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MANAGEMENT OF CHILDHOOD BRAIN TUMORS

Edited by

Melvin Deutsch, M.D.
University Health Center of Pittsburgh



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To Lisa and Sara

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CONTRIBUTING AUTHORS

A. Leland Albright, M.D.
Associate Professor, Neurosurgery
University of Pittsburgh
School of Medicine
Pittsburgh, PA 15213

Jeffrey C. Allen, M.D.
Associate Professor,
Pediatrics and Neurology
Departments of Neurology and Pediatrics
New York University Medical Center
550 First Avenue
New York, NY 10016

Silva Arslanian, M.D.
Assistant Professor, Pediatrics
Children's Hospital
University of Pittsburgh
School of Medicine
Pittsburgh, PA 15213

Laurence E. Becker, M.D., F.R.C.P. (C)
Professor, Pathology
Head, Division of Neuropathology
University of Toronto
Faculty of Medicine
The Hospital for Sick Children
Toronto, Ontario, Canada

Mitchell S. Berger, M.D.
Assistant Professor, Neurosurgery
University of Washington
Medical Center
School of Medicine
1959 N.E. Pacific Avenue
Seattle, WA 98195

William Cox, M.D.
Professor, Neurosurgery
Washington University
School of Medicine
660 South Euclid Avenue
St. Louis, MO 63110

Melvin Deutsch, M.D., F.A.C.R.
Professor, Radiation Oncology
University of Pittsburgh
School of Medicine
Pittsburgh, PA 15213

Gary R. Diamond, M.D.
Associate Professor, Ophthalmology
Hahnemann University
School of Medicine
Broad and Vine Streets
Philladelphia, PA 19102-1192

Jonathon L. Finlay, M.D.
Associate Professor, Pediatrics
Vice Chairman, Department of Pediatrics
Memorial Sloan Kettering Hospital
New York, NY

Thomas P. Foley, Jr., M.D.
Professor, Pediatrics
University of Pittsburgh
School of Medicine
Chief, Division of Endocrinology
Children's Hospital
Pittsburgh, PA 15213

Sarah J. Gaskill, M.D.
Resident, Neurosurgery
Department of Neurosurgery
Duke University
Durham, NC 22706

Harold J. Hoffman, M.D., F.A.C.S. (C)
F.A.C.S.
Professor, Surgery
Division of Neurosurgery
University of Toronto
Faculty of Medicine
Hospital for Sick Children
Toronto, Ontario, Canada

Venita Jay, M.D., F.R.C.P.C.
Assistant Professor, Pathology
Department of Pathology
University of Toronto
Faculty of Medicine
Neuropathologist
Hospital for Sick Children
Toronto, Ontario, Canada

David W. Johnson, M.D.
 Assistant Professor, Radiology
 University of Pittsburgh
 School of Medicine
 Pittsburgh, PA 15213

Richard E. Latchaw, M.D., F.A.C.R.
 Department of Radiology
 Swedish Hospital
 Ingelwood, Colorado
 Formerly Professor and Chairman
 Department of Diagnostic Radiology
 University of Pittsburgh
 School of Medicine
 Pittsburgh, PA 15213

Peter A. Lee, M.D., Ph.D.
 Professor, Pediatrics
 University of Pittsburgh
 School of Medicine
 Children's Hospital of Pittsburgh
 Pittsburgh, PA 15213

Arthur E. Marlin, M.D.
 Associate Clinical Professor, Orthopaedics and
 Pediatrics
 University of Texas
 Health Science Center
 7703 Floyd Curl Drive
 San Antonio TX 78284-7790

Jerrold M. Milstein, M.D.
 Associate Professor, Pediatrics and Medicine
 (Neurology)
 Children's Hospital and Medical Center
 University of Washington
 Seattle, WA 98195

Roger J. Packer, M.D.
 Professor, Neurology and Pediatrics
 George Washington University
 Director, Department of Neurology
 Children's National Medical Center
 111 Michigan Avenue, NW
 Washington, DC 20010

Dachling Pang, M.D., F.R.C.S. (C), F.A.C.S.
 Associate Professor, Neurosurgery
 University of Pittsburgh
 School of Medicine
 Chief, Pediatric Neurosurgery
 Children's Hospital
 Pittsburgh, PA 15213

Peter J. Savino, M.D.
 Clinical Professor, Ophthalmology
 University of Pennsylvania
 School of Medicine
 Thomas Jefferson University
 School of Medicine
 Chief, Neuro-Ophthalmology
 Willis Eye Hospital
 Philadelphia, PA 19104

Craig L. Silverman, M.D.
 Assistant Professor, Radiology
 University of Temple Hospital
 Philadelphia, PA 19104

Jeffrey A. Stevenson, M.D.
 Adjunct Clinical Professor of Radiation
 Oncology
 East Carolina University School of Medicine
 Director of Radiation Oncology
 Mercy Hospital of Janesville
 1000 Mineral Point Avenue
 Janesville, WI 53545

Lesley N. Sutton, M.D.
 Associate Professor Neurosurgery and Pediatrics
 University of Pennsylvania
 School of Medicine
 Philadelphia, PA 19104

Patrick R.M. Thomas, M.B.B.S.
 Professor, Radiology
 Washington University
 School of Medicine
 660 South Euclid Avenue
 St. Louis, MO 63110

Paul M. Zeltzer, M.D.
 Associate Professor, Pediatrics
 University of Southern California
 Director, Brain Tumor Program
 Children's Hospital of Los Angeles
 Los Angeles, CA 90033

PREFACE

In children, the central nervous system tumors are exceeded in incidence only by leukemia and are more common than any of the other malignancies of childhood. Childhood central nervous system tumors encompass a range of histologic varieties from the histologically benign-appearing pilocytic astrocytoma to the extremely malignant-appearing glioblastoma multiforme and the undifferentiated primitive neuroectodermal tumors. Similarly, the biologic behavior of childhood brain tumors varies not only according to histology but also with location of the tumor and age. Unlike primary central nervous system tumors in adults, many varieties of childhood brain tumors have the propensity to disseminate via the cerebrospinal fluid pathways. With improvements in length of survival, dissemination beyond the central nervous system is becoming a more common occurrence, especially for medulloblastoma.

Improvements in therapeutic outcome for adult primary malignant glioma over the past two to three decades can be measured by a few-months increase in median survival. In children, remarkable advances have been made in the treatment of brain tumors. In the first half of this century, the only afflicted children likely to survive were those with histologically and biologically nonaggressive tumors amenable to complete resection, such as cerebellar astrocytomas. Many tumor types that previously were almost 100% lethal, such as medulloblastoma and supratentorial malignant astrocytoma, can now be effectively treated, resulting in long-term survival for about half of all patients. However, some tumors, such as brainstem gliomas, still have a dismal outlook that has not changed appreciably over the past several decades.

Improvements in outcome have been ac-

complished through advances in the three main antineoplastic therapeutic modalities—surgery, radiation therapy, and chemotherapy. Improvements in neurosurgical technique concomitant with improvements in anesthesia and perioperative supportive care have resulted in decreased morbidity and mortality from neurosurgical procedures together with an increased likelihood of accomplishing a gross total resection of tumor. Radiotherapy has evolved from using orthovoltage (200–250 KV) equipment to supervoltage equipment with much-improved penetration, thus allowing for the administration of accurate homogeneous high doses to large volumes without significant effects on the overlying skin and soft tissues. Preliminary data indicate that multiagent chemotherapy as adjuvant therapy may be increasing the long-term survival rates of children afflicted with supratentorial malignant glioma and posterior fossa medulloblastoma. Undoubtedly, the advent of computerized tomography and now magnetic resonance imaging has contributed significantly to the management of the child with a brain tumor; diagnosis of intracranial tumor and hydrocephalus is now more accurately obtained without doing invasive, potentially dangerous procedures, and thus earlier diagnosis of tumor is possible. These imaging techniques also have allowed for a much more precise location of tumor for radiotherapy planning than was possible in prior times, when nucleotide scanning, angiography, and pneumoencephalography were used. Likewise, with these new imaging modalities, posttherapy evaluation is much easier and more accurate, allowing for determination of the amount of postresection residual tumor, surgically related complications such as hemorrhage, shunt malfunction, and recurrent tumor.

Along with the improvements in long-term

survival has come the realization that survivors may have a range of tumor- and treatment-related sequelae affecting neurologic, endocrine, and intellectual function. In addition, growth disturbances and second malignancies are potential late sequelae. Thus, it becomes increasingly more important to minimize these sequelae by early identification and intervention in order to improve the quality of survival. Similarly, optimization in the use of surgery, radiation, and chemotherapy must be sought in order not only to provide high rates of tumor control but also to decrease the incidence and severity of sequelae.

This volume outlines the diagnostic workup and pretherapy evaluation for the child with a

brain tumor. These include the pathological diagnosis, neurological and endocrine function assessment, and diagnostic radiology evaluation. The principles of neurosurgery, radiotherapy, chemotherapy, and also endocrine management as applied to children with brain tumors are presented, followed by a discussion of therapy and outcome for all the common childhood brain tumors. The final chapters are concerned with the posttherapy evaluation and management of recurrent tumor and the long-term sequelae of survivors—aspects of patient management that are increasingly important as more and more patients are being cured or are at least surviving longer.

1. INTRODUCTION

Melvin Deutsch

Over the past two decades, substantial advances have been made in the treatment of many of the common childhood malignancies. In the 1960s, patients cured of acute lymphocytic leukemia (ALL) were indeed rarities. Now over 90% of newly diagnosed children with ALL will attain remission and 60% will be long-term survivors. Survival rates for Wilms' tumor, childhood lymphoma, primary bone malignancies, and rhabdomyosarcoma have all improved dramatically over the past 20 years, due in large measure to the development of effective adjuvant chemotherapy regimens. The roles of surgery and radiotherapy have become better delineated. No longer is extensive surgical resection and radical radiotherapy considered mandatory for all children with solid tumors. Rather, mutilating surgery can often be avoided in favor of less radical resection, the judicious use of radiation, and chemotherapy. Few children with orbital rhabdomyosarcoma require exenteration, and similarly, few with rhabdomyosarcoma of the extremity require amputation. High-dose radiation therapy for Wilms' tumor and neuroblastoma is no longer uniformly administered. Rather, stage I and II Wilms' tumor or neuroblastomas usually do not require radiation, and for the advanced stages, moderate or low-dose radiation seems as efficacious as high-dose radiation, but with less long-term sequelae. Progress in the treatment of many of the common childhood malignancies has been expedited through the cooperative group mechanism whereby multiple institutions contribute patients for prospective randomized clinical trials. Compared to the adult population with cancer, a much larger

proportion of children with malignancy is treated in specialized centers and placed on prospective clinical trials.

Progress in the treatment of childhood brain tumors has been less remarkable, but nevertheless impressive. Of all the common childhood brain tumors, the greatest improvement in prognosis has occurred with medulloblastoma. Once a uniformly fatal disease, every decade has seen further improvements in five-year survival rates. At present, some subsets of medulloblastoma patients have a 70% five-year survival rate [1-4]. However, long-term survival rates for brainstem glioma, ependymoma, and high-grade astrocytoma are still less than 50% [5].

Multiple factors have contributed to the virtual elimination of the high operative mortality rates so common in past decades. Improvements in supportive care, use of shunts and corticosteroids to manage increased intracranial pressure and edema, improvements in anesthesia, and newer surgical techniques have practically eliminated operative mortality. It is now a rare occurrence for a child with medulloblastoma to die prior to initiation of radiotherapy [6, 7]. Even tumors in sites previously considered inaccessible such as the pineal region, can be approached safely for biopsy and resection.

The development of supervoltage radiotherapy (cobalt-60, linear accelerators) is probably the most important milestone in radiation therapy since Coolidge developed the 200 KV X-ray tube in 1913. Once supervoltage irradiation became available, it was possible to deliver homogeneous high doses to large volumes without the severe skin reactions associated with orthovoltage

or kilovoltage radiation. Undoubtedly, the advent of supervoltage radiation therapy was a factor in subsequent improved long-term survival rates in children with brain tumors. An example of this is seen in the report by McIntosh [8], who reported only one five-year survivor among 46 patients with medulloblastoma diagnosed in the five-year period from 1965 through 1969. In the next five-year period, 1970–1974, the five-year survival rate had increased to 39%. This improvement in outcome coincided with a change from 250 KV to supervoltage therapy equipment.

The marked benefits of chemotherapy for many of the common childhood malignancies have not yet been realized for childhood brain tumors. Only in the last ten years or so have large-scale clinical trials evaluating chemotherapy for childhood brain tumors been completed. Preliminary reports of the Children's Cancer Group (CCG) and Society International Oncology Pediatrics (SIOP) trials for medulloblastoma indicate a modest disease-free survival advantage with chemotherapy (vincristine, CCNU), especially for the poor-risk patient defined as having brainstem involvement and/or dissemination at diagnosis [9]. Similarly, a CCG study indicates benefit from chemotherapy for supratentorial malignant glioma. The same chemotherapy regimen was used as for the medulloblastoma study. However, this same regimen did not provide any benefit for brainstem glioma. Multiple drug regimens that have demonstrated activity for recurrent disease are currently being evaluated for newly diagnosed medulloblastoma, supratentorial primitive neuroectodermal tumors, and malignant glioma.

Recent developments in diagnostic neuro-radiology have literally revolutionized the management of the child with intracranial tumor. Computerized tomography (CT) and magnetic resonance imaging (MRI) are noninvasive, safe, and accurate methods for diagnosing intracranial mass lesions and also related conditions such as hydrocephalus, hemorrhage, edema, and calcification. Both imaging modalities provide an

effective method for postoperative assessment of extent of resection and the amount of residual tumor. In addition, CT and/or MRI are invaluable for follow-up assessment of a treated patient. Undoubtedly, these noninvasive, accurate modalities allow for the earlier detection of intracranial tumors both initially and at recurrence. Nowadays, probably any child with a seizure or persistent headache is evaluated by CT or MRI. Pneumoencephalography, with its risks and discomfort, is no longer performed and even angiography is seldom necessary for the preoperative evaluation of an intracranial tumor.

CT and MRI have greatly simplified the task of the radiation oncologist in designing treatment for the intracranial tumor. In prior years, malignant gliomas were often treated with whole-brain irradiation because of the inability to accurately localize such tumors by radiographic studies and clinical signs. Now, with CT and MRI, the radiation oncologist is able to accurately localize an intracranial tumor and, with the aid of computerized treatment planning, design the therapy so that the tumor volume is adequately covered by the high-dose volume, whereas normal uninvolved tissues are spared as much as possible [10]. CT and to a lesser extent MRI have also permitted development of accurate stereotactic neurosurgical procedures such as stereotactic biopsy, cyst drainage, insertion of radioactive isotopes into cystic lesions, and interstitial implantation of sealed radioactive sources.

Brain tumors and their treatment may produce long-term sequelae or deficits. Neurologic deficits caused by the tumor may persist in spite of successful treatment. Radiation necrosis, a rare complication of therapy, may cause symptoms and signs very similar to those at initial diagnosis. Endocrine dysfunction from tumor or from radiotherapy is now well recognized and fortunately can often be corrected by appropriate replacement therapy. Synthetic growth hormone is now available for the child with growth retardation posttherapy. As more and more children are surviving for long periods after treatment of intracranial brain tumors,

clinicians are becoming aware that a substantial proportion may have subtle but definite intellectual impairments. However, the majority of survivors appear to lead normal lives and few are impaired to the point of being non-self-sufficient.

Young age and radiation seem to be factors in predicting subsequent late effects. Thus, it is important to continue investigations concerned with limiting radiotherapy in terms of doses and volumes whenever possible. Again, cooperative group studies are important in this regard. The CCG is currently evaluating low-dose neuraxis radiotherapy for low-stage medulloblastoma (T1, T2, T3A, M0).

A devastating event for the survivor of one childhood malignancy is the development of a second primary tumor. Survivors of childhood brain tumors seem to be at an increased risk for developing second malignancies, as are the survivors of other childhood malignancies. This risk may be due to genetic or other etiologic factors responsible for the first tumor. However, there is increasing concern that treatment—radiotherapy and/or chemotherapy—may be responsible for an appreciable number of second malignancies. As more patients become long-term survivors due to better management, the occurrence of second primary tumors may become more commonplace.

Therefore, it is important that all children treated for brain tumors be followed indefinitely, not only for evidence of recurrent tumor, but also to detect late effects for which intervention may be warranted and also to detect at an early treatable stage second primary tumors, should they arise. The proper management of the child with an intracranial tumor requires the efforts of a multispecialty medical team and also the input of nurses, social workers, and psychologists.

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2. TUMORS OF THE CENTRAL NERVOUS SYSTEM IN CHILDREN

Laurence E. Becker

Venita Jay

In children, primary tumors of the brain are the most common solid neoplasms and are surpassed in frequency only by leukemia [1, 2]. The incidence, location, and natural history of brain tumors in children differ considerably from those in adults. There are significant contrasts between the two age groups in clinical symptomatology as well as temporal progression and outcome for particular tumors. These differences extend to other areas such as tumor morphology and pathology.

While major advances in imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), provide excellent anatomical localization [3, 4], pathologic confirmation is required to predict outcome and determine appropriate therapy. In addition to tumor biopsies, cerebrospinal fluid (CSF) cytology and biochemistry may be significant in some instances. Advances in immunodiagnosis have been made possible by the production of wide varieties of polyclonal and monoclonal antibodies.

A major contribution to tumor diagnosis and understanding will occur as developments in molecular genetics are more directly applied to diagnostic tumor biopsies. The objective grading of primary brain tumors to reflect accurately clinical behavior remains one of the most difficult problems facing the neuropathologist. Application of monoclonal antibodies, tumor kinetics, karyotypic analysis, and determination

of oncogene amplification will produce a better correlation of histologic appearance and prognosis and a more accurate prediction of biologic behavior.

Fundamental investigation of primary brain tumors has largely depended on the use of animal models. Many tumor models of the central and peripheral nervous system have been developed [5–17]. The most desirable model is one that is both histologically representative of the tumor and biologically comparable to its human equivalent. Animal models for human brain tumors present the same general advantages and disadvantages as animal models for most spontaneously occurring human disorders. They provide flexibility in designing experiments where several important variables can be carefully controlled. However, their application to the human *in vivo* situation is frequently questionable.

Cell culture has emerged in the last two decades as a versatile technique in the investigation of central nervous system (CNS) tumors [18–25]. The testing of *in vitro* chemosensitivity of a particular tumor is attractive. A tumor biopsy can be placed in short-term culture and its response to different agents studied, and therapy individually tailored. However, in a practical sense, this has not happened. The early cultures are often composed of a heterogeneous population of cells, so that drug effects can be difficult to interpret. If tumor cell lines could be

developed more effectively, the target cells would be more homogeneous and greater confidence could be placed on chemosensitivity assays.

In this chapter, we present the salient aspects of the pathology of brain tumors with a discussion of conventional morphology, ultrastructure, immunohistochemistry, and CSF examination, as well as comments on the current progress in understanding tumor biology.

Classification

A modification of the original World Health Organization (WHO) classification [26] was proposed in 1984 by a group of pediatric neuropathologists meeting under the sponsorship of the American Cancer Society [27] (table 2-1). Among the major changes was the transfer of glioblastomatous tumor to the glial category

TABLE 2-1. Classification of brain tumors in children

I. Tumors of neuroepithelial tissue	
A. Glial tumors	
1. Astrocytic tumors	
a. Astrocytoma (fibrillary, protoplasmic, gemistocytic, pilocytic, and xanthomatous)	
b. Anaplastic astrocytoma	
c. Subependymal giant-cell tumors (tuberous sclerosis)	
d. Giantocellular glioma	
2. Oligodendroglial tumors	
a. Oligodendroglioma	
b. Anaplastic oligodendroglioma	
3. Ependymal tumors	
a. Ependymoma	
b. Anaplastic ependymoma	
c. Myxopapillary ependymoma	
4. Choroid plexus tumors	
a. Choroid plexus papilloma	
b. Anaplastic choroid plexus tumor (carcinoma)	
5. Mixed gliomas	
a. Oligoastrocytoma	
1. Anaplastic oligoastrocytoma	
b. Astroependymoma	
1. Anaplastic	
ependymastrocytoma	
c. Oligoastroependymoma	
1. Anaplastic oligoastroependymoma	
d. Oligoependymoma	
1. Anaplastic oligoependymoma	
e. Subependymoma—subependymal glomerate astrocytoma	
f. Gliofibroma	
6. Glioblastomatous tumors	
a. Glioblastoma multiforme	
b. Giant-cell glioblastoma	
c. Gliosarcoma	
7. Gliomatosis cerebri	
B. Neuronal tumors	
1. Gangliocytoma	
2. Anaplastic gangliocytoma	
3. Ganglioglioma	
4. Anaplastic ganglioglioma	
C. Primitive neuroepithelial tumors	
1. Primitive neuroectodermal tumor, not otherwise specified (NOS)	
2. Primitive neuroectodermal tumor with	
a. Astrocytes	
b. Oligodendrocytes	
c. Ependymal cells	
d. Neuronal cells	
e. Other (melanocytic, mesenchymal)	
f. Mixed cellular elements	
3. Medulloepithelioma	
a. Medulloepithelioma, NOS	
b. Medulloepithelioma with	
1. Astrocytes	
2. Oligodendrocytes	
3. Ependymal cells	
4. Neuronal cells	
5. Other (melanocytic, mesenchymal)	
6. Mixed cellular elements	
D. Pineal cell tumors	
1. Primitive neuroectodermal tumor (see C above) (pineoblastoma)	
2. Pineocytoma	
II. Tumors of meningeal and related tissues	
A. Meningiomas	
1. Meningioma, NOS	
2. Papillary meningioma	
3. Anaplastic meningioma	
B. Meningeal sarcomatous tumors	
1. Meningeal sarcoma, NOS	
2. Rhabdomyosarcoma or leiomyosarcoma	
3. Mesenchymal chondrosarcoma	
4. Fibrosarcoma	

- 5. Others
 - C. Primary melanocytic tumors
 - 1. Malignant melanoma
 - 2. Melanomatosis
 - 3. Melanocytic tumors, miscellaneous
 - III. Tumors of nerve sheath cells
 - A. Neurilemoma (schwannoma, neurinoma)
 - B. Anaplastic neurilemoma (schwannoma, neurinoma)
 - C. Neurofibroma
 - D. Anaplastic neurofibroma (neurofibrosarcoma, neurogenic sarcoma)
 - IV. Primary malignant lymphomas
Classify according to local current standards
 - V. Tumors of blood vessel origin
 - A. Hemangioblastoma
 - B. Hemangiopericytoma
 - C. Neoplastic angioendotheliosis—angiosarcoma
 - VI. Germ-cell tumors
 - A. Germinoma
 - B. Embryonal carcinoma
 - C. Choriocarcinoma
 - D. Endodermal sinus tumor
 - E. Teratomatous tumors
 - 1. Immature teratoma
 - 2. Mature teratoma
 - 3. Teratocarcinoma
 - F. Mixed
 - VII. Malformative tumors
 - A. Craniopharyngioma
 - B. Rathke's cleft cyst
 - C. Epidermal cyst
 - D. Dermoid cyst
 - E. Colloid cyst of third ventricle
 - F. Enterogenous or bronchial cyst
 - G. Cyst, NOS
 - H. Lipoma
 - I. Granular cell tumor (choristoma)
 - J. Hamartoma
 - 1. Neuronal
 - 2. Glial
 - 3. Neuronoglia
 - 4. Meningioangioneurinomatosis
 - VIII. Tumors of neuroendocrine origin
 - A. Tumors of anterior pituitary
 - 1. Adenoma
 - 2. Pituitary carcinoma
 - B. Paraganglioma
 - IX. Local extensions from regional tumors
Type to be specified according to primary diagnosis
 - X. Metastatic tumors
 - XI. Unclassified tumors
-

and the introduction of the term *primitive neuroectodermal tumor* (PNET).

PNET is particularly relevant to childhood tumors. The term was introduced in an attempt to simplify nosology and bring together a group of tumors with different names but with histology that appears identical using currently available techniques. Confusion has arisen over the use of PNET as a concept and as a name for a tumor. In the suggested revision of the WHO classification, the term *primitive neuroepithelial tumor* is used as the general heading for the PNET group of tumors—that is, this term is used in the conceptual sense, and PNET is used as a name for a specific tumor. This system, when applied to children's tumors, works well with PNETs of the cerebrum and pineal gland (figure 2-1). However, there is a great reluctance to give up the term medulloblastoma for such tumors of the cerebellum. Therefore, we have found it convenient to retain medulloblastoma and parenthesize PNET of cerebellum.

Relative Incidence and Site

Since the prognosis of a cell tumor is closely linked to its anatomical site, standard site designations are recommended [27]. In our series of CNS tumors, 52% occur below the tentorium, 40% supratentorially, and 8% in the spinal cord [28].

Supratentorial tumors can be assigned to standard sites: hemispheric (35%), parasellar (40%), thalamic and basal ganglial (10%), pineal (10%), intraventricular (3%), and meningeal (2%). Infratentorial tumors occur in the cerebellum in 75% of cases and in the brainstem and fourth ventricle in 25% [28]. In both supratentorial and infratentorial locations, the most frequent tumor type is the astrocytoma [28–32].

When histology is related to location, 65% of tumors in the cerebral hemisphere are astrocytomas, 15% are PNETs, 15% ependymomas, and 5% other types [28]. Tumors in the parasellar region are divided into suprasellar

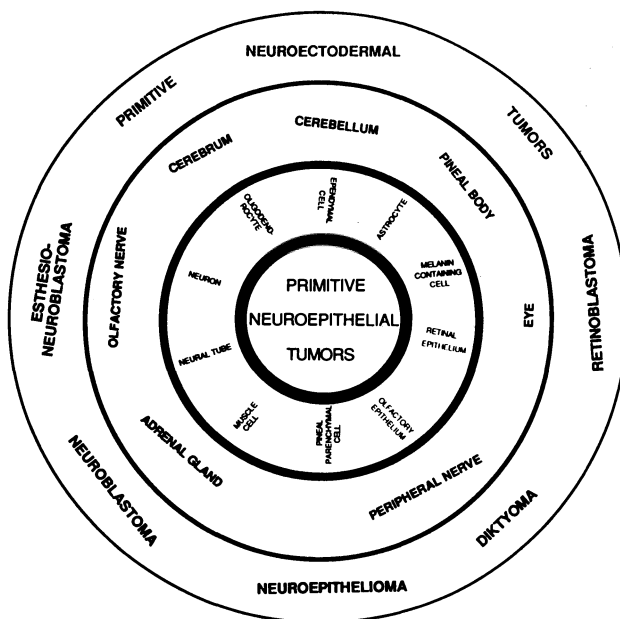


FIGURE 2-1. Primitive neuroepithelial tumors, the conceptual term for this wide variety of tumors. They may show a variety of cell types and occur in many locations. In nomenclature, some of these tumors retain specific designations and others, occurring in the cerebral cortex, pineal region, and cerebellum, are called primitive neuroectodermal tumors (PNETs).

(40%), optic nerve (40%), hypothalamic (15%), and pituitary-related (< 5%) types. Of the tumors in the suprasellar region, 85% are craniopharyngiomas and 15% germ-cell tumors. In the infratentorium, 50% are astrocytomas, 20% medulloblastomas (PNETs of cerebellum), 15% ependymomas, and 15% other types (schwannomas, meningeal tumors, hemangioblastomas, and chordomas).

Diagnosis

Traditionally, pathologic diagnoses depended on the recognition of histologic patterns using conventional techniques applied to paraffin-embedded sections or cytological preparations from CSF, and recognition of cellular characteristics using electron microscopy. However, recent advances in immunohistochemistry, using monoclonal and polyclonal antibodies, tumor biochemistry, cell culture, cell kinetics, karyotyping, and oncogene analysis, have widened the spectrum of diagnostic techniques that can

be applied to biopsy tissue and CSF samples.

Besides frozen sections and paraffin-embedded material, imprints and crush or smear preparations are invaluable adjuncts, particularly when dealing with small tissue samples [33–39]. These techniques provide an unsurpassed clarity of cytologic detail unaccompanied by the usual freeze artifact of frozen section preparations. Accuracy rates obtained by comparison of diagnoses from smear preparations with those from subsequent paraffin-embedded permanent sections range from 90% to 95% [36, 39].

Thus, used in conjunction, frozen sections, tissue imprints, and routine histology provide excellent detail of the pathology. For example, the whorling of meningothelium in meningio-

mas as well as psammoma bodies and intranuclear pseudoinclusions may be readily apparent on tumor imprints. In glial tumors, the presence of cell processes can be appreciated and a better assessment of cytologic atypia can be made. Tumor imprints or smears are also useful in diagnosis of PNETs and germinomas. In the latter, they may reveal the malignant nature of the germ-cell component better than paraffin sections.

Immunohistochemistry

Immunodiagnosis by identification of specific cell characteristics has become an indispensable tool in diagnostic pathology. In some instances, antisera to cell surface proteins and intracellular components can clearly label cell types. Of special importance are the intermediate filaments, so called because their diameter (10 nm) is intermediate between that of microfilaments (6 nm) and microtubules (25 nm). These filaments are widespread, being present in the cytoskeleton of almost all vertebrate cells [40]. Five classes of intermediate filaments are recognized, each suggesting a predominant differentiation toward a particular cell type: cytokeratin (epithelial), neurofilament (neuronal), glial fibrillary acidic protein (GFAP) (astroglial), desmin (muscle), and vimentin (mesenchymal and glial). A single cell may express at least two types of intermediate filaments simultaneously; astrocytes can express both vimentin and GFAP [41].

Application of polyclonal and monoclonal antisera for identification of intermediate filaments or other cell components forms the mainstay of immunodiagnosis. Routine immunohistochemical diagnostic methods include immunofluorescence, peroxidase–antiperoxidase, and avidin–biotin techniques [42–44]. The latter two methods are relatively easy to apply on paraffin-embedded tissue and have largely replaced immunofluorescence. In the CNS, major strides have been made in developing reliable astrocytic markers, such as antisera to GFAP.

GLIAL FIBRILLARY ACIDIC PROTEIN (GFAP)

Since GFAP was isolated by Eng and coworkers [45] and subsequently recognized as an astrocytic marker [46], its distribution in various CNS neoplasms has been widely studied [47–56]. This 48–50 kD protein is recognized as the chemical subunit of the intermediate filaments in the cytoplasm of glial cells [57, 58].

Both reactive and neoplastic astrocytes demonstrate positive staining with antisera to GFAP, the positivity being inversely correlated with the degree of anaplasia. This marker has helped in identifying poorly differentiated gliomas that involve the leptomeninges and, in the process, elicit a significant fibroblastic reaction simulating a mesenchymal tumor [47, 48]. It has also helped to identify the glial nature of unusual variants, such as the pleomorphic xanthoastrocytoma [59], which represents a distinctive form of supratentorial astrocytoma in young subjects. These tumors are superficial and involve the leptomeninges extensively. Although the tumor cells display marked pleomorphism, with bizarre giant cells, the prognosis appears relatively favorable with long survival times. The tumor cells contain large amounts of lipid and are immunoreactive for GFAP.

GFAP is also valuable in confirming the glial nature of primary CNS tumors that have metastasized to extracranial sites (figure 2-2), and in excluding the nonglial nature of those that superficially resemble astrocytomas [47]. Since GFAP is widely used as an astrocytic marker, a frequently encountered problem is the interpretation of GFAP positivity in tumors whose morphologic appearances are clearly not those of an astrocytoma. The presence of GFAP in nonastrocytic tumors such as oligodendrogliomas has been a subject of speculation [49, 50, 52, 56, 60]. We found GFAP positivity in cells with features typical of oligodendroglia in 9 of 14 oligodendrogliomas [60]. Some investigators consider such cells to be astrocytic [52], while others suggest that they

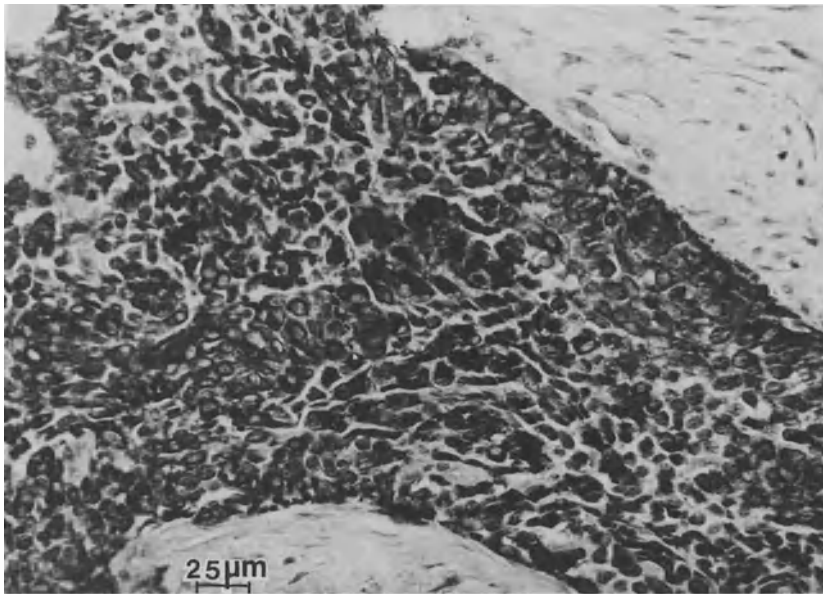


FIGURE 2-2. GFAP-positive tumor cells in an astrocytoma that has metastasized to the scalp.

represent transitions from oligodendroglia to astrocytes [56]. Alternatively, these cells may reflect the transient expression of GFAP by immature oligodendroglia during an early phase of development [56, 60]. In other words, GFAP positivity in itself does not render the diagnosis of an astrocytoma to any particular tumor, if the morphologic appearances are those of a nonastrocytic lesion. Of course, if GFAP positivity is found, the presence of an astrocytic component should be investigated.

GFAP-positive cells have been described in medulloblastomas (figure 2-3) and choroid plexus tumors [61–63]. These cells are believed to represent focal astrocytic differentiation in medulloblastomas and tanycytic differentiation in choroid plexus tumors.

VIMENTIN

Vimentin is a 57 kd protein subunit characteristic of various cell types such as fibroblasts, chondrocytes, macrophages, and endothelial cells [40]. It is also the first intermediate filament to appear in embryonal development, regardless of cell type, and is later replaced by the inter-

mediate filament specific for that particular cell type. Vimentin exists in developing, reactive, and neoplastic astrocytes and ependymal cells [41, 64]. Vimentin immunoreactivity may be found in meningioma and astrocytoma [65, 66].

S-100 PROTEIN

This 21 kd protein is one of the most extensively studied proteins of the nervous system. Its cytologic function remains unknown [67]. The protein has been localized to both nucleus and cytoplasm in a wide variety of cell types, and there are indications that it is not a single protein but is composed of several antigenically distinct proteins [67, 68]. This antigen has been detected not only in glial and nonglial tissues of the CNS and peripheral nervous system but also in cells of nonneuroepithelial origin (e.g., meningioma, keratinocytes of craniopharyngiomas, Langerhans' cells of skin, chondrocytes of bone, granular cell tumors, pleomorphic adenoma of salivary gland, myoepithelium of breast, and histiocytosis X) [69–72]. Although it cannot be included as a specific marker for glial or

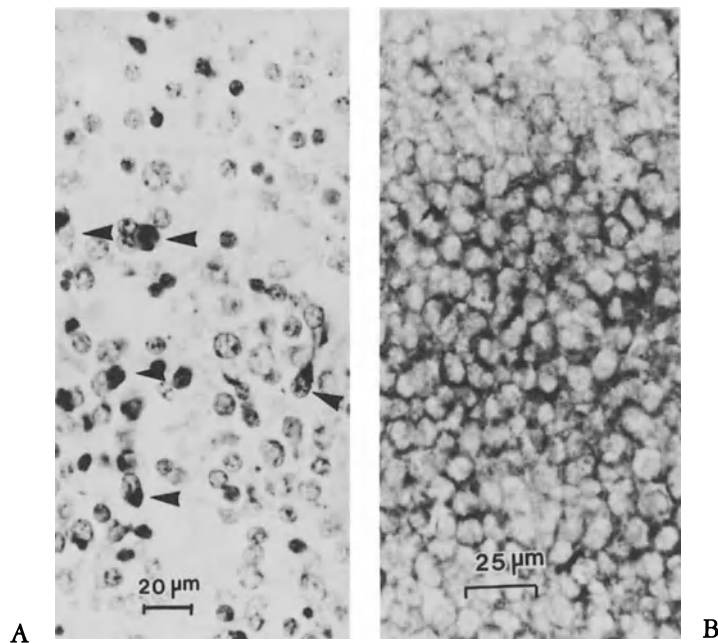


FIGURE 2-3. Cerebellar medulloblastoma showing A. focal immunoreactivity for GFAP (arrowheads), and B. diffuse immunoreactivity for neuron-specific enolase.

schwannian origin, S-100 is useful in diagnostic neuropathology for assessing conditions such as histiocytosis X and nerve sheath tumors.

NEURON-SPECIFIC ENOLASE (NSE)

Enolase is a cytoplasmic enzyme that catalyzes one of the late steps in the glycolytic pathway. NSE was assumed to be restricted to the neurons of the central and peripheral nervous system [73]. Hullin et al. [74] reported that immunoreactivity to NSE is present in all human organs, but at levels less than 3% of those found in human brain. Schmechel and associates [75] demonstrated its presence in several tissues of the amine precursor uptake and decarboxylation (APUD) system. Antisera to NSE have been useful for recognizing PNETs (figure 2-3B), peripheral neuroblastomas, melanomas, and APUD tumors [76, 77]. Several types of CNS tumors, including gliomas, ependymomas, choroid plexus tumors, and meningiomas, have

shown focal immunoreactivity for NSE [78]. However, the finding of NSE in nonendocrine tumors, such as lymphoma and breast and ovarian carcinoma [77], raises further questions about its absolute specificity as a neuronal marker [78, 79].

OTHER MARKERS

The application of the following markers, including enzymes and membrane proteins, to tumor diagnosis has been limited. Some of the less widely used astrocytic markers include enzymes such as glutamine synthetase [80] and 5'-nucleotidase [81]. Laminin, a basement membrane glycoprotein, has been observed in tumors such as schwannomas and fibroblastic meningiomas [82, 83]. It is expressed in vitro by immature astrocytes [84]. Laminin has not been detected in the cytoplasm of tumor cells in gliomas, and in the normal nervous system and neuroepithelial neoplasms it is expressed in regions of recognized basal lamina formation, including the junction between glial and mesenchymal elements [83, 85].

Another glycoprotein, fibronectin, has been

studied in nonglial and glial neoplasms [86, 87]. Fibronectins represent a family of structurally and immunologically related high-molecular-weight glycoproteins [88]. In one study, the GFAP-positive cells in glial tumors were fibronectin-negative; thus, the expression of fibronectin and that of GFAP appear to be mutually exclusive [86]. Fibronectin has also been demonstrated in vessel walls and tumor cells in meningiomas [87]. Keratin immunoreactivity has been observed in choroid plexus tumors [89–91]. Meningiomas characteristically stain positively for epithelial membrane antigen and desmosomal plaque proteins, in addition to mesenchymal markers such as vimentin [65, 66, 92–94].

A completely satisfactory immunohistochemical marker for oligodendrogliomas remains to be developed. However, about 90% of CNS oligodendrogliomas have been noted to be immunoreactive for Leu 7 [95–98]. This marker for human lymphocytes with natural killer activity also recognizes CNS and peripheral myelin-sheath elements including oligodendrocytes and Schwann cells [99]. Perentes and Rubinstein [100] reported anti-Leu-7-positive cells in 80% of schwannomas in a series of 47 nerve-sheath tumors; the 22 nonschwannian neoplasms in this series were negative.

Vandeveldt et al. [101] reported myelin-associated glycoprotein-positive cells in 3 of 11 canine oligodendrogliomas. Using the same monoclonal antibodies, Nakagawa et al. [96] found only a few immunoreactive cells in 1 of 30 human oligodendrogliomas. Immunopositivity to myelin basic protein (a component of CNS and peripheral myelin) has been reported in oligodendrogliomas [102], although other studies have failed to demonstrate its presence in this tumor [96]. Carbonic anhydrase C is an enzyme seen in normal glia [103, 104]. Kumpulainen et al. [105, 106] reported carbonic anhydrase positivity in mouse and human oligodendroglia and suggested that it might be useful for human oligodendroglia. However, in other studies, neoplastic and normal oligodendroglia have not

consistently shown immunoreactivity for carbonic anhydrase [96]. Other suggested oligodendroglial markers such as galactocerebroside [107] have not been systematically applied to human oligodendrogliomas. [Please see addendum.]

Monoclonal Antibodies

Monoclonal antibodies are directed against a single determinant on the antigen molecule for which they are specific; thus, they are more specific than polyclonal antibodies, although not necessarily more sensitive. The use of a panel of monoclonal antibodies (with various components being specific for different determinants of the antigen) enhances the sensitivity for diagnostic purposes (figure 2-4). The primary advantages of monoclonal antibodies are, therefore, their exquisite specificity and the long-term availability of a reagent that does not vary over time, thus providing a more specific and standardized set of reagents for immunodiagnosis.

Some monoclonal antibodies that have or will have direct relevance to brain tumor diagnosis are those raised against biochemically defined substances (GFAP, neurofilaments), antigens shared by lymphoid and neural cells, and antigens in human fetal brain [108–115]. McLendon et al. [115] applied three monoclonal antibodies to GFAP as a cocktail preparation and found that the quality of immunoperoxidase detection of GFAP closely approached that of a polyvalent anti-GFAP serum. Coakham, Garson, and associates [110, 113, 114] used a panel of seven monoclonal antibodies to characterize cerebral and spinal tumors. They used antibodies binding to most neuroectodermally derived tumors and tissues (UJ13A), fetal brain and tumors of neuroblastic origin (UJ181.4), schwannomas and normal and neoplastic neurons (UJ127.11), glial cells (FD 19), epithelial cells (LE 61), and leukocytes (2D1) in their study. They reported that in 12 cases the use of the monoclonal antibody panel was entirely respon-

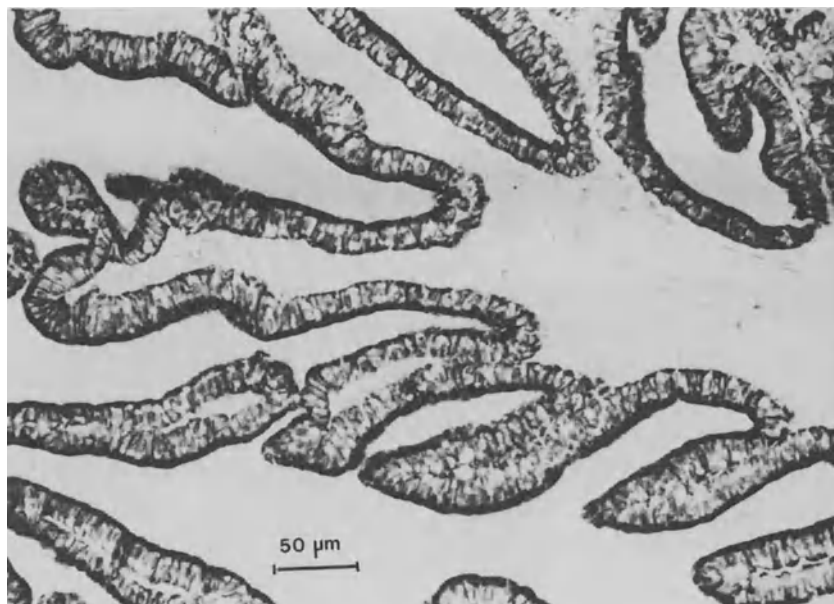


FIGURE 2-4. Cytokeratin immunoreactivity in choroid plexus papilloma shown by a monoclonal antibody. (Courtesy of Dr. H. Mannoji.)

sible for the final diagnosis, while in 22 cases, the panel made a significant contribution [114]. Since monoclonal antibodies represent a continuous supply of a well-defined monospecific reagent, such combinations may be superior to polyclonal sera for large studies extending over long periods of time. On depletion of a particular stock of polyclonal serum, an identical serum cannot be generated because of the biologic variables inherent in its production. Application of the monoclonal antibody technique is particularly useful in CSF cytology and fine-needle aspiration cytology [114].

CSF Studies

CYTOLOGY

CSF examination is of value in the investigation of patients with lymphohematopoietic disorders as well as primary CNS tumors [116–119]. The primary tumors in children with a propensity for seeding the CSF pathways include PNET, ependymoma, and germinoma.

Polmeteer and Kernohan [120] reviewed the Mayo Clinic autopsy experience (children and adults) of 20 years for the meningeal spread of primary brain tumors. The 42 cases with meningeal involvement included medulloblastoma (20), glioblastoma multiforme (6), ependymoma (5), oligodendroglioma (5), astrocytoma (3), retinoblastoma (2), and germinoma (1).

In assessing CSF cytology, one must take into consideration some normally encountered cell types such as ependyma, choroid plexus, macrophage, lymphocyte, and monocyte. Choroid plexus and ependymal cells are particularly common in direct ventricular samples.

Low-grade astrocytomas are rarely identified in the CSF [117, 119]. Large pleomorphic exfoliated cells may be found in glioblastoma multiforme, and dissemination into the CSF spaces is common in medulloblastoma and germinoma. In germinomas, subependymal implants are almost always found at autopsy.

Immunofluorescence and immunoperoxidase reactions of CSF cytospin preparations with monoclonal antibodies can also be employed in cytodiagnosis [112, 114].

BIOCHEMICAL MARKERS

Outside of a biopsy, examination of CSF for tumor cells is the most specific diagnostic aid. However, this investigation is worthless when leptomeningeal involvement has not occurred. In such a circumstance, biochemical marker studies may be useful [121–124]. Alpha-fetoprotein and chorionic gonadotropin are particularly helpful in diagnosis of intracranial germ-cell tumors. Other markers, such as polyamines and sterols, are relevant to the clinical outcome and management of gliomas but are not widely available.

Carcinoembryonic Antigen (CEA). CEA, a glycoprotein of fetal endodermal tissues, is normally absent in the brain; elevated levels occur with leptomeningeal metastases from CEA-producing systemic solid tumors [125–127]. In the diagnosis of primary CNS tumors, CEA has limited value, although Naganuma and colleagues [128] reported the presence of CEA in the CSF of two patients with mature intracranial teratomas.

Alpha-Fetoprotein. Alpha-fetoprotein has received much attention as a potentially useful marker for malignant, primary, CNS germ-cell tumors [129]. It is elevated in the CSF of patients with primary CNS embryonal carcinoma and endodermal sinus tumor. In these patients serum levels may be normal [123].

Human Chorionic Gonadotropin (HCG). Beta-subunit of HCG has been detected in the CSF of patients with intracranial choriocarcinomas and embryonal carcinoma [129]. The CSF level in a primary germ-cell tumor may exceed that in serum. The level decreases with therapy and rises with relapse [129].

Polyamines. Several reports have focused on the role of polyamines in human and experimental tumors [130–139]. Polyamines, including putrescine, spermidine, and spermine, are low-molecular-weight amines involved in

cell proliferation. Their levels are elevated in rapidly growing nonneoplastic tissue and tumor cells. The putrescine levels may reflect proliferative activity or growth fraction of tumors, whereas spermidine may be a marker of tumor cell death. These compounds are thought to be involved in nucleic acid metabolism and cell replication. In 1971, preliminary data indicated a possible relationship between elevated urinary polyamine levels and human cancers [130].

Polyamine levels in CSF are consistently increased in association with brain tumors, regardless of histologic type. Compared with subjects without tumor, those with untreated malignant CNS tumors have elevated CSF polyamine concentration [134]. However, polyamine increase may occur in nonneoplastic conditions (e.g., cerebrovascular disease, infection), although the increase is not as high as that caused by malignant brain tumors [134]. The polyamine concentrations in CSF do not bear any particular relationship to CSF protein levels; however, levels in samples containing blood may be elevated [134].

Polyamine concentrations are helpful in monitoring therapy. The values appear to relate to tumor burden and tumor growth rate. CSF polyamine levels show statistically significant differences between patients with malignant brain tumors who are responding to chemotherapy (clinical tumor regression) and those who are untreated [134]. Levels decline with improvement in clinical status. Thus, CSF polyamine determinations show promise as aids in early diagnosis, long-term evaluation of treatment, and short-term evaluation of the efficacy of a specific course of therapy. One study found that red blood cell (RBC) spermidine levels were higher in glioblastomas than other tumor types and that there was a highly significant correlation between the spermidine/spermine ratio in the tumor and in the RBCs [138]; the authors of that report proposed that RBC polyamine levels may be of use in monitoring patients with glioblastoma multiforme.

Polyamine levels in the CSF have been exten-

sively studied in patients with medulloblastomas. In one study [138], medulloblastomas showed the highest concentrations of all tumors. Takae et al. [139] found a significant increase in putrescine levels in children who had recurrent or metastatic medulloblastomas in sites close to the CSF pathways, compared with those in children whose disease status was stable after successful therapy. They proposed that increased CSF putrescine levels may be an early and sensitive quantitative marker of the progression of medulloblastomas.

Sterols. Desmosterol, the immediate precursor of cholesterol in the pathway of brain sterol synthesis, is a major constituent of the developing brain, where cholesterol biosynthesis is most rapid, while its content decreases with maturation [140]. In brain tumors, sterol synthesis is elevated and increased sterol levels have been reported in the CSF [140, 141]. However, there are conflicting reports about the usefulness of this marker [142], and desmosterol assay is complicated, making it impractical for clinical use [124].

GFAP. Elevated levels of GFAP in CSF have been detected by radioimmunoassay in glial and nonglial tumors as well as in nonneoplastic CNS disorders [143].

Cell Kinetics

While the histologic typing of a tumor has been greatly enhanced by advances in immunodiagnosis, a good histologic marker to determine malignancy and ultimate biologic behavior remains to be developed. Although increased cellularity, high mitotic rate, cellular pleomorphism, and factors such as necrosis and endothelial proliferation are used to determine the extent of anaplasia, these features do not accurately predict the growth potential of a particular tumor. Martin et al. [144] reported on automated image analysis of gliomas using morphometric, densitometric, and mitotic par-

ameters that they claimed allowed reproducible division of gliomas into four grades. Klinken and associates [145] also compared the predictive value of classic histologic grading and of two automatically retrieved nuclear parameters in patients with astrocytomas, and stated that nuclear count and nuclear area fraction correlated with survival.

Cell kinetic studies essentially provide information about the deoxyribonucleic acid (DNA) content and proliferative activity of tumors. In a normal nondividing cell, the DNA complement is diploid. In the life cycle of a cell, the following phases can be visualized: G0 (postmitotic cell, diploid), G1 (S phase, with DNA synthesis, variable DNA complement), and G2 (premitotic with tetraploid DNA complement). However, some nondividing cells are known to have a tetraploid DNA complement (e.g., 17% of the glial population in the Purkinje cell layer are said to be polyploid [146, 147]).

In cell kinetic studies, two principal methods have been applied: 1) flow cytometry, and 2) administration of tritiated thymidine before surgery, followed by autoradiography.

Recent advances have provided a method for rapid and accurate determination of the DNA content of individual cells [148–158]. Automated flow cytometry measures the amount of DNA per cell by quantitating the intensity of fluorescence emitted by a DNA-binding dye as the nuclei flow rapidly past a high-intensity laser beam [148, 157]. With these data, a histogram can be constructed with peaks corresponding to diploid and tetraploid cells as well as aneuploid cells. Thus, in a low-grade astrocytoma, there are two peaks, one for cells in the G0 or G1 phase and the second for cells in the G2 phase [151]. In contrast, malignant gliomas show a substantial population of cells in DNA synthesis with a wide distribution ranging from diploid to higher DNA complement. The distribution of the predominant ploidy varies in different regions of the same tumor [151]. Thus, malignant gliomas are heterogeneous with re-

spect to both ploidy and the distribution of ploidy in different areas of the same tumor. A tendency to change in the ploidy to a higher level in recurrent brain tumors has also been observed [154].

Mørk and Laerum [155] reported the presence of near diploid DNA content in a large number of poorly differentiated gliomas; thus, heteroploidy may not always correlate with aggressive biologic behavior. The characteristic histogram for benign tumors has a large diploid peak and a smaller tetraploid peak. However, two benign tumors (meningiomas and pituitary adenomas) have large numbers of aneuploid cells [149, 150].

Flow cytometry has also been applied to cultured cell lines from tumors and for analysis of CSF tumor cells [156, 158].

The other method employed in cell kinetic studies is tritiated thymidine-labeled autoradiography using tumor samples. In the first in vivo study of glioblastoma multiforme, multiple doses of tritiated thymidine were injected intravenously into a terminally ill patient and a labeling index of 0.6% was calculated [159]. The labeling index, which is the proportion of cells labeled shortly after a flash of tritiated thymidine, represents the percentage of cells in DNA synthesis preparing for mitosis in relation to the total cell population, and gives an approximation of the proliferative activity of the tumor in question [160–162]. Hoshino et al. [160] found that the labeling index not only differed among various gliomas but correlated reasonably well with histologic characteristics. As expected, in necrotic areas, the labeling index approached zero, while in viable areas, it was as high as 20%.

Growth fraction and cell cycle times are important parameters that are highly relevant to chemotherapeutic regimens. For example, drugs such as vinca alkaloids affect cells in a specific sensitive phase of the cycle, while drugs such as nitrosoureas that are cell-cycle nonspecific kill proliferating as well as nonproliferating cells. To obtain a sequential decrease in tumor size

with these drugs, courses of therapy must be repeated before the cells have had time to repopulate; this time factor can be assessed from knowledge of cell cycle times, growth fractions, and tumor cell kinetics.

In the past few decades, labeling indices obtained by autoradiographic analysis of tissue exposed to tritiated thymidine have been used for cell kinetic studies [160–164]; however, autoradiographic studies are laborious to perform and take several months to complete. Gratzner [165] developed a monoclonal antibody that could identify nuclei containing bromodeoxyuridine (BUDR). Anti-BUDR monoclonal antibody can be detected by direct conjugation of fluorescein isothiocyanate (FITC) to the monoclonal antibody, by indirect conjugation of FITC using an FITC-tagged secondary antibody, or by immunoperoxidase methods [166, 167]. Like tritiated thymidine, BUDR is incorporated into nuclear DNA during DNA synthesis, but it is neither radioactive nor myelotoxic in the doses used for in vivo labeling [166, 167]. Patients with brain tumors have been studied with this method by labeling cells in the S phase. Since this technique is nonradioactive and non-toxic in the conventional doses used, it can be used concurrently with histology to predict biologic outcome.

More recently, methods have been developed that rely on immunohistochemical localization of proteins expressed in the nuclei of proliferating cells to determine the populations of cycling cells. Burger et al. [168] reported on the potential application of monoclonal antibody ki-67 to CNS tumors. The antibody, which reacts with a nuclear protein expressed in the G1, G2, S, and M phases of the cell cycle, was demonstrated in frozen sections of all 40 neoplasms in that study, and a general agreement between the percentage of stained cells in gliomas and the histologic grade was apparent. Thus, the localization of such monoclonal antibodies as an indicator of malignancy may potentially be applied to routine diagnostic material. [Please see addendum.]



FIGURE 2-5. Cell culture from a cerebellar PNET with melanin (melanotic medulloblastoma), showing dark melanin-containing cells.

Cell Culture

Cell culture provides a dynamic picture of tumor growth patterns and is essential for investigating many aspects of tumor biology [18–25]. Unfortunately, the cell cultures usually survive for only a few passages, clearly limiting their usefulness. Nevertheless, these cultures are important for karyotypic analysis and for the potential preservation of tumor cells. The development of cell lines from these cultures provides a significant opportunity for understanding tumor behavior (figure 2-5). Combining cell culture techniques and the nude mouse model facilitates understanding of tumor growth patterns and assessment of tumor sensitivity to chemotherapeutic agents.

Tumors

This section will discuss the more commonly encountered neoplasms (astrocytoma, PNET,

ependymoma, and craniopharyngioma), which account for up to 88% of childhood CNS tumors, and will mention the unusual features of less frequent tumors.

ASTROCYTOMA

Astrocytomas are the most common tumor both above and below the tentorium. They occur throughout childhood with no particular age peak for incidence. The major sites are the cerebellum (35%), cerebral hemispheres (23%), brainstem (15%), optic nerve (11%), and hypothalamus (7%). However, astrocytomas may also occur in thalamus, basal ganglia, pineal region, and spinal cord.

The two important pathological issues with astrocytomas are related to histological subtyping and criteria for grading tumors.

Although traditionally astrocytomas are subtyped into pilocytic, fibrillary, protoplasmic, and gemistocytic forms, the histologic criteria for these designations are not rigorous and appellations vary widely from center to center. The proposed revision of the WHO classifica-

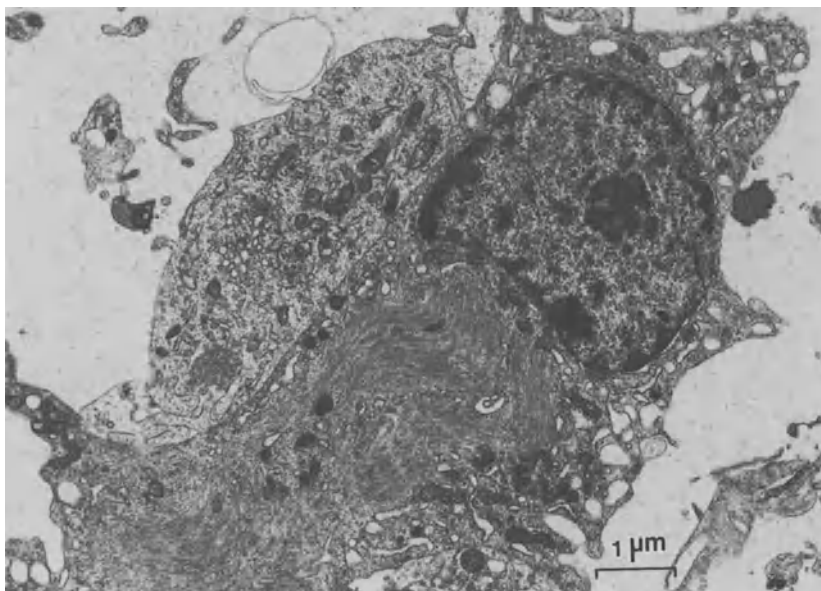


FIGURE 2-6. Electron micrograph of a tumor cell from a low-grade astrocytoma. Note the prominent bundles of intermediate filaments in the cytoplasm.

tion [27] of brain tumors suggests a diagnosis of astrocytoma followed by an optional designation, usually in parentheses, to indicate further characterization of the astrocytoma, if appropriate. The subtyping of astrocytomas is based on histological criteria that describe cell arrangements around blood vessels, axons, or other elements of neurophil, or that describe tumor cells in relationship to reticulin/collagen, emphasizing the propensity for local subarachnoid tumor growth. Immunohistochemistry, electron microscopy, karyotyping, and cell kinetics have not significantly assisted in the delineation of subtypes.

Often the anatomic site imprints characteristics on the tumor. For example, in optic nerve gliomas, a sequence of changes is apparent—from a minor increase in astrocytes and associated demyelination to gross distortion with growth of astrocytoma into subarachnoid space and a complex intermingling of reticulin/collagen with tumor. In other sites, such as the cerebellum, astrocytomas tend to be cystic. In the brainstem, astrocytoma may infiltrate be-

tween long tracts, leading to a designation of pseudopilocytic astrocytoma.

More important is clear documentation of astrocytic lineage, provided by classical stains such as phosphotungstic acid hematoxylin (PTAH), positive immunoperoxidase reaction with antiserum (e.g., GFAP), and identification of bundles of intermediate filaments on electron microscopy. Ultrastructurally, the neoplastic astrocytes have all the attributes of astroglial lineage with prominent cytoplasmic processes packed with intermediate filaments (figures 2-6, 2-7) [169–171]. Rare punctate adhesions and gap junctions can be identified. The diagnostic value of electron microscopy lies in identification of structural organelles that suggest a glial lineage in poorly differentiated tumors, which may or may not express markers such as GFAP.

An estimate of tumor growth potential is crucial to the management of a child with astrocytoma. Most astrocytomas in children are low-grade: easily recognizable astrocytes can be identified throughout the biopsy or resection.

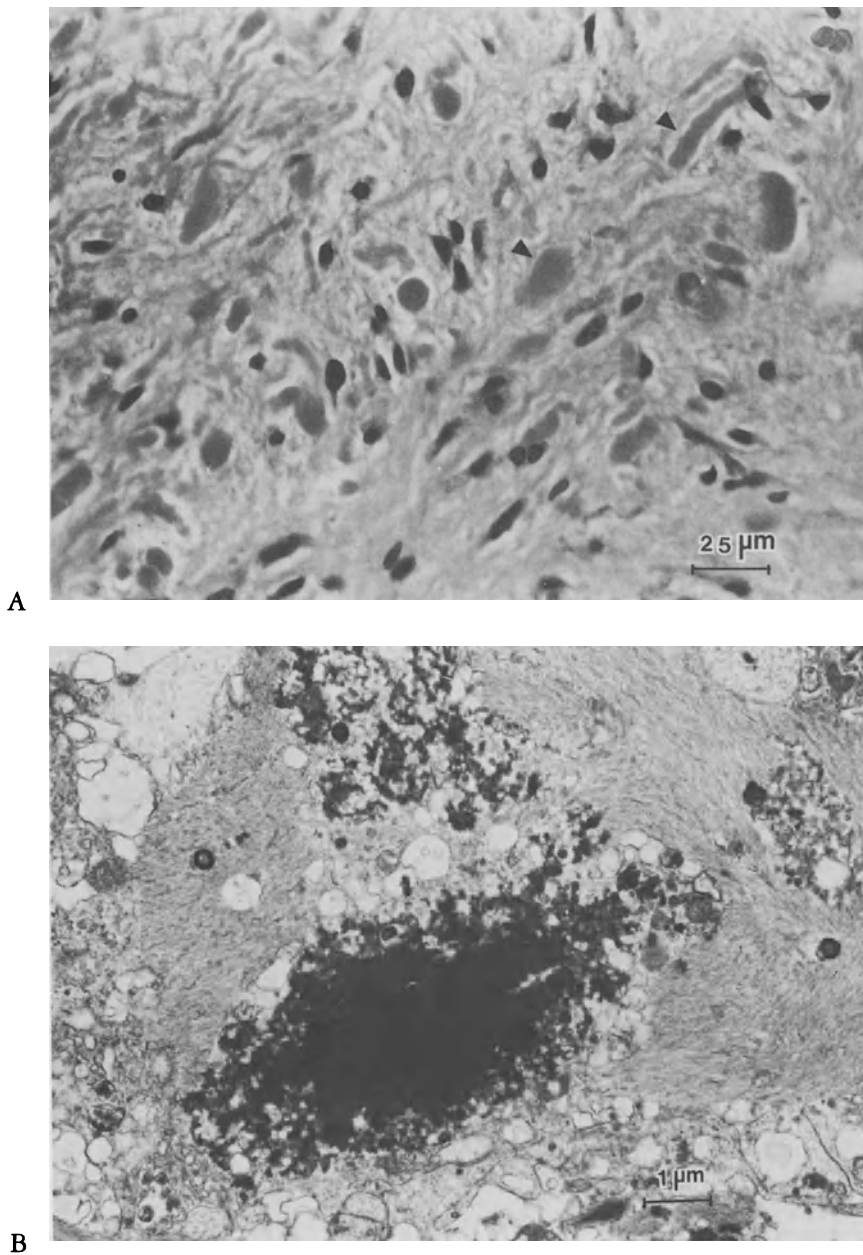


FIGURE 2-7. A. A low-grade astrocytoma with prominent Rosenthal fibers (arrowheads). B. Electron micrograph of a Rosenthal fiber showing a central dense area surrounded by intermediate filaments.

The tumor astrocytes are different from reactive astrocytes. The tumor nuclei are more variable in size, shape, and degree of chromatin staining. An occasional mitotic figure may be identified.

In contrast to astrocytomas in adults, the presence of knots of blood vessels with endothelial proliferation does not denote a more rapid tumor growth. These low-grade astrocytomas occur in optic nerve, hypothalamus, cerebellum, and brainstem.

The separation between the two groups of high-grade tumors, anaplastic astrocytoma and

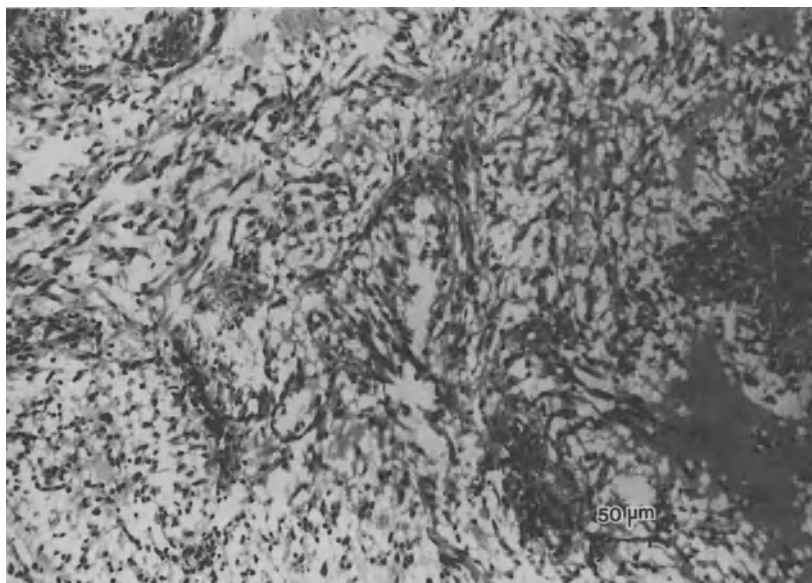


FIGURE 2-8. A low-grade pilocytic astrocytoma of the cerebellum, showing compact and cystic areas. Fibrillary cytoplasmic processes of the tumor cells are apparent. (Hematoxylin and eosin stain.)

glioblastoma multiforme, is not always clear-cut. Degree of nuclear pleomorphism, mitotic rate, and cellular atypia are more extreme in glioblastomas, which are rare in childhood. Typically, in glioblastoma multiforme large areas of necrosis are surrounded by a pseudopalisading of residual tumor cells, and prominent endothelial proliferation can be readily identified.

Unlike most astrocytomas elsewhere, brainstem astrocytomas appear to undergo a change in biologic behavior from low- to high-grade astrocytoma: there are anecdotal cases in which the biopsy shows a low-grade astrocytoma but the postmortem examination reveals a high-grade tumor. This sequence may result from a change in biologic activity or may merely reflect the more extensive tissue sampling available at autopsy.

Cerebellar Astrocytoma. The cerebellar astrocytomas usually occur laterally within the hemispheres, although vermian tumors are common in young children. These tumors often have a cystic component with a mural tumor nodule. The microscopic pattern is pilocytic, composed of fusiform cells with long bipolar fibrillary pro-

cesses arranged in compact areas that alternate with microcystic areas (figure 2-8). The cerebellar astrocytomas are, in general, well-differentiated, low-grade tumors. Microscopically, some cellular pleomorphism or vascular proliferation may be encountered but does not denote a worse prognosis. After surgical excision, the prognosis is excellent, the reported 25-year cumulative survival in one series being 94% [172]. Rarely, there may be malignant transformation. In the event of tumor regrowth, the recurrent cyst can be drained and the residual tumor excised. Although focal growth of astrocytoma into the subarachnoid space is common, seeding of low-grade cerebellar astrocytoma to the spinal cord is rarely reported [173].

Brainstem Astrocytoma. Brainstem astrocytomas are found predominantly in children between 3 and 8 years of age. These tumors most frequently originate in the pons with infiltration of the midbrain, medulla, and, occasionally, the cerebellum (figure 2-9). There is distortion of the contour of the brain stem, and the tumor

cells grow along various fiber tracts. This progressive intrinsic growth produces a combination of cranial-nerve and long-tract signs and symptoms. Histologically, most of the tumors are made up of stellate cells with distinctly fibrillary cytoplasmic processes. Unlike other childhood astrocytomas, which are usually low-grade, brainstem tumors may run an aggressive clinical course [174–178]. In one study, a pathologic diagnosis was available in 36 of 62 pediatric patients with brainstem glioma: of these cases, half were said to be malignant [175]. In all 13 cases of malignant brainstem gliomas in another series, the tumor showed frankly anaplastic areas as well as foci of low-grade tumor, thus underscoring the regional variability within a particular tumor and the relatively limited usefulness of a small biopsy sample [174].

Forty nine cases of brainstem gliomas managed at our center were reviewed [177]. Based on computerized tomographic scan characteristics, the patients were divided into four distinct groups. Group 1 (11 cases) consisted of isodense contrast-enhancing tumors that were dorsally exophytic into the fourth ventricle. All were surgically excised, and ten were low-grade astrocytomas. This distinct pattern of astrocytoma growth with extension into the fourth ventricle appears to have an excellent prognosis; 10 of these 11 patients survived, with a mean follow-up of 4.5 years. Group 2a involved hypodense nonenhancing intrinsic tumors of the brainstem. The 18 patients in this group did poorly, with a mean survival of 6.2 months. Group 2b, with seven patients who had intrinsic brainstem tumors with hyperdense exophytic components extending ventrally and laterally into the cerebellopontine and prepontine cisterns, also had a poor prognosis, with a mean survival of 12 months. Three of the four patients in group 3 (intrinsic cystic tumors with contrast-enhancing capsules) died, with a mean survival time of 11.5 months. Group 4 (nine cases) consisted of focally intrinsic tumors of the brainstem that were isodense and enhanced brightly on ad-

ministration of contrast media. Seven of these patients were alive with a mean follow-up of 2.3 years.

In yet another review addressing prognostic factors in pediatric brainstem gliomas, Albright et al. [178] reported that the following factors were associated with a worse prognosis: presentation with cranial nerve palsies; computed tomographic findings including hypodense tumor before contrast administration; a tumor that involved the entire brainstem; and a high-grade histology on biopsy. The histologic features associated with the poorest survival time in this series was the presence of mitoses. Morphologic features associated with the best prognosis were Rosenthal fibers and calcification.

A subset of brainstem gliomas characterized by exophytic growth into the fourth ventricle appears to be amenable to partial surgical excision, unlike the usual brainstem lesion, which is not resectable by virtue of its strategic location [177, 179]. These tumors are histologically low-grade astrocytomas and have been found to be compatible with long-term survival [179].

Cerebral Astrocytoma. Hemispheric astrocytomas are encountered in all lobes; we have seen the highest frequency in the frontoparietal lobes [28]. Temporal lobe tumors are most frequently low-grade astrocytomas with or without a ganglionic or oligodendroglial component. They may be well defined and cystic or appear diffuse and poorly delineated with infiltration of the centrum semiovale. About half of the glioblastomas, which are rare in childhood, are located in the cerebral hemisphere [180]. We have found low-grade cerebral astrocytomas to be twice as common as high-grade ones in children. In most instances, low-grade tumors are cystic with a high incidence of pilocytic histology. Astrocytomas of the thalamus and basal ganglia may be low- or high-grade and are similar in morphologic appearances to astrocytomas elsewhere.

Optic-Nerve–Hypothalamic Astrocytoma. We have found 18% of all astrocytomas in the

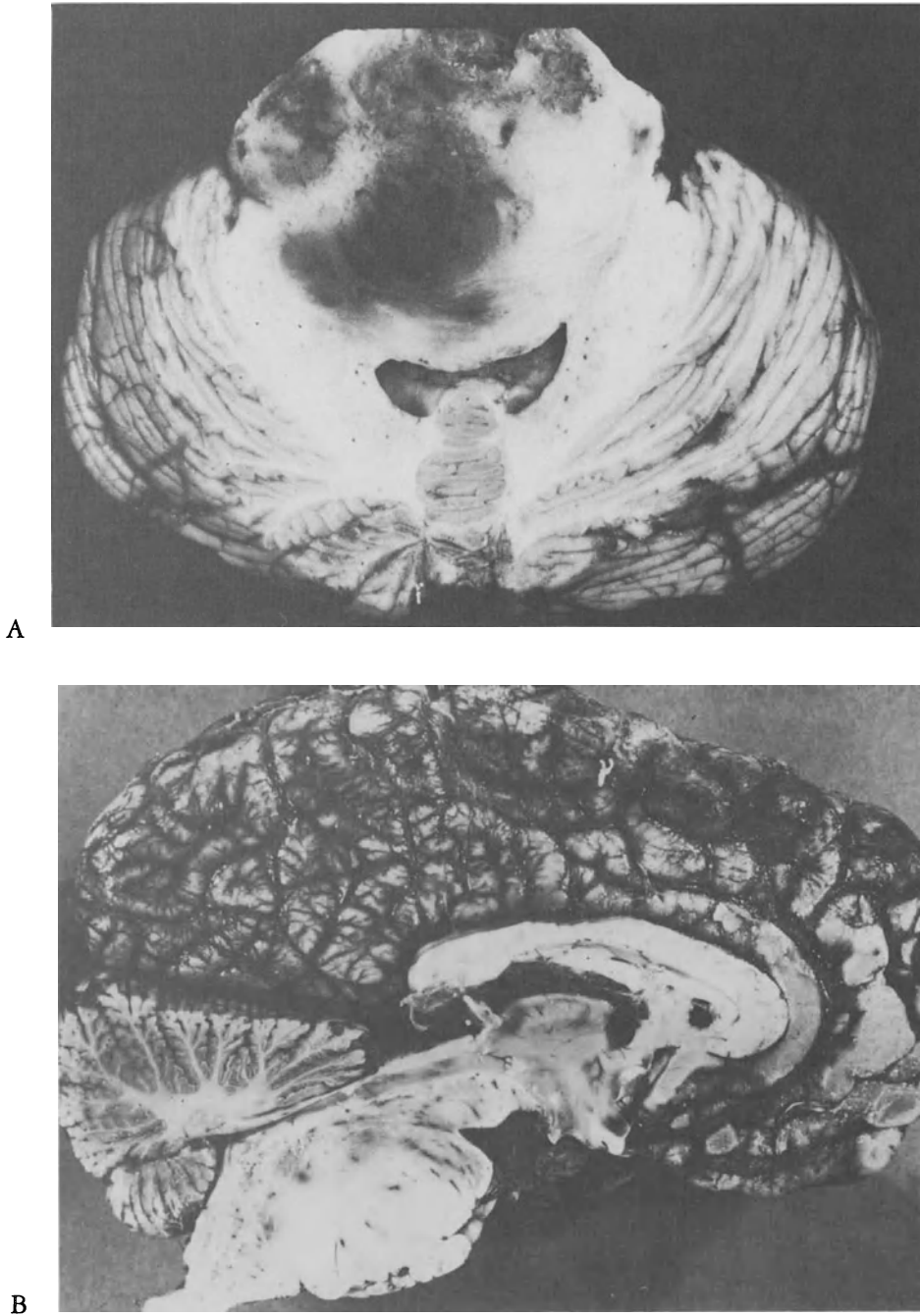


FIGURE 2-9. Brainstem glioma originating in the pons. A. A coronal section showing infiltration of the cerebellum. B. A midsagittal view revealing extreme distortion of the normal contour of the brainstem.

optic-nerve–hypothalamic region [28]. An association with von Recklinghausen's neurofibromatosis is well recognized [181–186], and up to 37% of optic gliomas may be encountered

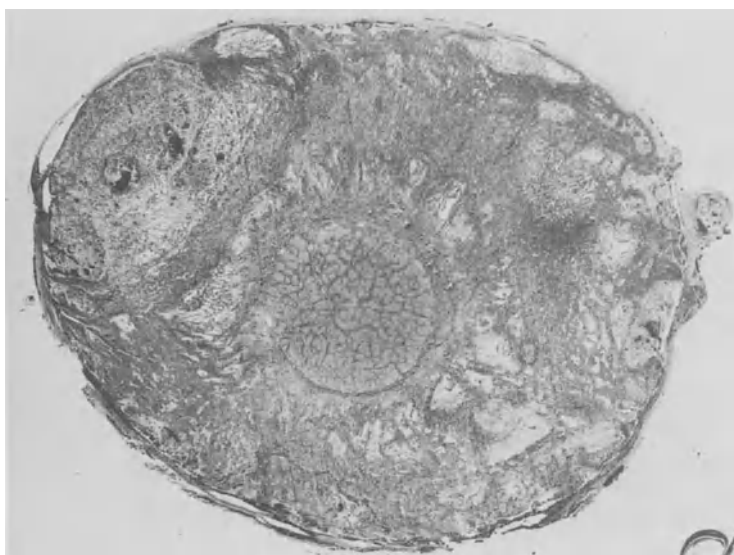


FIGURE 2-10. Cross section of an optic nerve glioma showing extensive subarachnoid spread with fibrosis. The compressed optic nerve can be seen in the center.

in this clinical setting [183]. The exact site of origin of the tumor may be difficult to determine, since the hypothalamic tumors may grow forward and the optic nerve tumors may grow backward into the hypothalamus. Anterior tumors can involve one or both optic nerves, the chiasm, or a combination. The posterior tumors affect the hypothalamus, the optic nerve, and the chiasm. Multiple anatomic locations may be involved by direct infiltration, and, rarely, multicentric optic nerve gliomas may occur, usually in the setting of von Reck-linghausen's neurofibromatosis [184]. When limited to the optic nerve, the tumor grows within the sheath to produce a fusiform enlargement. A cross section may reveal discernible optic nerve within the tumor (figure 2-10), or no recognizable nerve, due to replacement by tumor. Subarachnoid extension of the tumor may occur.

Histologically, two patterns may be encountered in an optic nerve glioma: the cells may be fibrillated and closely aligned, or they may lie in a loose framework of relatively low cellularity containing cystic spaces filled with mucoid material. With subarachnoid spread, the glial and

connective tissue elements may be intermixed. The hypothalamic tumors have the pattern of a pilocytic astrocytoma.

The posteriorly located tumors tend to have a poorer prognosis. At least 35% of our patients with optic gliomas have died, of whom 70% had posterior tumors. The growth rate of the tumor is unpredictable, with deterioration or death occurring over a span of 2 to 5 or more years. Unrelenting deterioration follows infiltration of structures about the third ventricle and the upper brainstem.

Gliomatosis Cerebri. Gliomatosis cerebri, a gliomatous growth in which the neoplastic process is very diffuse and widespread, with or without associated glioblastoma multiforme [187–189], is rare in children. There is enlargement of the cerebral structures, but the general configuration is preserved. Cervos-Navarro and colleagues [189], who described the ultrastructural findings in five patients, suggested that gliomatosis cerebri represents a neoplastic process with small, undifferentiated cells, where may be neoplastic astrocytes, oligodendroglia, or transitional astrocytic–oligodendroglial elements.

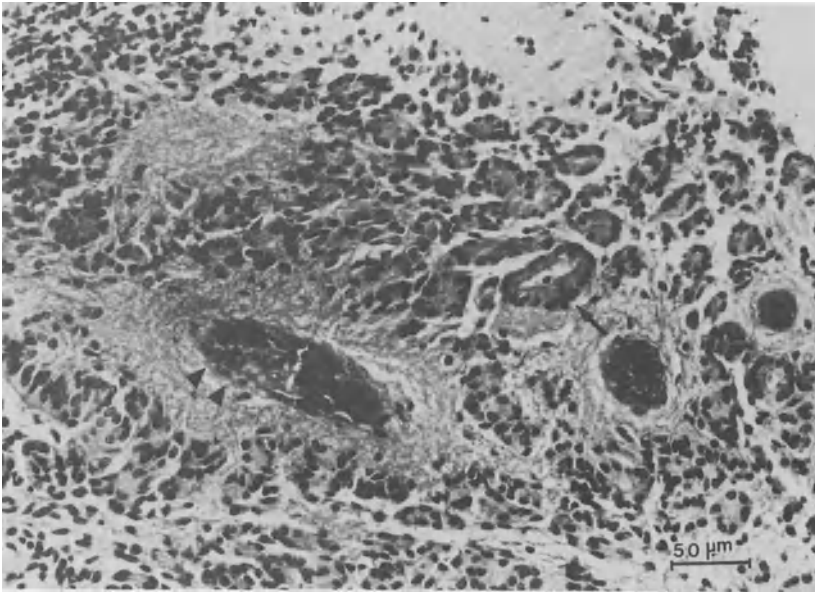


FIGURE 2-11. Ependymoma showing numerous ependymal rosettes with a clear central lumen bordered by cilia (arrow). Perivascular cell-free zones (arrowheads), another characteristic feature of ependymoma, are also seen. (Hematoxylin and eosin stain.)

EPENDYMOMA

In our series of ependymomas, 65% were located in the infratentorial compartment, 25% in the supratentorial compartment, and 10% in the spinal cord.

Supratentorial ependymomas can grow into the ventricular system or the hemispheres. Posterior fossa ependymomas grow into the fourth ventricle. The tumor may involve the cerebellum or brainstem, or grow through the foramina of Luschka and Magendie to cover the surface of the brainstem and fill the subarachnoid space. The tumor presents as a vascular grayish-red mass, usually with relatively well-defined margins in contrast to the diffuse infiltration of the astrocytoma.

Ependymomas express both glial and epithelial characteristics in concert with their putative origin from ependymal cells. Of diagnostic importance are the usual perivascular cell-free zones in which processes can be identified by immunoperoxidase reaction using antiserum to GFAP [51]. The nuclei are typically round to oval with a speckled chromatic distribution. In tumors with epithelial expression, true ependymal rosettes may be found. These have a dis-

tinct lumen and are surrounded by ciliated ependymal cells (figure 2-11). The identification of blepharoplasts (corresponding to the basal bodies of the ciliary apparatus) appearing as minute structures with PTAH stain toward the luminal surface has been emphasized, but such structures are least critical for establishing the diagnosis. Confirmation by ultrastructure examination is more valuable. The ultrastructural features of ependymomas include tight junctions, cilia, basal bodies, and microvilli (figure 2-12) [190]. The cytoplasm of tumor cells may contain intermediate filaments, which correspond to the immunopositivity seen with antisera to GFAP.

Variants of ependymomas include papillary and myxopapillary patterns. The myxopapillary ependymoma is confined to the region of filum terminale. It is characterized by cuboidal tumor cells surrounding a vessel. Between the cuboidal

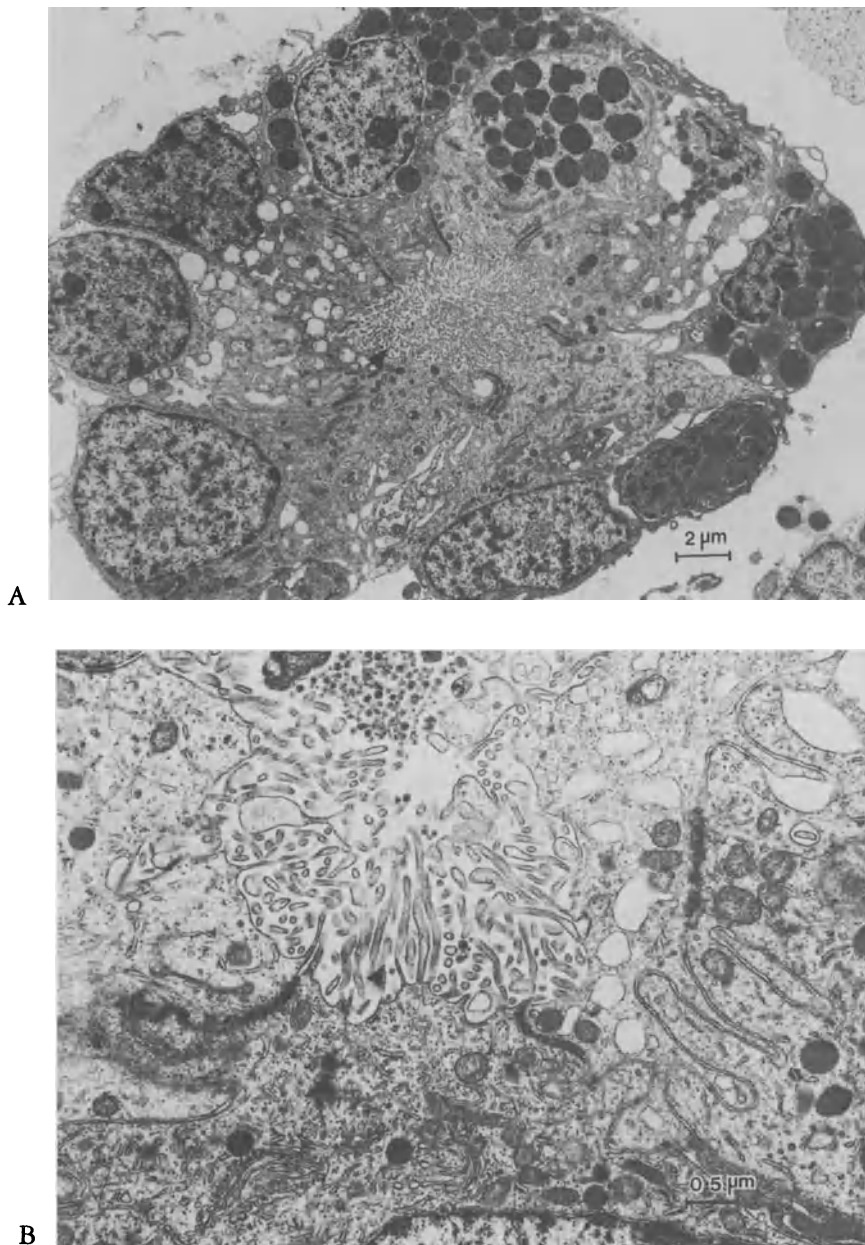


FIGURE 2-12. A and B. Electron micrographs of the tumor shown in figure 2-11, illustrating a true ependymal rosette. The central lumen and the microvilli (arrowhead) are clearly visible.

cells and the vessel is connective tissue that contains mucopolysaccharide.

Although only 15% of ependymomas have been regarded as anaplastic, showing increased

cellularity, mitoses, pleomorphism, and necrosis, the prognosis has been uniformly poor, with five-year survivals below 20% [28].

Ependymomas may infiltrate the subarachnoid space. In CSF preparations, ependymoma cells have dark, oval nuclei and tend to be oriented as a column or form small clusters.

PRIMITIVE NEUROEPITHELIAL TUMOR

The primitive neuroepithelial tumors arise in intracranial and peripheral sites of the nervous system (figure 2-1). In 1973, Hart and Earle [191] introduced the term PNET to designate a group of cerebral neoplasms unified by histologic, immunologic, and ultrastructural features. Before then, these tumors were referred to as cerebral or cerebellar medulloblastomas or cerebral neuroblastomas.

In the modification of the WHO classification [27], this group of neoplasms has been divided into the following categories: PNETs, PNETs with other elements such as astrocytes and oligodendrocytes, and medulloepitheliomas. All groups display similar histologic and biologic characteristics. The most frequently encountered childhood tumor from this group is the medulloblastoma (PNET of cerebellum).

Medulloblastoma (PNET of Cerebellum). Medulloblastoma is the most common primitive neuroepithelial tumor of the CNS, composing up to 20% of the intracranial tumors of childhood [28]. In children, most of these tumors arise in the cerebellar vermis, while in adults a lateral hemispheric location is more common. The tumors are soft, grayish-pink masses with focal areas of necrosis, hemorrhage, and cyst formation. Up to one third of cases show brainstem invasion [192].

Microscopically, there is a monotonous pattern of small, dark cells with round-to-ovoid nuclei, dense chromatin, numerous mitoses, and cellular necrosis. Hart and Earle [191] specified that at least 90% of cells should have this appearance for a tumor to be so designated. Endothelial proliferation may be present. The tumor cells may align around vessels (perivascular rosetting); occasionally, Homer–Wright rosettes (in which processes of tumor cells radiate toward a central core that has no lumen) may be seen. In some tumors, neuronal and astrocytic foci may be identified; rarely, oligodendroglial, ependymal, melanotic, or rhabdomyoblastic elements are present. The amount of connective

tissue stroma in these tumors is variable. In about 15% of cases, there is a significant collagen or reticulin component, presumably derived from the meninges secondary to leptomeningeal infiltration of tumor. This *desmoplast variant* shows a characteristic morphologic picture with aggregates of tumor cells with the appearance of central rarefaction simulating lymphoid follicles or germinal centers (figure 2-13). These nests are surrounded by a cuff of reticulin, which is characteristically absent within the nests.

These tumors frequently involve the leptomeninges. In cytologic preparations of the cerebrospinal fluid, the tumor cells show hyperchromatic nuclei with small nucleoli and scant cytoplasm.

By electron microscopy [193–195], the tumor cells show poorly developed cell junctions and primitive nuclei with margination of dense chromatin. Occasionally, the nuclei appear convoluted. The cytoplasm is poor in organelles, but microtubules can be identified in the short cytoplasmic processes. These processes may intertwine; in Homer–Wright rosettes, such processes point toward the center. With progressive neuronal differentiation, increased amounts of rough endoplasmic reticulum appear and cell processes containing microtubules are more prominent; rarely, neurosecretory granules may be found. In some tumors, foci of astroglial or ependymal differentiation may be identified.

By immunohistochemical techniques, positive staining for NSE and GFAP has been found in tumor cells (figure 2-3); however, the clinical significance of neuronal or glial differentiation is not clear. Packer et al. [196], in a review of 38 patients with medulloblastomas, stated that tumors with no histologic evidence of differentiation had a much better prognosis than those with differentiation, the four-year event-free survival rates being 70% and 32%, respectively. They also proposed that the degree and pattern of differentiation were prognostically important, since children with tumors showing multiple lines of differentiation had only a 10% four-year event-free survival. In contrast, Caputy

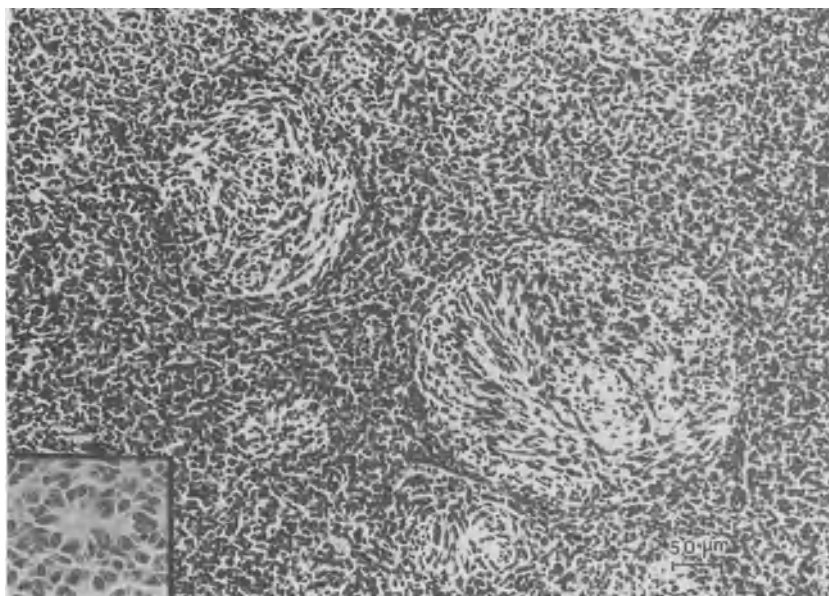


FIGURE 2-13. Desmoplastic medulloblastoma showing the characteristic appearance of follicles, created by aggregates of tumor cells with central rarefaction. The inset shows cells forming a Homer-Wright rosette with cytoplasmic processes radiating toward a central core, devoid of a true lumen.

et al. [197], in a series of 54 patients with medulloblastoma, found a significantly longer recurrence-free period in cases with cellular differentiation.

The prognosis in desmoplastic medulloblastomas was thought to be slightly better than in the classical medulloblastoma; however, in a recent study of childhood medulloblastomas, the desmoplastic variety had a slightly worse prognosis, and involved the vermis [192].

Extraneural metastasis of central nervous system tumors, considered rare in the past, is now being increasingly recognized [198–200]. In a recent review, Hoffman and Duffner [200] stated that 40.4% of cases occurred in children. The most common childhood brain tumor to spread outside the CNS axis is the medulloblastoma. Although CNS tumors can spontaneously spread beyond the confines of the cranial cavity, most instances of extraneural metastasis

occur after craniotomy or diversionary cerebrospinal fluid shunting.

PNET of Cerebrum. The cerebral tumors occur in children and young adults. Over 80% of the reported cases are hemispheric and about 10% are located around the third ventricle [201]. Grossly, the tumors appear sharply demarcated from the adjacent brain; however, extensive infiltration, often across the midline, may be seen. The tumors may be cystic and show areas of necrosis or calcification. The histologic appearances, ultrastructural features, and immunohistochemical staining patterns are similar to those of the cerebellar medulloblastoma (PNET of cerebellum).

Medulloepithelioma. Medulloepitheliomas are thought to represent the most primitive of the primitive neuroepithelial tumors, with a morphology reminiscent of the primitive medullary plate and neural tube epithelium. The tumor manifests in early life and most frequently arises in the cerebral hemispheres, although cases have also been described in the brainstem, cerebellum, peripheral nerves,

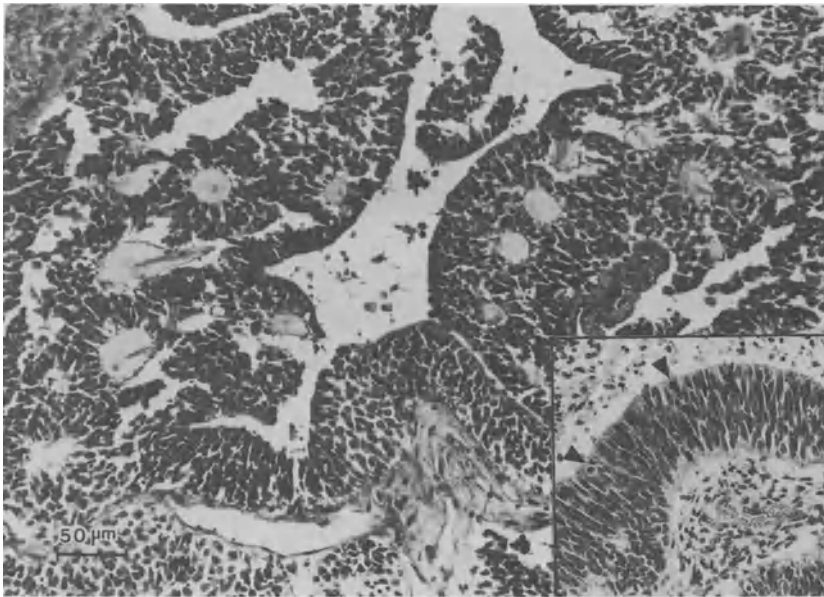


FIGURE 2-14. Cerebral medulloepithelioma displaying tubules, trabeculae, and papillary structures. (Hematoxylin and eosin stain.) The inset shows the pseudostratification of tumor cells with mitoses (arrowheads) toward the luminal aspect. Distinct internal and external limiting membranes surround the tumor cells.

and cauda equina [202–207]. This highly malignant tumor has a marked propensity for invading the leptomeninges. Grossly, it presents as a soft grayish-pink mass with necrosis. Microscopically, tubules, trabeculae, ribbons, and papillae are seen (figure 2-14). The tubules are lined by a pseudostratification of primitive cells with more frequent mitoses toward the luminal aspect. The cells rest on a distinct basement membrane. Electron microscopy also confirms their primitive nature; they contain large nuclei, sparse organelles, and scanty cytoplasm. There may be evidence of maturation along neuronal, astrocytic, oligodendroglial, ependymal, or choroid plexus epithelial lines. Differential diagnosis from a teratocarcinoma rests on the identification of endodermal and mesodermal derivatives in the latter.

The following subtypes of PNETs show very prominent differentiation toward one of the cell lines, and thus have distinctive histological patterns: PNETs with ependymal differentiation have primitive cells with true ependymal rosettes and tubules, with the luminal surface of the cells bearing cilia and blepharoplasts

[208–210]. Tumors with very prominent astrocytic or neuronal differentiation may also be encountered. PNETs of the pineal gland (pineoblastoma) are similar to PNETs elsewhere, except for the rare appearance of retinoblastomatous differentiation consisting of Flexner–Wintersteiner rosettes with or without fleurettes or melanin pigment [211]. This differentiation is of interest, since the pineal gland in lower vertebrates is photoreceptive. PNETs with striated muscle (medulloblastoma) are rare tumors in which smooth or striated muscle elements are found in a typical medulloblastoma [212–214]. The origin of the muscle component has been variably interpreted. This tumor has been regarded by some as a malignant teratoma with prominent neuroepithelial and focal mesenchymal differentiation [212]. Stahlberger and Friede [214] proposed that medulloblasts and myoblasts proliferate from

two different cell lines, the probable origin of the myoblast being differentiation of peripheral mesenchymal, perivascular, or leptomeningeal stroma. Yet another explanation of the appearance of muscle proposes a multipotential differentiation of neural crest cells. PNETs with melanin are a rare subtype containing melanin pigment (e.g., melanotic medulloblastoma) [215].

Astroblastoma. The very existence of astroblastoma is controversial. Since the initial description by Bailey and Cushing [216], only a few reports have appeared in the literature [217–220]. Bailey and Cushing proposed that the tumor arose from a precursor of the astrocyte, which they called the spongioblast [216]. The tumor has a characteristic microscopic appearance with tumor cells arranged around abundant blood vessels with thick walls. These blood vessels may be infiltrated by lymphocytes and plasma cells. GFAP positivity has been described within the tumor cells. Astrocytomas have been observed with focal areas having an arrangement typical of astroblastomas, but rarely is such a tumor with that histology exclusively recognized.

Polar Spongioblastoma. Polar spongioblastoma is a well-circumscribed tumor arising in the first two decades of life, with an aggressive growth pattern and a propensity for leptomeningeal spread [212,213]. The histologic pattern is one of cells aligned in rows of parallel palisades separated by relatively acellular areas. Such a morphologic pattern has been described in astrocytoma, oligodendroglioma, and medulloblastoma [212]. Golden and associates [174] described frequent occurrence of spongioblastomalike areas in tumors otherwise indistinguishable from high-grade astrocytoma or glioblastoma in an autopsy study of 13 brainstem gliomas. As a separate entity, polar spongioblastoma remains poorly documented, and detailed studies of a tumor with this histology exclusively are lacking.

CRANIOPHARYNGIOMA

Craniopharyngioma characteristically occurs in a suprasellar location near the pituitary stalk and infundibulum (figure 2-15), although it may occur within the sphenoid bone or the third ventricle [222,223]. The tumor may extend forward to the chiasm, laterally toward the internal carotid artery, or posteriorly into the posterior cranial fossa.

Craniopharyngiomas are thought to arise from the remnants of Rathke's pouch. The characteristic brownish fluid contained within the cyst shows cholesterol and squamous debris. Microscopically, solid and cystic areas are apparent with islands of polygonal epithelial cells, cells with squamous differentiation, trabeculae of tumor cells enclosing cystic spaces (ameloblastomatous pattern), and loose areas of stellate cells. Calcification, cholesterol clefts, and foreign-body giant-cell response to the keratin are frequent. A vigorous reactive gliosis is elicited wherever the tumor comes in contact with neuropil, and Rosenthal fibers are numerous in these foci. In surgically removed specimens it is common to find islands of tumor embedded in the gliotic tissue (figure 2-16); such microscopic foci of tumor extension may account for recurrences, despite an apparently adequate surgical excision. In a review of the experience with craniopharyngiomas at this center, Hoffman [224] reported adequate removal of tumor by microsurgical excision in 21 of 29 patients with no clinical evidence of recurrence after nine years. No deaths were recorded, and the principal causes of morbidity were the patients' endocrine deficits.

GERM-CELL TUMORS

Germ-cell tumors are composed of interrelated neoplasms that demonstrate a hierarchical order of increasing differentiation and malignant behavior [225–231]. Each represents the malignant correlate of a normal stage of embryonic development: the primordial germ cell (germinoma), the pluripotential stem cell of the embryo (embryonal carcinoma), the



FIGURE 2-15. Craniopharyngioma showing a cystic and a solid component, with extensive calcification seen as whitish speckled areas.

embryonic differentiated derivative (teratoma), the extraembryonic derivative (endodermal sinus tumor), and the trophoblast (choriocarcinoma). In the CNS, the germinomas arise in the pineal and suprasellar location, while the nongerminomatous germ-cell tumors preferentially involve the pineal gland. The latter are also characterized by an earlier age of onset compared with germinomas. A significant number of suprasellar germinomas occur in females.

Germ-cell tumors infiltrate locally and spread by growth into the subarachnoid space. Invasion of the quadrageminal plate is frequent. The histology of the intracranial germ-cell tumors is similar to that of its extracranial counterpart. Jennings et al. [231], in a review of 389 intracranial germ-cell tumors, stated that two factors appeared dominant in predicting the outcome: tumor histology and extent of disease dissemination. A histologic diagnosis of germinoma was associated with a significantly longer survival. A poorer prognosis was found in patients whose tumors had infiltrated the hypothalamus, third ventricle, or spinal cord.

Germinoma. Germinoma is the most commonly encountered tumor of the germ-cell group. Microscopically, it presents a classic picture with two populations of cells: the neoplastic germ cell and the reactive lymphocytic component (figure 2-17). The former are characterized by large vesicular nuclei, prominent nucleoli, and pale, ill-defined cytoplasm. They occur in sheets or may be interspersed among the lymphocytes. The tumor cells contain abundant glycogen. Electron microscopy reveals cells with scant cytoplasm and large, rounded nuclei that have prominent nucleoli and few cytoplasmic organelles but prominent glycogen aggregates. A few primitive junctions can usually be identified, and occasionally desmosomes may be seen.

In addition to the tumor cells and lymphocytes, macrophages and focal granulomatous response may be present [228]. Also of significance is the finding of clusters of syncytiotrophoblastic cells immunoreactive for HCG

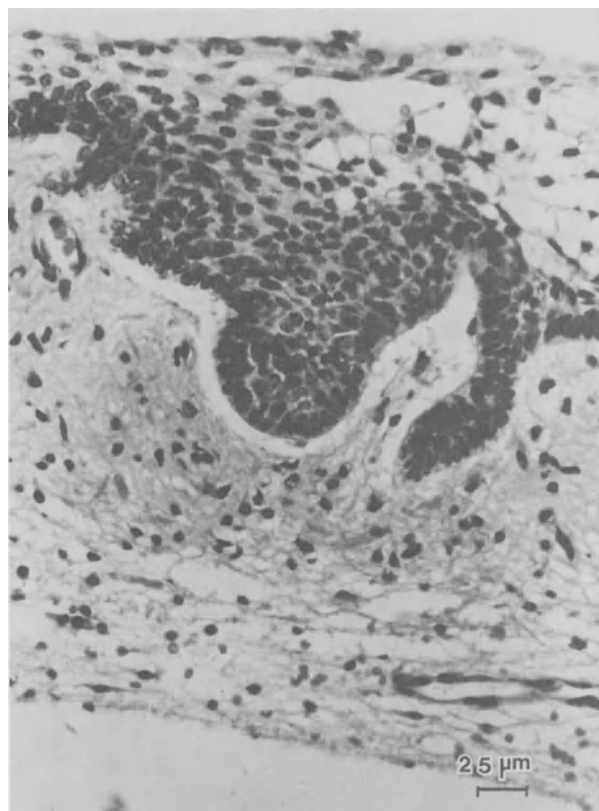


FIGURE 2-16. A surgically resected craniopharyngioma showing islands of tumor embedded in gliotic neurophil. (Hematoxylin and eosin stain.)

[230]. The presence of such cells does not imply associated choriocarcinoma.

Embryonal Carcinoma. Among the least frequently reported intracranial germ-cell tumors, the embryonal carcinoma is conceptually the most primitive. The tumor is very poorly differentiated, and is composed of sheets of columnar to cuboidal cells with large nuclei, prominent nucleoli, and a high mitotic rate.

Endodermal Sinus Tumor (Yolk Sac Tumor). Initially thought to represent merely a morphologic variant of embryonal carcinoma, the endodermal sinus tumor has come to be regarded as a specific entity, primarily because of its elaboration of various protein

markers (such as alpha-fetoprotein and alpha-1-antitrypsin) and its characteristic histologic appearance. The classic morphologic feature of this uncommon tumor is the formation of *Schiller–Duvall bodies* represented by vascular tufts invaginating a space surrounded by a layer of tumor cells. This structure is reminiscent of the yolk sac or endodermal sinus of lower animals. The tumor cells contain (PAS)-positive diastase-resistant cytoplasmic globules, which may be intracytoplasmic as well as extracytoplasmic [226, 227, 229]. Immunoreactivity with antisera to alpha-fetoprotein and alpha-1-antitrypsin has been observed [226, 227, 229].

By electron microscopy, embryonal carcinoma and endodermal sinus tumor resemble adenocarcinoma and may have extensive junctions, lumina, and microvilli.

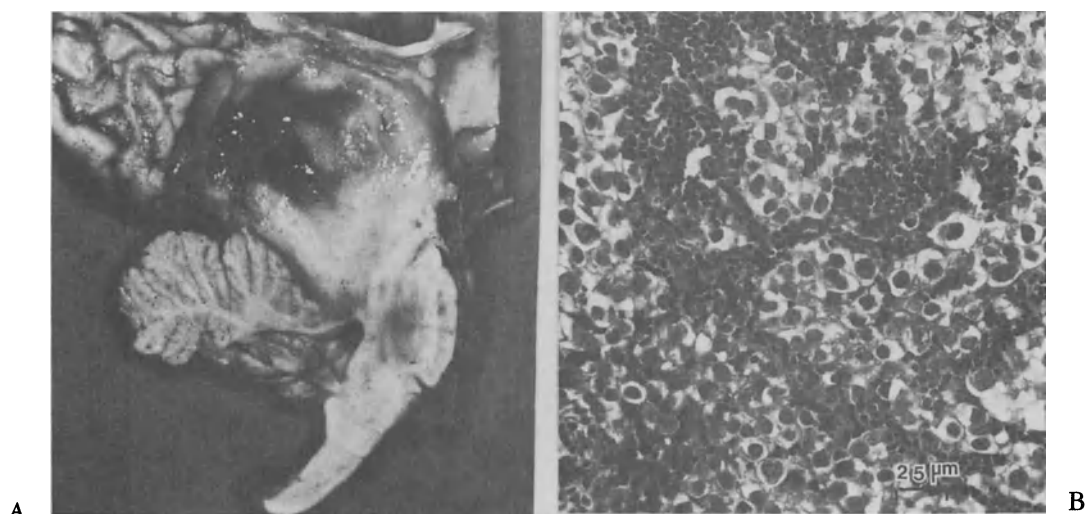


FIGURE 2-17. A. A pineal germinoma extending superiorly into the third ventricle and inferiorly into the tectum of the midbrain. B. A germinoma showing an admixture of the tumor cells (with large vesicular nuclei, prominent nucleoli, and pale cytoplasm) and the reactive lymphocytic component. (Hematoxylin and eosin stain.)

Teratoma. Teratoma is the designation for a tumor containing the derivatives of the three germ layers. Two principal forms are observed: in the immature variety, the histology is reminiscent of embryonic or fetal tissues; in the mature type, the morphology is that of adult tissue. This distinction has important prognostic significance, since the more frequent immature variety is more aggressive. Also, the immature type is more often associated with other primitive germ-cell tumors such as embryonal carcinoma.

Choriocarcinoma. Extragenital choriocarcinomas are rare. When they occur, they are seen as hemorrhagic lesions characterized histologically by the presence of syncytiotrophoblastic giant cells overlying cords of cytotrophoblasts.

CHOROID PLEXUS TUMORS

Choroid plexus tumors account for less than 1% of all intracranial tumors, the benign choroid plexus papillomas being more frequent than their malignant counterparts [89–91, 232–234]. These neoplasms morphologically mimic the cytoarchitecture of the normal choroid plexus and have a propensity to hypersecrete CSF [235, 236]. They occur in early childhood, with many patients being under one

year of age. Grossly, they present as soft vascular cauliflower-like fronds. Of the 17 cases seen at our center, ten were located in the lateral ventricle, three in the third ventricle, and three in the fourth ventricle. Microscopically, there is a striking resemblance to normal choroid plexus with cuboidal epithelium lying on a basement membrane and containing a fibrovascular core (figure 2-18).

By electron microscopy, basement membrane, villi, and microvilli are seen. We have observed an abnormal microtubular arrangement in the apical cilia varying from $5 + 0$ to $8 + 1$ in choroid plexus tumors [89].

Rarely, the malignant form, known as choroid plexus carcinoma, is encountered. There is increased cellularity, atypia, necrosis, mitotic activity, and piling up of cells with loss of the papillary structure. Since both benign and malignant varieties are friable and detachable, they can seed the CSF pathways.

In a study of 18 choroid plexus tumors, we have found immunoreactivity for GFAP, S-100

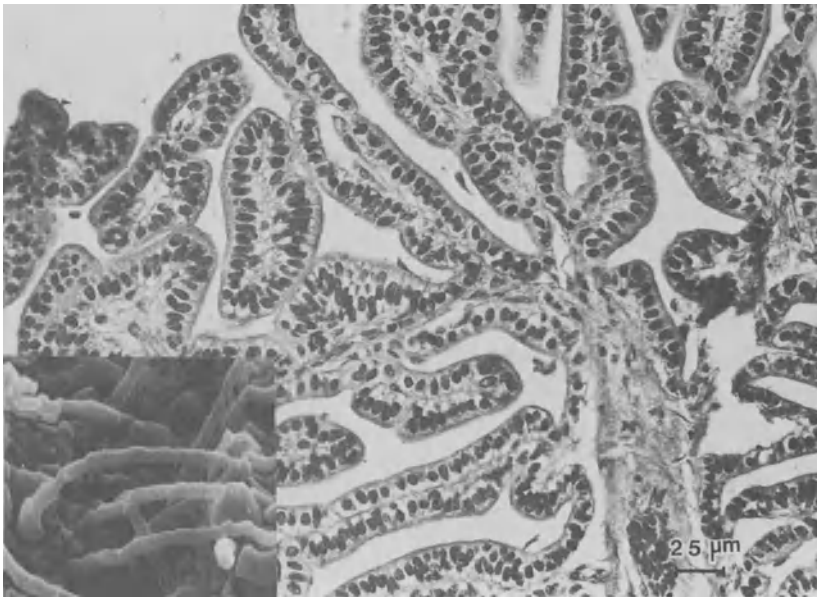


FIGURE 2-18. A choroid plexus papilloma showing papillary formations with a fibrovascular core and columnar-to-cuboidal epithelium. (Hematoxylin and eosin stain.) The inset shows a scanning electron micrographic view in which microvilli can be readily appreciated.

protein, and internal organ cytokeratin [89]. Choroid plexus tumors have true epithelial characteristics in contrast to ependymomas, which infrequently show keratin positivity. Miettinen and associates [91] also demonstrated immunoreactivity for keratin in normal human choroid plexus tissue as well as choroid plexus papilloma. Coffin et al. [90] reported positive staining with antisera to 45–54 kD cytokeratin, keratin, CEA, and S-100 protein in choroid plexus papillomas and carcinomas. On the basis of their findings, they proposed that 45–54 kD cytokeratin and keratin are reliable markers for choroid plexus tumors; in their study, positive CEA staining was correlated with more aggressive tumors, and S-100 immunoreactivity with better-differentiated tumors.

OLIGODENDROGLIOMA

Oligodendrogliomas are uncommon in childhood and represent 1%–2% of all primary

intracranial neoplasms [237–239]. These tumors present as a pink, friable mass infiltrating the adjacent white matter. The tumor cells have small, round, dark nuclei with characteristic perinuclear haloes, which are attributed to poor fixation and autolysis. A delicate vascular meshwork separates the tumor cells. Microcystic change or calcification are commonly found. Ultrastructurally, oligodendrogliomas show a two-cell population of light and dark cells, with a paucity of cell processes, sparse endoplasmic reticulum, Golgi complexes, and microtubules [60, 240–243]. Polygonal crystalline structures may be encountered in the cytoplasm. Robertson and Vogel [240] described laminar structures in oligodendrogliomas. These rows of folding processes have been interpreted as a manifestation of the oligodendroglial capacity to form myelin.

A few recent studies have attempted to correlate histologic features in oligodendrogliomas with prognosis [244–247]. Gaining prognostic information from histologic grading of oligodendrogliomas has been difficult. Mørk et al. [246], in a study of 208 oligodendrogliomas, reported that microcysts, necrosis,

subpial infiltration, and cell density were the only histologic features of prognostic significance. Median postoperative survival was six years longer in patients having tumors of low cellularity with microcystic change and without necrosis than in those who had higher cellularity, necrosis, and no microcystic change. The presence of subpial tumor-cell infiltration indicated a poorer prognosis. Burger and coworkers [244] reported a significant association with malignancy for two parameters—necrosis and mitotic rate. Sotrel and colleagues [247] presented the clinical and pathologic data on oligodendroglial tumors in 38 children. Nine cases were said to have an astrocytic component. They suggested that childhood oligodendrogliomas may be treatable when amenable to surgical resection, despite their propensity for widespread cortical and subpial invasion and focal anaplasia.

MIXED GLIOMA

Mixed gliomas can occur in a variety of locations and combinations (e.g., astrocytic–oligodendroglial, astrocytic–ependymal, oligodendroglial–ependymal, and oligoastro-ependymal). Both low-grade and high-grade forms occur. These tumors have a roughly equal proportion of various cell types.

Subependymoma (Subependymal Glomerate Astrocytoma). A subependymoma is usually found as an incidental lesion at postmortem examination, much more often in adults than in children. It occurs as a nodular, discrete mass in the wall of the lateral or fourth ventricle and rarely is large enough to obstruct the CSF flow. Microscopically, the tumor is distinctive with irregular clumps of cells that have nuclear features reminiscent of ependymal cells, lying in a fibrillary glial background. This tumor has been visualized as a neoplasm of subependymal glial, astrocytic, ependymal, or combined origin. Both blepharoplasts and cytoplasmic processes filled with glial filaments have been found on electron microscopy [212, 248, 249]. Thus, the

tumor is included as a mixed glioma in the modification of the WHO classification [27].

Ganglioglioma. Gangliogliomas have a predilection for the third ventricle and the temporal lobe. In the series from our center, most were cystic, calcified, and located in the cerebral hemispheres, particularly the temporal lobe [250]. They show an admixture of astrocytic and neuronal elements with prominent calcification. Nests of small, round cells with dark nuclei resembling lymphocytes are frequently found. The neoplastic neurons need to be differentiated from normal trapped neurons within an infiltrating astrocytoma. The presence of clusters, binucleate or multinucleate forms, and the bizarre morphology of the former aid in the distinction (figure 2-19). Bielschowsky staining often impregnates the processes of the neuronal elements. NSE and neurofilament may be demonstrated in the neuronal component.

Gangliogliomas are low-grade, slow-growing tumors; malignancy is exceedingly rare and involves the glial component.

Subependymal Giant-cell Tumor. Subependymal giant-cell tumors have a characteristic location, histology, and clinical association with tuberous sclerosis. They occur adjacent to the lateral ventricular walls near the foramen of Monro. They contain large cells with abundant eosinophilic, glassy cytoplasm typically arranged in fascicles and oriented around hyalinized blood vessels (figure 2-20). The cell processes stain positively by the Holzer and Mallory's PTAH stains. Multinucleated tumor cells, as well as cells with marked variation in nuclear size and moderate pleomorphism, may be present, but they do not imply biologically aggressive behavior. The subependymal giant-cell tumors are slow-growing, low-grade neoplasms.

There has been speculation about the origin of this tumor cell. Russell and Rubinstein [213] pointed out the histologic similarity between the characteristic subependymal tubers with giant astrocytes and the tumor cells, and

suggested that the tumors originated in such foci. Globus [251] proposed that these cells presented neuronal features and originated from "spongioneuroblasts," cells capable of differentiating in both neuronal and glial directions. By immunohistochemical studies [252–255], both the presence and absence of GFAP have been described in this tumor. Of seven subependymal giant-cell tumors studied by immunohistochemistry and electron microscopy in our center, immunoreactivity for GFAP was found in four cases. However, the tumor cells may be negative for GFAP [252] and immunoreactive for NSE [253]. Ultrastructurally, the most consistent feature is the presence of numerous dense bodies, presumably primary lysosomes, as well as other organelles including prominent Golgi complexes and rough and smooth endoplasmic reticulum in the cytoplasm. Neurosecretory granules, microvilli, synapses, and bundles of intermediate filaments have also been described in rare cases [254]. These findings suggest that the tumor may be composed of ultrastructurally unique cells probably best thought of as *hybrid cells*, in addition to cells with neuronal and astrocytic characteristics. Until the exact histogenesis of the tumor cells is resolved, these tumors are best designated as *subependymal giant-cell tumor* rather than subependymal giant-cell astrocytoma.

MENINGIOMA

Meningiomas are rare in childhood. Of 1283 intracranial tumors of infancy and childhood encountered at The Hospital for Sick Children, Toronto, over 51 years (1934–1985), 13 (1%) were meningiomas [256]. The mean age of the patients was 11.3 years. There was a striking male preponderance (10 males, 3 females). The tumor locations were as follows: cerebral convexity (3), parasagittal region (2), medial sphenoid wing (2), olfactory groove (2), and optic canals (1).

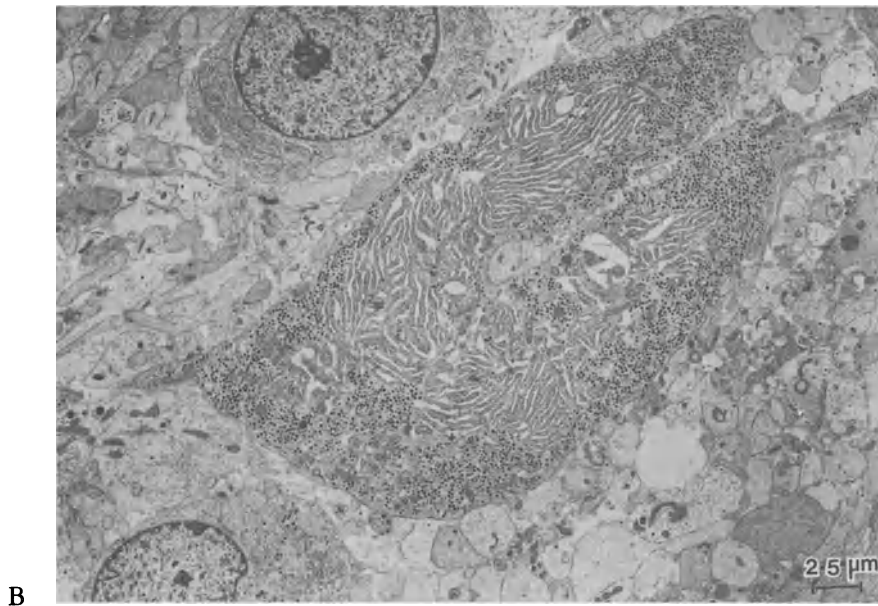
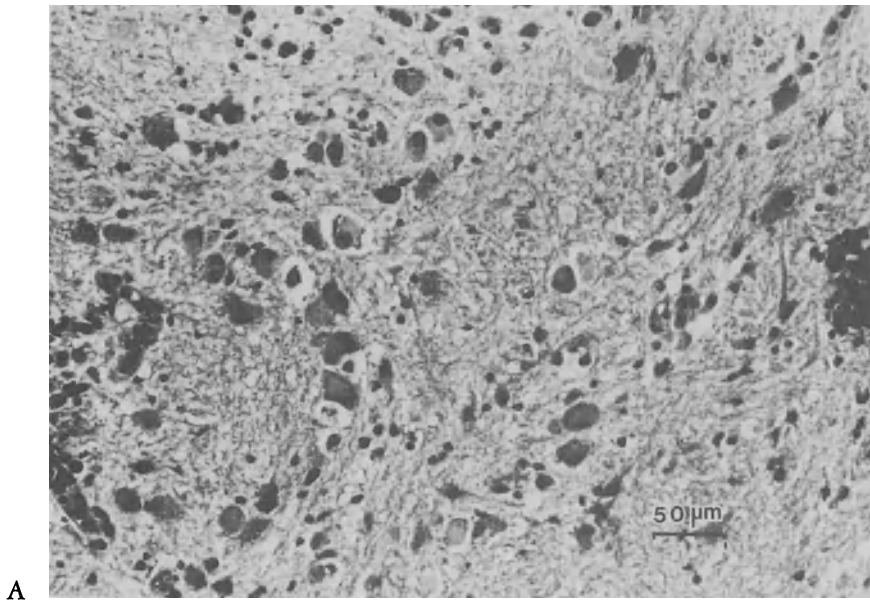
Meningiomas are well circumscribed and well delineated from underlying brain. Micros-

copically, several patterns are identified (meningotheial, fibroblastic, transitional), but only papillary and angioblastic meningioma are specifically related to prognosis. The tumor cells may show intranuclear pseudoinclusions, an appearance created by cytoplasmic invagination into the nucleus. The papillary meningiomas, although lacking overt microscopic features of anaplasia, are associated with frequent recurrence and metastatic potential.

The angioblastic meningioma is more aggressive than the other subtypes. It is also regarded as the hemangiopericytoma of the meninges by some authors is [257, 258]. Hemangiopericytoma has been categorized in the revised WHO classification as a tumor of blood vessel origin [27]. Pitkethly et al. [259] divided 81 tumors designated as angioblastic meningiomas into hemangioblastic and hemangiopericytic types, according to histological appearance. The hemangiopericytic tumors appeared at an earlier age and had a more rapid evolution of symptoms. There was also a tendency for local recurrence and development of extracranial metastases. Based on these observations, they suggested that meningeal hemangiopericytoma was an entity distinct from angioblastic meningioma.

Malignant meningiomas are exceedingly rare in children. In our review of 13 intracranial meningiomas in children [256], seven cases were completely excised and examined histologically. Only one tumor had histologic appearances of a malignant meningioma.

Immunohistochemical and morphologic studies indicate that meningiomas possess both epithelial and mesenchymal features. Immunoreactivity to epithelial membrane antigen, presence of desmosomes, immunolocalization of desmosomal plaque protein, and presence of intracytoplasmic inclusions immunoreactive for secretory component are epithelial traits, while immunoreactivity for vimentin is a mesenchymal feature. The characteristic positivity for epithelial membrane antigen and the coincident expression of vimentin intermediate filament and



desmosomal plaque protein are helpful in differentiating meningiomas from other mesenchymal tumors such as fibromas and schwannomas [65, 66, 92–94].

The following tumors are relatively infre-

quently encountered in pediatric practice and are only briefly outlined.

Acoustic Neuroma (Schwannoma, Neurilemoma). Bilateral acoustic nerve neuromas may be

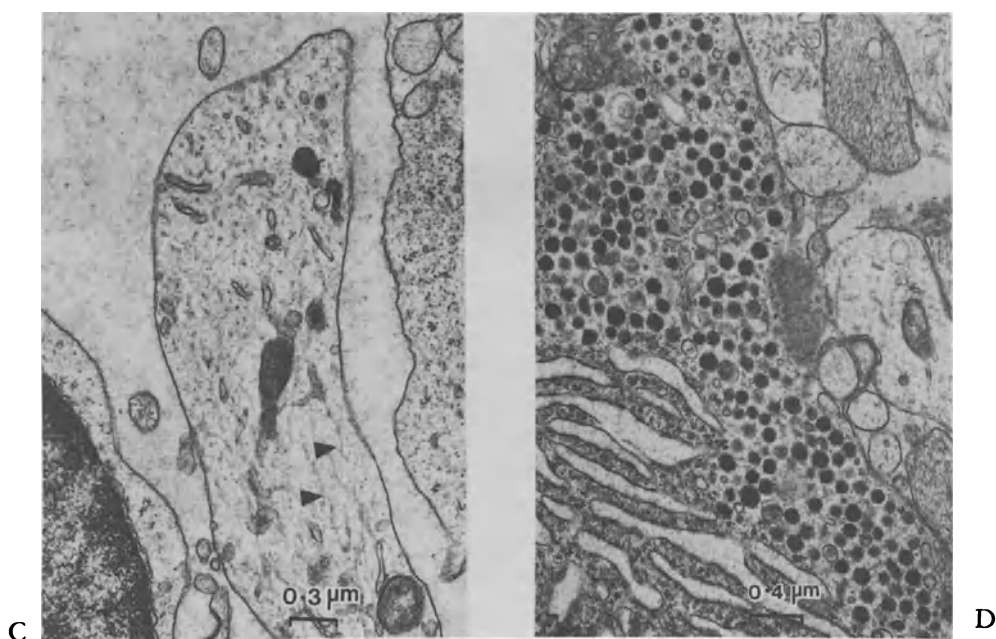


FIGURE 2-19. Ganglioglioma. A. Neuronal and glial components. B. An electron micrograph showing a large neuron with prominent dense-core granules and endoplasmic reticulum surrounded by numerous intertwining cytoplasmic processes. C. An electron micrograph showing microtubules (arrowheads), intermediate filaments, and mitochondria in the cytoplasmic processes. D. An electron micrograph showing the dense-core granules in higher magnification.

encountered with von Recklinghausen's disease, in addition to low- and high-grade astrocytomas and optic nerve gliomas. These tumors, which may be solid or cystic, account for 1%–2% of infratentorial tumors. Microscopically, the hallmark is the finding of Antoni type A and type B areas, the former characterized by parallel rows of nuclei arranged as Verocay bodies, and the latter containing loosely arranged cells.

Chordoma. Chordomas are tumors of notochordal remnants and can occur at any level of the craniospinal axis [260–262]. They account for less than 1% of all intracranial tumors. The majority of these tumors occur in the fourth

decade of life. They are rare in children before puberty, but may be seen even in infancy [261]. Chordomas are immunoreactive for epithelial markers such as cytokeratin and epithelial membrane antigen as well as S-100 and vimentin [262].

Pituitary Adenoma. Pituitary adenomas are rare in childhood. We have encountered only four cases, all in children over ten years old. These adenomas tend to be more aggressive in children than in adults, and extend outside the sella [263]. With recent advances in electron microscopy and immunohistochemistry, a classification that accurately reflects hormone production of the tumor is now appropriate: prolactin cell adenoma, growth hormone and prolactin cell adenoma, adrenocorticotrophic hormone (ACTH) cell adenoma, and undifferentiated cell adenoma (oncocyctic and nononcocyctic adenoma) [264–266].

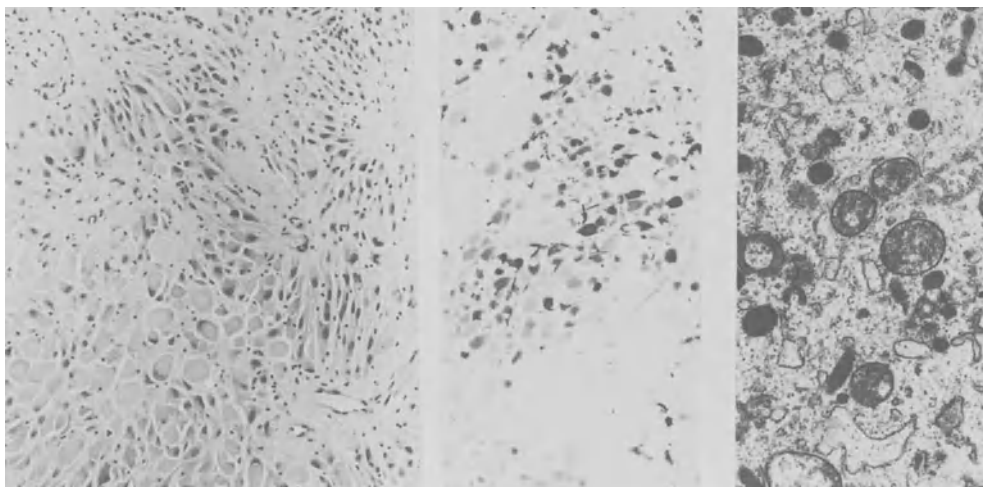


FIGURE 2-20. Subependymal giant-cell tumor. A. The characteristic arrangement of plump eosinophilic tumor cells in fascicles, oriented around hyalinized blood vessels. (Hematoxylin and eosin stain.) B. Scattered tumor cells immunoreactive for GFAP (arrow). C. Electron micrographs showing prominent dense bodies in the cytoplasm.

Hemangioblastoma. Hemangioblastoma is a vascular neoplasm known for its association with retinal hemangioblastomas and a number of extra-CNS lesions (von Hippel–Lindau disease) [267–270]. The cerebellar tumor is discrete and characteristically presents as a cyst with a mural nodule. These highly vascular tumors show two components: vascular channels with endothelial cells and pericytes, and foamy stromal cells that may aggregate in small clusters.

Others. Nonneoplastic, malformative lesions may be considered in the differential diagnosis of CNS neoplasms: dermoid and epidermoid cysts, histiocytosis X, hamartomas, primary bone lesions such as giant-cell tumor, arachnoid cysts, and vascular malformations. [Please see addendum.]

Current and Future Perspectives

To date, most tumor research in neuro-oncology has focused on phenotypic differences between neoplastic and normal cells; only recently have investigations been initiated to understand events at the genotypic level. The properties

of malignant cells that distinguish them from their normal counterparts, such as unregulated proliferation, immortalization, loss of contact inhibition, expression of new antigens, and metastatic potential, must be determined by genes that regulate cell growth. Oncogenes produce such cellular transformation [271–277]. If the latent tumorigenic potential of the proto-oncogenes, a subset of genetic targets that has remained highly conserved throughout evolution, is expressed, the resulting active oncogenes will induce the malignant transformation. Thus, detection of specific genetic defects at the molecular level will eventually complement cytogenetic studies of malignant cells.

Genes that confer the malignant phenotype were first recognized as components of the genomes of ribonucleic acid (RNA) tumor viruses. Two technical approaches, one involving the transfer of genetic material from one cell to another (gene transfer), and the second involving the study of oncogenic RNA tumor viruses (retroviruses), identified a group of

genes (oncogenes) that were capable of transforming a normal cell to a malignant cell. Oncogenes detected by gene transfer are homologous to the transforming genes found in retroviruses. Potential oncogenes are present in cellular DNA of the somatic cell genome, and may be activated by qualitative changes (e.g., mutations) or quantitative changes (e.g., gene amplification or rearrangement).

Three tumors that exemplify the application of molecular genetics to clinical management are retinoblastoma, neuroblastoma, and Wilms' tumor, which occur in childhood. Specific chromosomal deletions are associated with these tumors. Both unilateral and bilateral cases of retinoblastoma may be associated with a deletion of chromosome region 13q14 [278, 279]. Deletion or inactivation of the alleles in this region may play an important role in the development of retinoblastoma.

Approximately one third of children who appear to be homozygous for deletion of a specific band in the short arm of chromosome 11 develop Wilms' tumor [280–282]. The deletion may be associated with duplications leading to homozygosity of the nondeleted alleles in the tumor cells [282]. Children with the rare syndrome known as the AGR (aniridia, genitourinary abnormalities, and mental retardation) triad often develop Wilms' tumor at a very early age and have deletion in the short arm of chromosome 11 [280].

An example of the influence of genetic information on treatment decisions and determination of prognosis may be found in the *N-myc* oncogene amplification by neuroblastomas [283–287]. Three cytogenetic abnormalities have been identified with increasing frequency in human neuroblastoma cells [288–292]. Double minute chromatin bodies are found in 20%–30% of primary tumors and about half of neuroblastoma-derived cell lines. Homogeneously staining regions are found in over half of neuroblastoma cell lines but rarely in primary tumors. Partial deletion of the short arm of chromosome 1 has been identified in

about 70% of both primary neuroblastomas and tumor-derived cell lines. Both double minutes and homogeneously staining regions are considered to be cytological manifestations of amplified genes.

The *N-myc* gene was first identified as a gene amplified up to 140-fold in human neuroblastoma cell lines and fresh tumor tissues. Brodeur and colleagues [284] found *N-myc* amplification in 24 of 48 stage 3 and 4 tumors but in none of the 15 stage 1 and 2 tumors. *N-myc* amplification is correlated with advanced stages of disease and adaptation to growth in vitro, both of which are associated with a poor prognosis. The estimated progression-free survival at 18 months was 70%, 30%, and 5%, respectively, for patients whose tumors had one, 3–10, and more than ten copies of *N-myc*. *N-myc* expression has also been noted in retinoblastomas, a significant association since both tumors are derived from neural ectoderm [286].

Tumor growth factors generally have been identified through their mitogenic effects on cells in culture. Two of these, the epidermal growth factor and platelet-derived growth factor (PDGF), are well-characterized molecules that are active on glial cells [293]. Epidermal growth factor is a potent mitogen for a variety of cells, including those of neuroectodermal origin [294]. Direct evidence that an oncogene may code for a growth factor emerged from the amino acid sequence of PDGF, which showed a virtual identity between one of its constituent polypeptide chains and a part of the transforming protein of the simian sarcoma virus [295, 296]. There is evidence suggesting that the transforming capacity of this virus can be ascribed to its synthesis and release of a PDGF-like growth factor [295–298]. The simian sarcoma virus induces gliomas at a very high frequency in primates [299]. Tumor lines from several different gliomas have been shown to secrete a PDGF or PDGF-like molecule [300, 301]. [Please see addendum.]

An understanding of the molecular-genetic events that contribute to neoplastic disease may benefit clinical practice in three areas: the refinement of tumor diagnostic classification with attendant effects on prognosis and choice of therapy; the development of simple noninvasive methods to predict cancer risk; and the potential exploitation of oncogene product identification in developing effective therapeutic strategies. These experimental developments, and the information they have generated, require integration into the background of the conventional pathologic approach to brain tumors, since they provide important insights into areas such as tumor biology, assessment of individual cancer risk, prognostication, and therapy.

Note

The addendum to this chapter appears on page 511 of this book.

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3. DIAGNOSTIC RADIOLOGY OF CHILDHOOD BRAIN TUMORS

David W. Johnson

Richard E. Latchaw

Techniques of Neuroradiology

VENTRICULOGRAPHY AND MYELOGRAPHY

Neuroradiology has evolved rapidly since Roentgen first discovered the X-ray in 1895. Fractures and foreign bodies were the first to be appreciated. However, intracranial disease had to demonstrate some effect on the surrounding bone or normal physiologic calcifications to be appreciated on the skull radiograph.

Luckett was the first to describe air in the ventricles of a patient 19 days after head trauma [1]. Dandy described the technique of injection of air directly into the ventricles and later into the spinal subarachnoid space [2, 3]. Positive contrast ventriculography started with Lipiodol and Thorotrast, but was considered more toxic and was used with less frequency and only when air ventriculography was inadequate. Thorotrast was discontinued when it was later found to be an alpha-particle emitter with a half-life of 1.4×10^{10} years. Pantopaque, less toxic than Lipiodol, was used since the late 1940s. However, this agent also had significant side effects. As a result, water-soluble contrast agents, desirable because of their complete absorption from the central nervous system (CNS), were developed. In recent years, metrizamide (Amipaque), a nonionic contrast, has replaced Pantopaque and other more toxic water-soluble agents for myelography. Most recently,

nonionic agents such as Iohexol (Omnipaque) and Iopamidol (Isovue) have appeared; both show less toxicity to the CNS than metrizamide.

ANGIOGRAPHY

Cerebral angiography in humans was first performed by Moniz in 1927 by direct percutaneous puncture of the carotid artery [4]. Since that time, catheter techniques, usually via the common femoral artery, have developed [5]. Angiography has evolved into interventional techniques, such as embolization of hypervascular tumors and arteriovenous malformations and balloon occlusion of aneurysms. It is not now used in the routine workup of most intracranial tumors.

COMPUTED X-RAY TOMOGRAPHY

Computed tomography (CT) was developed by Hounsfield in England in 1972 [6]. Because of its ability to better differentiate tissues of very similar linear attenuation coefficients, it has greatly modified the approach in neurodiagnosis and has caused pneumoencephalography to become a lost art. Many tumors have an abnormal blood-brain barrier. Intravenous iodine contrast agents cross the abnormal blood-brain barrier and improve tumor conspicuity. Positive contrast cisternography and ventriculography with CT is only performed with water-soluble

agents, because Pantopaque is too dense on CT and is used only to detect communication of cystic lesions with the ventricular system, delineation of cystic suprasellar masses, determination of communication between the ventricular and the subarachnoid space, and sites of cerebrospinal fluid (CSF) leakage. Computed tomography has also challenged the need for routine angiography, which is now limited to primary vascular abnormalities, delineation of very angiographically characteristic tumors such as meningioma and hemangioblastoma, and occasionally, arterial mapping in presurgical planning. Computed tomography has proved to be a valuable adjunct in water-soluble contrast myelography, and is the imaging method of choice in the use of positive contrast cisternography and ventriculography.

MAGNETIC RESONANCE IMAGING

Nuclear magnetic resonance imaging (MRI) is the new imaging modality. Like CT, it provides tomographic images of the body, but it does not use ionizing radiation. Though more costly than CT, MRI has proven useful in the detection of a variety of disease processes, primarily because of its great sensitivity to altered water content in the brain and spinal cord.

Placed in a strong external magnetic field, charged particles (in this case hydrogen protons) will align with the force lines of the field. Adding energy at the resonance frequency of the protons to the volume will perturb these protons to a higher energy state. The return of a large enough population of these protons to a lower energy state will result in a detectable radiofrequency (RF) pulse that is quantified and given a gray scale value. Low signal intensities relative to surrounding tissue are assigned a dark shade; high signal intensities relative to the surrounding tissues are assigned a white shade. Air and bone, for different reasons, have no detectable signal and are therefore black. There are three magnetic properties of body tissue that describe each RF pulse: proton (hydrogen) density, spin-lattice

(T1) relaxation, and spin-spin (T2) relaxation. The relative effects of T1 or T2 relaxation on the image can be varied by manipulating two operator-dependent parameters: pulse repetition time (TR) and echo time (TE). It is beyond the scope of this chapter to describe the physics of MRI, and we refer the reader to other works that treat this subject in greater depth. However, for the practicing clinician confronted with these images, it is sufficient to say that most images emphasize either T1 relaxation effects or T2 relaxation effects. These are otherwise referred to as T1-weighted (T1W) or T2-weighted (T2W) images. The purist refuses to use the terms T1 weighting or T2 weighting, but for the clinician these terms are useful. T1 weighting occurs when a short TR (< 1000 ms) and a short TE (< 30 ms) are used. CSF will appear dark relative to brain tissue because of its long T1 relaxation time relative to brain tissue. T2 weighting occurs when a long TR (> 2000 ms) and a long TE (> 80 – 100 ms) are used. On these images, CSF will appear white relative to brain tissue. This is because of its long T2 relaxation time relative to brain tissue. There are also images that emphasize proton density. These will have a long TR (> 2000 ms) and a short TE (< 80 ms). Here, CSF will appear darker than or may have the same signal as white matter. T1W images are more pleasing to the eye and better define anatomy than spin density or T2W images but are less sensitive to the presence of abnormal water content, a sensitive indicator of pathology in the brain.

Gadolinium-DTPA is a paramagnetic contrast agent, used intravenously to enhance the contrast of tissues and tumors without a blood brain barrier (BBB) relative to surrounding tissues. Its enhancement effect is best appreciated on T1W images due to shortening of the T1 relaxation time of neighboring water protons. This means enhancement will result in a higher signal and cause that tissue to appear white. This brief introduction to MRI should help orient the reader to the images that follow in this chapter.

Supratentorial Tumors

ASTROCYTOMA AND GLIOBLASTOMA MULTIFORME

The noncontrast CT scan of the typical astrocytoma usually reveals an area of low density, often with little mass effect. Sometimes the area of low density is very subtle and can be masked by artifact from the surrounding bony structures. White-matter edema, which also has low density, often surrounds the tumor and further obscures its true location and margins. Glioblastoma, with hemorrhage or calcification, will also have increased density. If hemorrhage is large enough, the tumor mass itself may be obscured, confusing the neoplastic etiology of the hemorrhage with other processes such as angioma.

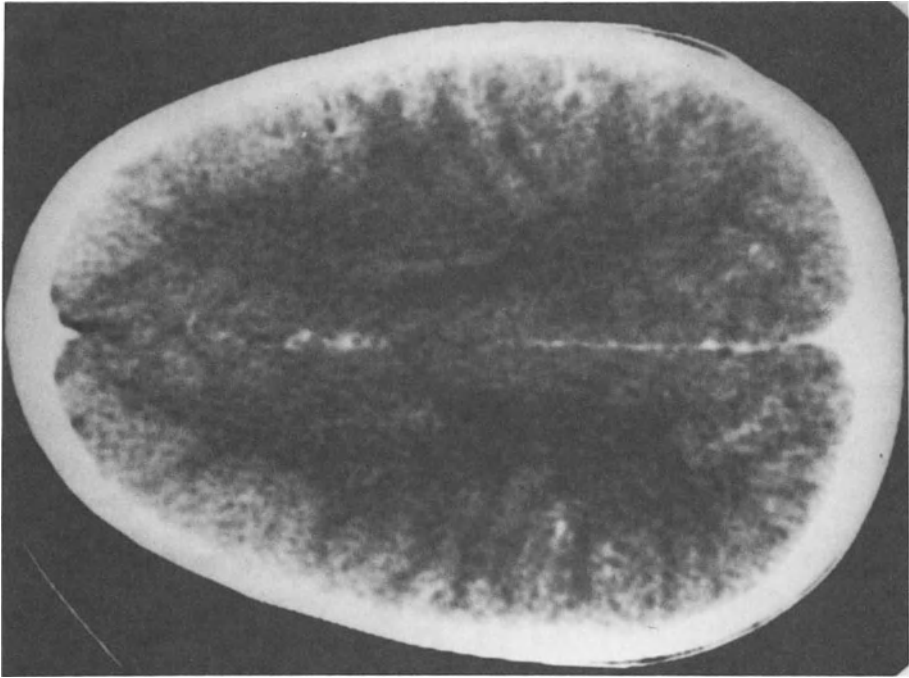
There is no typical appearance of astrocytoma on the post-contrast scan. There are many different degrees of enhancement that astrocytoma can display. The most subtle type of astrocytoma has minimal or no enhancement at all with a conventional intravenous contrast dose of about 40 gm of iodine (figures 3-1A, 3-1B). This has led to the use of a delayed high-dose contrast technique, in which a double dose of contrast is administered followed by delayed scanning one hour later. This allows for a higher blood iodine level and more time for contrast to cross the relatively intact blood-brain barrier. Most tumors will show more enhancement with a double dose of contrast than with a single dose [7]. We believe this technique should be reserved for those individuals with nonenhancing mass effects who also have normal renal function. Enhancement ranges from poor or patchy with ill-defined margins to a more homogeneous enhancement with well-circumscribed borders. Rim or ring enhancement is also seen with astrocytoma (figure 3-2). This rim will vary in thickness, unlike the uniformly thin rim of enhancement seen in most cerebral abscesses. Whole-mount pathological studies of untreated glioblastoma multiforme have revealed a close correlation of the rim of viable

neoplasm and the enhancing rim seen on CT [8]. The central area of low density within the rim corresponds to necrotic tissue, and the perilesional area of low density represents edema with infiltrating tumor. The central low density may also represent viable neoplasm that enhances more slowly than the rim [9]. Astrocytoma can also appear very complex, with formation of multiple cystic or necrotic areas interspersed with variably enhancing solid tumor (figure 3-3). These features tend to indicate a higher-grade tumor. It is difficult to accurately predict the contents of the cystic lesion. Despite the presence of a sharp border, the contents can range from proteinaceous fluid to necrotic tissue to solid tissue with intracellular microcysts.

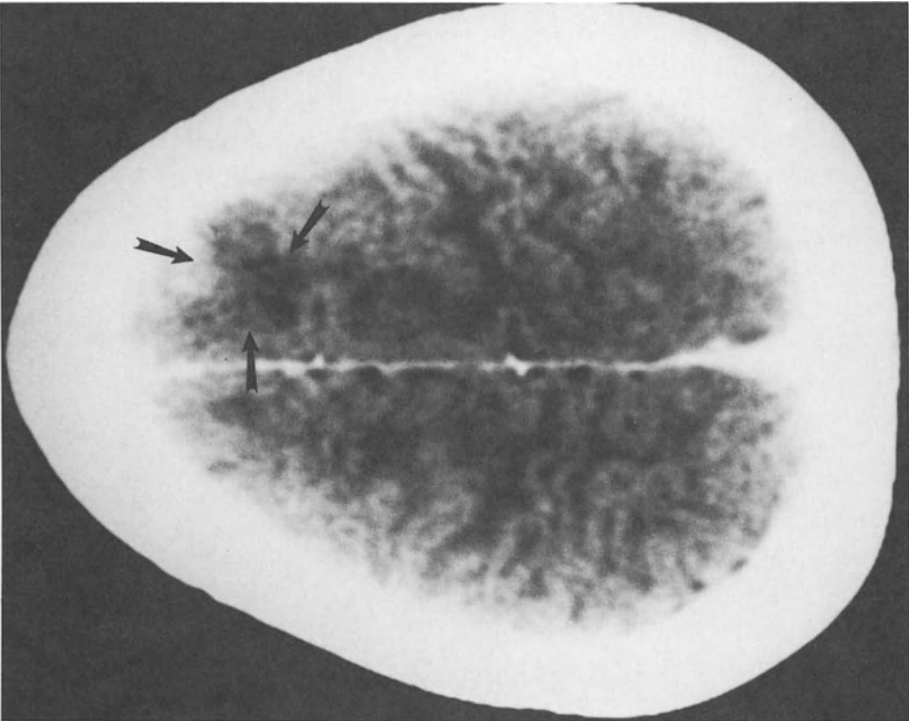
While it may be said that low-grade astrocytomas tend to enhance less and high-grade astrocytomas/glioblastomas tend to enhance more, studies have shown that the degree of enhancement correlates poorly with histologic grade [10]. High-grade tumors can show very little if any enhancement (figure 3-4) and lower-grade tumors can enhance vividly. The margin of enhancement, if seen, does not necessarily mark the boundary of the tumor. The surrounding tissue may be infiltrated with tumor cells.

If the tumor extends to the ventricular or cortical surface, the tumor may spread along the CSF pathways (figure 3-5). This may manifest itself as a leptomeningeal enhancement or as new focal areas of tumor bordering the ventricular or cortical surfaces. Multifocal glioma, a rare form, appears as multiple noncontiguous simultaneously occurring foci of tumor that do not border the ventricular or cortical surface [11]. According to Rubinstein, they represent between 2.5% and 4.9% of all primary gliomas [12].

The appearance of calcification suggests a low-grade tumor and may be the only clue to its presence. Some calcifications may be dense enough to be seen by plain film radiography (figure 3-6). Unfortunately, the pattern of calcification is not specific. Tumor type cannot be



B



A

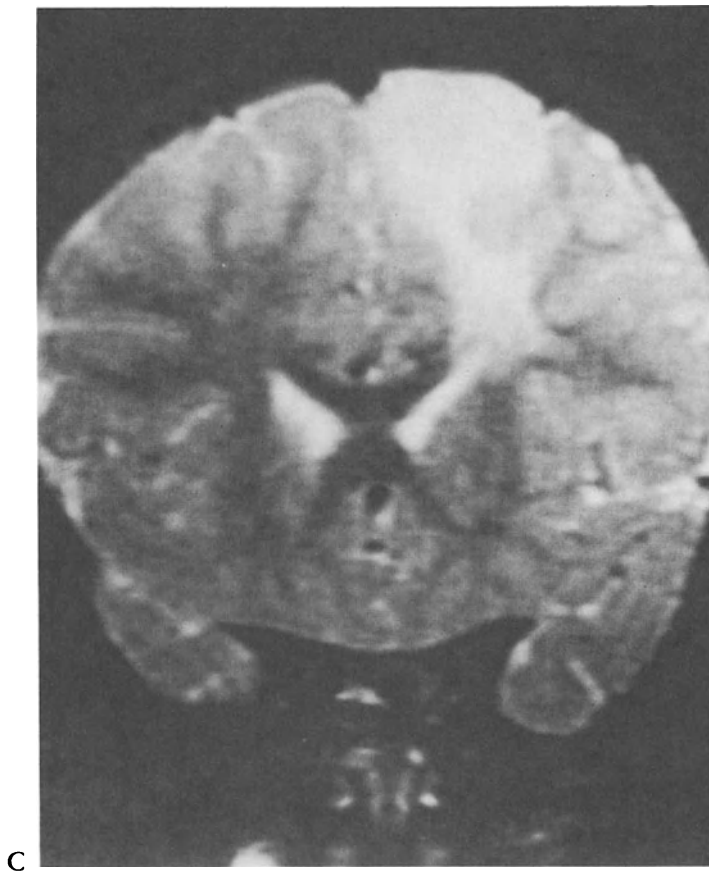


FIGURE 3-1. A four-year-old male with astrocytoma. A and B. An IV contrast-enhanced CT scan at two levels shows only a subtle area of decreased density in the left frontal lobe at the convexity (arrows). No enhancement is seen and no abnormality is seen in the white matter near the left frontal horn. C. Coronal MRI (TR/TE 3000/120) shows increased signal in the tumor at the cortex. There is also increased signal in the white matter extending to the frontal horn not detected by CT. (Used with permission from Latchaw RE, *Computed Imaging of the Head, Neck and Spine*, second edition, 1990, in press.)

predicted, and nonneoplastic processes such as old inflammatory changes and angioma must also be considered.

There is a subset of patients with clinical manifestations of glioma and negative initial CT scans. Hylton and Reichman report eight cases who returned two weeks to 39 months

later with a positive CT scan [13]. They felt this group probably represented benign gliomas undergoing anaplastic differentiation to more malignant forms.

MRI is more sensitive than CT in the evaluation of suspected intracranial tumor [14, 15], but cannot discriminate between different tumors on the basis of T1 or T2 relaxation times [16, 17]. Astrocytoma commonly exhibits a low signal on T1W and a high signal on T2W sequences (figure 3-1C). However, the T2W spin-echo sequence is more sensitive to the presence of edema than the T1- or the spin-density-weighted sequences. The ability to detect tumor is possible on the basis of the greater water content often seen in tumor-bearing tissue. This distinction is very non-specific when one considers that pathologic

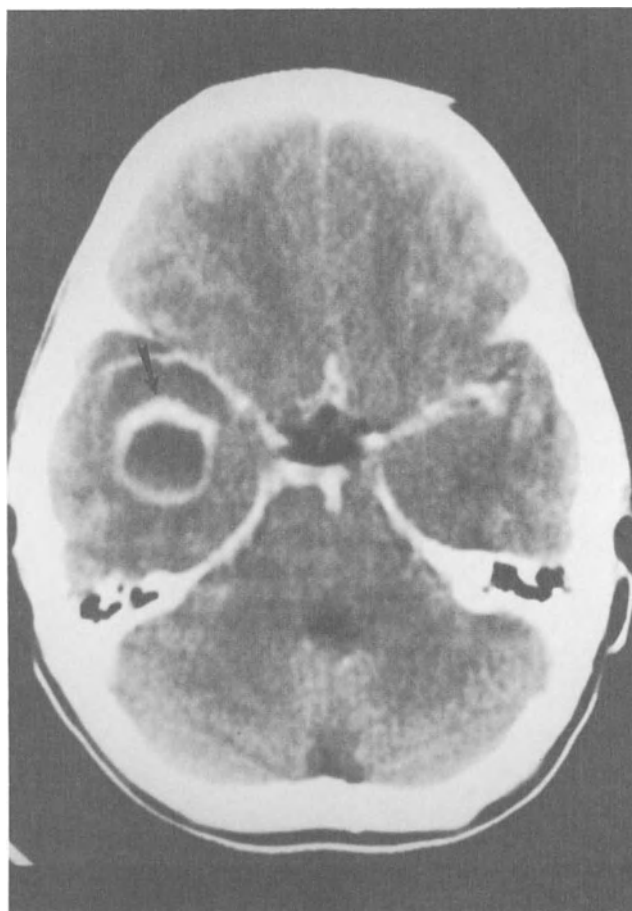


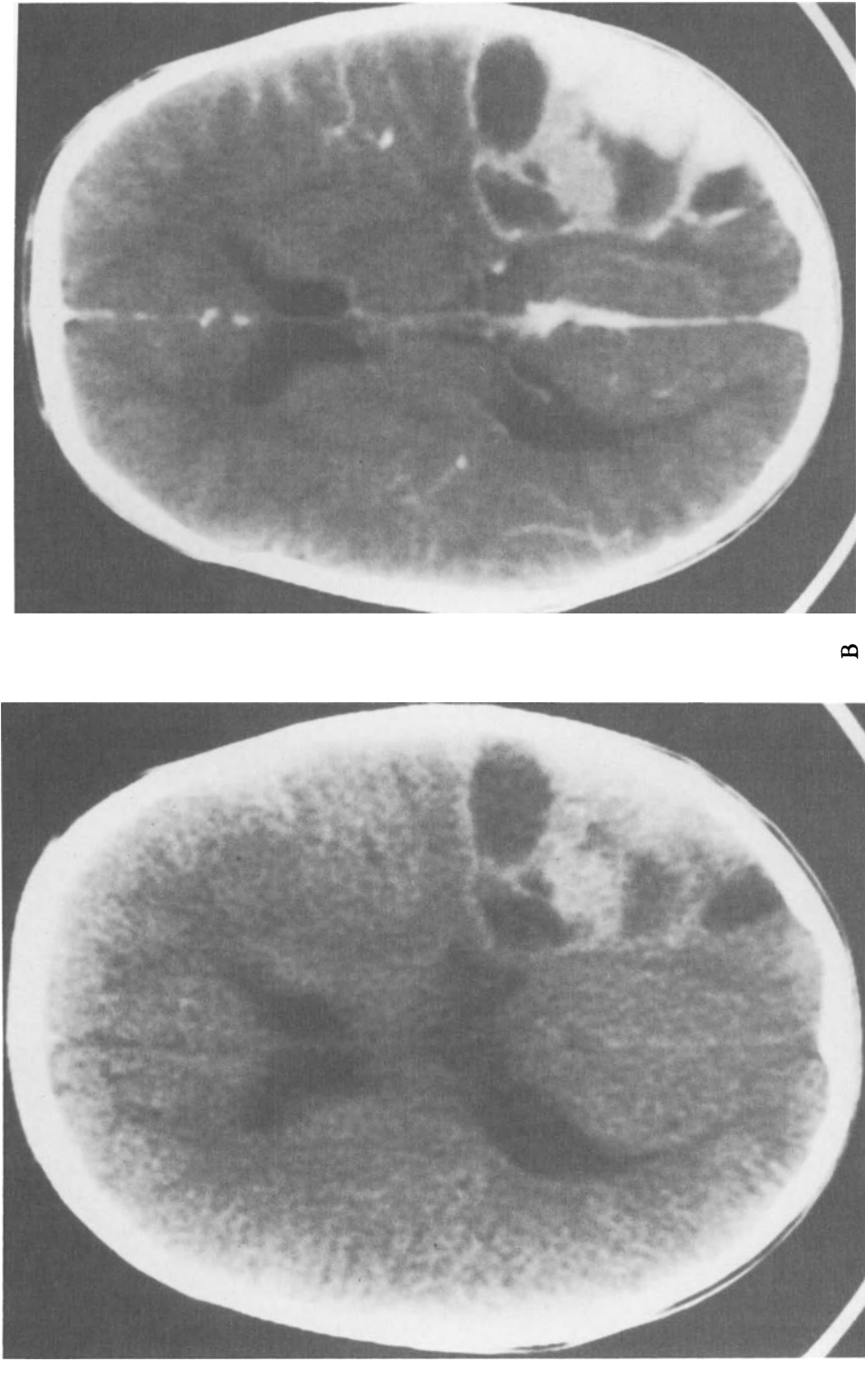
FIGURE 3-2. A two-year-old male with astrocytoma. The IV contrast-enhanced CT shows a ring-enhancing lesion with a central low density in the right temporal lobe. Note the thickened rim anteriorly (arrow), a feature more compatible with tumor than with abscess.

processes such as infarct, demyelination, and inflammation also increase parenchymal water content. Furthermore, as is the case with CT, on MRI, tumor margins can be obscured by surrounding edema. Lower-grade tumors having a water content closer to that of normal brain will be closer to normal brain in signal characteristics. We are aware of one case, an adult with gliomatosis cerebri at autopsy, who had tumor in many areas where MRI demonstrated a normal signal.

Intravenous administration of gadolinium-DTPA will lead to enhancement of those areas of tumor that have a breakdown of the blood-brain barrier much like CT [18, 19]. Gadolinium research is ongoing in the area of contrast agents. It remains to be seen if the use of con-

trast agents in MRI will better define the true extent of tumor and if they will be more sensitive than iodine and CT to the more intact blood-brain barrier.

Research in MRI characterization of tumor cysts of astrocytoma has revealed a dependence of T1 relaxation time on protein concentration [20]. Increasing protein concentration results in decreasing T1 relaxation time. MRI appears to be better than CT in differentiating cystic from solid portions of tumor, but the appearance of a rather edematous, soft, well-demarcated



A

B

FIGURE 3-3. A three-year-old female with anaplastic astrocytoma. A. A noncontrast CT shows a complex, well-circumscribed mass in the left parietal lobe. Areas of solid tumor and tumor cyst and/or necrosis are seen. B. IV contrast-enhanced CT shows variable enhancement in the solid portions of tumor and better margination of the cystic and/or necrotic areas.

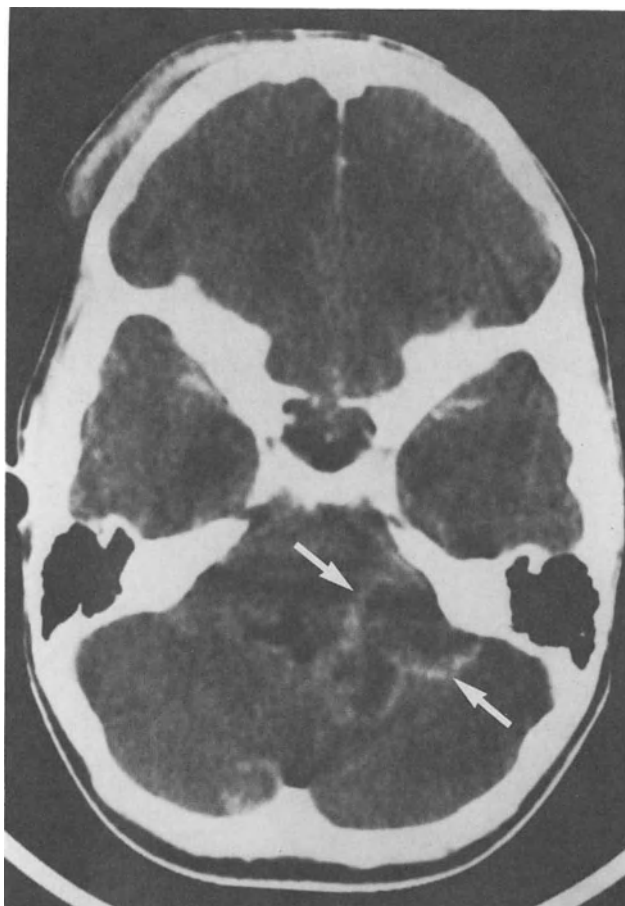


FIGURE 3-4. A five-year-old male with glioblastoma multiforme. An IV contrast-enhanced CT shows a rim-enhancing tumor in the left middle cerebellar peduncle and hemisphere (arrows). Enhancement is less in this higher-grade tumor than in those tumors shown in figures 3-2 or 3-3.

tumor on MRI sometimes cannot be differentiated from the very proteinaceous tumor cyst.

By CT, the calcified, nonenhancing or partly enhancing tumor often cannot be differentiated from angioma. MRI may reveal flow void in feeding arteries or draining veins and may also reveal hemosiderin, the legacy of an old hemorrhage. These features, while not pathognomonic of angioma, are not seen in low-grade astrocytoma. Angiography may further characterize the small angioma, but frequently these lesions are angiographically occult.

OLIGODENDROGLIOMA

Oligodendroglioma is rare in children. When it does occur, it is located in the cerebral hemispheres [21]. This tumor usually has all the

CT and MRI features common to astrocytoma. This tumor calcifies more frequently than astrocytoma. Vonofakos et al. found calcifications in 20 of 22 patients with oligodendrogliomas [22]. Calcification varied from central to peripheral in location, and linear to nodular in appearance. There are no distinguishing features of oligodendroglioma calcification. Another feature that is more common to oligodendrogliomas is the nonenhancing, well-circumscribed, low-density lesion seen by CT [23]. This can occur without (figure 3-7) or with (figure 3-8)

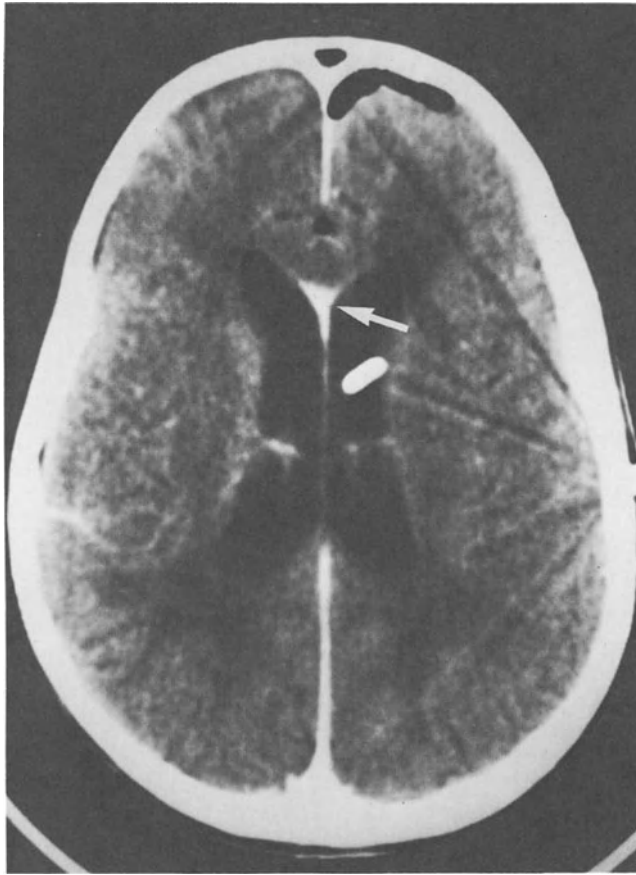


FIGURE 3-5. A 14-year-old female with brainstem glioma. IV contrast-enhanced CT shows enhancement and thickening of the anterior septum pellucidum (arrow).

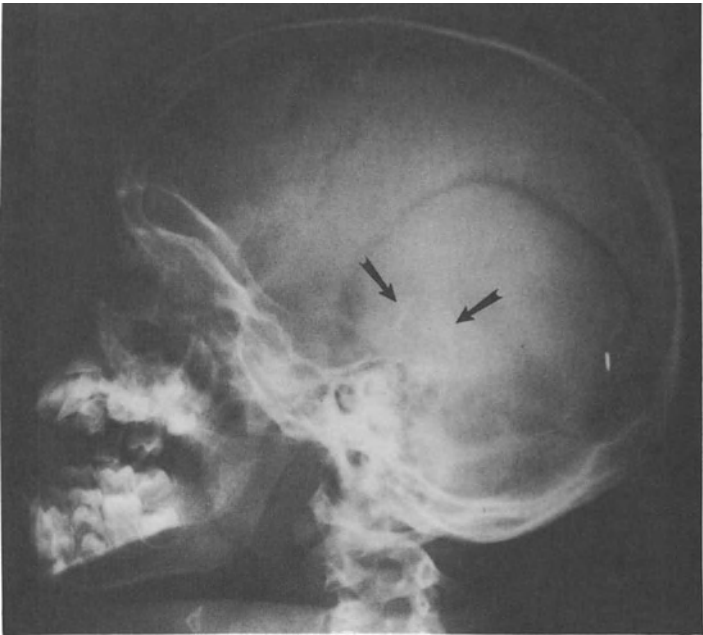
mass effect. While oligodendroglioma may become cystic, attenuation coefficients are not specific for cysts. Solid neoplasms with low densities have been described [24]. MRI may serve to differentiate arachnoid cysts from cystic neoplasm. However, a well-margined, relatively “wet” but solid tumor can have T1 and T2 relaxation times similar to a proteinaceous cyst.

PRIMITIVE NEUROECTODERMAL TUMOR (PNET)

Rorke has attempted to subclassify PNET according to five lines of cellular differentiation

[25]. These five subtypes are 1) PNET, not otherwise specified, 2) PNET with glial differentiation, 3) PNET with ependymal differentiation, 4) PNET with neuronal differentiation, and 5) PNET with bipotential differentiation. Those that differentiate along neuronal cell lines include the primary intracranial neuroblastoma, which if located in the cerebellum is otherwise known as medulloblastoma [26]. Rorke also includes the pineoblastoma and pineocytoma in this classification. Primary intracranial neuroblastoma is different from the metastatic type in which metastasis to the orbits, base of the skull, and calvarium is typical. Parenchymal metastasis from an extracranial site is very rare [27].

Typically, PNET is located in the hemisphere and is large at presentation. In one series



A



B

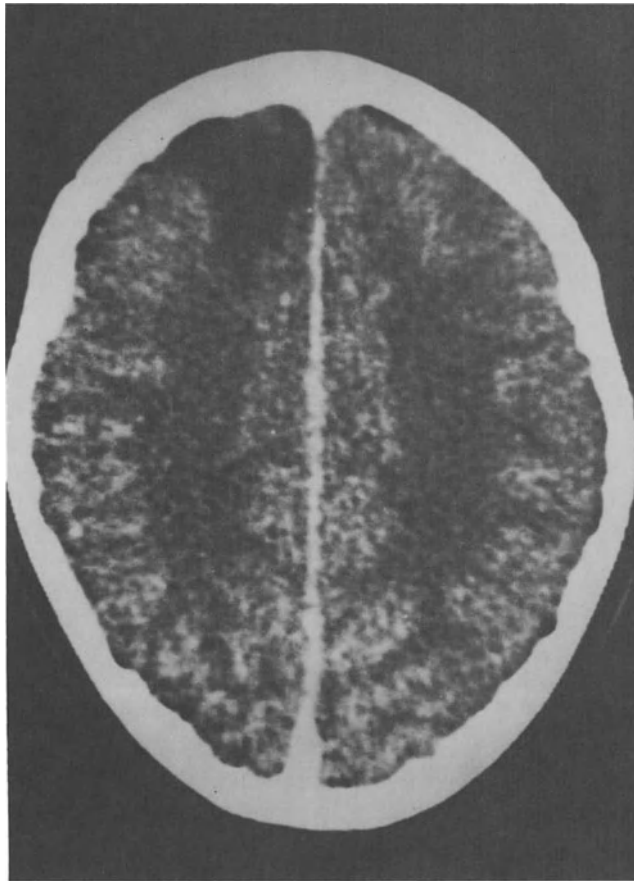


FIGURE 3-7. An 11-year-old male with oligodendroglioma. An IV contrast-enhanced CT scan shows a wedge-shaped, low-density mass in the right frontal lobe. Without mass effect, this has the appearance of an old infarct or arachnoid cyst.

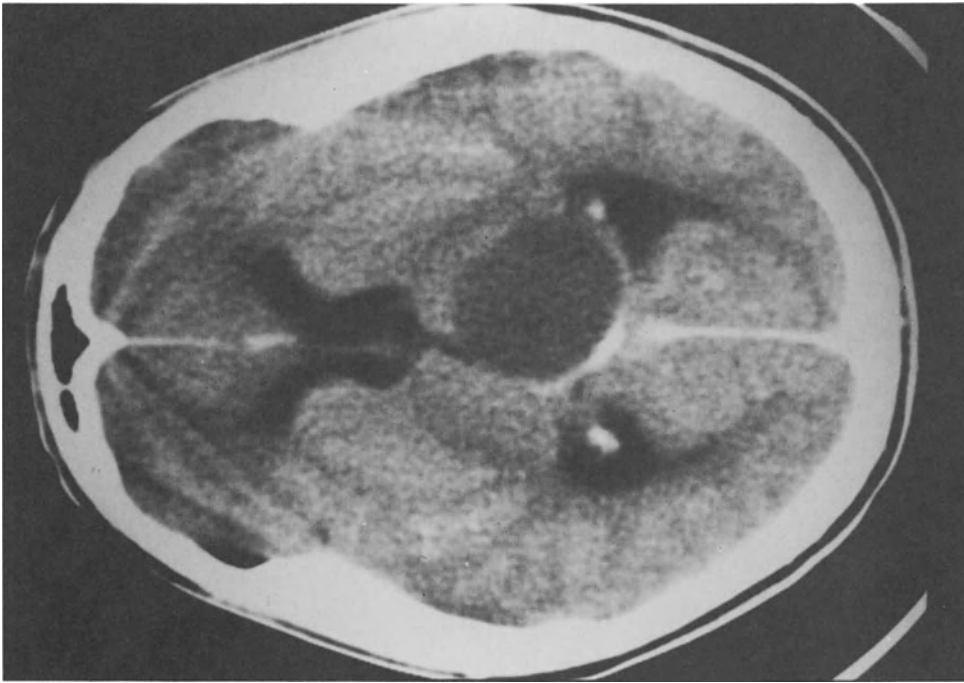
of 17 patients, over half of tumors were at least 7.5 cm in size [28]. PNETs frequently spread via the CSF pathways and despite aggressive therapy have a high recurrence rate.

In primary neuroblastoma, Kingsley and Harwood-Nash reported localized thinning, vault expansion, or erosion of the inner table of the skull over the site of the tumor [29].

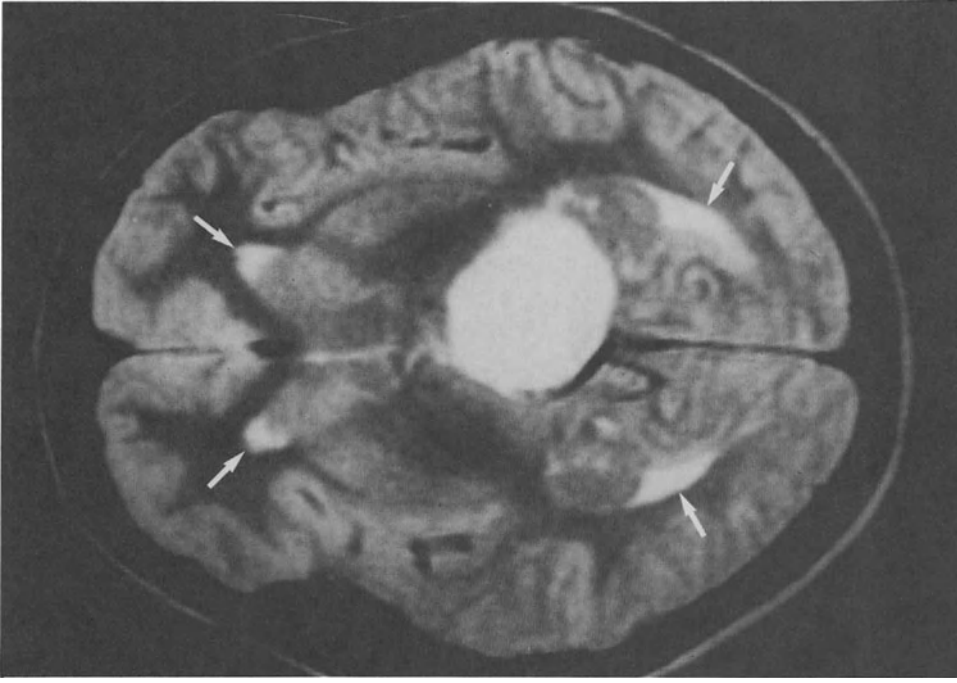
They found no changes in the skull typical of metastatic neuroblastoma. In the primary form, elevated intracranial pressure can lead to sutural diastasis if the sutures have not closed. Sutural diastasis also can occur in the secondary form because of epidural deposits of tumor extending to the sutural margins [30, 31].

There are several CT features that may suggest the diagnosis of PNET. The first to consider is the large size and sharp margin of the tumor mass (figure 3-9). Few pediatric tumors in the supratentorial compartment reach such a large size at presentation. Sometimes the mass her-

FIGURE 3-6. A 17-year-old female with a 15-year history of low-grade astrocytoma. A. One of the original skull films (this one after biopsy) shows faint gyriform calcifications just above the mastoids (arrows). B. A recent CT shows dense calcification in the tumor. Atrophy secondary to irradiation is also seen.



A



B

FIGURE 3-8. A 15-year-old female with oligodendroglioma. A. An IV contrast-enhanced scan shows a well-margined, low-density mass in the left thalamus with mass effect. No enhancement is seen. B. Axial MRI (TR/TE 2000/56) shows a hyperintense signal in the mass. At surgery this tumor was soft but not cystic. Also note periventricular high signal (arrows) and large ventricles, MRI evidence of obstruction of the lateral ventricles, and transependymal absorption of CSF. (Used with permission from Latchaw RE, *Computed Imaging of the Head*, Neck and Spine, second edition, 1990, in press.)

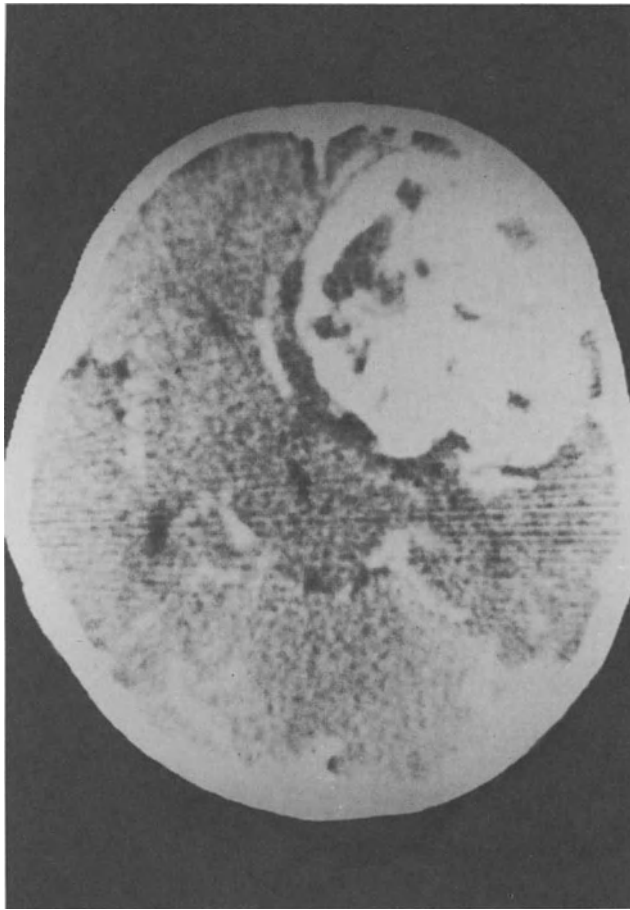


FIGURE 3-9. A four-year-old male with PNET. An IV contrast-enhanced CT scan shows a large, well-margined tumor in the left frontal lobe. There is dense contrast enhancement with several nonenhancing areas compatible with necrosis.

niates beneath the falx or through the tentorium. Astrocytoma is frequently smaller at presentation, but if diffusely infiltrative may involve most of the hemisphere. Such astrocytomas tend to be lower-grade tumors and will fail to demonstrate sharp margins. The second feature to consider is the internal characteristics. The solid portion of the mass is typically isodense to hyperdense on noncontrast CT. Calcification and cystic/necrotic change is frequent. These studies report calcification in 50%–70% of cases and cystic/necrotic change in 40%–80% [28, 32, 33]. These same studies

report only one hemorrhage in 53 patients. However, Zimmerman reports hemorrhage in 2 of 3 patients with primary craniocerebral neuroblastoma [31].

With contrast, these tumors nearly always enhance, revealing the sharp margin and outlining any cystic or necrotic change within the mass. Sometimes the mass appears lobulated with an adjacent thin-walled cyst. Subependymal or subarachnoid seeding, if present, will also enhance.

The angiographic findings of PNET are nonspecific. Altman reports a varied appearance from avascular mass effect to moderate vascularity [28]. Angiography is not now commonly used in the workup of PNET.

No series of PNET studied with MRI has



FIGURE 3-10. A nine-month-old female with leukemia. An IV contrast-enhanced CT scan shows a durally based enhancing mass in the right frontal lobe (arrows).

yet been published. Generalizations can be made from studies of other cystic, calcified neoplasms. We know that unless the calcification is large, it will not be imaged on MRI. If imaged, calcification must be differentiated from flow-void signal and the low signal of hemosiderin. Cystic and necrotic change will have a low signal on T1W images. On spin-density-weighted images, this signal will be greater than that of CSF, and with longer TE the signal will fall off more rapidly than that of CSF. MRI will display the anatomy of the mass and surrounding brain in three planes and as with other tumors will be more sensitive to the extent of surrounding edema but may not reveal the outer margins of the tumor.

LEUKEMIA/LYMPHOMA

CT is much less sensitive than CSF studies in the detection of leukemic or lymphomatous meningitis, even with contrast [34,35]. The positive CT scan in the face of negative CSF cytology is the exception rather than the rule [36]. Sulcal enhancement, venous infarction, and hydrocephalus are very infrequent findings. Pagani et al. [34] and Enzmann et al. [37] reported no hydrocephalus in 169 patients with CNS leukemia. Brant-Zawadski and Enzmann [35] reported only four patients with infarction. The most consistent positive CT finding in

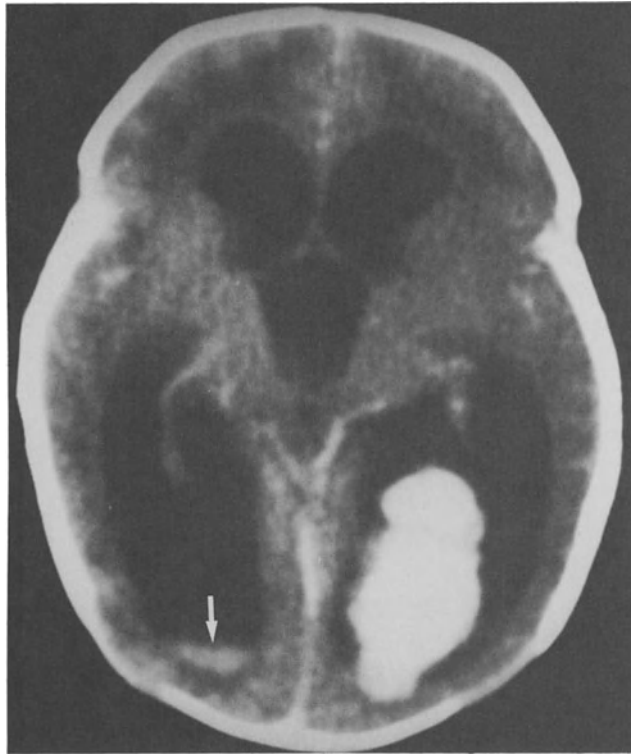


FIGURE 3-11. A three-day-old female with choroid plexus papilloma. The axial IV contrast-enhanced CT shows a homogeneously enhancing left atrial mass and hydrocephalus. There is also a small amount of blood in the right occipital horn (arrow).

CNS leukemia and lymphoma is the parenchymal mass. Noncontrast CT demonstrates an isodense or slightly hyperdense mass with a variable amount of surrounding edema. With contrast there is usually intense enhancement of the mass with variable definition of the margins (figure 3-10) [36]. Central low density is rare. There may be more than one mass, and such masses are usually contiguous with a meningeal or ependymal surface. Subependymal enhancement is also seen but is not pathognomonic [38]. The chloroma, typical of acute myelogenous leukemia (AML), has a similar appearance and tends to abut the meningeal surface like meningioma [39].

In these immunocompromised patients, the major differential is cerebritis or abscess. Cerebritis will enhance poorly and more diffusely,

and abscess will show rim enhancement, but the correct diagnosis may depend on the clinical history of sepsis and positive CSF cultures. Acute subdural, subarachnoid, and intracerebral hemorrhage may occur with leukemia and is hyperdense on CT. Infarction will have a low density and if subacute will enhance in a vascular distribution. The CT findings in the treated patient will be discussed later.

CHOROID PLEXUS PAPILLOMA

The plain skull roentgenogram usually reflects nonspecific effects of increased intracranial pressure. In infants, the sutures are split, and in older children there is erosion of the dorsum sellae. Rovit reported that calcification was visible in 4.1% of skull films [40]. Noncontrast CT scan reveals a well-circumscribed lobulated intraventricular mass most commonly in the trigone of the lateral ventricle. Hydrocephalus is also present due to either overproduction of CSF or obstruction of the CSF pathways over the con-

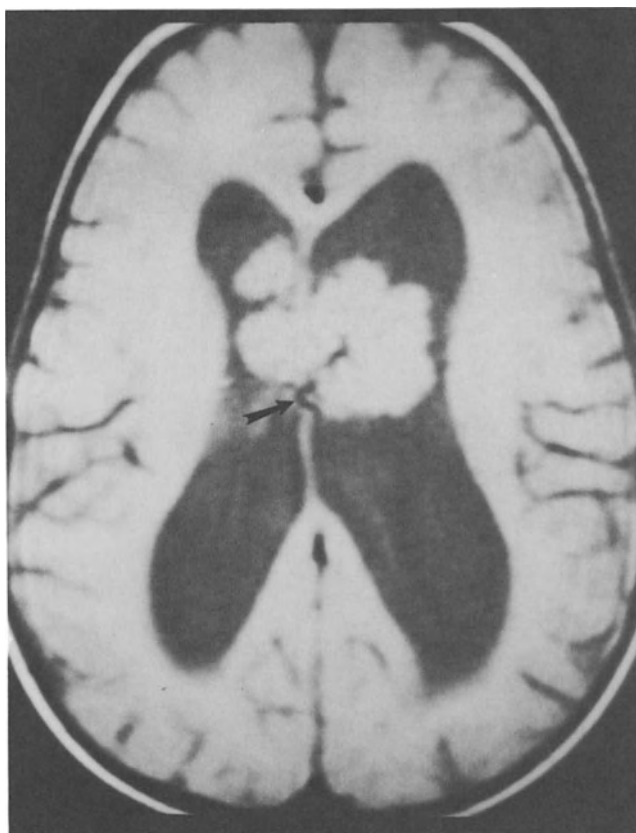


FIGURE 3-12. A one-year-old female with choroid plexus papilloma. The axial MRI (TR/TE 2500/25) shows a cauliflower-like mass in both frontal horns. An enlarged vessel is seen posterior to the mass (arrow).

vexity from repeated occult hemorrhages or both. It can be isodense relative to brain parenchyma, but the presence of hemorrhage or calcification will cause it to be hyperdense, and there may be intraventricular blood. Homogeneous enhancement of the mass occurs with intravenous contrast 100% of the time (figure 3-11) [41, 42]. Malignant infiltrating forms may show invasion of nearby brain parenchyma. Angiography is often necessary to determine the location of the vascular pedicle and is an aid in preoperative planning.

MRI of choroid plexus papilloma reveals an isointense, cauliflower-like intraventricular mass and will often reveal the vascular pedicle (figure 3-12). If hemorrhage has occurred, there will be evidence of methemoglobin and/or hemosiderin.

EPENDYMOMA

Unlike ependymoma of the posterior fossa, supratentorial ependymoma is more commonly located in the parenchyma than in the ventricle and is larger than that found in the posterior fossa (figure 3-13) [43]. The incidence of subarachnoid seeding from supraventricular ependymoma is uncommon. One of the 11 cases of seeding reported by Kim and Fayos [44] was from a supratentorial ependymoma.

Of their 20 childhood ependymomas studied by CT, Armington et al. found that 85% were larger than 4 cm, 70% were moderately well or very well margined, 55% were cystic, 30%



FIGURE 3-13. A 13-year-old female with supratentorial ependymoma. An axial IV contrast-enhanced CT shows a large rim-enhancing mass with central low density in the right hemisphere. (Used with permission from Latchaw RE, *Computed Tomography of the Head, Neck and Spine*, 1984, p. 218.)

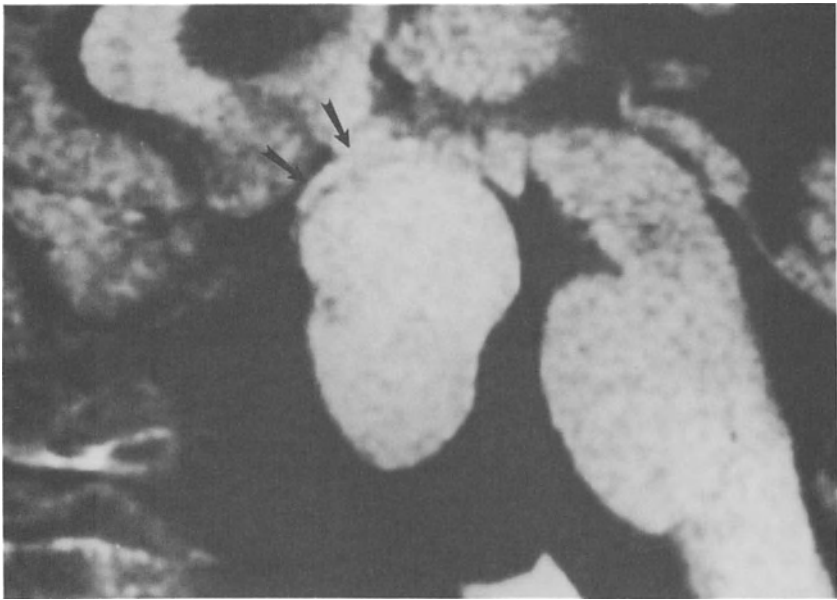
had calcification, and 95% had moderate to intense enhancement; only one had intratumoral hemorrhage [43]. Eighty percent of the more benign types were hypodense or isodense on noncontrast CT, while all the ependymoblastomas and malignant ependymomas were hyperdense on noncontrast CT. Other features found to distinguish the more malignant forms included less distinct margination, more intense enhancement, and fewer calcifications. The differential diagnosis of the hemispheric type includes low- and high-grade astrocytoma,

oligodendroglioma, ganglioglioma, and primitive neuroectodermal tumor.

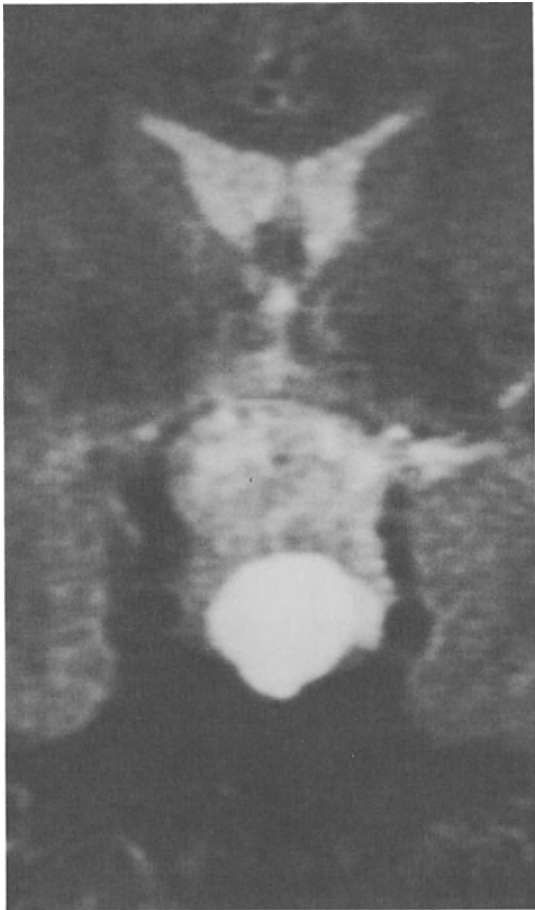
PITUITARY ADENOMA

There are several features of the microscopic anatomy of the normal pituitary gland that seem to relate closely to radiologic imaging. Those features are 1) the degree of tissue compactness and cellular granularity, 2) the presence of colloid cysts, and 3) the degree of tissue vascularity [45,46]. The normal gland will exhibit variability in these features. Clinically silent abnormalities also known to occur in the pituitary include infarcts and cysts.

The pituitary gland is best imaged in the coronal plane using thin sections with intravenous contrast. The anatomical relationships



A



B

of the sella turcica, cavernous sinus, carotid siphons, sphenoid sinus, optic chiasm, and the pituitary gland are best demonstrated in this plane. Axial images may be helpful in the very large macroadenoma.

The density of the normal anterior lobe on noncontrast CT scans may be homogeneous or heterogeneous with a repetitive pattern of low-density areas alternating with areas of relative isodensity with brain. The pattern is related to the cytoarchitecture of the gland [46]. The dense areas correlate closely with areas of compact glandular tissue with increased granularity, and the lucent areas correspond to loosely packed tissue and decreased granularity. Colloid cysts, known to occur in the pars intermedia, appear as lucent foci. The density of the posterior lobe is variable but is generally less than the nonenhanced anterior lobe. In the anterior lobe, contrast enhancement tends to be best in those areas that have the greatest degree of tissue compactness [46]. The anterior portion of the posterior lobe, because of its great vascularity, can enhance more than the anterior lobe, however.

Normal gland heights are variable and tend to be greater in females of childbearing age. In a population unselected for age, the average gland height in females was 4.8 ± 1.3 mm and 3.5 ± 1.5 mm in males [47]. Schwartz et al. reports a mean gland height of 6.9 ± 1.1 mm in women of childbearing age [48]. Roppolo et al. found a normal gland height of 3.3 ± 0.4 mm in prepubertal children [45].

The normal bony margins of the sella turcica also demonstrate some variation. A flat bony plate of uniform thickness forms the floor of the sella often with a keel-shaped bony septum intersecting at right angles and dividing the sphenoid sinus into two compartments of

roughly equal size. Variations of normal include sloping of the floor and bony thinning [45].

Typically the microadenoma on noncontrast CT scan is hypodense or isodense with the remaining gland. One report found greater density and better margination in types secreting growth hormone [49]. The most common post-contrast CT appearance of the microadenoma is a homogeneous hypodensity within the enhanced gland. Less commonly, there is homogeneous dense enhancement or heterogeneous enhancement of the tumor. The degree of enhancement is related to the degree of vascularity of the tumor. Other associated CT findings include erosion of the sellar floor, upward deviation of the diaphragm, and deviation of the infundibulum. One study of prolactin-secreting adenomas with surgical correlation found the focal hyperdense or hypodense lesion to be the only statistically significant CT finding of microadenoma [50]. They found that normal scans occurred in six patients with surgically proven microadenoma. They concluded that the usual CT signs are neither sensitive nor specific in the diagnosis of prolactin-secreting microadenoma, and the CT scan findings must be evaluated in the light of the clinical and endocrinologic findings.

Macroadenomas may enlarge enough to fill the suprasellar cistern. The margins of the tumor are typically sharp on imaging studies and tend to compress and displace but may invade the cavernous sinus and erode through the dorsum and floor of the sella. The nonenhanced CT typically demonstrates a hyperdense mass relative to brain. Low densities within the mass are found less commonly and occasionally may be largely cystic [51]. Acute hemorrhage will be hyperdense and with time will become

FIGURE 3-14. A 17-year-old female with pituitary macroadenoma. A. A sagittal MRI (TR/TE 600/25) shows an isointense sellar and suprasellar mass compressing and elevating the optic chiasm (arrows) and anterior third ventricle. B. A coronal MRI (TR/TE 3000/100) shows hyperintense signal in the mass relative to the brain parenchyma. In the inferior half of the mass, the signal is higher, compatible with cystic change.

hypodense on CT. In one large series, significant hemorrhage and necrosis was found in 9.5% of cases, although symptoms of pituitary apoplexy were present in only 0.6% [52]. Rilliet et al. reported calcification in 7% of pituitary adenomas by microscopic examination, and by roentgenologic examination, calcification was seen in 1.7% of pituitary adenomas [53]. The incidence of calcification seen by CT is probably higher because this report included plain films, conventional tomograms, and CT when available. Calcification was found to be either diffuse, patchy, rim-like, dense, or well circumscribed in appearance. Contrast enhancement of macroadenomas is usually homogeneous and dense. Areas of hypodensity correlate with cystic or necrotic change. Occasionally, there is only rim enhancement of a hypodense tumor.

Bromocriptine therapy can have a profound effect on the CT appearance of pituitary adenoma. In adult series, 65% reduction in size of macroadenomas with an incidence of new tumoral hypodensities in 35% have been reported [54]. Tumor shrinkage was rapid but not total, with regression of visual symptoms. Another series of microadenomas in adults treated with bromocriptine reported either a reduction in volume or disappearance of the abnormalities seen on the pretreatment scan [55].

Regardless of the pulse sequence, the MRI appearance of the normal anterior lobe of the pituitary gland is homogeneous on spin-echo images. The posterior lobe has a high signal on the T1W sagittal image, the result of increased lipid content.

Two retrospective studies of microadenomas having the appropriate clinical findings and positive CT scans have found that noncontrast MRI may be normal in some cases although CT scans are positive [56, 57]. The small size of the gland requires the use of a small voxel volume, which is achieved by thin sections and a 256×256 acquisition matrix. This is achieved at the sacrifice of signal intensity but can be optimized

by using higher field strengths, more excitations, and using spin-echo sequences that maximize signal to noise. The most common nonenhanced MRI characteristic of microadenoma is a low signal on T1W images and, though somewhat more variable, a high signal on T2W images within the tumor [57, 58]. Like CT, other signs suggestive of tumor are upward bulging of the diaphragm due to increased gland height, deviation of the infundibulum, and sloping of the floor of the sella. With gadolinium, microadenomas tend to enhance less than surrounding normal gland. Like CT with iodine, gadolinium enhancement is dependent upon tumor vascularity.

Macroadenomas lend themselves particularly well to MRI (figure 3-14). Tumor extent is usually well visualized in all three planes. The sagittal and coronal images are quite graphic in demonstrating anatomical relationships and mass effects on the optic chiasm, anterior third ventricle, cavernous sinus, carotid siphons, brainstem, and sphenoid sinus. The relationship of the tumor to the carotid siphon is particularly well visualized and rivals preoperative angiography in demonstrating vascular displacement and encasement by tumor [58]. Intratumoral cysts and hemorrhage can be detected. A series of patients treated with bromocriptine has not yet been described, but a report of two patients revealed what may represent blood and cystic change [57]. Another report of 28 patients noted no differences in the internal characteristics between the various types of adenomas [58].

CRANIOPHARYNGIOMA

Craniopharyngioma by CT usually appears as a well-marginated, partially calcified suprasellar mass with areas of low density that represent cyst formation (figure 3-15). The mass can be ovoid, lobulated, or irregular in shape. It can be large enough to encroach upon the optic chiasm and cause visual symptoms. It can extend further upwards to fill the third ventricle and cause obstructive hydrocephalus. Extension

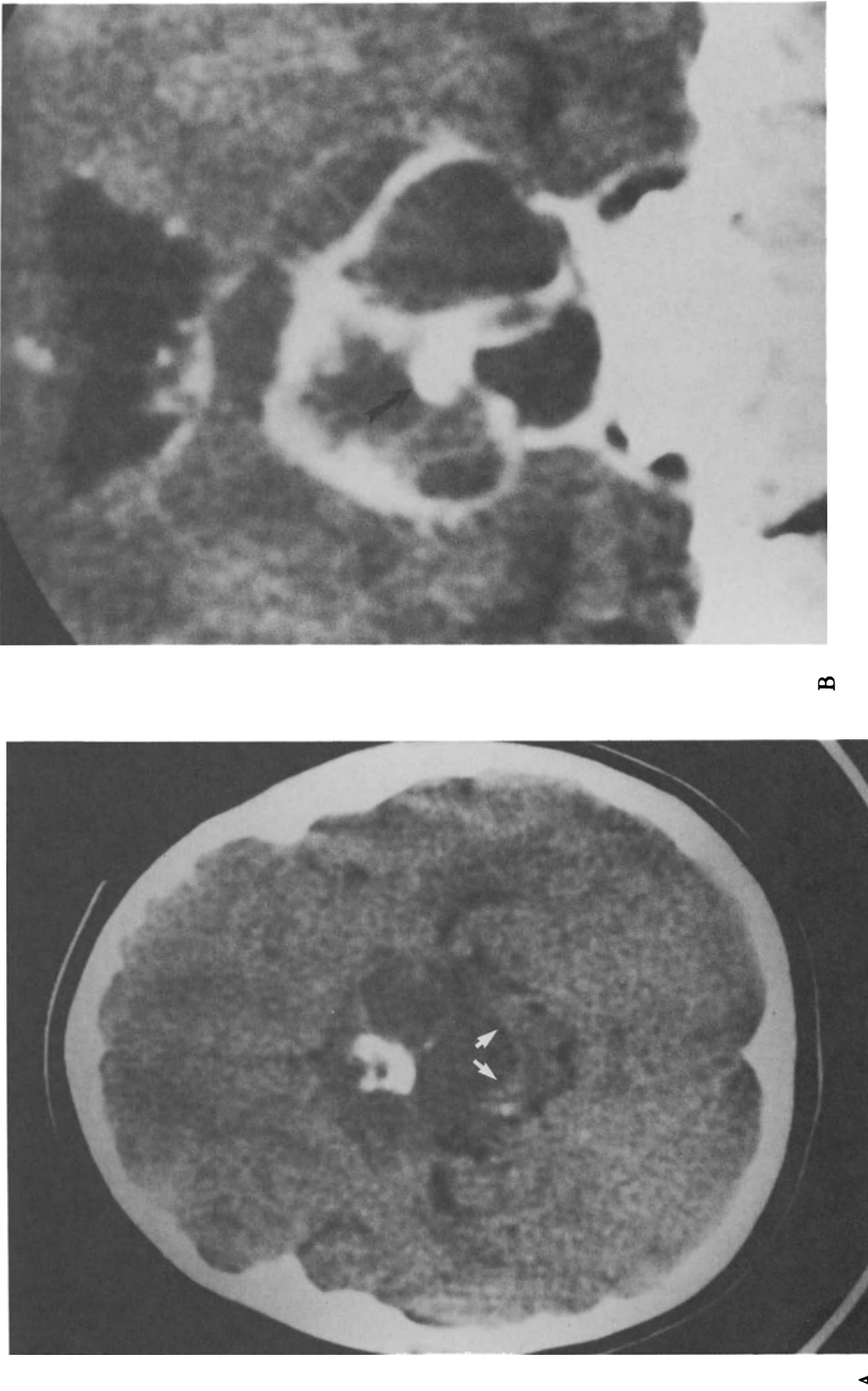


FIGURE 3-15. A six-year-old female with craniopharyngioma. A. An axial noncontrast CT shows a cystic mass filling the suprasellar cistern compressing the midbrain (arrows) and other surrounding structures. There is calcification in the center of the mass. B. A coronal IV contrast-enhanced CT shows a large multiloculated cystic mass in the suprasellar cistern filling the sella. Enhancing rims identify multiple cyst cavities. The central calcification (arrow) is difficult to distinguish from enhancement.

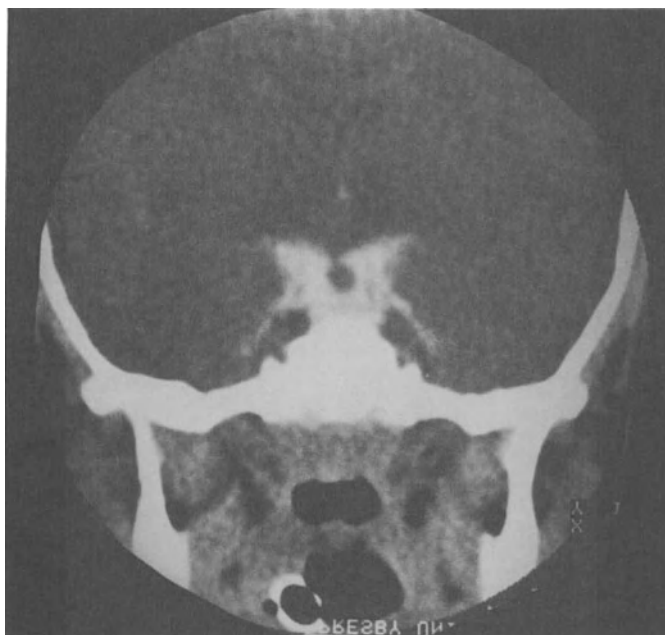


FIGURE 3-16. Hamartoma of the infundibulum. Intrathecal contrast-enhanced coronal CT shows a small mass arising from the infundibulum. (Used with permission from Latchaw RE, *Computed Tomography of the Head, Neck and Spine*, 1984, p. 253.)

downward can fill and enlarge the sella turcica, compress the pituitary gland, and even erode bony margins [59]. The CT density of the cystic portion of the tumor is variable and is dependent upon the protein and cholesterol concentration. The density can range from isodensity with CSF to greater density than brain parenchyma. Calcification is often seen in the rim of the cyst but also can appear as a bulkiness in the more solid portions of the tumor. Those tumors that are predominantly cystic may show little enhancement. Solid portions of the tumor usually enhance well. The CT appearance of the typical craniopharyngioma is fairly specific; however, several features are common to other lesions. Rim calcification is often seen in giant aneurysms. Calcification is also seen in meningiomas of the tuberculum sellae, and although less common, is also seen in pituitary adenomas. The differential diagnosis of the hypodense cystic form of craniopharyngioma would include Rathke's cleft cyst, epidermoid cyst, and arachnoid cyst. The solid enhancing form would include meningioma,

glioma, metastasis, granuloma, and pituitary adenoma.

By MRI, the cystic portion of the tumor can range in signal intensity from isointense with CSF to hyperintense relative to brain, reflecting the varying protein and cholesterol content [60]. The T2W scans further characterize the cystic portions by demonstrating a high signal. Even if bulky, the signal void of calcification may be difficult to identify on the T1W or T2W sequences either because of adjacent flow void signal in vessels or, on the T1W sequences, because of the low-intensity signal of adjacent CSF.

HAMARTOMA

Hamartomas can occur in many regions of the brain and represent mature, disordered, and/or ectopic foci of tissue. In the region of the hypothalamus, they usually occur in the tuber

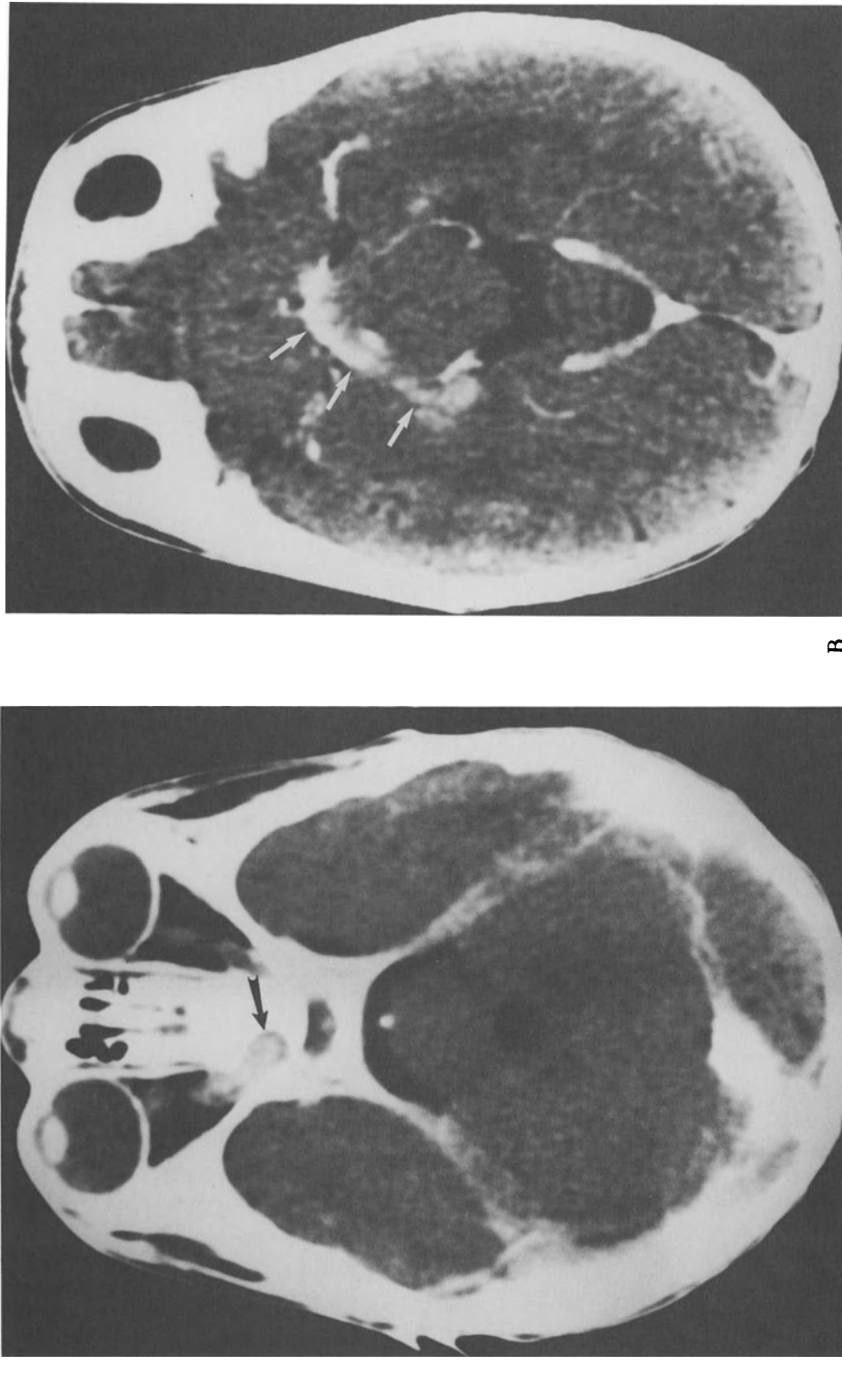


FIGURE 3-17. A ten-month-old female with optic chiasm glioma. A. An axial IV contrast-enhanced CT shows an enlarged enhancing optic nerve on the right with a widened optic canal (arrow). B. The same study through the chiasm shows enhancement of the chiasm and the optic tract on the right (arrows).



FIGURE 3-18. A 20-month-old female with an astrocytoma. An axial contrast-enhanced CT shows a very large enhancing mass in the hypothalamic/chiasmatic region.

cinereum or mammillary bodies [61]. Appearances range from focal enlargement of the infundibulum or mammillary bodies to larger masses approaching 3 cm in size [62]. On CT there is little if any enhancement with IV contrast. Small hamartomas are better appreciated with contrast-enhanced cisternography (figure 3-16). By MRI the mass is isointense to surrounding normal tissues on T1W images [15]. On T2W images, the mass tends to have an isointense to slightly hyperintense appearance relative to surrounding normal brain.

TUMORS OF THE DIENCEPHALON AND THE OPTIC PATHWAY

On the noncontrast CT, these tumors will be isodense. Intraorbital optic nerve glioma will cause fusiform widening of the nerve, and extension through the optic canal may cause bony erosion (figure 3-17A). The optic chiasm may

only be subtly enlarged and is best studied in the coronal and 0° axial planes using thin sections (≤ 3 mm) to minimize partial volume averaging. Daniels et al. found that the vertical diameter of the normal optic chiasm should be no greater than 6 mm [63].

Tumor calcification is very uncommon in the untreated patient. Cystic or necrotic change will be evident as low-density areas within the tumor. The smaller tumors tend to enhance poorly; with increasing size, there is moderate to vivid enhancement. Enhancement of the optic tracts indicates posterior tumor extension (figure 3-17B). With increasing size, however, the exact origin of the tumor, whether in the optic chiasm or in the hypothalamus, will be obscured (figure 3-18).



FIGURE 3-19. A four-year-old female with optic chiasm glioma. A coronal MRI (TR/TE 600/20) shows low signal intensity and enlargement of the optic chiasm.

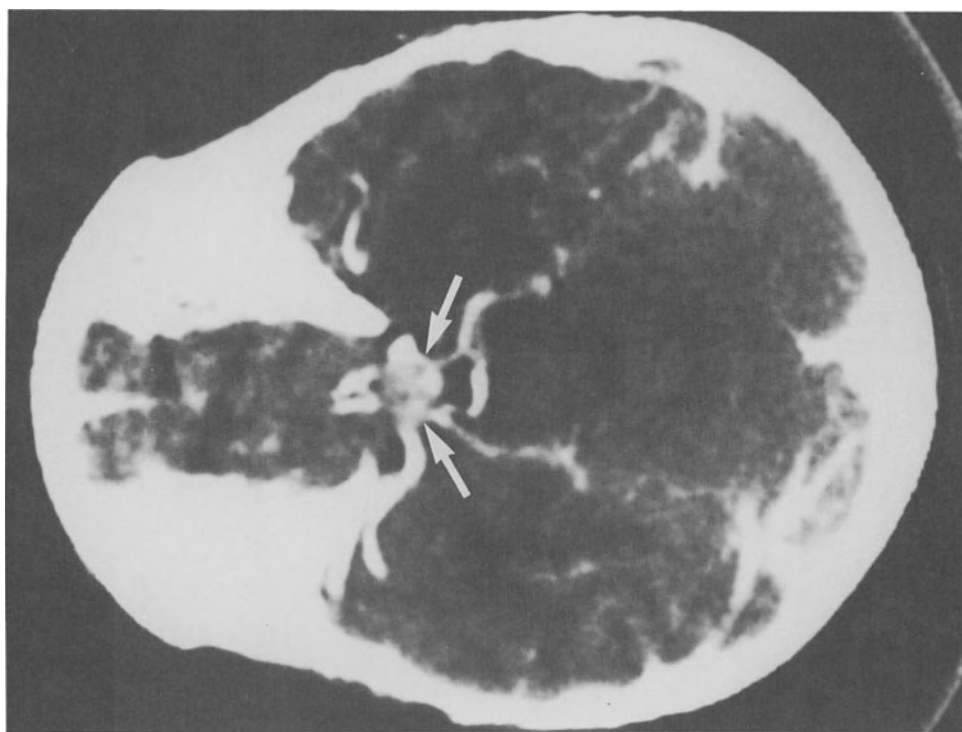
The anatomy of the optic nerves, chiasm, and hypothalamus is accurately depicted on T1W images, particularly in the coronal and sagittal planes (figure 3-19). The signal intensity on T1W images will usually be similar to normal brain tissue and can appear hyperintense on T2W sequences, but low-grade tumors can also be isointense depending entirely upon how much edema is present in the abnormal tissue [64]. Enhancement characteristics of these tumors with gadolinium are similar to those seen with postcontrast CT, but it remains to be seen if there will be better delineation of posterior tumor spread along the optic tracts.

PINEAL REGION TUMORS

Pineal region tumors represent a rather diverse group of neoplasms that fall into the broad categories of pineal-cell, germ-cell, and glioma. There are different conclusions in the radiological literature as to the ability of CT to differentiate the various tumor types [65, 66]. So far, MRI has not demonstrated better diagnostic specificity than CT [67], and it is doubtful that gadolinium-DTPA will add more to what is already known about the enhancement characteristics of these tumors. There is considerable overlap in the appearance of several tumor types that occur in the pineal region, and in the absence of a few rather specific identifying characteristics, at best only a differential diagnosis can be offered. The following discussion of the typical appearances of the common tumor types is not intended to lead



A



B

FIGURE 3-20. An 11-year-old male with pineal germinoma. A. An axial IV contrast-enhanced CT shows an enhancing pineal mass (arrows). B. From the same study, a lower axial section reveals an enhancing mass in the suprasellar cystern (arrows). (Used with permission from Latchaw RF, *Computed Imaging of the Head, Neck and Spine*, second edition, 1990, in press.)

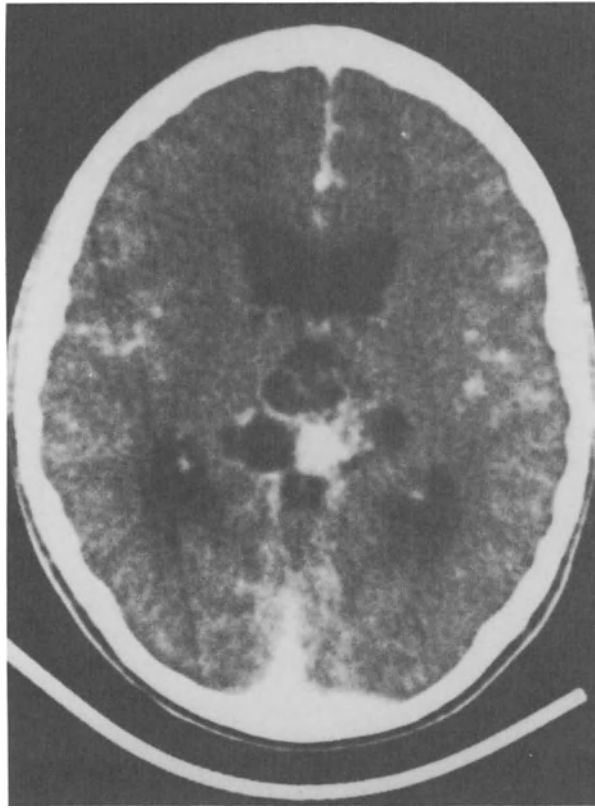


FIGURE 3-21. A 13-year-old male with pineal teratoma. An IV contrast-enhanced CT scan shows a complex, partly solid and enhancing, partially cystic pineal region mass. (Used with permission from Latchaw RE, *Computed Tomography of the Head, Neck and Spine*, 1984, p. 254.)

the reader to conclude that any great specificity exists in imaging of this area.

Calcification of pineal tumors occurs commonly and is a nonspecific finding. Pineal body calcification in children below the age of six years may be due to neoplasm and requires follow-up CT examinations [68].

Germinomas (atypical teratomas) account for over 50% of pineal-region tumors in childhood [69]. Skull films show calcifications in two-thirds of these tumors [70]. Noncontrast CT usually demonstrates an isodense or slightly hyperdense mass that vividly enhances with intravenous contrast (figure 3-20A). These tumors usually arise from within the pineal body,

but displaced normal pineal calcification may indicate a parapineal origin. Similar findings characterize the *ectopic pinealoma* or *suprasellar germinoma* and those unilateral types of germinoma that occur in the basal ganglia and thalamus (figure 3-20B).

The pineal body is the most common site of intracranial teratoma (figure 3-21). Less commonly, teratomas will occur in the sellar and suprasellar regions and midline in the posterior fossa. The benign types will usually demonstrate low attenuation within the mass, consistent with fat, and high attenuation due to the presence of calcification. There are also reports of tooth-shaped calcifications by CT [68]. Contrast enhancement is not uniform owing to the mixed nature of the lesion, and margination is variable. The malignant forms have more vivid contrast enhancement, may fail to demonstrate

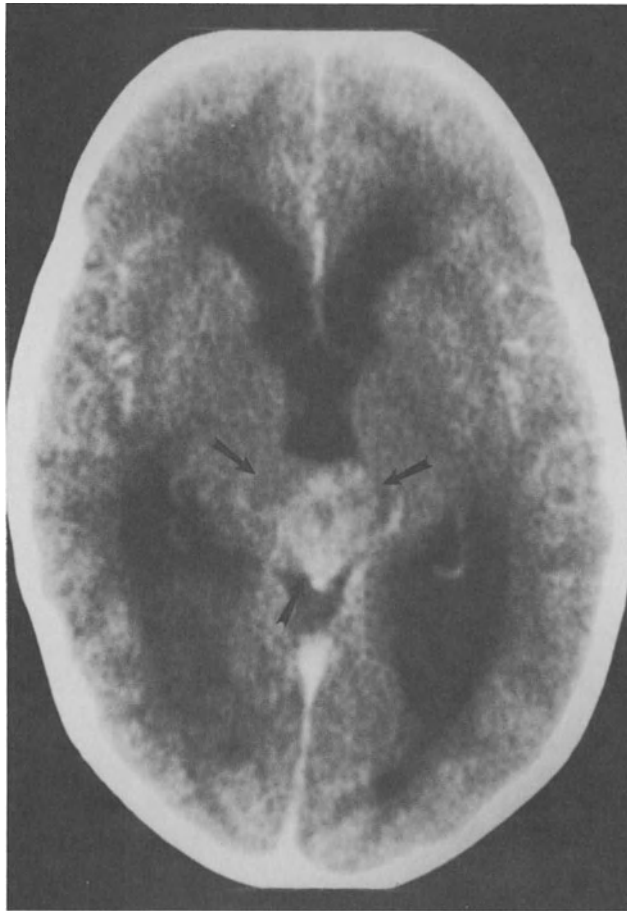


FIGURE 3-22. A two-year-old male with a pineal mixed glioma. An IV contrast-enhanced CT shows a poorly enhancing, poorly margined pineal mass (arrows) causing obstructive hydrocephalus.

fatty attenuation, and can look very similar to germinoma [66].

Dermoid and epidermoid tumors occur in the pineal region much less commonly than teratoma. Both can have fat and mural calcific densities, although epidermoid tumors will more frequently have densities close to CSF [65]. Fat and cystic elements have the same MRI characteristics in this region as they do elsewhere in the brain.

Embryonal cell carcinoma and its variant, endodermal sinus tumor, have been reported to have greater density than the surrounding brain parenchyma on noncontrast CT and will vividly enhance with contrast [65, 71]. This carcinoma can also demonstrate calcification and cystic change.

Pineal-origin tumors are less common than germinomas, and in one report represented about 12% of pineal region tumors [69]. Like germinomas, they may be isointense to slightly hyperintense on noncontrast CT, may enhance vividly with contrast, and may have variable margination. However, calcification occurs in 80%, a higher rate than that of germinomas [70].

Glioma can arise from within the pineal body, tectum of the midbrain, thalamus, and hypothalamus. Its precontrast density tends to be lower than surrounding normal brain, and

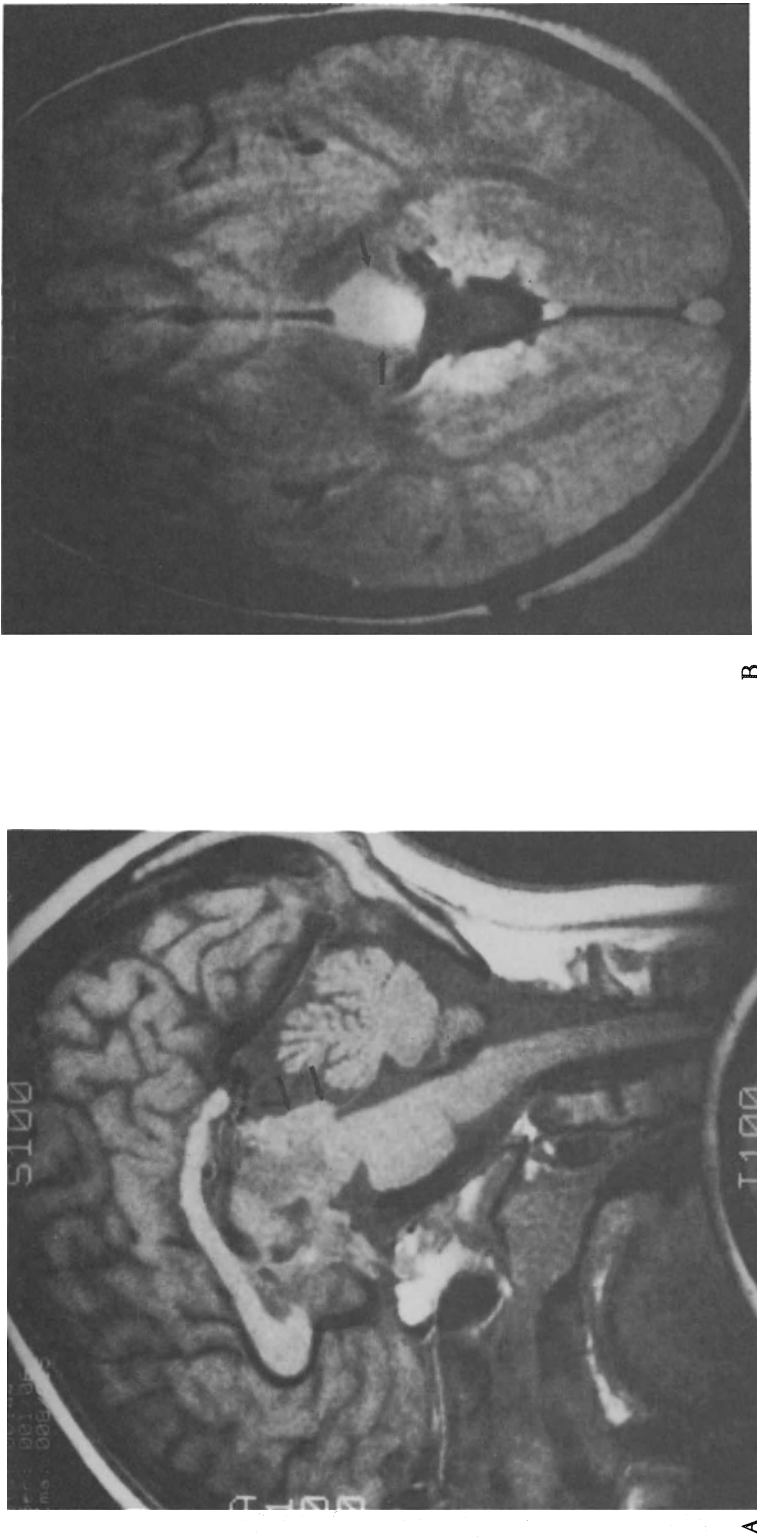
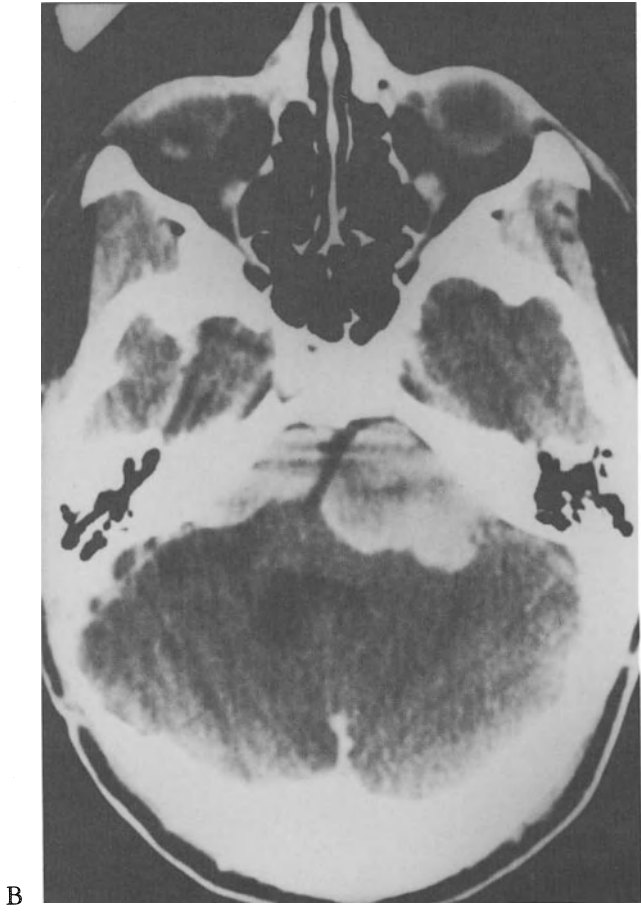
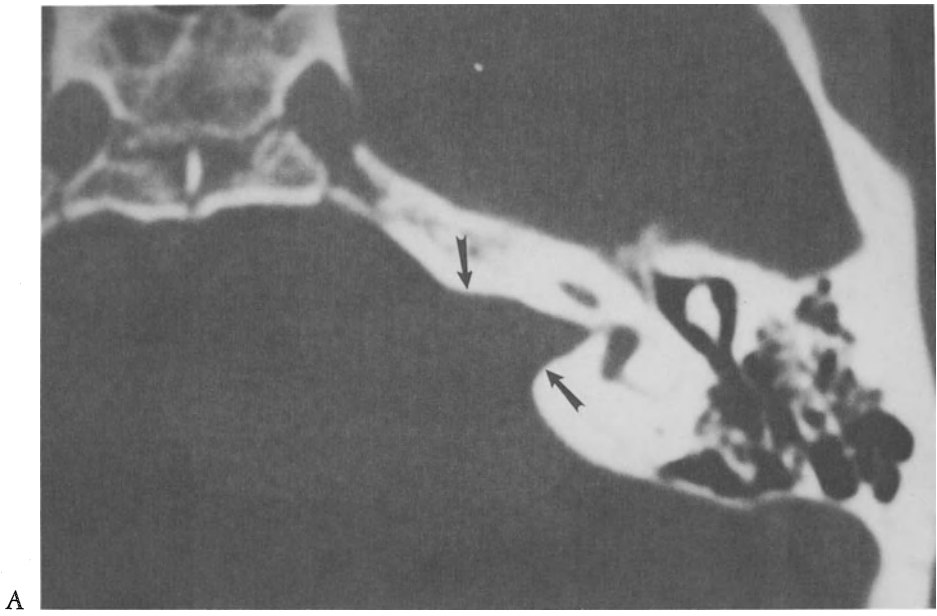


FIGURE 3-23. A seven-year-old female with a tectal glioma A. Sagittal MRI (TR/TE 600/20) shows enlargement of the tectum of the midbrain (arrows). B. Axial MRI (TR/TE 1667/30) shows a hyperintense signal in the posterior third ventricle and tectum (arrows). (Used with permission from Latchaw RE, *Computed Imaging of the Head, Neck and Spine*, second edition, 1990, in press.)



the enhancement pattern is more irregular and less intense than germinoma or pineal parenchymal tumors (figure 3-22).

The sagittal midline MRI graphically depicts the relationship of the mass to the surrounding vascular structures, tectum of the midbrain, aqueduct, and third ventricle (figure 3-23). Tectal gliomas will be isointense to hypointense on T1W images and hyperintense on T2W images. Calcification is not reliably detected. The signal characteristics of four biopsy-proven pineal germinomas have been described and are nonspecific [67]. They were found to be nearly isointense with normal adjacent brain tissue on both T1W and T2W series.

ACOUSTIC NEUROMA

Although the occurrence is rare, the CT appearance of acoustic neuroma in children is not unlike the adult form [72] and is more commonly associated with neurofibromatosis. A proper evaluation of the internal auditory canals requires high-resolution imaging using thin slices and computer algorithms to enhance fine bony detail. If the tumor is small, the noncontrast CT will usually be normal. In the past, air cisternography was performed to better outline the small intracanalicular tumor [73], but this procedure has been replaced by gadolinium-enhanced MRI. As the intracanalicular tumor enlarges with time, there is pressure erosion of the bony canal, which manifests as widening best seen on the bone algorithms (figure 3-24A). Continued enlargement will result in protrusion of the tumor into the cerebellopontine angle cistern and progressive compression of the brainstem and cerebellum. Occasionally, the tumor may arise outside the internal auditory canal and despite reaching a large size will not alter the bony canal itself. With contrast, there will

be marked enhancement of the mass (figure 3-24B). The enhancement tends to be homogeneous with sharp margins. Nonenhancing areas, if present, represent cystic necrosis or arachnoid cyst formation [74].

MRI of acoustic neuromas has a distinct advantage over CT because of the lack of artifact from the surrounding petrous bone [75]. The entire course of the seventh and eighth nerve complex is reliably imaged, using a 3-mm slice thickness. CSF will be imaged surrounding these nerves in the normal internal auditory canal on T1W sequences. The small intracanalicular neuroma will fill the canal and displace CSF. Very long TR imaging (up to 4000 ms) will better image the small intracanalicular neuroma than short TR imaging because of the greater contrast between the signal of CSF and the tumor [76]. Larger tumors are easily seen on both short and long TR sequences. The signal intensity is usually isointense to slightly hypointense to the brainstem on T1W sequences and on T2W sequences is hyperintense. Cystic or necrotic areas will have a lower signal on T1W scans and a higher signal with T2 weighting than the tumor itself. Meningiomas tend not to "turn white" with T2 weighting, as do neuromas. But in the individual case, accurate differentiation may not be made between the two tumor types. Because of vivid enhancement of neuromas, gadolinium-enhanced MRI has improved sensitivity of detection of intracanalicular tumors over nonenhanced MRI [77].

TUBEROUS SCLEROSIS

The clinical triad of seizures, mental retardation, and skin lesions including depigmented areas, adenoma sebaceum, and shagreen patches does not necessarily indicate the presence of intracranial disease. One study found that 80% had both definite or suggestive clinical features

FIGURE 3-24. A 16-year-old male with neurofibromatosis. A. Computer-enhanced bone algorithm of the left internal auditory canal shows widening of the bony canal (arrows). B. Axial IV contrast-enhanced CT shows bilateral cerebellopontine angle-enhancing masses compressing the brainstem and fourth ventricle.

and a negative CT scan [78]. Four percent had definite clinical features and a normal CT scan, and 16% had no clinical features and a positive CT scan. Imaging is generally reserved for those few cases where a suspected diagnosis needs confirmation or for the management of obstructive hydrocephalus.

The most common lesion is the subependymal tuber. It frequently calcifies, is often located at the foramen of Monro, and is often multiple, bilateral, and almost symmetrical in distribution (figure 3-25). A tuber located at the foramen of Monro, if large enough, can lead to obstructive hydrocephalus. If the tuber is not calcified, it is isodense or slightly hyperdense with surrounding tissue, and its presence may be betrayed only by a small subependymal bump outlined by CSF in the ventricle. *Candle guttering* is an old term from air ventriculography showing these subependymal bumps. A benign lesion does not enhance with contrast. Occasionally, a tuber can undergo degeneration into the giant-cell astrocytoma. This lesion is larger than the typical subependymal tuber, is isodense on noncontrast CT, and may or may not contain calcification. With contrast this tumor will enhance, although it has a more benign course than other giant-cell tumors. Cortical tubers also occur, often calcify, and are less numerous than the subependymal tubers [79]. Noncalcified tubers will be isodense to hypodense on noncontrast CT and, like the calcified types, fail to enhance with contrast. White-matter low densities, if present, can be large, are poorly marginated, and do not enhance with contrast. They are thought to represent heterotopias or myelination defects [80].

MRI can accurately delineate the subependymal tubers causing bumps along the ventricular lining contrasted against the low signal of CSF on the T1W sequence; the tubers themselves are isointense with surrounding normal parenchyma. Calcification, unless large, may go undetected. T2W scans demonstrate high signal in the tubers and in areas of demyelin-

ation. If there is obstructive hydrocephalus, transependymal CSF flow will also be seen in the periventricular white matter as a hyperintense signal.

MENINGIOMA

Convexity meningiomas may thicken the calvarium, occasionally with radially oriented bone spicules producing a "hair-on-end" appearance on plain skull films. Hyperostosis also can be seen at the base of the skull due to meningiomas of the sphenoid wing. Sphenoid wing meningiomas can occasionally mimic fibrous dysplasia. Meningiomas of the planum sphenoidale can cause either hyperostosis or blistering of the planum, also known as *pneumo-sinus dilataans*. A large meningioma can also cause bone erosion, but this is less common than hyperostosis. If there are enlarged meningeal feeders, the lateral skull film may demonstrate enlarged vascular grooves.

The nonenhanced CT scan typically demonstrates a mass that is isodense or slightly more hyperdense than brain parenchyma. The margins may be difficult to identify; however, the extra-axial nature of the tumor can be suggested by buckling of the white matter around the lesion [81]. Calcification, if any, can be sparse to globular to solid in appearance. Small noncalcified tumors can be overlooked on axial scans, particularly over the convexities and along the floor of the anterior and middle cranial fossae. Beam-hardening artifact from the petrous bones can also obscure meningiomas in the cerebellopontine angle.

Contrast enhancement is usually homogeneous and intense, revealing a durally based, sharply marginated mass. Contrast enhancement aids detection of small tumors and accurately delineates the tumor margins, but subtle calcification will be obscured. Occasionally the tumor can be so densely calcified that contrast enhancement is not apparent.

The appearance of peritumoral edema is variable. Abundant edema is more typical of an intra-axial tumor, such as glioma, or of

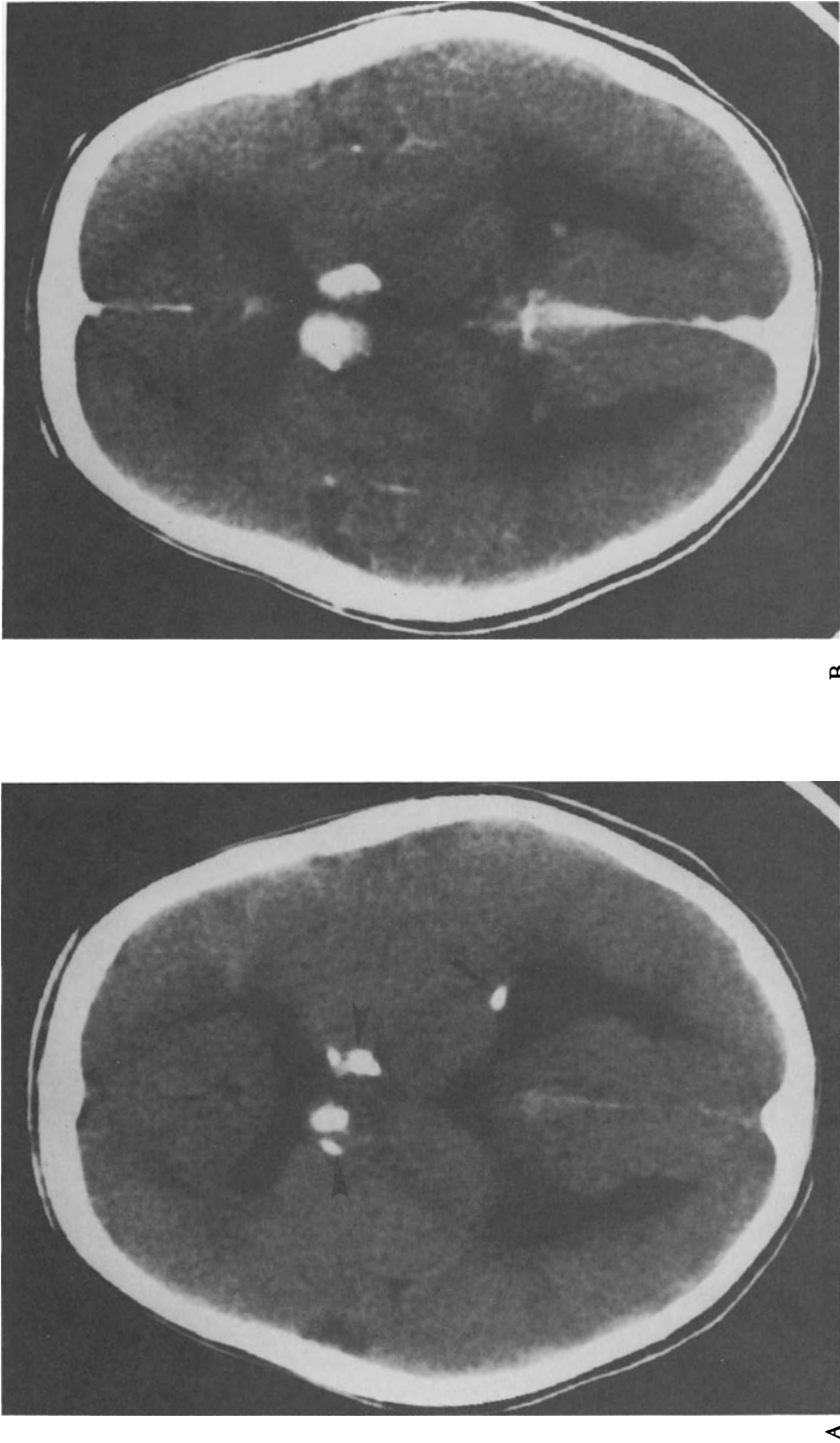


FIGURE 3-25. A three-year-old male with tuberous sclerosis. A. An axial noncontrast CT shows bilateral calcified subependymal tubers at the foramen of Monro (arrowheads) and one along the margin of the left atrium (arrow). B. With IV contrast, the tubers at the foramen of Monro enhance. The atrial tuber seen on the noncontrast study is now out of the plane of section.

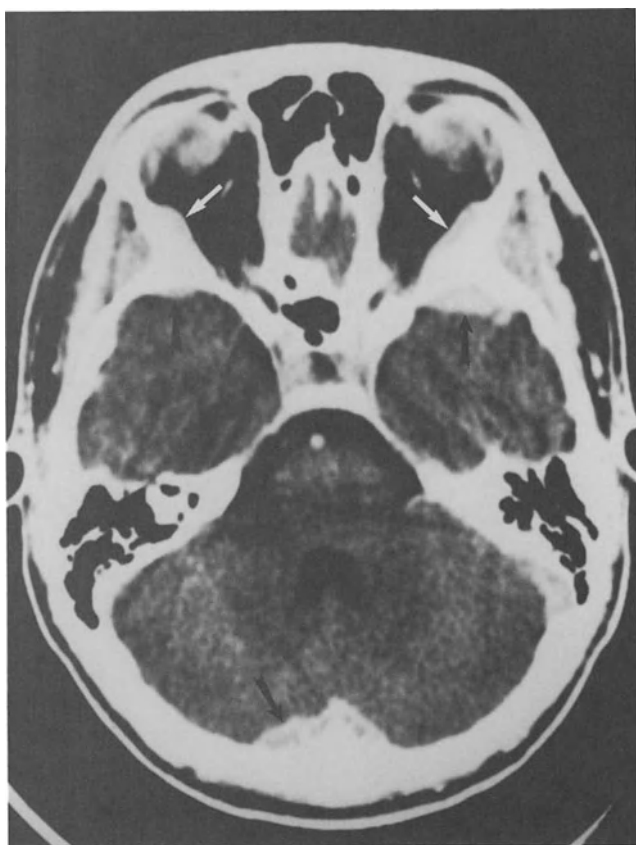


FIGURE 3-26. A 17-year-old male with a history of abdominal neuroblastoma. An IV contrast-enhanced CT scan shows epidural tumor deposits along the greater sphenoid wings (black arrows) and orbits bilaterally (white arrows) and in the posterior fossa (single black arrow).

metastasis. Indeed, if the intra-axial lesion is located in the cortex, sharing a margin with the dura, the differentiation from extra-axial tumor is difficult. Size, location, histological type, and malignant degeneration are not related to the amount of edema.

In 15% of a large series of adults studied by Russell et al. atypical CT features of meningioma occurred and were closely correlated with atypical histological features [82]. Those histological features included tumor necrosis and hemorrhage, cystic change, lipomatous transformation, and scarring. The most common atypical appearance was the central area of low density, suggesting a more malignant tumor. There is little in the literature about atypical features of childhood meningioma, but Sano et al. describe cyst formation, which tends to occur in the sarcomatous type [83].

The most common feature of the typical meningioma on MRI is its poor contrast with surrounding brain on most spin-echo sequences [84]. Generally, most meningiomas are slightly hypointense relative to white matter on T1W images and slightly hyperintense to white matter on T2W images [85]. Small tumors are particularly difficult to visualize even when their location is known from a contrast-enhanced CT scan. As with CT, one depends with MRI upon buckling of the white matter and distortion of other anatomical structures. Prominent vessels may be identified as a hypointense rim or mottling within the tumor suggesting

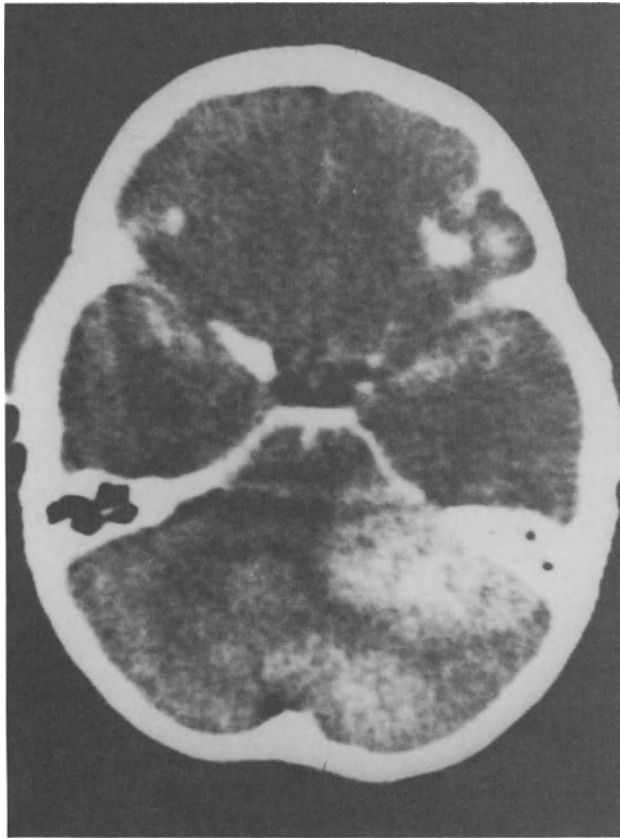


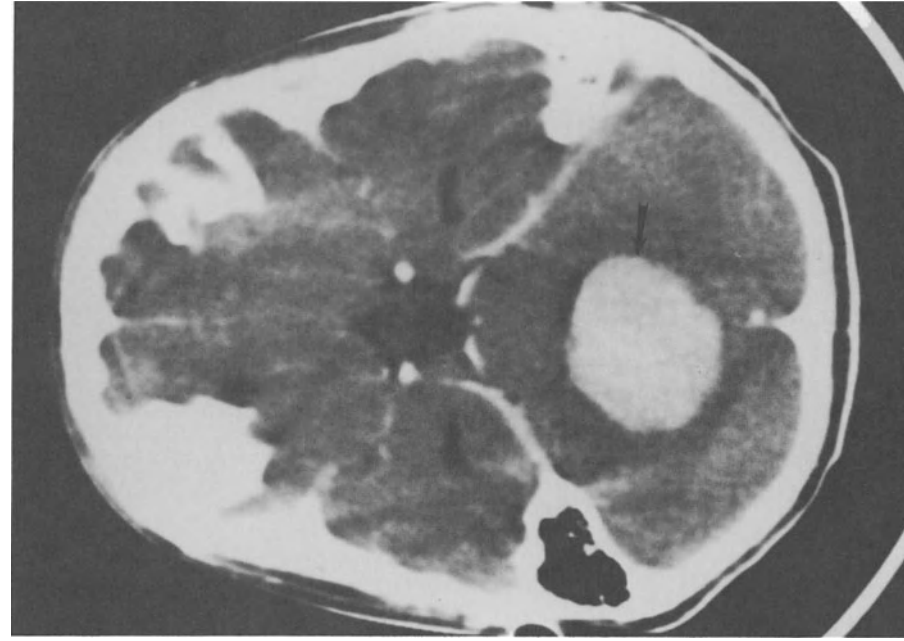
FIGURE 3-27. A two-year-old male with retroperitoneal rhabdomyosarcoma metastatic to the CNS. An axial IV contrast-enhanced CT scan shows a large, enhancing, durally based mass along the right petrous bone compressing and invading the right cerebellar hemisphere and brainstem.

hypervascularity [84]. Gadolinium-DTPA enhances meningiomas on the MRI scan in the same way that iodinated contrast agents enhance meningiomas on CT. Bydder et al. report a series of six adults with meningiomas [86]. All enhanced with gadolinium-DTPA and correlated closely with CT.

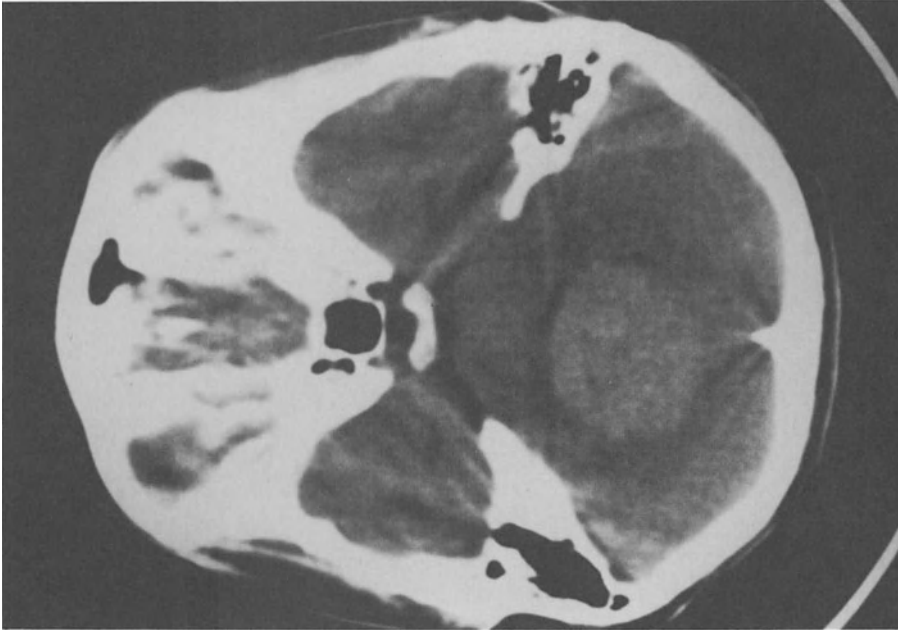
INTRACRANIAL METASTASIS

There are no features of intracranial metastasis that distinguish them from primary tumors, except when metastasis occurs in multiple locations. Primary intracranial tumors tend to be single, rather than multiple. In the appro-

priate setting of a known extracranial tumor, the presumptive diagnosis of metastatic tumor to the brain is reasonably assured, but confirmation still requires tissue biopsy. Intracranial metastasis may be the presenting manifestation of an undiagnosed extracranial primary. The majority of cerebral metastases are non-specific in appearance, so a clue to the site of origin is not usually possible. Some tumors, however, have a propensity to metastasize to the bony structures. Metastatic neuroblastoma tends to go to the base of the skull, calvarium, and orbits but is not limited to those areas (figure 3-26) [27, 31, 87]. It can also present in the hemispheres as primary cerebral neuroblastoma tends to do [27]. Neuroblastoma metastatic to bone leads to erosions and spread of tumor along the epidural space and sutures where further erosions or sutural diastasis may



B



A

FIGURE 3-28. An eight-year-old female with medulloblastoma. A. CT without contrast enhancement shows a large intrinsically dense tumor filling the fourth ventricle. B. Contrast enhancement is homogeneous and dense identifying a sharp margin (arrow). (Used with permission from Latchaw RE, *Computed Imaging of the Head, Neck and Spine*, second edition, 1990, in press.)



FIGURE 3-29. A four-year-old female with medulloblastoma. CT with contrast shows diffuse sulcal/cisternal enhancement in the posterior fossa. Note also hydrocephalus evidenced by enlargement of the temporal horns.

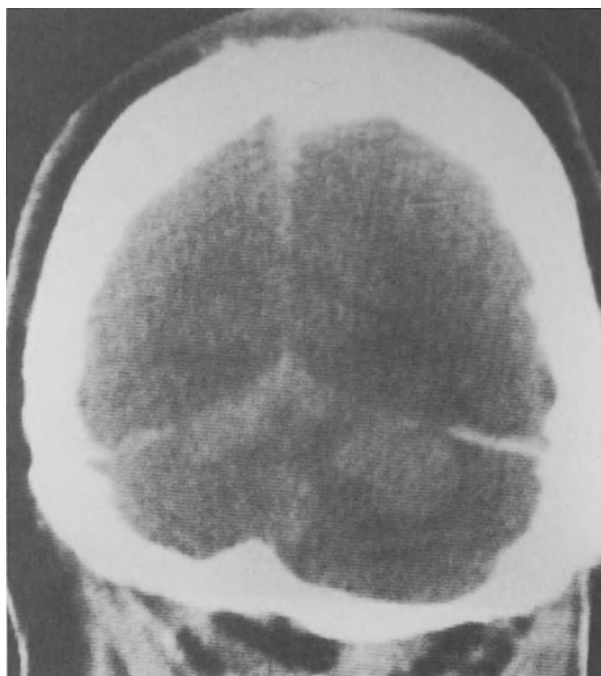
occur [27]. Bone spiculation may also be seen [87].

Other tumors metastatic to the brain are also rare but include rhabdomyosarcoma (figure 3-27), osteosarcoma, and Wilms' tumor. As with other tumors of the brain, enhancement and degree of margination with these tumors is variable. There are no radiological features that distinguish one metastatic tumor from another.

Infratentorial Tumors

MEDULLOBLASTOMA

In children, medulloblastoma typically is found in the vermis along the roof of the fourth ventricle. At the time of presentation it usually fills the fourth ventricle and is about 4–6 cm in size [88]. It is well margined, and usually limited to the vermis. In young adults, medulloblastoma is found in the cerebellar hemisphere and is desmoplastic. Extension into the cerebellopontine angle or into the supratentorial compartment is rare [88, 89], but subarachnoid spread is very common and has been reported in 30%–50% of cases [90, 91]. Recurrence is usually at the primary site, and less commonly to the quadrigeminal, basal, and suprasellar cisterns and into the upper cervical



cord [92,93]. Seeding of the supratentorial subarachnoid space has been seen in the subfrontal region and has been attributed to shielding of the eyes during radiation therapy [94].

The typical appearance of medulloblastoma on noncontrast CT is a central, solid, hyperdense mass that fills the fourth ventricle (figure 3-28A). Low-density areas, if present, represent necrosis or cyst formation. Calcific or hemorrhagic density is not usually seen [89,95,96]. There is typically homogeneous enhancement with IV contrast (figure 3-28B). Leptomeningeal metastasis manifests as either sulcal-cisternal enhancement (figure 3-29), ependymal or subependymal enhancement, thickened irregular tentorial enhancement, and occasionally as communicating hydrocephalus only [97]. The desmoplastic type tends to enhance less (figure 3-30).

MRI has been primarily helpful in better definition of the anatomical relationships. The sagittal T1W image accurately demonstrates a medulloblastoma filling and enlarging the fourth

FIGURE 3-30. A 21-year-old female with medulloblastoma, desmoplastic type. Coronal CT with contrast shows minimal enhancement of tumor in the superior vermis and hemispheres bilaterally. (Used with permission from Latchaw RE, *Computed Tomography of the Head, Neck and Spine*, 1984, p. 216.)

ventricle (figure 3-31). Cystic or necrotic areas, if present, will have a low signal on T1W images and a high signal on T2W images. As with CT, there will be vivid enhancement of the tumor with gadolinium-DTPA.

CEREBELLAR ASTROCYTOMA

Like medulloblastoma, cerebellar astrocytoma can be quite large at initial presentation [88]. Imaging studies usually suggest a well-marginated tumor that can present either in the vermis or hemisphere. It can be totally solid, with or without a few small cysts, or largely cystic with a mural nodule. Hemorrhage and necrosis also occur. Calcification occurs in about 25% of cases [98].

Solid tumors can appear either hypodense or hyperdense on noncontrast CT. The tumor

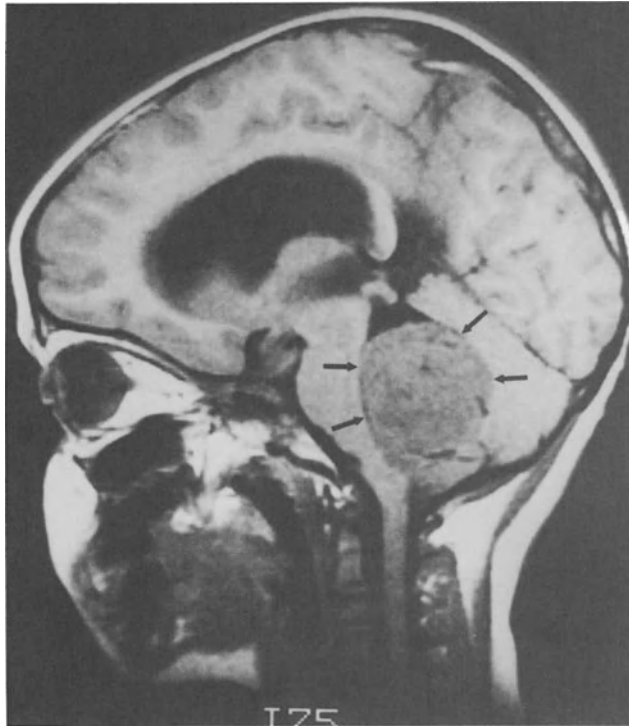


FIGURE 3-31. A five-year-old female with medulloblastoma. Sagittal MRI (TR/TE 600/20) shows the fourth ventricle enlarged and filled with a sharply marginated tumor. The brainstem is displaced anteriorly and vermis is displaced posteriorly and superiorly (arrows). (Used with permission from Latchaw RE, *Computed Imaging of the Head, Neck and Spine*, second edition, 1990, in press.)

enhances well with iodine, usually with sharp margins (figure 3-32). Cystic forms can have a variety of enhancement patterns. There may be variable enhancement around the margins of the cyst, or enhancement of a mural nodule (figures 3-33 and 3-34A) [88, 99]. Because of the increased protein content of the cyst, it will often have a greater density than CSF.

The multiplanar aspect of MRI can accurately demonstrate the relationship of the tumor with the fourth ventricle, brainstem, and surrounding cerebellum. The higher protein content of the tumor cyst can differentiate cyst fluid from the adjacent fourth ventricle. Solid portions of the tumor will have a higher signal on T2W images (figure 3-34B) and will en-

hance with gadolinium. The infiltrating type of cerebellar astrocytoma has CT and MRI features similar to its cerebral counterpart.

EPENDYMAL NEOPLASMS

In the fourth ventricle, ependymal neoplasms commonly arise from the floor and grow to fill the ventricular cavity or protrude through the foramina of Luschka without invasion of the cerebellum.

The tumor mass on noncontrast CT is usually isodense relative to surrounding brain tissue but can also be hypodense or hyperdense [100]. About 50% show calcification on CT [88, 100]. Enhancement can either be homogeneous or nonhomogeneous. The calcified nonhomogeneously enhancing mass originating from the floor of the fourth ventricle differentiates this tumor from medulloblastoma or cerebellar astrocytoma (figure 3-35). Spread is usually through the lateral recesses toward the cerebellopontine angle or the foramen of Magendie to extend along the dorsal



FIGURE 3-32. A six-year-old female with cystic cerebellar astrocytoma. CT with contrast enhancement identifies a solid, well-margined tumor in the brachium pontis with surrounding edema compressing the fourth ventricle and brainstem. (Used with permission from Latchaw RE, *Computed Imaging of the Head, Neck and Spine*, second edition, 1990, in press.)

side of the medulla and spinal cord (figure 3-36).

The multiplanar aspects of MRI, particularly the sagittal image, reveal the anatomical relationships of the ependymoma and may identify its origin from the ventricular floor. Its internal characteristics, however, are nonspecific, particularly if the foci of calcification are not large enough to be visualized as areas of absent signal [14].

HEMANGIOBLASTOMA

This tumor is usually well circumscribed and can be entirely solid, partly cystic, or predominantly cystic with a mural nodule. In the younger age group, there is an increased association between hemangioblastoma and von Hippel–Lindau syndrome. Because these tumors are very

vascular, hemorrhage is very common. Calcification does not occur. Jeffreys reports multicentricity in 7% of cases [101]. Tumors can recur in the tumor bed or arise in a new area following surgery.

The vascular nature of these tumors provides several distinct appearances on angiography: 1) a solid, vascular tumor, often with enlarged feeding arteries and draining veins; 2) a vascular rim surrounding a central lucent area; 3) a dense mural nodule with an adjacent avascular area

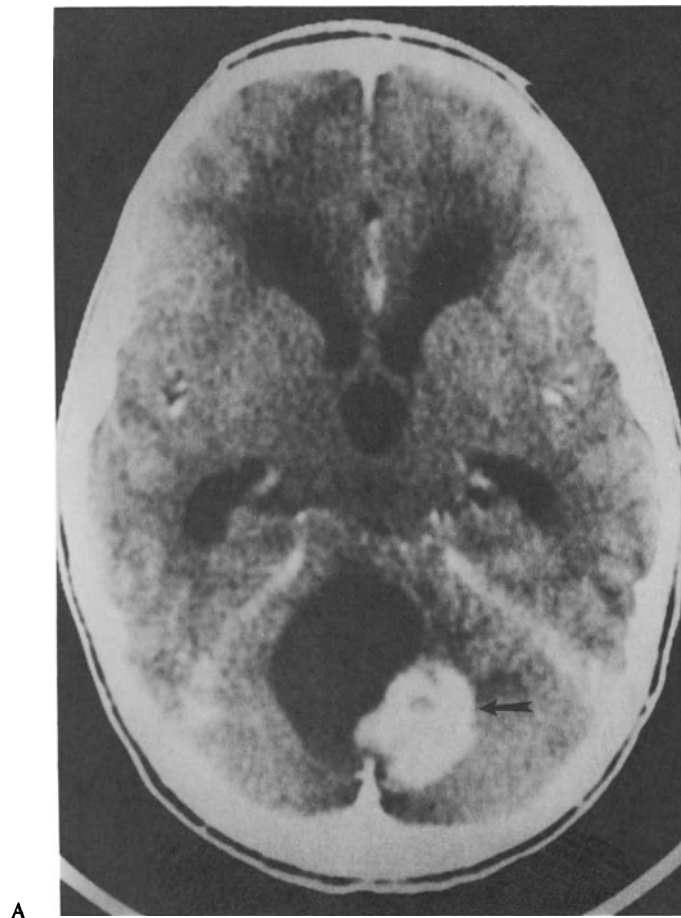


FIGURE 3-33. A four-year-old female with cystic cerebellar astrocytoma. A. CT with contrast shows a midline cyst and enhancement of a mural nodule (arrow). Third and lateral ventricles are enlarged with periventricular lucency, suggesting transependymal CSF absorption. B. A sagittal midline reformatted image shows tumor in vermis causing forward displacement of the brainstem and fourth ventricle.



FIGURE 3-34. Another four-year-old female with cystic cerebellar astrocytoma. A. CT with contrast shows a large eccentric cyst and enhancing mural nodule lateral to tumor cyst (arrow). B. Axial MRI (TR/TE 3000/75) at the same level as in A shows high signal in the mural nodule. (Used with permission from Latchaw RE, *Computed Imaging of the Head*, Neck and Spine, second edition, 1990, in press.)

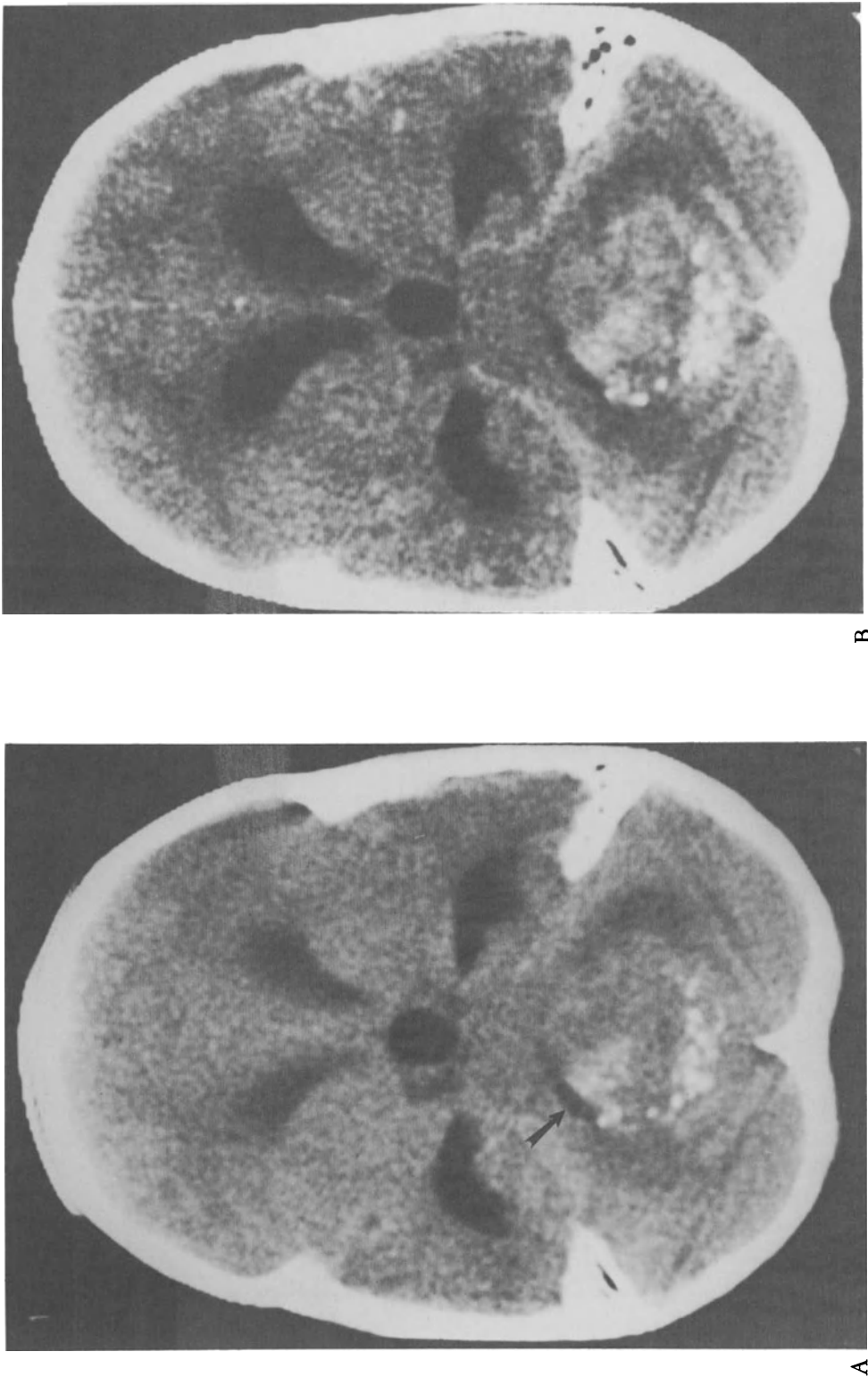
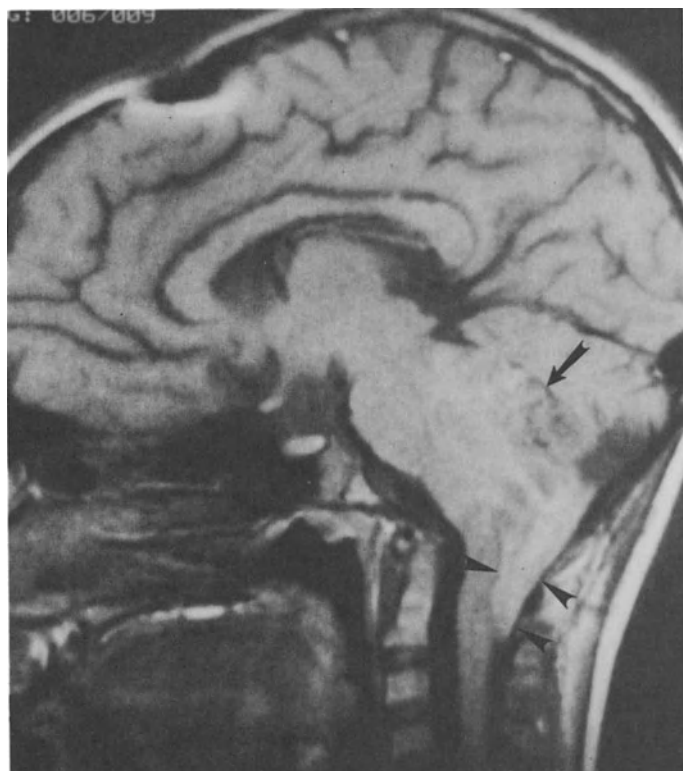


FIGURE 3-35. A five-year-old male with ependymoma. A. CT without contrast reveals a fourth-ventricular tumor with flecks of calcification and obstructive hydrocephalus. There is a small crescent of residual fourth ventricular lumen on the right (arrow). B. CT with contrast enhancement shows minimal enhancement of tumor, typical of ependymoma. (Used with permission from Latchaw RE, *Computed Imaging of the Head, Neck and Spine*, second edition, 1990, in press.)



outlined by displaced normal vessels corresponding to the cyst. Occasionally dense nodule can have a central lucency [102] (figure 3-37A). Angiography is more sensitive than CT in detecting tiny nodules. Seeger et al. found that angiography detected 55 hypervascular nodules, whereas CT found only 16. One patient in Seeger's series had 27 nodules at angiography, but only two were found at CT [103].

CT with contrast differentiates the cystic and solid components of the tumor mass (figure 3-37B). These lesions have several distinguishing features that can differentiate them from other neoplasms of the posterior fossa. Although a large cyst with a small, densely enhancing mural nodule is a very common appearance and can look quite similar to the cystic cerebellar astrocytoma, Ganti et al. found that the mural nodule of the hemangioblastoma is generally smaller (13 mm or less) than the mural nodule

FIGURE 3-36. An 11-year-old female with ependymoma. Sagittal midline MRI shows a fourth-ventricular mass with no clear margin with the brainstem and a cauliflower-like posterior margin (arrow). Note also growth of tumor behind the cervical cord through the foramen magnum (arrow-heads). (Used with permission from Latchaw RE, *Computed Imaging of the Head, Neck and Spine*, second edition, in press.)

of the cystic cerebellar astrocytoma, and all hemangioblastomas were found to border the pia-arachnoid [104]. The overall size of the mass at presentation is smaller than the cerebellar astrocytoma. Naidich et al. found that 75% of hemangioblastomas were less than 4 cm in size and that 70% of cerebellar astrocytomas were greater than 5 cm in size [88]. This may be because cerebellar astrocytomas tend to occur in a younger age group than hemangioblastoma, when the skull can expand more, allowing the tumor to grow larger before discovery. Because the mass is typically hemi-

spheric, the tumor displaces of fourth ventricle rather than filling it like medulloblastoma. If large, hemangioblastoma also can cause hydrocephalus. When there is an enhancing rim, it is typically very thin, unlike the case of metastasis [104]. Occasionally there is little contrast enhancement in the solid portions of the tumor.

MRI can characterize the lesion according to its cystic and solid components and can identify the flow-void signal in enlarged feeding vessels and draining veins (figure 3-37C). Hemorrhage into the solid portion of the tumor or into the surrounding brain substance can also be identified. High signal on T1W and T2W sequences has been attributed to the presence of methemoglobin, while a low signal on both T1W and T2W sequences has been attributed to hemosiderin [105]. The low signal in an aging hematoma, if linear, can look like the flow void signal in vessels. Differentiation from arteriovenous malformations may therefore require angiography.

BRAINSTEM TUMOR

This tumor causes diffuse enlargement of the brainstem, although it is also capable of exophytic growth and can even encase the basilar artery (figure 3-38, 3-39). This intra-axial infiltrating lesion can involve the pons, medulla, cerebellar peduncles, and midbrain. Cystic or necrotic change does occur and is more common than calcification or focal hemorrhage [106]. Seeding is not usually seen.

The CT appearance is a typically isodense or hypodense mass, with variable degrees of enhancement (figure 3-39). The degree of enhancement correlates poorly with histologic grade. Despite the presence of Hounsfield artifact (beam attenuation secondary to the petrous bones) in the posterior fossa, the CT detection rate for brainstem gliomas in children is 96% [106]. Water-soluble contrast cisternography has also been employed to better outline the brainstem with the surrounding basilar cisterns and the fourth ventricle (figure 3-40). This pro-

cedure permits precise measurement to evaluate subtle intra-axial enlargement and can also localize an extra-axial component that may be biopsied [107].

The advent of MRI has challenged the use of plain CT and contrast cisternogram CT scanning for the evaluation of the brainstem [108, 109]. The midline T1W sagittal image clearly identifies the anatomical relationships of the brainstem, fourth ventricle, and cerebellum. Measurements can be employed to detect subtle enlargements of the brainstem [110]. Brainstem gliomas typically exhibit a low signal on T1W and a high signal on T2W MRI (figure 3-41). Sagittal imaging can also evaluate extension into the cervical spinal cord [15]. MRI better evaluates abnormal anatomy and extent of tumor than CT for evaluation of the brainstem because of the lack of artifact and better contrast between normal and edematous, possibly neoplastic tissue. Gadolinium-DTPA may enhance the tumor margins (figure 3-42).

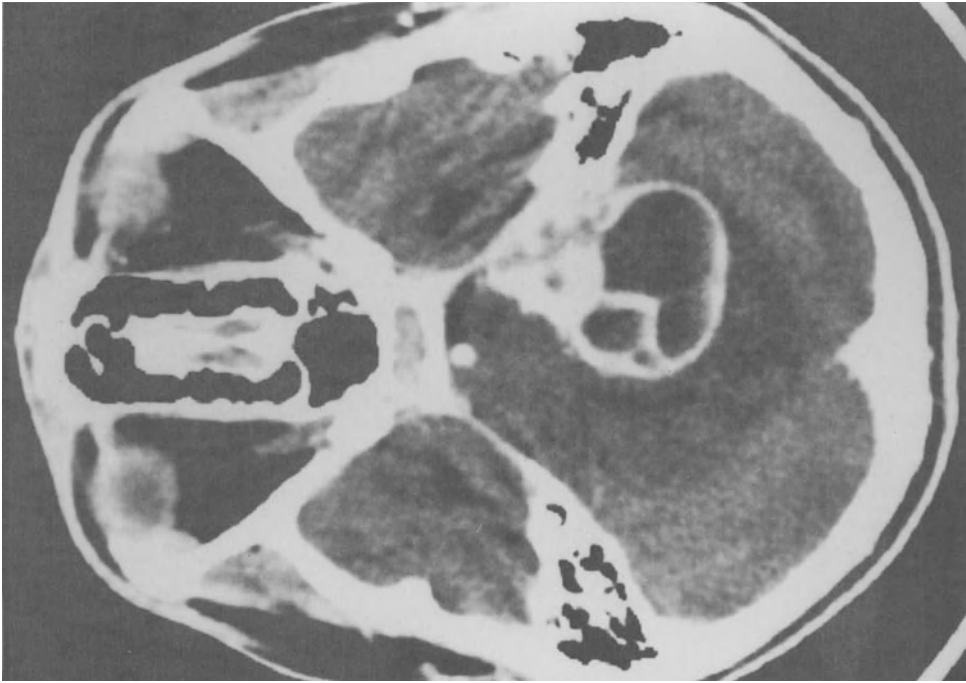
CHOROID PLEXUS PAPILLOMA

In children under the age of 10, only 10% of choroid plexus papillomas occur in the fourth ventricle. By contrast, in the adult, choroid plexus papilloma is more common in the fourth ventricle than in the third or lateral ventricles and can occur in the cerebellopontine angle. For a more complete discussion of this subject, please refer to the section on supratentorial tumors (page 67).

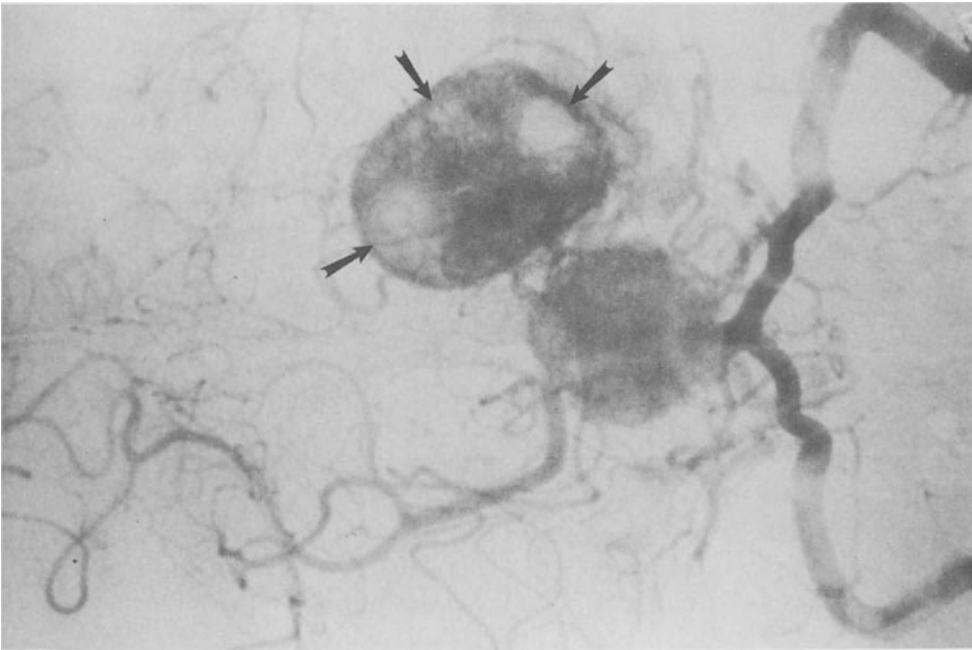
DERMOID AND EPIDERMOID TUMORS

Dermoid and epidermoid tumors are both cystic tumors of maldevelopmental origin. Dermoids most frequently occur in the posterior fossa in the midline and may communicate with the surface of the skin via a dermal sinus [12]. They can also occur in the subfrontal region and can be more eccentric in location. In the spine, their most common location is the lumbosacral region.

Dermoids characteristically contain fat and frequently have mural calcifications [111].



B



A

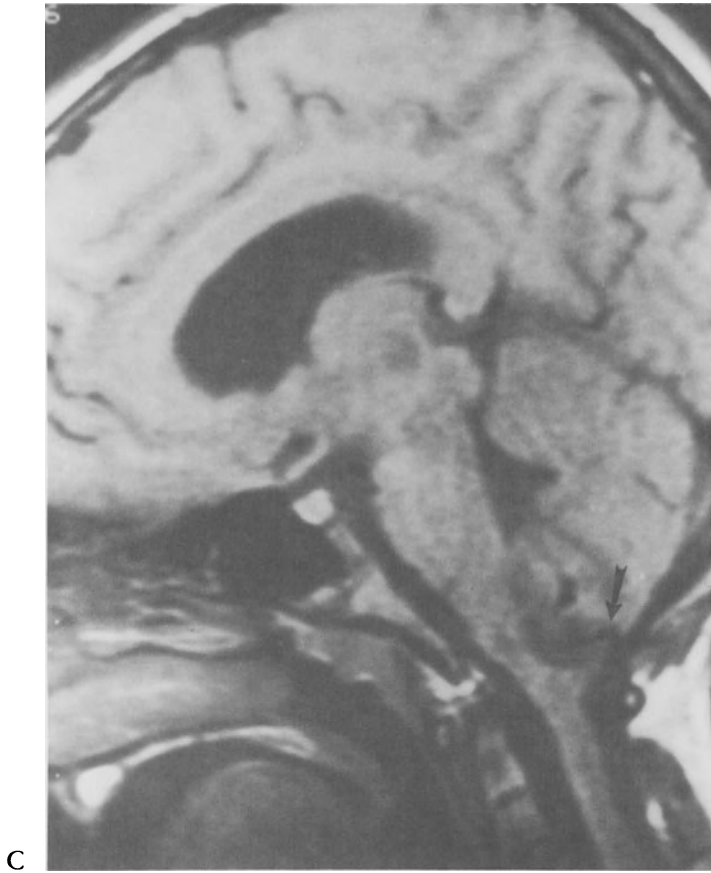


FIGURE 3-37. A 12-year-old male with von Hippel-Lindau syndrome. A. Vertebral angiogram shows two densely vascular lesions. The one on the patient's left has three cysts (arrows). B. CT with contrast enhancement done after surgery and two years later than the angiogram shows a partially cystic, partially solid mass in the left brachium pontis. C. Midline sagittal MRI (TR/TE 600/20) shows a midline mass in the inferior fourth ventricle compressing the inferior vermis with flow-void signal in a vessel supplying the mass (arrow).

Rarely, teeth are present. CT accurately reflects their composition of fat and calcium when present. A fat-fluid level in the ventricle or in the cistern is indicative of rupture of the cyst [112]. MRI, like CT, will identify the fatty elements, but calcification may be missed if small.

Epidermoids may present in the midline, but they are more commonly eccentric in lo-

cation. Most commonly they present in the cerebellopontine angle, but they also occur in the supratentorial compartment in the middle cranial fossa. Intraventricular epidermoids are rare. CT attenuation values of the cystic contents are closer to CSF, reflecting the combination of desquamated epithelium and cholesterol crystals [111, 113, 114]. Epidermoids calcify less frequently than dermoids, and there is no enhancement with contrast. Malignant change that showed contrast enhancement has been reported [115]. The main differential diagnosis to consider is arachnoid cyst. MRI may be able to differentiate epidermoid from arachnoid cyst depending upon the cyst content. If the content is proteinaceous, it will have a high signal on T1W scans in contradistinction to the arachnoid cyst. However, the

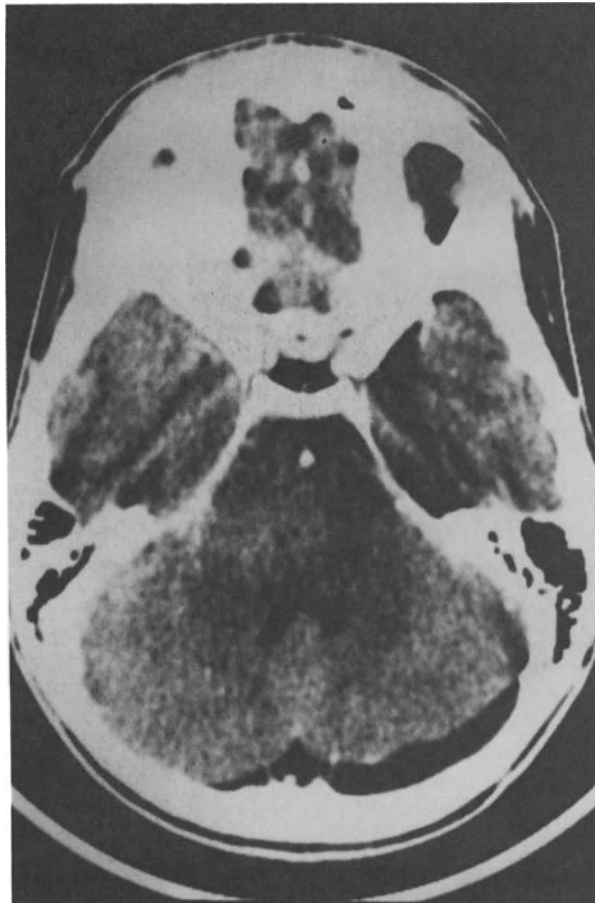


FIGURE 3-38. A 9-year-old female with brainstem glioma. Axial IV contrast-enhanced CT shows enlargement of the pons with posterior displacement of the fourth ventricle and partial encasement of the basilar artery.

more similar the content is to CSF, the more difficult the differentiation.

POSTTHERAPY CHANGES

The radiological manifestations of radiation injury to the brain are multiple and include the following: 1) atrophy, 2) calcification, 3) edema, 4) demyelination, 5) radiation necrosis, 6) large vessel occlusive vasculopathy, and 7) tumor induction. Diffuse necrotizing leukoencephalopathy is most commonly known to occur following methotrexate chemotherapy and is potentiated when used with radiation therapy.

The most common abnormality following radiation therapy is generalized enlargement of the ventricular and cisternal spaces [116] (figure 3-6B). This finding is more common in

those patients who have also been treated with chemotherapy. The etiology is not entirely clear.

Dystrophic calcification is also a common finding. The time of appearance varies from several months to years following irradiation, with or without intrathecal or systemic methotrexate [117, 118, 119, 120]. The most common locations are the putamen and globus pallidus and the deeper layers of the cerebral and cerebellar cortex. Calcification in the brainstem can also occur (figure 3-43). The patho-



FIGURE 3-39. A five-year-old female with brainstem glioma. Axial IV contrast-enhanced CT. There is diffuse enlargement of the pons with encasement of the basilar artery (arrow) and posterior displacement of the fourth ventricle (arrowheads). Contrast enhancement is seen in portions of the tumor.

genesis is related to a microangiopathy leading to focal hypoxia and subsequent calcification. Most patients reported with calcification have received about 4000–5000 rads (40–50 Gy), but Kramer and Lee report a ten-year-old who received 550 rads (5.5 Gy) [121].

Radiation injury is classified according to time of onset. Acute reactions are those that occur during therapy. The early delayed reactions occur within weeks to a few months after therapy, and the late delayed reactions occur months to years later [122]. There are no reports of CT findings in the acute stage

because the syndrome is self-limiting; interruption of therapy reverses the symptoms, and few if any patients get scanned. Early delayed reactions are due to demyelination. These patients will have low density on CT and high signal on T2W MRI in the white matter with mass effect. Subsequent scans will show partial resolution of associated edema, but there should be residual evidence of demyelination. Radiation necrosis is a well-documented complication of radiation therapy to the brain; it is more likely to occur when higher doses are given. The usual time of onset is about two years after therapy, with a range of several months to years. Typical doses required are about 6000 rads (60 Gy), but the dose can be less if given over a shorter period of time [123]. The CT appearance is nonspecific and can simulate recurrent tumor. The lesion usually has low density on noncon-

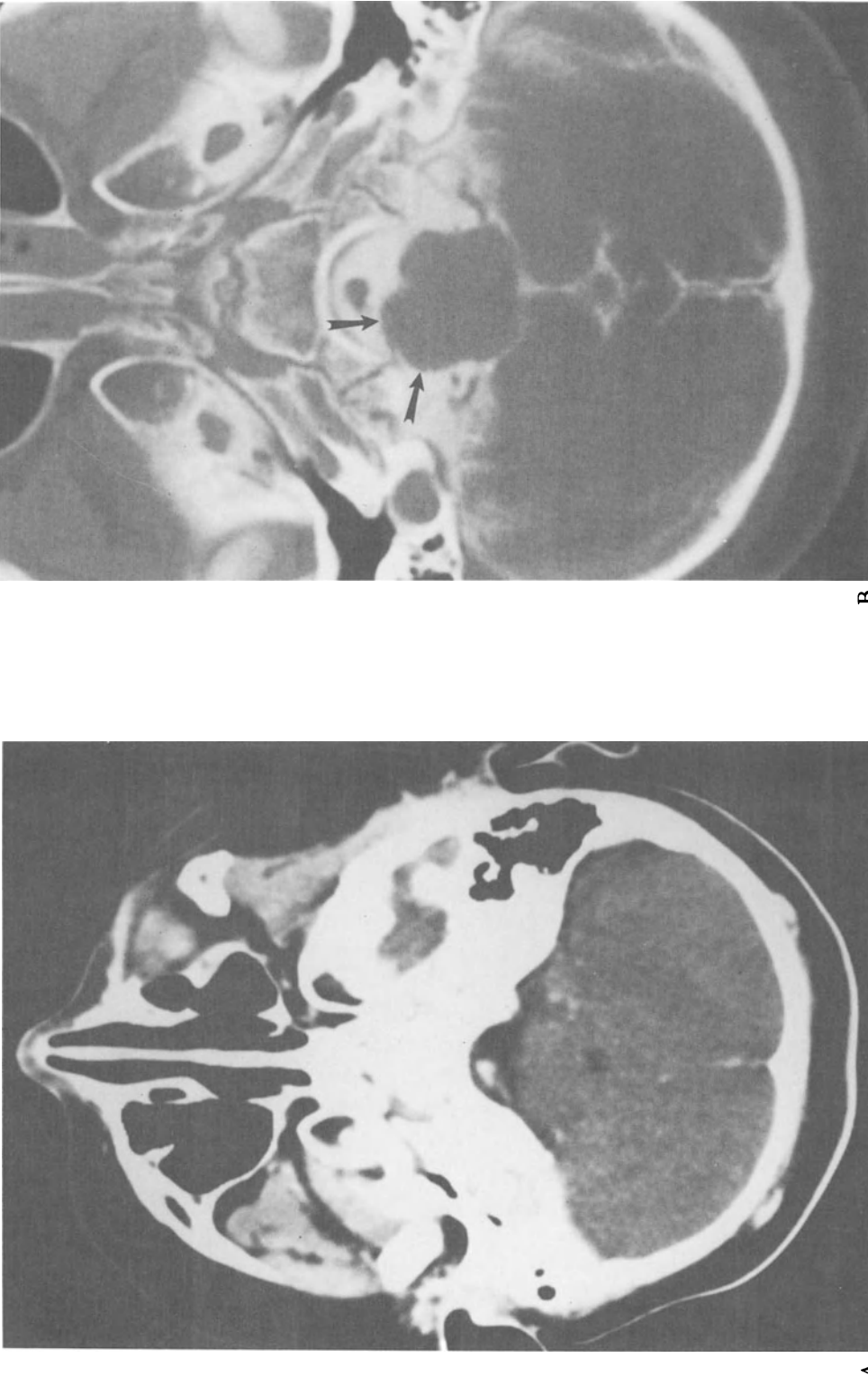
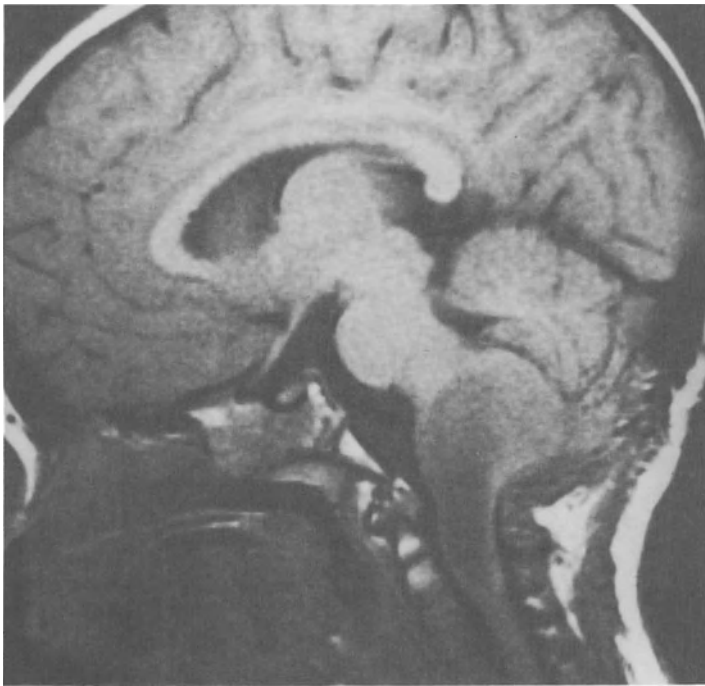
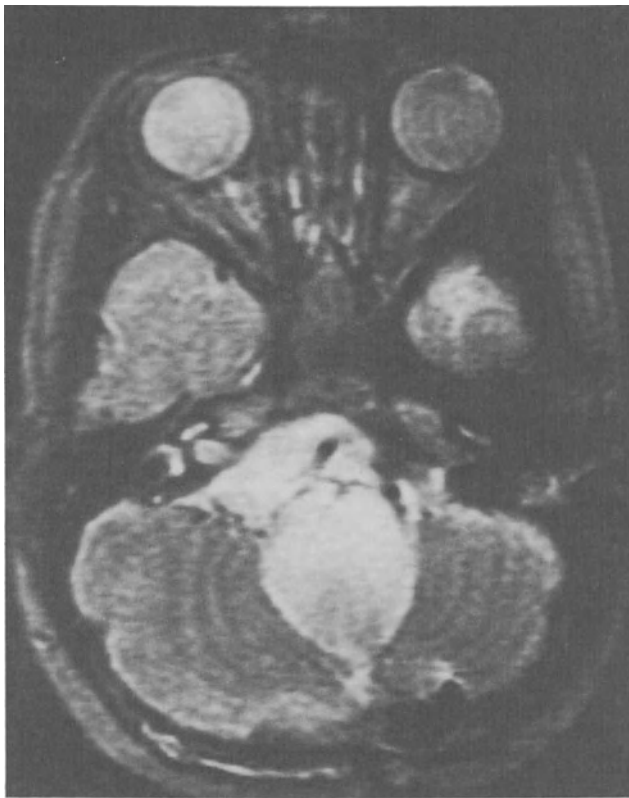


FIGURE 3-40. A three-year-old female with brain-stem glioma. A. Axial IV contrast-enhanced CT shows no obvious abnormality. B. Axial cisternal enhanced CT shows enlargement of the right olive (arrows).



A



B

FIGURE 3-41. A one-year-old female with brainstem glioma. A. Sagittal midline MRI (TR/TE 600/20) shows a large hypointense mass in the medulla and upper cervicle cord with a large extension of tumor expanding posteriorly, compressing the inferior vermis. B. Axial MRI (TR/TE 2500/75) through the largest diameter of the mass, which shows a hyperintense signal relative to normal cerebellar hemisphere.



FIGURE 3-42. A five-year-old male with presumed brainstem glioma. Axial MRI (TR/TE 600/20) with gadolinium shows a rim-enhancing tumor in the medulla.

trast CT, with or without mass effect, but can also be isodense or occasionally hyperdense. There may or may not be enhancement with contrast. The enhancement pattern may be patchy and irregular or there may be solid or rim enhancement. Differentiating radiation necrosis from recurrent tumor in most cases is not possible but can be suggested with knowledge of the isodose curves [123]. A definitive diagnosis will require surgical biopsy.

Disseminated necrotizing leukoencephalopathy is a complication of combined radiation therapy and chemotherapy. This is seen most commonly in those patients receiving either intrathecal or intravenous methotrexate. The effect tends to be diffuse; however, a focal lesion may develop due to a high concentration of methotrexate near the shunt tip [124]. The noncontrast CT demonstrates a nonspecific white-matter low density, symmetric or asymmetric in distribution, that usually fails to enhance with contrast. The changes are usually irreversible; however, reversible CT changes have been described in a child receiving ir-

radiation and intrathecal methotrexate [125].

Reports have documented the occurrence of occlusive vasculopathy following radiation therapy [126, 127]. At angiography, a nonspecific pattern of arteritis is seen with stenoses and occlusions of larger vessels. Collateral pathways can form, producing a telangiectasia or moyamoya pattern. Histologic sections show dense hyalinization and intimal thickening leading to luminal stenosis or occlusion. CT and MRI reveal infarction that follows a vascular distribution and a temporal sequence typical for stroke. Reported radiation doses vary widely, ranging from 1000–8500 rads (10–85 Gy) [127]. The wide range may be attributable to a decreasing sensitivity to radiation effect with age.

MRI of radiation injury of the brain has not proven better than CT in the detection of calcification or in the differentiation of tumor from radiation necrosis. It is more sensitive to

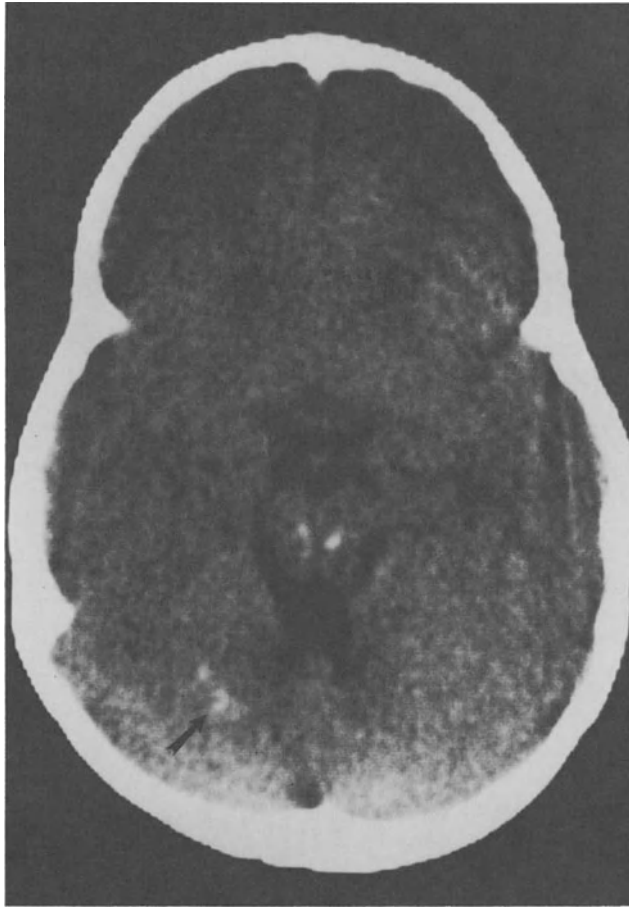


FIGURE 3-43. A four-year-old male with retinoblastoma and a history of radiation therapy. A noncontrast CT shows paired symmetric calcifications in the midbrain and a single calcification in the right cerebellar hemisphere (arrow).

the extent of injury due to its greater sensitivity to the presence of excess water in the affected areas [128, 129].

The appearance of new tumors induced by radiation therapy is identical to that of their spontaneously occurring counterparts. Knowledge of the portals may offer the only clue as to the origin. New primary tumors may be confused with recurrence of the original tumor, as in the case of radiation-induced fibrosarcoma of the pituitary gland.

Spinal Tumors

In recent years, myelography, the mainstay of spine imaging, has been strongly supplemented by CT. Often done in combination with the use of water-soluble contrast material, the myelogram can survey long areas of the spine, allowing a focused CT examination to be done for those areas in question. This procedure is being challenged by MRI, which can achieve excellent definition of CSF and the spinal cord without being invasive. Intramedullary lesions are better characterized as being solid, cystic, hemorrhagic, or a mixture of these. However, myelography is still better in the evaluation of filling of the nerve root sleeves, and CT still remains the method of choice for evaluating bone de-

struction or remodeling. Spinal angiography is used in the workup of hemangioblastoma and arteriovenous malformation with possible embolization.

Tumors of the spinal canal are classified into

three broad categories according to location: intramedullary (within the cord substance), intradural–extramedullary, and extradural (figures 3-44, 3-45, and 3-46). The tumor location is usually easily distinguished on

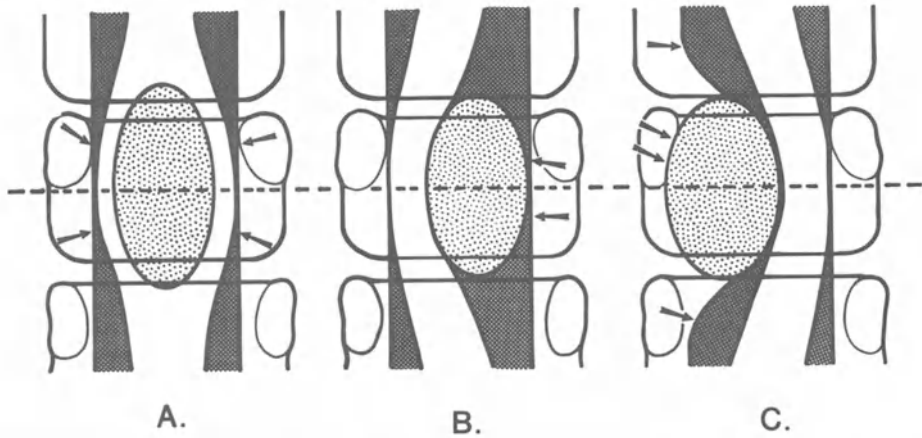


FIGURE 3-44. Anteroposterior view. A. Intramedullary mass (black dots on white background): note the smooth widening of the cord (solid white) displacing CSF (white dots on black background) and the acute angle it makes with the dural sac (arrows). B. Intradural–extramedullary mass: note the compression of the cord and the acute angle the mass makes with the dural sac (arrows). C. Extradural mass: note the compression of the cord and the obtuse angle the mass makes with the dural sac (arrows). Pedicular erosion is also depicted (paired arrows).

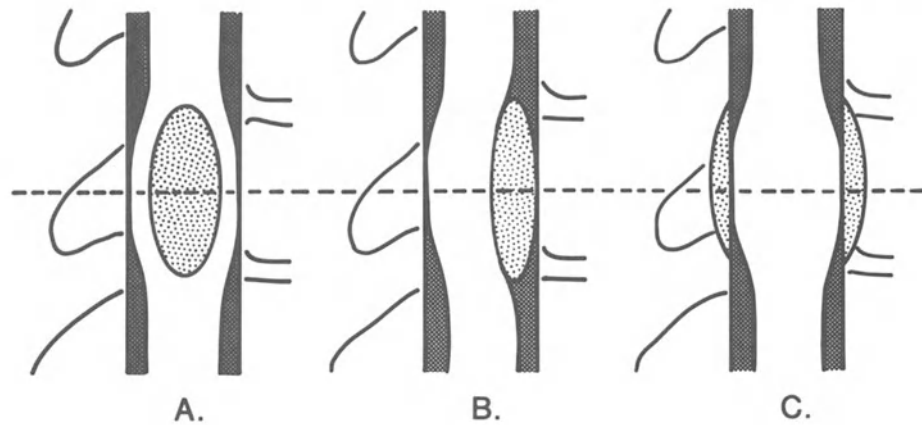


FIGURE 3-45. Viewed at right angles to figure 3-44.C demonstrates cord widening and may simulate an intramedullary process, as in A.

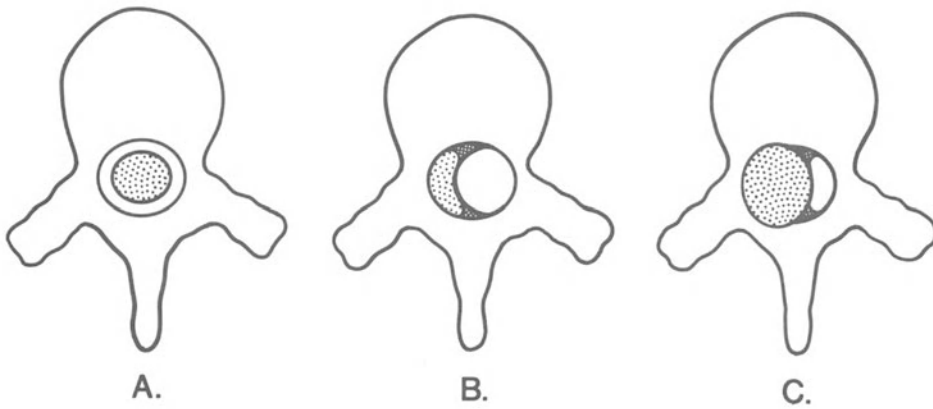


FIGURE 3-46. A–C. Cross-sectional view at level of dotted lines in figures 3-44 and 3-45 clearly demonstrates the location of the masses in relation to the dura and spinal cord.

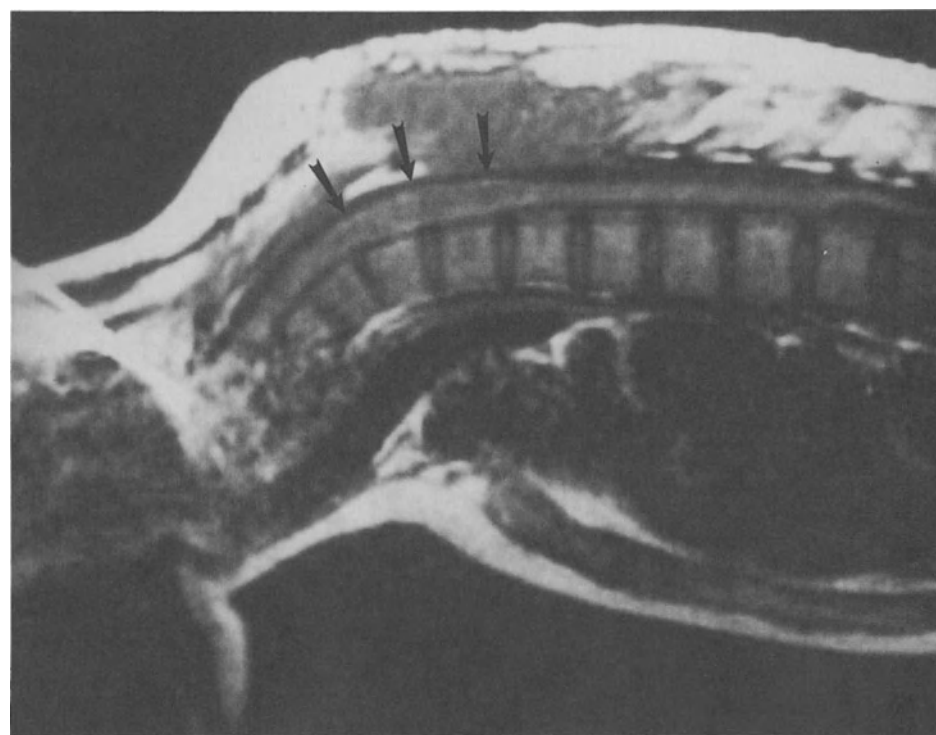
myelography, provided that both projections are obtained. But occasionally, CT is needed to better localize the tumor to a specific compartment. Occasionally, in the case of *drop metastasis*, the surface of the cord can be so diffusely coated as to look like an intramedullary process despite its extramedullary location. MRI has provided a less invasive way to image the contents of the thecal sac and has proven very useful in better characterizing intramedullary tumors.

INTRAMEDULLARY TUMORS

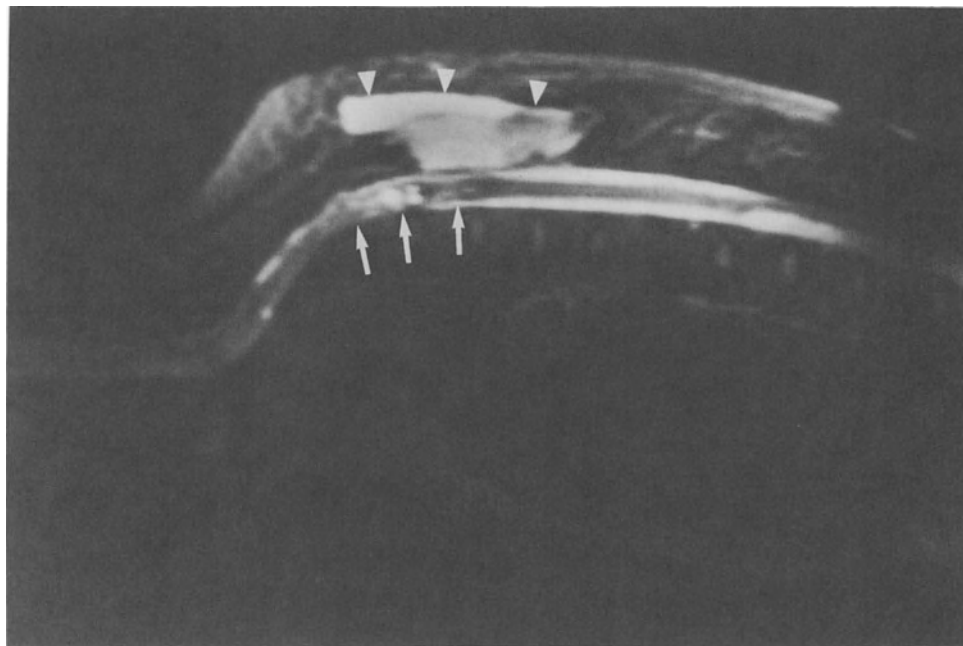
Astrocytoma is the most common intramedullary tumor of the spinal cord. Less common than astrocytoma is ependymoma. On myelography, CT, and MRI, smooth widening of the cord is seen (figure 3-47), which may be limited to only a few segments or in rare cases may extend the entire length of the cord from the foramen magnum to the conus medullaris. These tumors have been called giant or gigantic tumors of the spinal cord [130]. The tumor itself may be small with a large cystic component, or it may obstruct the central canal, causing hydromyelia. CT scanning performed

several hours after water-soluble myelography may demonstrate uptake of contrast into cystic regions of the cord.

MRI can better characterize the internal structure of the tumor than CT. Much like astrocytomas of the brain, solid portions of the tumor will show a low signal intensity on short TR sequences and a high signal intensity on long TR sequences due to the increased water content of the tumor. Very proteinaceous cysts may have signal characteristics similar to solid tumor. There are two studies in the literature that report the inability of MRI to reliably differentiate cystic from solid portions of the tumor [131, 132]. Both found intraoperative ultrasound more helpful in determining the presence and extent of cysts. Jungreis et al. found a significant difference in the T1 and T2 relaxation times of the fluid contents of syrinx and tumor cyst [20]. As expected, the fluid in the syrinx is most like CSF. Therefore, the lower the protein content in the tumor cyst is, the better it will be visualized and the more like the syrinx it will appear. Morphologically, syringohydromyelia will have a well-margined, multiloculated, or septated appearance. Tumor



A



B

FIGURE 3-47. A 17-year-old female with neurofibromatosis and astrocytoma of the upper thoracic cord. A. Sagittal midline MRI (TR/TE 600/20) shows widening of the upper thoracic cord. The intramedullary mass is isointense to hypointense (arrows) relative to normal cord below. B. MRI (TR/TE 3500/120). The signal is heterogeneous within the mass but has predominantly a high signal (arrows). A collection of fluid is seen in the laminectomy site following recent surgery (arrowheads).

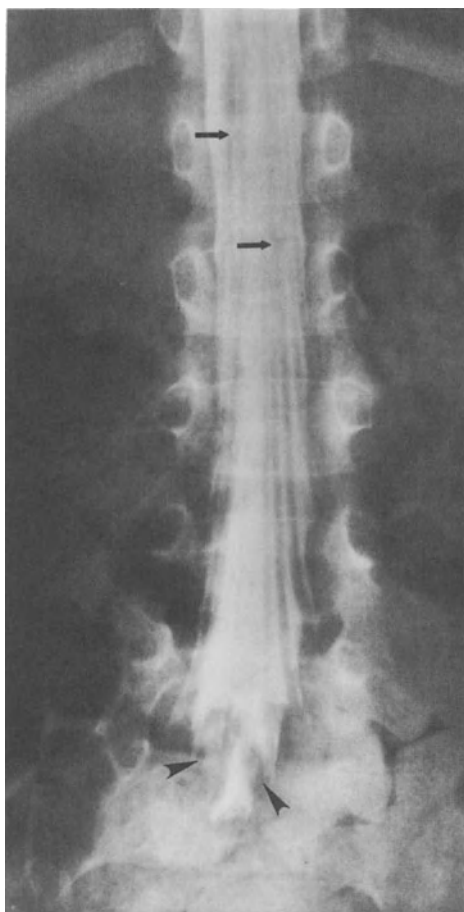


FIGURE 3-48. A five-year-old male with drop metastasis from glioblastoma multiforme in the cerebellum. Subarachnoid deposits of tumor are best seen in the tip of the caudal sac (arrowheads), but at least two other deposits are seen on nerve roots at the L1 and L2 levels (arrows).

cysts generally will not look septated, but in our experience sharpness of margination may vary.

Tumor enhancement is seen on MRI scans with gadolinium-DTPA [133]. As in the brain, gadolinium enhancement appears to improve lesion detectability and probably will become necessary in spinal cord tumor evaluation. Though they originate from the intramedullary space, ependymomas of the conus may develop an extradural component and will

appear like any other extramedullary tumor such as neurofibroma or meningioma.

INTRADURAL EXTRAMEDULLARY TUMORS

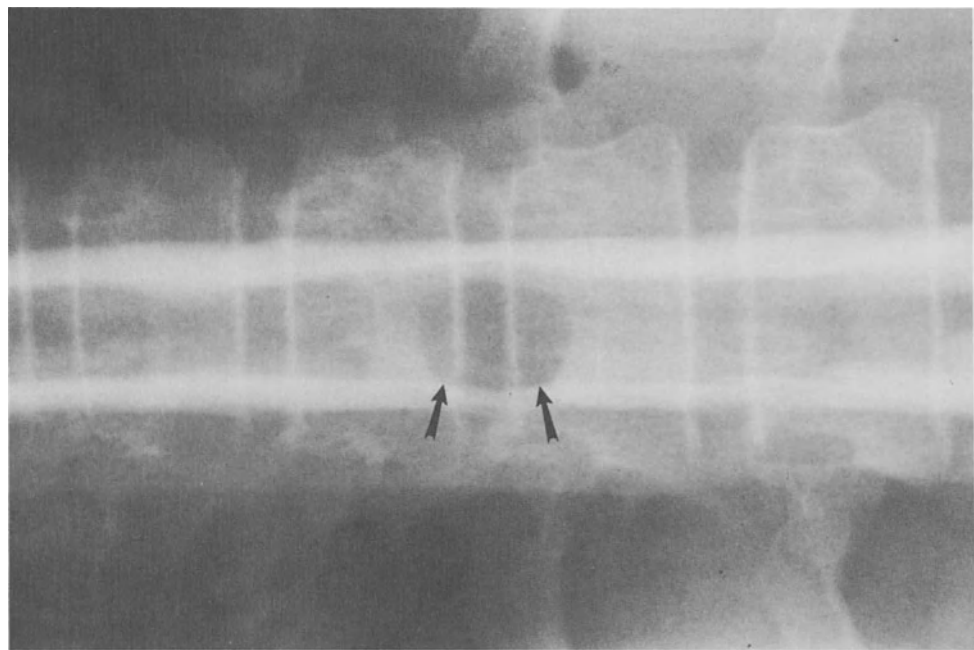
Drop metastases from intracranial tumors are the most common cause of intradural extramedullary tumors. Most commonly, these tumors display multiple nodular implants of varying size on the cord, nerve roots, and meninges (figure 3-48). Less commonly, there may be a single large mass compressing the cord (figure 3-49). Occasionally, there may be a diffuse coat of tumor on the cord having the appearance of an intramedullary tumor (figure 3-50). If there is coating of the nerve roots, they will appear diffusely thickened. There are no radiologic features to distinguish one metastatic tumor type from another.

Noncontrast MRI is less sensitive than myelography and contrast-enhanced CT for detecting drop metastasis [134]. Preliminary work with gadolinium-enhanced MRI in the detection of intradural extramedullary tumors has shown significantly better results [135].

Though rare in children, neurofibroma and meningioma present in this location. In association with von Recklinghausen's disease, neurofibromas may be multiple and may extend through the neural foramen, widen it, and form a *dumbbell tumor*. Multiple dumbbell tumors may be seen on a coronal MRI projection (figure 3-51) [136]. Meningiomas are usually solitary, but may also extend through the neural foramen and form a dumbbell tumor.

EXTRADURAL TUMORS

The most common extradural tumor in children is neuroblastoma. Typically there is a paravertebral mass of varying size, widening of one or more neural foramina, and intraspinal extension of tumor that compresses the thecal sac and its contents (figure 3-52). However, regardless of the origin of the tumor, the myelographic findings will be the same. Myelography shows smooth compression of the thecal sac with compression of the cord or cauda equina



A



B

FIGURE 3-49. A nine-year-old male with drop metastasis from medulloblastoma. A. A frontal view of the lower thoracic cord. An oval, well-circumscribed filling defect is seen through the cord shadow (arrows). B. The lateral view shows the mass anterior to the cord. The ventral surface of the dura and the mass form acute angles (arrows), locating it beneath it beneath the dura. (Compare with figures 3-44B and 3-45B.)

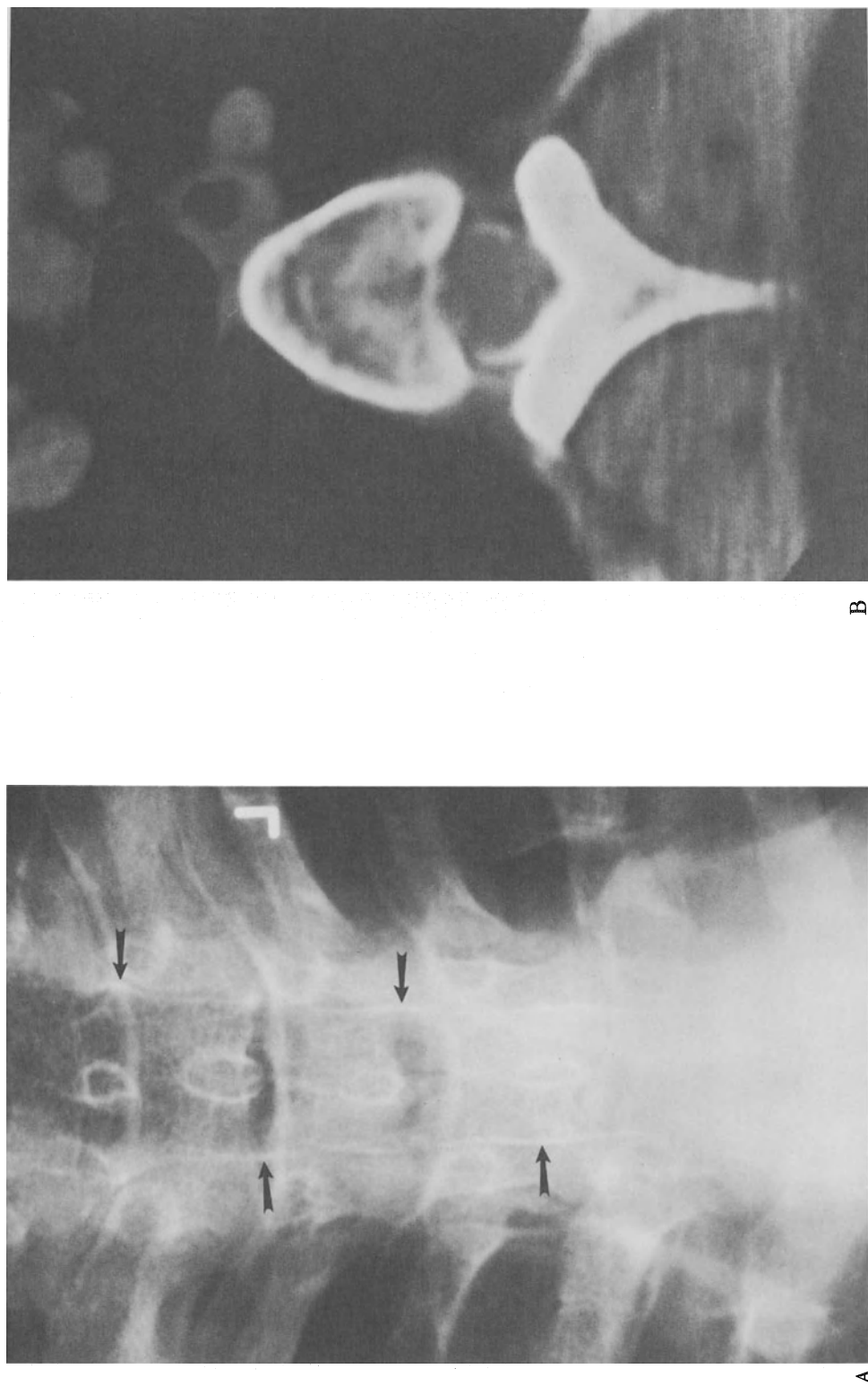
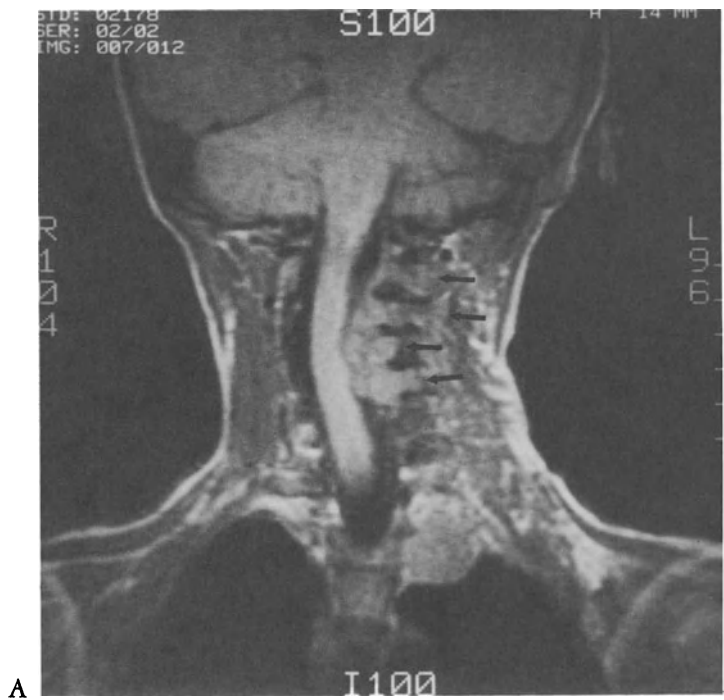
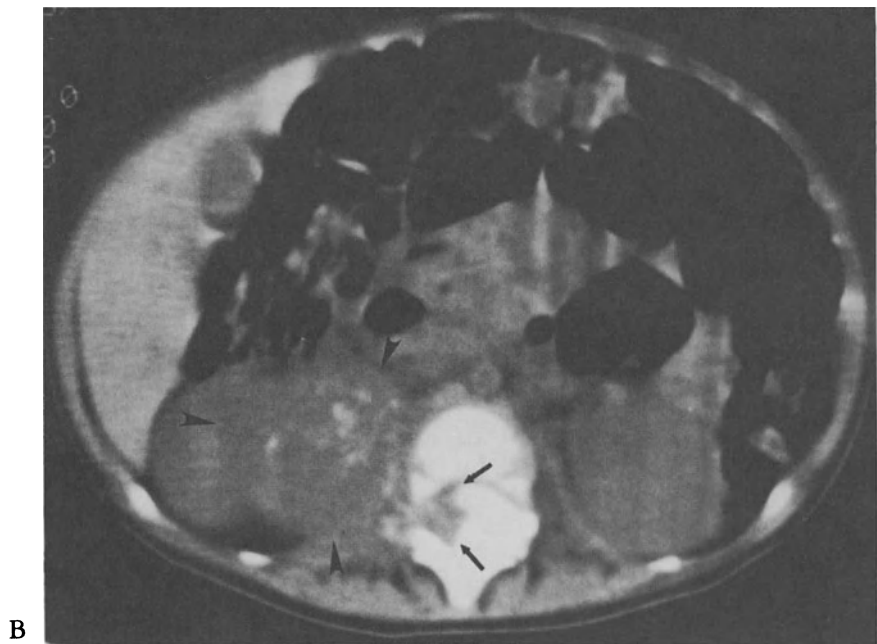


FIGURE 3-50. A 21-year-old female with cerebellar medulloblastoma. A. A frontal view of a myelogram at the level of the upper thoracic cords shows diffuse widening of the cord shadow, indistinguishable from an intramedullary process. Only a thin stripe of intrathecal contrast outlines the cord (arrows). At the time of posterior fossa surgery, extensive leptomeningeal tumor seeding to the level of C1 was seen. B. Axial CT following the myelogram shows widening of the upper thoracic cord.



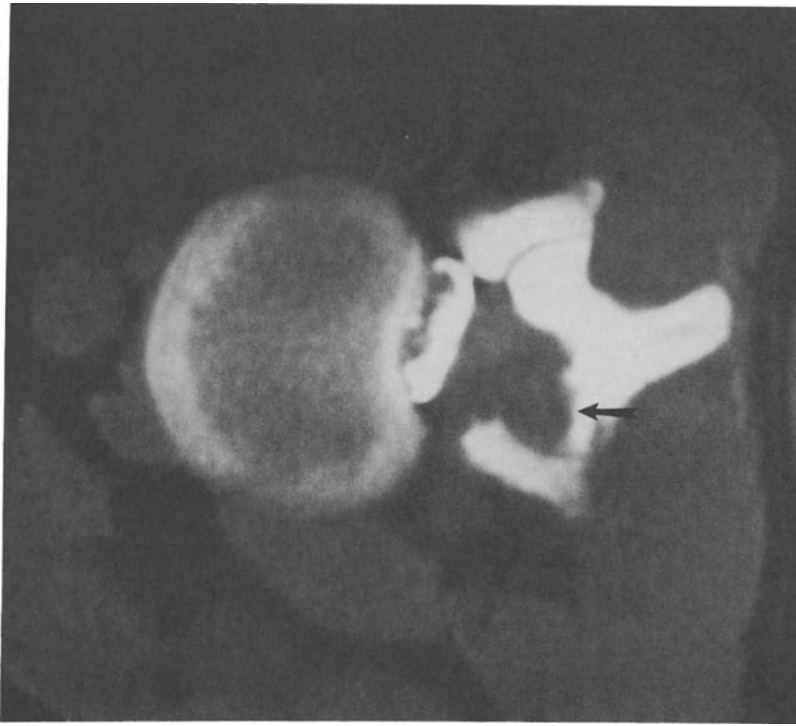
A

FIGURE 3-51. A four-year-old female with neurofibromatosis. Coronal MRI (TR/TE 800/25) shows dumbbell tumors compressing the cord and extending through multiple neural foramina on the left (arrows). (Used with permission from Burke et al., *Radiology* 162:797–801, 1987).

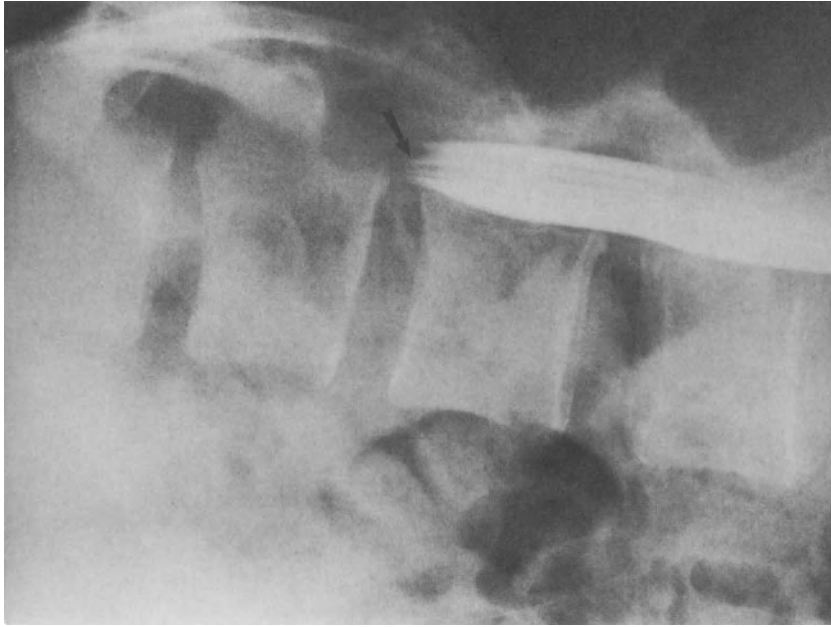


B

FIGURE 3-52. An eight month-old male with neuroblastoma. Abdominal CT following myelography shows a large right-sided paraspinal mass (arrowheads) with intraspinal extension and compression of the thecal sac and contents (arrows).



B



A

FIGURE 3-53. A 19-year-old male with giant-cell tumor of L1. A. Water-soluble contrast injected below the lesion demonstrates a block at the L1–L2 disc space (the patient is head down). Compare with figure 3-44C. There is feathering of the contrast column due to minute extensions of contrast around the crowded cauda equina (arrow). B. Axial CT following the myelogram just below the block shows a right dorsolateral mass compressing the thecal sac and eroding the right interior facet (arrow).

(figure 3-53A). CT following myelography shows smooth compression of the thecal sac by the extradural mass (figure 3-53B).

Bone erosions are better defined on CT than on plain films or myelography. Both primary and metastatic tumors of the bone can cause erosions. MRI has proven itself useful in evaluation of tumors in this location, and recent literature suggests improved visualization of extradural tumors with gadolinium-DTPA [137].

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4. NEUROLOGICAL ASSESSMENT

Jerrold M. Milstein

This chapter will try to develop a clinical and laboratory strategy to help direct the physician to the diagnosis of a central nervous system neoplasm and possibly the tumor type producing the symptoms and signs. Given the ambiguity of symptoms that are seen in children and particularly in the very young infant, the first task is to keep the diagnosis of a brain tumor in mind. Often, the family practitioner or pediatrician focuses on the most probable source of the symptom and neglects to consider brain tumor. It is not unusual for nonneurologic subspecialists to be the first to consider a diagnosis of brain tumor in children referred for evaluation of visual problems or recurrent vomiting.

With the above in mind, there is a group of symptoms and signs that can be considered as general and nonspecific and others that are very specific for a particular tumor. The symptoms and signs will be addressed in the initial part of this chapter. The next section will address the inherent differences between young children and adults as these affect the clinical examination and choice of studies necessary to make a definite diagnosis. Finally the discussion will address some of the procedures considered part of the neurologic evaluation and how they may be properly used in the early management of childhood brain tumors.

Symptoms

Perhaps the most common symptom brought to a physician's attention and associated with a brain tumor is headache [1, 2]. In the older literature, this was felt to be one of the most

important presenting symptoms of tumor in a child, but today headache is one of the more common symptoms seen by physicians, particularly child neurologists. As would be suspected, this is rarely associated with a tumor, but it should not be disregarded, and additional history is often helpful. Those headaches that have been persistent for many years without change with a normal examination are more likely to represent nonneoplastic disease. On the other hand, headaches of recent onset may be more meaningful. The underlying basis for tumor-associated headache is increased intracranial pressure or traction on the meninges. Headaches in this setting are characterized by onset in the morning after a prolonged recumbent position, which allows intracranial pressure to increase. They may also occur after a nap. Once the child is awake, active, and in an upright posture, venous pressure is reduced and the intracranial pressure is also relieved. The other symptom frequently associated with headache is vomiting, and this too occurs more often in the morning. The vomiting is not always associated with nausea and rarely is projectile. Once the child has vomited, he is usually hungry again, and eating seems to have little influence on the symptom. Both of these symptoms, headache and vomiting, should be considered as nonspecific, since they occur often and rarely are associated with localizing findings.

Seizures occur often in childhood, but again are rarely associated with a brain tumor. When seizures are caused by a tumor, it is usually supratentorial and adjacent to cortex. It may be subcortical as well as involving the surface of

the brain. Typically the seizure will have some focal features, but even generalized seizures that originate in the subcortical regions, such as typical absence, have been observed with brain tumors. While the majority of tumor-related seizures occur with supratentorial lesions, older reports have commented that seizures occur with infratentorial tumors. Actually, the observed motor activity may suggest a seizure, but the phenomenon may be decerebrate posturing resulting from an infratentorial mass.

Weakness or paresis is frequently seen with brain tumors, yet this symptom rarely prompts the diagnosis. Paresis, even in childhood, is much more common with other disorders of the nervous system. If paresis is progressive over time, then tumor becomes probable. Suspicion should also be raised when a motor symptom appears to be localized, such as a monoparesis. The nature of the motor symptom is also a factor. Usually with central causes of paresis the complaints are of weakness, but on further questioning, the patient or his parent will observe a change in how a limb is being used, rather than noting a loss of power. Other features may appear that are more difficult to use for localization. A loss in coordination may seem to point toward cerebellar involvement, but this may be a manifestation of deficits arising from many different sites within the central and peripheral nervous system. Even ataxia may be due to tumor at various sites within the central nervous system. Unusual movements are most frequently seen with involvement of the basal ganglia, structures that are located deep within the hemispheres and adjacent to the internal capsule. Examples of these symptoms include chorea, dystonia, and athetosis. These unusual movements are often unilateral when associated with a tumor.

In general, sensory symptoms are unusual complaints in childhood, but because of their rarity should be evaluated vigorously. Lesions of the central nervous system produce a loss of sensation or a distortion rather than discomfort or pain. Sensory symptoms are difficult for a

young child to characterize and interpret for parents and physicians. If pain is part of the complaint, then consideration must be given to tumors of the peripheral nervous system, including rootlets of the spinal cord and brainstem. Disturbed perceptions of tactile sensation are termed *paresthesias*. If the complaint is an alteration of taste, smell, or vision, then these symptoms are considered as hallucinations and may have some structural origin in the brain. If the complaint is auditory and associated with voices talking to the patient, and particularly if the statements perceived by the patient are voices talking about the patient, then psychiatric illness should be considered. The spontaneous sensation of an unusual smell or taste is associated with lesions involving the anterior and medial temporal lobe. In adults they are more likely to be caused by a tumor, while in children, these hallucinations are rare complaints and generally are not associated with tumors. Loss of a particular sensation is more worrisome and must be given attention. Loss of vision or hearing has a greater implication, suggesting involvement of peripheral structures such as the retro-orbital region or lesions along the acoustic pathways. Visual losses in the child are often recognized through observations by the parents, who witness the child misjudge a short distance or bump into an object that is away from the central area of vision. Unilateral visual losses are quite hard to detect, since normal vision in the unaffected eye is sufficient for a reasonable field of vision. Depth perception requires binocular vision within one meter. The judgment of distances greater than one meter depends on other clues. Homonymous field cuts are recognized more readily, since they result in loss that affects both eyes. The complaint is usually that of a single eye having lost vision, but in reality both are affected, resulting in an inability to see anything in the field that has been lost, regardless of which eye is being tested (figure 4-1). Defects of this type involve the optic tract or structures up to and including the occipital cortex. When a field cut

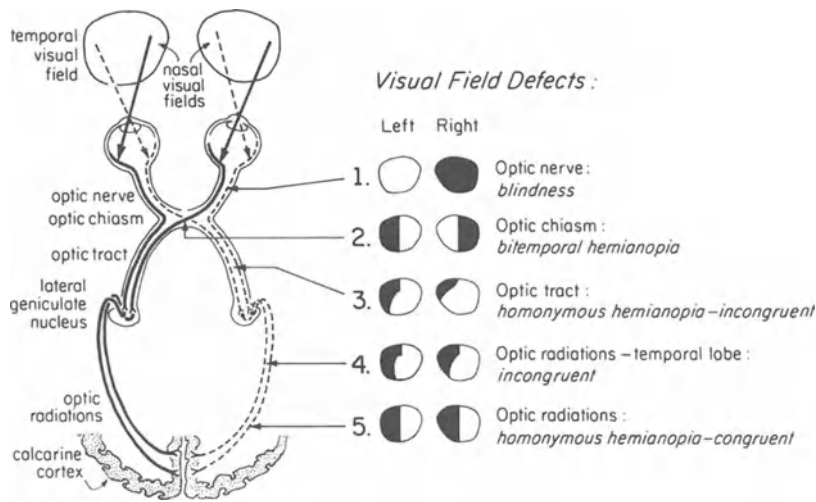


FIGURE 4-1. Visual pathways with typical field cuts at various sites along the pathway from the retina to the occipital cortex.

is incomplete, the more congruous the defect, the closer to the cortex will be the lesion. Other field cuts are seen with lesions involving the optic chiasm. The way visual fibers cross or remain uncrossed determines the field cuts from a lesion. With lesions affecting the central part of the chiasm, the visual loss will be bitemporal, while lesions affecting the inferior side of the chiasm will produce a superior bitemporal defect.

Disturbances of ocular motility are detected very early, since most parents probably recognize abnormalities within a day or so of onset. If the child has had long-standing intermittent strabismus, the changes may not be recognized as quickly. An older child may complain of diplopia even prior to the parents recognizing a limitation in ocular motility. The strabismus or diplopia is accentuated by gazing in the direction that requires the function of the paretic muscle. For example, weakness of the medial rectus on the left will result in worsening diplopia when gaze is turned toward the right. Lesions, and specifically tumors, may produce ocular motility deficits by local

infiltration of the particular nerve or its brain-stem nuclei. The other mechanism resulting in ocular motility disturbances is increased intracranial pressure that shifts the brain, with resulting pressure on the brainstem or cranial nerves.

Nystagmus, a rhythmic movement of one or both eyes, can easily be observed by parents, but there may be no other associated symptoms that can be discerned by the patient. When symptoms are present, the most common is vertigo or dizziness. The possible source of nystagmus ranges from disturbances in vision, particularly macular losses, to lesions in the brainstem, cerebellum, and upper cervical spinal cord. Several types of nystagmus have been described. The most common is the jerk type, with both a rapid and a slow component. Frequently it is best seen when the gaze is directed laterally, with the fast component being in the direction of gaze while the slow component is back to the midline. This type of nystagmus is associated with a variety of disorders, from intoxication to tumors that affect the brainstem and cerebellum. Vertical nystagmus is also a jerk type of nystagmus, but here the nystagmus occurs with gaze directed upward and downward. The latter is occasionally seen with in-

creased intracranial pressure, while the former is often associated with midbrain dysfunction. The other form of nystagmus is pendular. This is often seen when there is visual loss present from birth and is therefore rarely associated with intracranial tumors. Variations of pendular nystagmus may occur with macular losses, but are rarely associated with intracranial tumors. Cerebellar hemisphere lesions typically result in nystagmus that is more dramatic as the gaze is directed toward the side of the lesion.

Decreased or lost hearing is rarely associated with primary neoplastic processes in childhood. When present, it is usually due to an extensive tumor with other features suggesting brainstem involvement. When the eighth nerve is involved, there is often tinnitus and/or vertigo accompanying the hearing loss. The vertigo may appear as a problem in coordination as observed by the parent.

Alterations in hearing may take the form of hallucinations. Unlike visual hallucinations, auditory hallucinations have a high incidence of being associated with psychiatric disease. The nonpsychiatric types of hallucinations represent distortions of what is present in the environment. Those associated with psychiatric processes usually have voices as part of the hallucination, and the voices often speak to the patient or about the patient.

Changes in school performance are a major concern with any child. While tumors are rare causes, they must remain in the differential. Other features may be present to suggest the possibility of tumor, such as seizures, headache, and morning vomiting. The basis for school-performance changes must be sought in a systematic manner beginning with a reasonable history and competent examination. At times, more in-depth psychometrics will help document changes and may even give a clue as to the anatomic site of involvement. Changes in behavior may accompany the deterioration in school performance. The changes may be subtle and insidious over months and apparent only when a long period of time is considered.

Losses of memory may be part of the process and may be ascribed to daydreaming or possibly absence seizures. Regardless of the large number of potential etiologies, tumor must remain on the list of possibilities.

Personality and behavior are manifestations of brain function. Changes observed in a child may represent a normal developmental change, but if this occurs in dramatic manner or at a time that is unlikely to be associated with a developmental change, other causes must be sought. Increased intracranial pressure will often be associated with headaches, but irritability may also be seen. Fluctuations in personality and increased lability have been associated with cortical diseases as well as brainstem dysfunction. Swings from euphoria to depression are the frequent manifestations of this disorder. In the adult population this has been titled *pseudobulbar*, but this terminology is misleading and confusing. Certainly this is most commonly seen in the adult population with bilateral cortical disease. In childhood, it is more often seen as a feature of brainstem disease, partly because of the higher incidence of brainstem involvement.

During childhood, while language is developing, it is unusual for language to be affected in a recognizable way. Rarely, it is lost as part of a seizure process or a structural abnormality involving the dominant hemisphere.

In addition to language problems, speech may be affected without any language disturbances. Distortions, giving the impression of intoxication, may be part of frontal-lobe dysfunction, while more classic dysarthria is felt to be part of brainstem or cerebellar involvement. In many children, alterations in speech are observed with cerebellar or lower brainstem tumors.

Closely associated with a disturbance of speech is bulbar dysfunction, which may manifest as drooling and swallowing problems. This is more often seen with brainstem tumors, but may be due to increased intracranial pressure. Symptoms of bulbar involvement may be seen

with brainstem infiltration by a cerebellar tumor.

Control of bowel and bladder function is a complex neurologic function that can be disturbed by dysfunction in many regions of the nervous system. In the absence of other symptoms, changes in these functions should direct the physician toward tumors involving the spinal cord. When there are associated symptoms, then the assessment should be directed toward the appropriate region of the neuraxis. The symptom may be part of a seizure, which expands the number of possible sites even further. Often, as part of spinal cord involvement, there is pain which may reflect the specific site of the tumor. When pain is present, then extramedullary involvement is more likely. Lesions of the spinal cord, producing bowel and bladder dysfunction without pain, often are intrinsic.

Symptoms associated with spinal cord tumors may be referable to an extremity served by that portion of the spinal cord. Usually the symptoms will be loss of motor strength and/or sensations in a multisegmental pattern if the tumor is intrinsic to the cord. In those instances where the symptom is pain and/or unusual sensations, paresthesia, and dysesthesia, then the lesion is often extrinsic to the cord itself, even though there may be infiltration of the cord. The distribution is often more of a radicular pattern in those situations. Un-

usual and distorted sensations without loss of sensation or motor strength are suggestive of cortical lesions. When this is secondary to superficial cortical lesions, the areas affected most dramatically are those with the largest cortical representation, such as the thumb, fingers, hand, face, or tongue. The motor changes will often be more difficult to define based on symptoms, since patients will usually describe the problem as one of weakness even though the extremity is not weak. Patients also have a difficult time accurately describing motor symptoms other than weakness or changes in coordination.

When unusual limb symptoms occur, they may be manifestations of focal seizures, even in the absence of typical tonic-clonic seizure activity (table 4-1). The symptom in that situation is often more likely to be intermittent than continuous. When stereotyped movements are also seen, then the diagnosis of seizure is clearer. Intermittent sensory symptoms may also represent seizure activity. If obvious seizure activity is present and particularly if it is focal or spreading from a focus, the responsible lesion is often well localized to the sensorimotor cortex. Imaging studies will often demonstrate a structural lesion within or adjacent to the cortex. It would be rare for a deep subcortical or brainstem lesion to manifest focal seizure activity.

Because of the compactness of a variety of

TABLE 4-1. Seizure type with clinical features and typical anatomic location

Seizure type	Clinical features	Anatomic site
Generalized	Symmetric motor activity (tonic and/or clonic) with loss of consciousness	Subcortical or rapidly propagated from focal site
Focal	Localized motor or sensory activity that may spread to become generalized	Localized area of cortex
Absence	Brief loss of awareness with or without some subtle motor activity such as eyelid flutter	Subcortical and midline
Partial, complex	May resemble generalized or focal	Localized area of cortex, often temporal lobe
Partial, simple	May resemble absence	Localized area of cortex, often temporal lobe

TABLE 4-2. Brainstem syndromes with clinical features and anatomic localization

Eponym	Clinical signs	Anatomic site
Weber	Ipsilateral third-nerve palsy with contralateral hemiparesis	Cerebral peduncle at level of third-nerve fibers
Parinaud	Paralysis of upward gaze	Pressure on the collicular plate
Horner	Ptosis, anhydrosis, myosis	Disruption of sympathetic fibers beginning at the hypothalamus down through the brainstem reticular formation
Millard–Gubler	Ipsilateral facial paralysis and contralateral paralysis of tongue and limbs	Pontine tegmentum
Foville	Ipsilateral facial paralysis and contralateral paralysis of tongue and limbs with paralysis of ipsilateral lateral rectus and conjugate ocular deviation	Pontine tegmentum
Brissaud–Sicard	Facial spasm and paralysis of contralateral limbs	Lateral pons
Nothnagel	Contralateral hemiataxia with possible ipsilateral cerebellar signs and external ophthalmoplegia	Dorsal midbrain involving tegmentum, brachium conjunctivum
Gasperini	Ipsilateral dysfunction of cranial nerves V through VIII with contralateral sensory disturbance and paresis of conjugate gaze toward side of cranial nerve dysfunction	Caudal and lateral pontine tegmentum
Babinski–Nageotte	Cerebellar ataxia, nystagmus, ipsilateral Horner and contralateral hemiparesis, and sensory loss	Pontomedullary junction
Vernet	Paralysis of soft palate and the muscles of swallowing and sternocleidomastoid with hemianesthesia of soft palate and upper pharynx and contralateral hemiparesis	Medulla oblongata

nuclei in an extremely small region of brain with very specific functions, symptoms involving the brainstem are often stereotyped and similar from patient to patient. Destruction of portions of the brainstem by vascular compromise results in well-recognized brainstem syndromes (table 4-2). Tumors may mimic some of these syndromes, but since tumors rarely follow isolated vascular distributions, the symptoms and findings may have features more or less associated with a specific syndrome. Occasionally a brainstem tumor, particularly if there is an exophytic component, can produce vascular compromise and result in one of the readily recognized syndromes.

If sufficient intracranial pressure is present from a supratentorial lesion, the brainstem may be compromised, but more often isolated cranial nerves will be affected. The most frequently affected are the oculomotor (CN III) and abducens (CN VI) nerves, leading to diplopia. This symptom is often due to the nerve being compressed or stretched as the brainstem is being displaced downward. If the pressure is producing a pressure-cone effect, then the symptoms are more vague, with headache, lethargy, and morning nausea and vomiting.³ If the pressure is sufficient, then other symptoms of brainstem compromise will be present such as respiratory and heart rate changes.

When these occur, there are often other clues that intracranial pressure is elevated secondary to a space-occupying lesion.

The hypothalamus has a major role in endocrine function, serving as the site of synthesis of many of the trophic hormones that control end-organ function. Tumors in this region notoriously affect endocrine function, often in unpredictable ways. Endocrine dysfunction may not only result from tumors in the hypothalamus, but may be seen with increased intracranial pressure producing an indirect effect on either the hypothalamus or the pituitary gland. The entire hypothalamic-pituitary system is sensitive to these changes. Most often the presenting symptom is secondary to decreased function. Maturation is also highly vulnerable to hypothalamic disturbances such that either premature or delayed maturation may occur.

Because of the close anatomic relationship of the hypothalamus, pituitary gland, and optic chiasm, tumors originating in any of these sites may produce effects in the adjacent structures. One of the more common tumors of childhood arising in this region is the craniopharyngioma. Typical features include headache, an inferior bitemporal hemianoptic visual loss, and endocrinopathies. Similar clinical findings may be seen with an optic nerve glioma, but these often produce more unilateral or unusual visual defects. Tumors of the pituitary fossa are extremely rare in children, with the chromophobe adenoma being the most common. If the lesion extends beyond the sella, the visual change is often a superior bitemporal hemianopsia (figure 4-1). The superior field cuts are more difficult for the patient or his parents to recognize until the loss begins to extend below the horizon.

Diabetes insipidus, a common symptom associated with a hypothalamic tumor, is fairly easily recognized, with large urine output and a concomitant increase in fluid intake. In childhood, this may take the form of nocturnal enuresis and/or frequency during waking hours. The increased intake becomes so apparent that even trying to deprive the child of water will

result in some very industrious means of getting water. While diabetes insipidus is occasionally seen in the preoperative phase of the illness, more often the symptoms and findings are seen in the postoperative period, and the patient must be observed for this treatable complication. When the symptom is subtle, it may be necessary to stress the child to confirm its presence. Most of the tests involve some form of water deprivation with monitoring for signs of dehydration. Chronic treatment has been made simpler by the use of vasopressin, which can be conveniently given by nasal spray (DDAVP), and dosing can be monitored by the patient or parents at home.

Both multiple endocrine adenomatosis I and II have higher incidences of tumors. Type I has been associated with pituitary adenomas, while type II has been seen with multiple neurofibromas. In the latter situation, there is occasionally an associated pheochromocytoma and/or thyroid medullary carcinoma.

Signs

WITHOUT SPECIFIC ANATOMIC SITE

Visual loss becomes easier to document as the child becomes older. With young infants and toddlers, suspicion of visual loss should lead to more exacting means of documentation. Ophthalmologic evaluation can result in fairly accurate measures of acuity and funduscopic exam may reveal atrophy, but neither of these observations are specific for any particular tumor, nor do they imply a specific anatomic location of the tumor. As discussed previously, field defects are often described by patients and parents as loss of vision of one eye. Examination of visual fields by confrontation in young children will demonstrate the field defect, but rarely will it be so well defined as to permit determination of whether the defect is congruous.

Assessing ocular motility may demonstrate an isolated third or sixth cranial defect, but as noted previously, these findings have little

localizing powers. The same holds true for pupillary changes, under most circumstances.

Papilledema has been long recognized as a sign of increased intracranial pressure, but does not localize the particular lesion or identify its histology.

Paralysis, whether of the upper or lower motor neuron, has limited localizing value. With lower motor changes, the involvement may be anywhere from the spinal cord to the peripheral myoneural junction. In most instances, lower motor neuron weakness is limited to particular motor groups that have more specific localization. Upper motor neuron types of paralysis or weakness may result from lesions anywhere above the spinal cord segment where the anterior horn cell axon is found. Usually the type of deficit is helpful in localization, since most lesions resulting in upper motor neuron findings will have hemiparetic, quadraparetic, or paraparetic distributions. In the hemiparetic, the lesion must reside above the cervical cord in the contralateral pyramidal tract. Quadraplegics will often have lesions of the upper cervical cord or other sites where both pyramidal tracts are in very close proximity. Quadraplegia may result from a diffuse process. Lesions resulting in paraplegia are almost always below the cervical cord.

Adventitious movements are usually manifestation of basal ganglia dysfunction. The most common is chorea, which has been seen frequently with basal ganglia tumors. With tumor or other structural lesions, chorea usually is unilateral, whereas with inflammatory processes it usually is bilateral. The other adventitious movements include tremor, rigidity, ballismus, and akinesia/bradykinesia, which occur less frequently but occasionally are seen with tumors.

WITH SPECIFIC ANATOMIC SITES

In the past, well-defined abnormalities on neurologic examination were of great help in localizing tumors, but now it is often easier to obtain computerized tomography (CT) and magnetic resonance imaging (MRI). However, before CT

or MRI is performed, a reasonable neurologic exam should be completed. Visual field testing, if performed with some care, can provide helpful information. Hemianoptic losses can be produced by a variety of extensive lesions. If the defect is complete and identical in both eyes, then the tumor may be residing anywhere along the optic pathways beyond the chiasm through the calcarine cortex. This has been termed a congruous homonymous hemianopsia. If the defect is incomplete and less congruous, then some refinement in localization can be accomplished. Each visual field from either eye begins as a more or less distinct tract after the chiasm and is segregated even within the lateral geniculate body. Distal to the geniculate body, the fibers begin to intermix until they ultimately merge at the calcarine cortex, the final destination of visual fibers. Therefore, the more congruous the particular field deficit is, the closer the lesion is to the cortex (figure 4-1). In adults and older children, it may be possible to determine this congruity, but as a practical issue, it has little value for diagnosis, especially in young children.

A distinct sensory and motor change can be seen with fairly complete blocks within the spinal canal. Lesions may interfere with autonomic pathways, resulting in an inability to perspire below the level of a block. This has been termed a *sweat level* and is assessed by running a hand over the surface of the trunk beginning in the gluteal region and moving cephalad. The areas below the block will be dry and no resistance to movement will be felt. As the hand reaches the normally innervated segments, more resistance will be encountered secondary to the presence of moisture on the skin. When the child is active and distressed, as he may be with a spinal cord lesion, this finding is even more exaggerated.

Findings Associated with Specific Tumors

Skin lesions in the form of pigmentary or vascular changes have been recognized as often

being part of neurocutaneous diseases. These diseases have also been associated with some very specific types of tumors. The cafe-au-lait spots and freckles not associated with solar burns are often the only external manifestation of neurofibromatosis. Neurofibromatosis has been associated with cutaneous neurofibromas and also central nervous system tumors, mostly astrocytomas. Of the neurofibromatosis-associated tumors, optic nerve gliomas are very common, while acoustic neuromas in children are rare. Spinal cord astrocytomas and neuroblastomas have also been reported. A tumor outside the nervous system that may have neurologic symptoms and be associated with neurofibromatosis is the pheochromocytoma. Elevated blood pressure may be sufficient to produce central nervous system symptoms such as headache.

Depigmented lesions are part of tuberous sclerosis. Usually the intracranial lesions of tuberous sclerosis are periventricular glial nodules or hamartomas that remain static, but occasionally these continue to grow and pathologically are giant-cell astrocytomas.

Cutaneous vascular lesions may be isolated and benign, but, if present in a patient with progressive neurologic symptoms, suggest an intracranial vascular tumor. When there are multiple vascular lesions, including retinal lesions, this may be part of the von Hippel-Lindau syndrome and associated with cerebellar hemangioblastomas. Similar vascular tumors have also been noted in other sites of the nervous system. When the cutaneous vascular lesion involves the face, it is often part of Sturge-Weber syndrome. This is frequently associated with focal seizures having their origin in the underlying cortex, where the typical "railroad track" calcifications are seen radiographically. While not common, other vascular tumors and malformations have been seen with Sturge-Weber.

Skin lesions of the basal cell nevi syndrome identify children at greater risk of developing medulloblastoma. Other characteristics of this

entity are retardation and skeletal anomalies.

Oral and oral-labial papillomas have been labeled *Cowden's syndrome* and are associated with meningiomas.

Diabetes insipidus has been seen with almost all hypothalamic tumors, but in two it is classically found—craniopharyngiomas and histiocytosis X. Diabetes insipidus appears early in the spectrum of symptoms and may precede other symptoms.

Limitation of upward gaze has been termed *Parinaud's phenomenon* and is associated with increased intracranial pressure, particularly when there has been hydrocephalus and dilation of the posterior third ventricle. Tumors of the pineal region that compress the collicular plate will also have associated Parinaud's.

Tumors outside the nervous system may produce neurologic symptoms and signs in the absence of metastases. This has frequently been observed in adults as part of a paraneoplastic syndrome, but a fairly common tumor of young children also produces a characteristic neurologic syndrome. Infants with neuroblastoma may have unusual eye movements termed *opsoclonus* or *dancing eyes*. It occurs without evidence of tumor within the central nervous system. Many other unusual movements have also been seen with neuroblastoma. Whenever the evaluation of a child with ataxia, myoclonus, and ocular mobility problems fails to reveal a lesion within the central nervous system, neuroblastoma should be considered. Most have been in the thorax, with the second most common site being the abdomen.

Neurologic Examination

The purpose of the neurologic examination is to make a diagnosis and localize the disease process within the nervous system [4]. The exam begins with a history that should be spontaneous, allowing the patient or parent(s) to describe their observations in their terms. Then the physician should try to refine the

symptom(s) into a medical scheme that has more meaning for localization.

The essence of the history in a patient with a brain tumor is change. Typically, the child was normal until a specific change became apparent, and thereafter, progressive symptoms become more evident. Other neurologic illnesses, such as degenerative diseases, may produce similar changes and initially may be difficult to distinguish from tumors. Additional history will often direct the physician toward a suspected tumor. Other nonspecific features, but with decreasing reliability, include headache, paralysis, focal seizures, visual disturbances, coordination disturbances, speech and language problems, intellectual changes, and personality changes. It should be remembered that these symptoms may be seen with a variety of illnesses, and it becomes incumbent on the physician to draw upon clinical judgment to arrive at the correct diagnosis. Past medical history and family history may add more information to help develop a stronger case for one or another illness, but ultimately the patient must be examined.

Examining a child should include a general physical examination as well as a neurologic one. Findings on the general exam may result in a definitive diagnosis even though localization will still require a neurologic exam. Examples of this include the child with numerous cafe-au-lait spots with progressive blindness (neurofibromatosis and optic nerve glioma), the child with facial and retinal hemangioma and cerebellar dysfunction (von Hippel-Lindau and cerebellar hemangioblastoma), and the young child with an abdominal mass and ocular bobbing (neuroblastoma). The general exam should also include vital signs, auscultation of the head, and head circumference. The latter is especially important with younger children.

The neurologic examination should not be intimidating to the pediatrician or oncologist, and it does not necessarily have to be performed by a child neurologist. Unfortunately, the

further from neurologic training the physician is, the less confident he may be in his findings on the neurologic exam. As this confidence falls, so does the reliability of the exam.

With older children, the traditional neurologic exam routinely performed on adults is applicable and often easily accomplished. With younger, frightened, and less cooperative children, the exam must be modified to obtain the greatest amount of meaningful information [5]. The traditional exam approaches the patient's nervous system by assessing individual components and then combining the components to arrive at a specific diagnosis and location of disease. The exam evaluates cranial nerves, motor system, sensory system, reflexes, and cerebellar function. Table 4-3 describes the components of each of these particular subdivisions.

Another aspect of the exam that is difficult to address briefly is higher cortical function. Most physicians assess this in a casual manner and often use some easily performed tests during a routine exam such as recall of simple objects, following simple directions, simple mathematic processes, knowledge of current events, and orientation. Even in older children these assessments are very superficial and occasionally misleading. Historical information from the school may be helpful. In younger children, even the history of intellectual function measured either by parents or by teachers is not reliable. Objective assessment of intellectual skills in the clinic setting is difficult. Because the assessment is performed in an unusual environment, the results will likely be an underestimate of the actual skill. Many factors may result in a poorer performance than that of which the child is capable, while nothing will cause a child to perform at a level greater than that of which he is capable. In cases where there is a marked discrepancy between a child's actual and expected performance, it is then possible to make a definitive statement from the clinical assessment regarding intellectual function.

TABLE 4-3. Neurologic examination by system with clinical assessment

System	Function/Assessment
<i>Cranial</i>	
I Olfactory	Smell
II Optic	Vision, fields, and funduscopy
III Oculomotor	Eye movements: vertical and medially Pupil reactivity: light and accommodation
IV Trochlear	Eye movements: medially and down
V Trigeminal	Facial sensation and jaw closure
VI Abducens	Eye movements: laterally
VII Facial	Facial movements and taste
VIII Auditory	Hearing and vestibular function
IX Glossopharyngeal	Sensation of palate and pharynx and taste
X Vagus	Motor of palate and pharynx
XI Spinal accessory	Shoulder and neck muscles
XII Hypoglossal	Tongue movements
<i>Motor</i>	
Tone	Resistance to passive movement: hypotonia, spasticity
Strength	Movement against resistance: lower motor effects
Movements	Abnormal and extraneous movements: chorea, dystonia, athetosis, tremor, myoclonus
<i>Sensory</i>	
Primary	Temperature, pain, light touch
Posterior column	Position, vibratory, deep pain
Cortical	Graphesthesia, two-point discrimination
<i>Reflexes</i>	
Stretch	Tendon reflexes at joints
Pathologic	Toe signs and persistent developmental
<i>Cerebellar</i>	
Posture	Tremor, titubation, hypotonia
Gait	Tandem, broad-based
Synergy	Smoothness of movement
Meter	Underreaching or overreaching
Speech	Fluency and clarity

More often, the child will be closer to normal, and small changes are hard to recognize.

Most physicians, and particularly neurologists, feel that if a neurologic exam is to be performed, it must be complete without skipping any component. In young children, and probably even in adults, a pertinent exam is acceptable as long as it is accurate and provides meaningful information that will result in the correct diagnosis. There are many components of the exam that are uncomfortable for the

patient and that are rarely of much value except for special situations. Examples of these include corneal sensation and pain recognition. Generally, the sensory exam in very young children is difficult and not very helpful unless there is possible dysfunction from a particular illness or anatomic lesion. Then the exam should be performed in a compassionate and gentle manner with the testing beginning in the area where it is suspected that there is significant loss and then progressing toward areas where

sensation should be normal. Signs of uneasiness in the child usually indicate that an area of normal sensation has been reached. The child should not observe testing for pain sensation, since visual observation will often result in a misleading response.

Infants, toddlers, and frightened children pose the greatest challenge to the clinician. Encroaching on their space, particularly by touching or holding, will almost always assure an unsuccessful exam. Allowing the child to receive the comfort and "protection" that a parent can provide will serve the examiner well. Relying on perhaps less information than might be obtained by the more traditional type of exam, but with patience, the examiner can learn surprisingly more than might have been predicted. Observation and opportunism are the keys to success. Much can be learned by watching the child. Playing with small objects and even introducing smaller objects will give some measure of visual acuity. Presenting the object from various fields and watching for a change of attention and visual fixation will also give a clue as to fullness of visual fields. Most authorities recommend that the funduscopic exam be deferred until late in the session. Frequently, when the child is still relaxed in the lap or arms of a parent, the fundi are easiest to visualize. If possible, not touching the child improves chances of success. The more the child is touched or held by the examiner, the less likely will be a successful funduscopic exam. As objects and toys are introduced, observing ocular motility will provide information regarding third- and sixth-nerve function. If the child is eating, then normal chewing and swallowing indicate that the fifth, ninth, tenth, and twelfth cranial nerves are probably functioning normally. Facial mobility and eye closure with blinking indicate that the seventh nerve is functioning well. Speech is another indicator of ninth-, tenth-, and twelfth-nerve function, but it also indicates that coordination of bulbar function is intact and eliminates significant apraxia as well as bulbar dysfunction. Apraxia is the

inability to carry out purposeful movements in the absence of motor or sensory impairment. If the language content is also appropriate for age, then some assessment of cortical function has been completed.

Motor function testing can be partially performed by watching how the child plays with toys. The smoothness of movements also provides information regarding cerebellar function. How a child uses his or her hands and the type of thumb and finger placement on small objects can also indicate developmental level. Sitting and standing provide information regarding development as well as strength. Resisting the removal of a toy is a measure of hand strength. Tone assessment requires a quiet and relaxed child. This may be best done by examining the child in a parent's lap. Lower-extremity motor functions can be assessed by allowing the child to walk and run. Adventitious movements are frequently noticeable as the child sits quietly, and some cerebellar function can be evaluated as the child becomes more active and participates in simple clinic games.

There are no simple methods to test reflexes. Pathologic reflexes can be tested without discomfort. Notoriously these are performed using a noxious stimulus stroked up the foot. Most child neurologists have discovered that the same information can be obtained with a simple gentle stroke upon the sole. In the same light, if a sensory exam is pertinent, then it too can be done gently by remembering to assess areas of suspected deficit first and then to progress towards areas of normal sensation.

A special problem exists in assessing infants and young children. We tend to assume that all patients should be able to perform motor and language skills equally well. The young child may not have reached the developmental level necessary for that skill, and so we must recognize that expectations should be appropriate for the child's age. Knowing this will also allow recognition of a persistent, more primitive reflex or behavior that should have disappeared by the child's chronologic age.

Diagnostic Procedures

With the improvements in imaging technology that have occurred over the past two decades, some long-standing diagnostic studies are now of limited value. In many ways, the newer methods are providing more and better information with less discomfort and danger to the patient. Today, pneumoencephalograms are almost unheard of, and most recent neurology graduates have never seen this procedure, let alone performed one. There have also been some tradeoffs with the newer procedures. Because some studies were uncomfortable for the patient and not always diagnostic, clinicians had a greater respect for selection and performance of each test. Today we perform almost all of the newer tests with less selectivity and repeat them after short intervals if the initial study is negative.

The studies available range from neuropsychologic to electrophysiologic to imaging and finally to assays of body fluids such as cerebrospinal fluid (CSF). The first group is becoming more important, since we are now beginning to see more survivors, and concerns are being raised as to the long-term sequelae of therapy. In some rare instances, presurgical neuropsychologic assessments may be performed. There is little evidence that any of the neuropsychologic tests have ever provided sufficient information to be categorized as a specific diagnostic test for brain tumors.

Classically, the neurophysiologic tests were the mainstay of neurologic diagnosis. Their use faded somewhat with the newer imaging methods, but they still may be helpful. As noninvasive tests, they may provide enough information to warrant further investigation, and if negative may eliminate the need for other studies. An example of this is the evaluation of headaches, a frequent problem of children. The most utilized of the neurophysiologic tests is the electroencephalogram (EEG). Changes demonstrated may be subtle, such as asymmetric slowing, to more obvious, such as focal slowing and surrounding spikes (table 4-4). The latter changes clearly point out a very localized lesion with destructive changes and irritability surrounding it. Whether this represents a tumor cannot be stated unequivocally, but it would clearly suggest the possibility. The EEG only directs thinking toward possible diagnosis, and further investigation is necessary to make a definitive diagnosis.

Another group of tests are the evoked potentials. These include somatosensory, auditory, and visual. The first is uncomfortable and may have value in assessing spinal cord lesions and monitoring spinal cord and posterior fossa surgery, but adds little, if anything, to confirm the diagnosis of a spinal cord tumor. Auditory evoked potentials have been proposed as a test to confirm a brainstem tumor, but the clinical exam coupled with imaging studies are clearly sufficient. On those occasions where surgery is

TABLE 4-4. Seizure type with electroencephalographic features

Seizure type	Electroencephalographic features
Generalized	Generalized replacement of background activity with symmetric repetitive spikes followed by generalized slowing
Focal	Localized spike- and/or slow-wave discharge that may spread to become generalized
Absence	Generalized synchronous spike-wave discharge, usually three per second, replacing a normal background and often provoked by hyperventilation
Partial, complex	Localized spike- and/or slow-wave discharge that may spread to become generalized when a seizure occurs
Partial, simple	Localized spike- and/or slow-wave discharge that remains confined even during a clinical seizure and usually in the temporal lobe

undertaken for diagnosis and treatment, then auditory and somatosensory potentials may help detect changes during surgery that may limit or allow greater resections. Preoperative studies may be helpful, since the deficits seen at surgery and including positioning of the head would be recognized earlier.

Electromyography (EMG) has very limited value in arriving at a diagnosis of brain or spinal cord tumors. Once a spinal cord tumor is diagnosed, then looking for its extent up and down the cord might be augmented with EMG, but the need for myelography will not be eliminated.

Imaging has progressed dramatically from plain skull films in the past two decades. The changes of split sutures and luckenschadel, which were signs of increased intracranial pressure, have been replaced by ultrasonic studies in young infants and CT and MRI in all children. The standard today is rapidly becoming the MRI scan, and with the use of Gadolinium enhancement, more specific information regarding tumor type will be possible. CT with contrast will still have a significant role in preoperative diagnosis and post-operative follow-up. Other limits of MRI include the need for the patient to remain immobile during the procedure, which may take upwards of an hour. Sedation and anesthesia under these conditions is often complicated. While ultrasound is logistically easier to perform under a variety of conditions, it is not as definitive as either CT or MRI. Lesions found with this modality require further studies. Over time, with increasing confidence in CT and MRI, the use of angiography has declined. Certainly there are conditions where it can be helpful, but these are few and are related to suspected vascular tumors and malformations. Even myelography may become obsolete with better MRI. Newer and higher-power magnets will provide better resolution of the cord and its surrounding elements, and may eventually replace myelography. This would eliminate the

discomfort and even the slight risk of increasing a spinal cord deficit with a spinal tap.

The study of CSF in brain tumors has proven to be of some value [6]. Few consistent markers have been found that are sufficiently diagnostic to eliminate the need for other studies, including biopsy. Some tumors are known to secrete polyamines, and follow-up CSF studies after treatment have measured these compounds. If elevated, recurrent tumor is likely. The enthusiasm for this procedure appears to be declining. Studies are also underway exploring whether or not treatment of tumors that produce elevated levels of polyamines might respond to chemotherapy directed at reducing polyamine production. Other tests on spinal fluid may be informative, but rarely diagnostic. CSF cytology has been used frequently in follow-up of leukemics, and is often sufficient to document relapse. CNS tumors occasionally will shed cells that will be found with examination of CSF, but prior to diagnosis, these cells can only be used as a suspicious marker and increase the possibility of the tumor being a medulloblastoma or ependymoma. In any instance where there is a suspicion of increased intracranial pressure, performing a spinal tap is not risk-free. The incidence of herniation after a spinal tap in patients with elevated pressure from a brain tumor is less than 5%. Thus, if other studies are definitively, a spinal tap poses an unnecessary risk [7].

Some of the newer and unproven tests include position emission tomography (PET). Predictably, this will be used more frequently in those institutions where it is available, but it is unlikely that PET will lead to earlier diagnosis. From an investigational standpoint, we may acquire considerable insight into tumor biology by studying the metabolism of these tumors both in vivo as well as in vitro. Both MRI and PET offer this possibility.

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5. ENDOCRINE AND SYSTEMIC MANIFESTATION OF BRAIN TUMORS IN CHILDREN

Silva Arslanian

Thomas P. Foley, Jr.

Peter A. Lee

After leukemias, brain tumors are the second most common malignancy of childhood. Tumors within or above the sella turcica often profoundly alter endocrine function through involvement of the hypothalamic–pituitary axis. Tumors remote from the hypothalamic–pituitary axis may produce endocrine dysfunction by infiltration to the axis or through increased intracranial pressure. Metastatic malignancy in the pituitary associated with disseminated neoplasms is rare during childhood, occurring more frequently among adults. However, in children the most common malignancies associated with metastasis to the pituitary are histiocytosis X, leukemia, and lymphoma. Cranial irradiation for childhood head and neck tumors and leukemias are becoming a more frequent cause of acquired hypopituitarism.

Evaluation of the endocrine function of the hypothalamus and pituitary is indicated in three groups of children. The first consists of patients with signs and symptoms consistent with dysfunction involving the anterior or posterior pituitary lobes. A second group of patients requiring investigation is composed of those discovered to have radiologic evidence of space-occupying lesion in the hypothalamic–pituitary region. These patients often present to the

neurologist or ophthalmologist with neurologic evidence of a space-occupying lesion in the hypothalamus or pituitary. A third group of patients in need of endocrine evaluation is made up of those who have completed brain tumor therapy, whether it has involved surgery, radiotherapy, chemotherapy, or any combination modality. In our experience, among 42 patients with hypopituitarism associated with brain tumors, 12 patients (29%) initially presented to the endocrinologist with symptoms and signs of hypothalamic–pituitary deficiency, 14 patients (33%) were evaluated just prior to surgery because of the diagnosis of brain tumor, and 16 patients (38%) were seen in consultation after surgery [1].

In this chapter, we will outline the more common varieties of intracranial tumors that are associated with hypothalamic–pituitary dysfunction in children, as well as the endocrine and systemic manifestations of these tumors, their diagnostic evaluation, and management strategies.

Endocrine Dysfunction

The three major symptoms of juxtasellar or intrasellar masses are headaches and, because of the anatomic location of these tumors, dis-

turbances of vision and endocrine dysfunction [2, 3]. A discussion of nonendocrine-related manifestations is not within the realm of this chapter.

Intrasellar and suprasellar neoplasms disturb endocrine function through involvement of the hypothalamus, the pituitary gland, or both. The clinical manifestations of endocrine dysfunction are classified according to inadequate or excessive hormone production and correlation with clinical findings. Hypopituitarism can involve one, several, or all hormones. Generalized hormone deficiency is usually attributable to tissue destruction by tumors or infiltrative conditions. Hypothalamic abnormalities may cause generalized hypopituitarism or may involve only selective releasing factors and hormones. Increased hormone production, which occurs rarely, may be due to functioning pituitary adenomas or to excessive stimulation of a normal pituitary gland by hypothalamic-releasing hormones or deficiency of hypothalamic-inhibiting factors. A brief summary of the most significant clinical manifestations of hypothalamic-pituitary hormonal deficiency or excess follows.

HORMONE DEFICIENCY

1. Growth hormone (GH) deficiency is characterized by short stature, a subnormal growth velocity of less than 4 cm/year over at least one year (figure 5-1), and a delay in skeletal maturation. In the very young child, less than two years of age, recurrent hypoglycemic episodes may be the presenting symptom of GH deficiency, before abnormalities of growth become apparent.

2. Thyroid-stimulating hormone (TSH) deficiency causes hypothyroidism with subtle and slowly progressing clinical signs and symptoms that include weakness, lethargy, pallor of skin, edema of eyelids, cold intolerance, and constipation. In the postpubertal female patient, TSH deficiency might be responsible for menorrhagia. A reduction in growth velocity

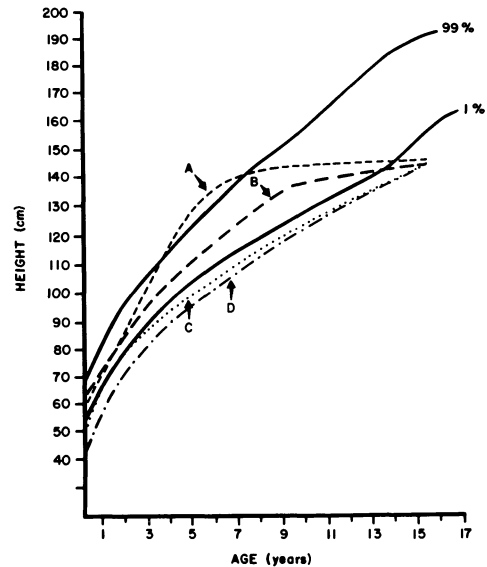


FIGURE 5-1. Examples of four growth curves during childhood that result in short stature after age 15 years. Curve A, small dashed lines, is representative of accelerated growth during early childhood, but cessation of growth around age eight years; this curve is seen in children with precocious puberty that begins between ages two and three years. Curve B, large dashed lines, is representative of abnormal growth that developed at age nine years; the growth rate before age nine years was normal, since the curve was parallel to the normal first and ninety-ninth percentile curves. This curve is seen in children with acquired disease that caused deficiencies in the secretion of GH or thyroid hormones, or an excess in the secretion of ACTH or hydrocortisone. Curve C, the dotted line, is representative of a child with normal growth during infancy, mild growth deceleration around age 2 to 3 years, and normal linear growth rate with short stature thereafter. This curve is seen in normal children with constitutional delay of growth and adolescence. Curve D, the dash-dot line, is representative of children who are short at birth and remain short throughout childhood. The linear growth rate is normal, indicative of normal hormonal secretion. This curve is seen in children with abnormalities of fetal growth for various reasons. (Reproduced with permission from the design by S. Peter Nissley, M.D.)

or cessation of growth in a previously normal child is of particular importance and may be indicative of acquired growth hormone and/or thyroid hormone deficiency (figure 5-1).

3. Adrenocorticotrophic hormone (ACTH) deficiency: If suppression of the hypothalamic–pituitary axis by exogenous glucocorticoids is excluded, tumors of the hypothalamic–pituitary region are the most common cause of pituitary ACTH deficiency. In such cases, other pituitary deficiencies coexist and usually precede or follow the loss of ACTH reserve. Patients with secondary adrenal insufficiency are not hyperpigmented but otherwise have clinical features similar but usually more mild than those seen in patients with Addison's disease. However, since mineralocorticoid secretion is maintained, electrolyte abnormalities, orthostasis, and hypotension are less frequent. While the clinical symptoms are usually chronic, an acute presentation can occur in the undiagnosed patient during stress or in treated patients who do not receive proper steroid coverage during surgery or infection.

4. Gonadotropin deficiency manifests itself at the time of puberty as lack of sexual development and arrest or regression of pubertal changes. In the older female patient, it may manifest itself by cessation of menses.

5. Antidiuretic hormone (ADH) deficiency: Destruction of at least 80% of arginine vasopressin (AVP)-synthesizing neurons is necessary before polyuria occurs. After symptoms occur and before diagnosis, patients with ADH deficiency and no other hypothalamic disturbance may rely upon their thirst mechanism to maintain water homeostasis. Patients with central nervous system (CNS) tumors may have diabetes insipidus present and diagnosable before treatment. Most commonly, however, diabetes insipidus becomes manifest during or within hours after surgery with acute onset of polyuria, polydipsia, hypernatremia, hyperosmolality, and diminished renal concentrating ability.

HORMONE EXCESS

1. GH excess is rare in pediatrics. In the majority of cases, it is due to a somatotroph adenoma. When this condition begins during childhood, a time when open epiphyses permit exaggerated skeletal growth, it presents with the findings of overgrowth known as gigantism. Recently in a small percentage of adult patients, acromegaly has been described in association with carcinoid tumors of either the pancreas or the lung; these tumors secrete GH-releasing factor and cause somatotroph hyperplasia rather than a true adenoma of the pituitary.

2. TSH hypersecretion is very rare and causes clinical symptoms of thyrotoxicosis. In children these symptoms include sleep restlessness, poor school performance, nervousness, and increased appetite with or without weight loss.

3. ACTH excess: Cushing's syndrome refers to a group of symptoms and signs that occur as a result of increased circulating concentrations of cortisol from any cause. The eponym *Cushing's disease* applies only to cases of hypercortisolism of pituitary or hypothalamic origin. Thus, it is ACTH-dependent. Cushing's disease is uncommon in childhood. The clinical manifestations of chronic hypercortisolism are progressive obesity producing a rounded face, prominent cheeks, double chin, and a "buffalo hump." Contrary to the findings in adults, children have generalized obesity, and the muscular wasting in the limbs is not as evident. The face is plethoric and striae are common over the abdomen, buttocks, and thighs. Frontal and temporal hairlines are low, and there is often a growth of downy hair over the back and arms. Mild hypertension and glucose intolerance are common. Sustained hypercortisolism profoundly affects growth. Short stature and obesity may be the only presenting features of Cushing's syndrome in the child (figure 5-1). Osteoporosis, hypercalciuria, and renal calculi can also result from prolonged hypercortisolism.

4. Precocious puberty: True or complete pre-

precocious puberty indicates an activation of the hypothalamic–pituitary–gonadal axis at an unusually young age. In precocious sexual development, an increase in circulating sex steroids will be found, together with accelerated physical growth (figure 5-1) and bone maturation. In girls, breast budding and progressive enlargement, sexual hair growth, and eventually menses will occur, while in boys, progressive testicular and penile enlargement and sexual hair growth will take place. Between 50% and 70% of boys with precocious puberty have a space-occupying lesion of the CNS, most commonly localized in the posterior hypothalamus, the pineal gland, or the median eminence, or one which exerts pressure on the floor of the third ventricle. These tumors are generally hamartomas, teratomas, gliomas, or germinomas, but occasionally may be optic gliomas and astrocytomas.

5. Hyperprolactinemia is responsible for a significant amount of reproductive and sexual dysfunction in the human. It has recently been suggested that hyperprolactinemia is the most common hypothalamic–pituitary disorder currently recognized in adults: of all pituitary tumors, 40% are prolactinomas. However, prolactinomas are rare in children, and hyperprolactinemia may presumably be due to compression of the pituitary stalk and disruption of the tonic inhibition of prolactin by dopamine from the hypothalamus.

Tumors in the Hypothalamic–Pituitary Area

CRANIOPHARYNGIOMA

Craniopharyngioma is the most common brain tumor associated with hypothalamic–pituitary dysfunction in childhood. It arises in the pituitary stalk from residual cells of Rathke's pouch. Although present at birth, the tumor grows very slowly and may not give rise to symptoms or signs for years. In reviewing 1002 cases from the world's literature, Banna found the greatest

frequency of presentation to be in the first two decades of life [4]. Within these ages the peak occurrence has been found to be at eight years with smaller peaks at four and 13 years [5].

The duration of the clinical history is variable, being rarely as short as days, not uncommonly as long as several years, and in most cases encompassing several months. In a study of 42 children with craniopharyngioma, clinical symptoms were present before diagnosis for a mean of 14 months but ranged from one day to 48 months [6]. In about 45% of cases, the tumor is confined to the suprasellar region; in the rest, it involves both suprasellar and intrasellar structures [7]. The tumor mass grows forward to compress the optic chiasm, downward to compress the pituitary gland, and upward to impinge on the third ventricle. Thus, the clinical picture largely depends upon the size of the tumor and the extent of involvement of neighboring structures. It is rare for patients to present initially with endocrine disorders and more usual for the neurological symptoms to be the principal and earliest manifestations [6–8]. However, it is not unusual for patients with craniopharyngioma to present to the endocrinologist because of symptoms related to hypopituitarism, particularly growth failure (figure 5-1). Figure 5-2A depicts the growth pattern of a 14-year-old girl who presented initially for evaluation of short stature, and was found to have a calcified craniopharyngioma (figure 5-2B). Signs and symptoms of endocrine dysfunction are the reason for initially seeking medical action in 7%–25% of patients with craniopharyngioma [5, 6, 9].

In the Endocrine Clinic of Children's Hospital of Pittsburgh, slightly more than half of the patients with organic hypopituitarism have craniopharyngiomas. Of those, 56% presented initially for evaluation of signs and symptoms related to hypothalamic–pituitary dysfunction. Short stature or deceleration of linear growth is the most frequent complaint, followed by polyuria and polydipsia in the prepubertal age group and hypogonadism with delayed puberty

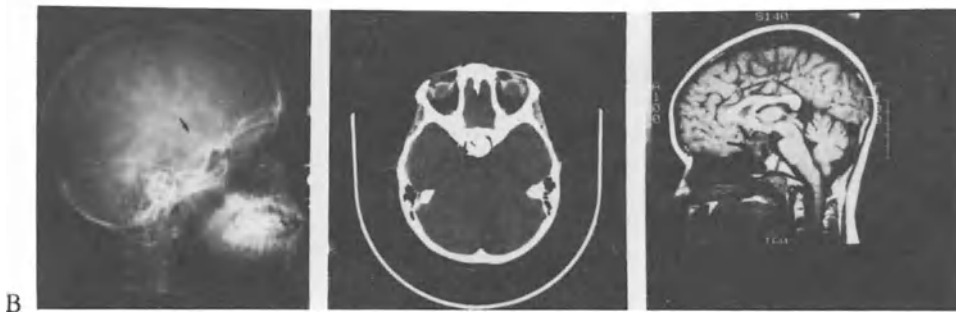
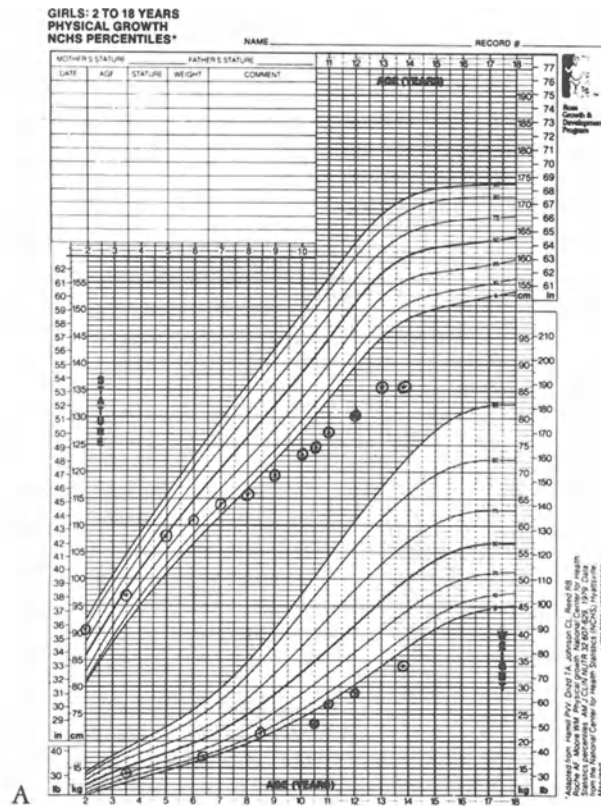


FIGURE 5-2. A. Growth curve of a patient with craniopharyngioma. B. Skull X-ray, CT scan, and MRI of the same patient, demonstrating a calcified craniopharyngioma (arrows).

in the postpubertal age group. Growth failure with delayed bone maturation is secondary to hypothalamic–pituitary GH deficiency with or without TSH deficiency. Polyuria and poly-

dipsia are due to ADH deficiency, which may result in partial or complete diabetes insipidus. Gonadotropin deficiency becomes manifest only at or after the age of puberty. It presents with lack of pubertal development or progression, or primary or secondary amenorrhea. Gonadotropin deficiency is inapparent and undiagnosable in the prepubertal child. Symptoms related to

ACTH deficiency with resultant hypocortisolism are usually vague, consisting of fatigue, lethargy, or lack of energy that is frequently attributed to nonendocrine causes. The degree of ACTH deficiency is rarely severe enough for the patient to present initially in adrenal crisis, or to interfere with normal glucose homeostasis leading to clinical hypoglycemia. Approximately one third of children with craniopharyngioma will have signs and symptoms indicative of endocrine dysfunction (table 5-1), although in a small proportion of them, this will be the initial presenting complaint [1, 3, 5, 6, 9–13].

Table 5-2 cites the reported incidence of hypothalamic–pituitary hormonal deficiency before any tumor treatment intervention [1, 6, 12]. The most common hypothalamic–pituitary abnormality on initial evaluation of children with craniopharyngioma is GH deficiency, present in about 80% of cases. The next most common abnormalities are corticotropin and

gonadotropin deficiency. The frequency of the latter cannot be accurately determined, since many patients are appropriately prepubertal in development at the time of peak tumor occurrence, which is around eight years of age. Deficiencies of TSH and ADH are present, but are much less common. Unlike all other pituitary hormones, prolactin secretion, which is controlled by a tonic dopaminergic inhibitory influence of the hypothalamus, tends to be only moderately increased or normal in children with craniopharyngioma, even though the hypothalamus is frequently compressed by the tumor [12, 14]. Occasionally the hyperprolactinemia accounts for the clinical presentation of the patient with amenorrhea and galactorrhea.

GERMINOMA

Germinomas are germ-cell tumors identical to seminomas of the testis and dysgerminomas of the ovary. They may be found in the pineal

TABLE 5-1. Principal signs and symptoms of endocrine dysfunction at presentation: Craniopharyngioma

Study	Percentage of patients		
	Retarded growth	DI	Hypogonadism
Matson et al., 1969	38	9	
Hoff et al., 1972	25	25	50
Banna et al., 1973	42	12	20
Thomsett et al., 1980	45	2	
Newman et al., 1981		9	
Carmel et al., 1982	30	9	
Sung et al., 1982	33	7	10
Calvo et al., 1983	22	27	16
Arslanian et al., 1985	50	22	
Mean	36	14	24

TABLE 5-2. Hypothalamic–pituitary hormone deficiency in children with craniopharyngioma at presentation

Study	Percentage of patients				
	GH	FSH/LH	ACTH	TSH	ADH
Newman et al., 1980	67	33	50	13	10
Thomsett et al., 1980	72	38	24	24	17
Arslanian et al., 1985	94	50	47	33	17
Mean	78	40	40	23	15

gland region and are often erroneously called *pinealoma*, or in the suprasellar region and improperly called *ectopic pinealomas* [15, 16]. In 1947, in a classic paper, Friedman concluded that most pineal and suprasellar tumors producing pineal tumor structures were identical to testicular and ovarian germ-cell tumors. He proposed that they be called germinomas. The belief that most pineal and suprasellar tumors resembling pinealomas are of germinal origin has received further support by other investigators who have verified the histological identity of these tumors with seminomas and tumors of the ovaries [17, 18]. Germinomas occur more commonly during the second decade of life, and those located within the suprasellar-hypothalamic region do not exhibit a sex predominance. Germinomas of the pineal occur mainly in males, especially between 10 and 15 years of age [19–22]. Because of their proximity to the hypothalamus, germinomas are often manifested by abnormalities of the neuroendocrine system well before symptoms and signs indicating involvement of the central nervous system and before they can be detected radiologically. Over the years, a characteristic clinical triad for CNS germinomas has become apparent. The components of this triad are diabetes insipidus (DI) as the first symptom and anterior pituitary dysfunction and visual disturbance with few or no radiological signs of CNS involvement. Table 5-3 presents the frequency of endocrine manifestations in patients with CNS germinomas [22–26].

It is important to emphasize that diabetes insipidus is the most frequent symptom, present in about 80% of the patients; in more than half of them, it may be the first symptom. Additionally, the time lag between the first signs of polyuria and the discovery of the tumor must be emphasized. In a series of 14 histologically proven germinomas, the CT scan was initially normal in six. Repeated studies led to their detection 1 to 3 years later [26]. In these cases, diagnosis of the tumor and of its origin is difficult. In such cases, the presence of tumor markers takes on an important diagnostic significance because the sole treatment of these tumors is radiotherapy. The tumor markers studied in patients with germinomas are 1) human chorionic gonadotropin (hCG) in plasma and in the spinal fluid when possible (this is the tumor marker of trophoblastic cells), and 2) alpha-fetoprotein in plasma, which is the tumor marker of endodermal sinus cells. In one study, 2 of 6 patients with normal first neuroradiological examination had an elevated plasma hCG. Plasma concentrations of hCG increased when the tumor became visible on computed tomography (CT) scan after a lag time of one year [27].

Varying degrees of anterior pituitary dysfunction are present before treatment in patients with germinomas. GH deficiency is the most common anterior pituitary abnormality with or without TSH and ACTH deficiency [19, 23, 24, 28, 29]. Hypogonadotropic hypogonadism

TABLE 5-3. Frequency of endocrine dysfunction in patients with germinoma

Study	Percentage of patients			
	DI	Retarded growth	Hypogonadism	Hypothalamic dysfunction
Takevchi et al., 1978	83	39	17	28
Izquierdo et al., 1979	85			38
Sklar et al., 1981	70	50	20	40
Sung 1982	75	33	25	
Pomarede et al., 1982	100	36	0	73
Total	83%	40%	16%	45%

is more frequently encountered than precocious puberty; it occurs as pseudoprecocious puberty secondary to the ectopic production of hCG by the tumor cells, rather than true precocious puberty. The sexual precocity has been limited almost exclusively to males [24, 30–32]. Since ovarian follicular development depends upon stimulation by both luteinizing hormone (LH) and Follicle-stimulating hormone (FSH), the LH properties of hCG alone should not be capable of producing true precocious puberty in females. This is further supported by the reports of hCG-secreting tumors that did not result in signs of sexual precocity in prepubertal females [33, 34].

Multiple abnormalities of hypothalamic function have been reported in patients with CNS germinomas. The most common are hypodipsia, or adipsia and less commonly hyperphagia and obesity [22–24, 29, 34]. These symptoms are thought to be secondary to destruction of the ventromedial hypothalamus.

TUMORS OF OPTIC PATHWAYS AND HYPOTHALAMUS

Tumors presenting near the optic chiasm, pituitary region, and hypothalamic region account for almost half of tumors in the supratentorial compartment. After craniopharyngiomas, gliomas are the second most frequent tumors encountered in this region [35, 36]. These tumors arise in the optic apparatus, either anterior (prechiasmatic/retro-orbital), chiasmatic, or posterior (postchiasmatic, hypothalamic). There is general agreement that these tumors are pilocytic astrocytomas that may be extremely slow-growing, with occasional cystic changes and malignant degeneration.

Visual abnormalities are the most common presenting complaint, followed by headaches and hypothalamic dysfunction. The latter is more frequent with posteriorly located lesions of the chiasm and the hypothalamus. The endocrinopathy is characterized by two distinct clinical presentations: precocious puberty and the diencephalic syndrome.

The incidence of precocious puberty associated with optic gliomas has been reported to vary between 12.5%–22.5% [37–40]. The mechanism underlying the sexual precocity has not been well documented. In the case of gliomas of the chiasm with a posterior location, the mechanism may be similar to that of precocious puberty from hypothalamic hamartoma involving the tuber cinereum and the median eminence [41]. An intrinsic neurosecretory production capable of inducing precocious puberty has been hypothesized in *slow-growing hamartomas* and gliomas [42, 43]. Indeed some hypothalamic hamartomas have been demonstrated to be a source of luteinizing-hormone-releasing factor (LRF) and ultrastructurally, have been shown to be composed of unipolar and bipolar cells interspersed among glial cells and to contain membrane-bound electron-dense granules giving a positive fluorescence with LRF antiserum [44, 45].

The diencephalic syndrome was initially described by Russell in 1951 [46]. In its broadest definition, it comprises a diencephalic tumor with emaciation and minimal neurological signs. The characteristic signs are extreme emaciation, hyperkinesis, alert appearance, vomiting, inappropriate euphoria, and nystagmus with decreased visual acuity [47–50]. The majority of reported cases have been in children less than one year of age, and therefore the syndrome has since been referred to as the *diencephalic syndrome of infancy*. The type of emaciation seen with these tumors does not appear to be limited to infancy, since a similar cachexia occurs in older patients with anorexia nervosa and hypothalamic glioma [51]. In a review of 67 cases of diencephalic syndrome, 16% of the tumors were reported as gliomas, and another 15% as “spongioblastoma, ganglioglioma and dysgerminoma with astrocytes” [47]. The relationship between the neoplasm and the endocrine abnormalities has been difficult to ascertain. This has resulted in part from the heterogeneity of the tumors observed. However, a constant finding of the diencephalic emacia-

tion syndrome has been reported to be elevated serum GH concentrations [49, 52–55]. Normalization of the basal GH concentrations concurrent with clinical remission after tumor irradiation also has been described [52, 54]. Results of GH stimulation tests after completion of therapy rarely have been reported and have yielded either complete GH deficiency or normal GH responses [52, 54, 56]. The mechanism underlying the apparent excessive GH secretion remains unresolved. The pathogenesis of the emaciation in this syndrome is not known; however, the striking increase in weight and growth following tumor irradiation has been noted in this syndrome [48, 54].

The association of optic gliomas and neurofibromatosis has been well established in the literature [57]. Another very rare association of optic gliomas has been with the Beckwith-Wiedemann syndrome, reported in only three patients [58, 59].

ARACHNOID CYSTS

Intracranial arachnoid cysts are extracerebral anomalous CSF accumulations surrounded by a connective tissue membrane covered on its inner surface by arachnoid cells of mesothelial nature [60]. They are encountered more frequently in children because they are predominantly congenital, and they can be produced by trauma, infection, radiation, or surgery [61, 62]. The incidence of intracranial arachnoid cysts is about 1% of all intracranial tumors [63]. Of these, only 12% are suprasellar in location [64, 65]. Though rare, they are included in the differential diagnosis of tumors occurring within or above the sella.

The clinical symptoms and signs result from the following mechanisms: 1) increased intracranial pressure without lateralizing signs (midline syndrome), consisting of hydrocephalus in infants and very young children, and headache, vomiting, papilledema, and macrocephaly in the older patients; 2) the so-called *bobble-bead doll syndrome*, which appears with masses compressing structures neighboring the third ven-

tricle [66, 67]; and 3) direct compression of adjacent structure by the cyst, visual field disturbances, and the hypothalamic-pituitary syndrome. In the latter, the commonest abnormality is precocious puberty due to premature activation of the hypothalamic-pituitary-gonadal axis [67–70]. This early activation is believed to be secondary to increased intracranial pressure, since decompression following shunting has been reported to reverse the clinical picture [69]. Other associated endocrinologic manifestations include amenorrhea, dwarfism, retarded skeletal maturation, hypothyroidism and inappropriate ADH secretion with a tendency to hyponatremia [69–73].

PITUITARY TUMORS

Pituitary tumors in childhood and adolescence are rare, and account for only 1% of all intracranial tumors [74, 75]. Recently the detection rate of these tumors has increased because of advances in neuroendocrine and neuroradiologic evaluation. There are two different types of proliferative lesions in the hypophysis: hyperplasia and the adenoma. They differ in the central control of their growth and in their functional activity. Function and growth of an adenoma are partially or completely independent of the hypothalamic regulatory factors, whereas both are fully controlled in hyperplasia [76]. Furthermore, pituitary adenomas are divided into two types based on their clinical symptomatology. The first type presents with signs of endocrine hyperfunction, whereas the second has endocrine hypofunction and signs of compression of visual pathways. Most pituitary adenomas in children (unlike the case in adults) are associated with hypofunction. Growth retardation is the most common finding, followed by delayed puberty in the adolescent child and diabetes insipidus [77, 78]. The diagnosis is suggested by the presence of endocrine abnormalities and visual field defects and confirmed by neuroradiological abnormalities of the sella turcica. The hypersecreting group is subdivided according to the hormone produced [79].

Among the hypersecreting pituitary adenomas, only GH and ACTH hypersecretion has been reported in children, leading respectively to the clinical pictures of gigantism and Cushing's disease [80–85]. This is in contrast to adults, where prolactin-, TSH-, and gonadotropin-secreting tumors have been reported.

HISTIOCYTOSIS X

Histiocytosis X is a term introduced by Liechtenstein in 1953 to include those disorders that were previously termed Hand–Schüller–Christian disease, eosinophilic granuloma, and Letterer–Siwe [86]. The disorder may be disseminated or solitary and most frequently involves the bone. Clinically the most common manifestations are skeletal lesions, chronic otitis, skin eruptions, seborrhea of the scalp and external ear canals, hepatomegaly, and pulmonary infiltrates. Involvement of the hypothalamic–pituitary area by this disease is well recognized [87]. The endocrinopathies associated with histiocytosis X are believed to be secondary to histiocytic infiltration of the hypothalamus and pituitary. Characteristically, the endocrine manifestations include DI, often preceding GH or other anterior pituitary hormone deficiencies. DI due to ADH deficiency occurs in as many as 50%–70% of the patients and growth retardation in 40%–50% of affected children [88–90]. The latter is postulated to be secondary to poor nutrition, inadequate control of DI, complications of radiotherapy and chemotherapy, and more importantly, GH deficiency [88, 89, 91]. Although rare, isolated cases of histiocytosis X with panhypopituitarism have been reported [92]. The high frequency of involvement of the hypothalamus in histiocytosis X underscores the need for full hypothalamic–pituitary evaluation at intervals, especially in patients with DI or recent growth deceleration, to diagnose GH deficiency.

NEUROFIBROMATOSIS

Neurofibromatosis (von Recklinghausen disease) is an autosomal-dominant disorder with an

incidence of 1 in 3000 live births. The characteristic features of the fully developed syndrome are café-au-lait skin pigmentation, pigmented freckles and moles, subcutaneous nodules and neurofibromatous tumors, and/or general predilection to malignancy [93].

A variety of endocrine manifestations have been reported in association with neurofibromatosis. In childhood, sexual precocity is the commonest associated endocrinopathy [94–96]. Retarded somatic and sexual development is also relatively common [96, 97]. The sexual precocity is usually central, complete, and isosexual. It is commonly due to the involvement of the hypothalamic region, probably disrupting the inhibition of gonadotropin production in the prepubertal child. Different types of intracranial neoplasia that are known to occur in neurofibromatosis can be responsible for the precocity.

As pointed out earlier, gliomas of the optic pathways are an integral part of neurofibromatosis [57], and at least 75% of these lesions occur in children under the age of 12 years [98]. Frequently, patients presenting with precocious puberty are found to have optic gliomas in association with neurofibromatosis. In other instances, a diffuse hypertrophic gliosis found in central neurofibromatosis or hydrocephalus or both may be the cause of precocity. The presence of neurofibromatous involvement of the CNS may not always be evident on radiologic examination because of the small size of the gliomas. Clinically silent cerebral lesions are frequent and may well be the cause of sexual precocity in some children. Thus, when patients with neurofibromatosis present because of advanced or retarded growth, a thorough neuro-radiologic and neuroendocrine evaluation is warranted.

Diagnostic Evaluation

ABNORMALITIES OF GROWTH HORMONE SECRETION

During postnatal life, linear growth is regulated by the secretion of GH from the pituitary gland.

The secretion of GH is regulated by two small peptides that are secreted by hypothalamic neurons. GH-releasing factor (GRF) stimulates GH secretion and somatotropin release-inhibiting factor (SRIF), also known as somatostatin, inhibits GH secretion [99]. GH mediates its growth-promoting or mitogenic effects upon most tissues in the body by the stimulation of a small peptide that is known by two names, insulin-like growth factor I (IGF-I) and somatomedin C (Sm-C). IGF-I/Sm-C stimulates metabolism and mitogenesis of chondrocytes, and requires the presence of normal nutrition and the normal secretion of thyroxine and hydrocortisone for optimal stimulatory effect on linear growth during childhood [99]. Tumors, radiation therapy, granulomas, and other space-occupying lesions in the area of the hypothalamus and pituitary may cause an increase or decrease in the secretion of the hypothalamic peptides, GRF and SRIF, and GH. Tumors that increase the secretion of GH cause an increase in the production of IGF-I/Sm-C, as seen in adults with acromegaly and children with gigantism; a persistent decrease in GH secretion causes a decrease in IGF-I/Sm-C production, as seen in children with hypopituitarism. When these changes occur during childhood and adolescence, there is an acceleration or deceleration of linear growth velocity, respectively. Therefore, the most important clinical assessment of GH secretion is the change in growth velocity, as measured in cm/year, and not necessarily the absolute height of a child at one given point in time [100]. For instance, a child with normal GH secretion may be short or tall, but growing at a normal growth velocity; the short or tall stature would not be caused by abnormalities in GH secretion whenever the growth velocity is normal, but by other familial or nongenetic conditions (figure 5-1). The plot of height at various ages on a standard growth chart is an exceedingly important assessment of GH as well as thyroid and glucocorticoid secretion (figures 5-1 and 5-2A).

The integrity of hypothalamic-pituitary se-

cretion of GH is determined by specific physiologic and provocative or pharmacologic tests [99, 101, 102]. In patients suspected of having GH deficiency, the collection of a single specimen for the measurement of GH in serum is usually of very limited value, since low concentrations of GH normally occur throughout the day and do not imply impaired GH secretion. Only at the time of an acute biologic stress reaction during the fasting state may the value of GH exceed 7–10 ng/mL (depending upon the normal value for the laboratory) in a single serum specimen and indicate normal GH secretion.

There are two physiologic tests that are useful in the evaluation of GH secretion: exercise and sleep. The exercise test is an excellent screening test for GH deficiency, and can be performed on an outpatient basis [101]. It must be performed in the fasting state, and the child must have the physical capability to perform strenuous exercise for 20 minutes. Specimens for GH are collected before exercise, at the conclusion of exercise at +20 minutes, and 20 minutes after exercise at +40 minutes. A GH value that exceeds the normal range for the laboratory in any of the three specimens indicates normal GH response, but the failure of a rise in GH to normal does not indicate GH deficiency. Sampling of blood (less than 1.0 mL per specimen) every 20 minutes from an indwelling venous catheter for 24 hours is the most accurate test of GH deficiency, particularly partial GH deficiency as seen in children after radiation therapy for solid tumors and for systemic malignancies like leukemia [102, 103]. However, this test requires hospitalization and skilled nursing personnel. Furthermore, the laboratory must have the capability to measure GH accurately in less than 50 μ L of serum or plasma. Although the cost to perform 72 GH determinations for this test is an important factor to consider, the psychological, physical, and monetary costs to the patient for chronic GH therapy are considerable, and the cost-effectiveness of this test may justify its use in the diagnosis of partial GH

deficiency or in situations where there are conflicting data and the diagnosis of GH deficiency is uncertain.

The provocative tests using certain pharmacologic agents to stimulate GH secretion are the most widely performed tests for the diagnosis of GH deficiency [99, 101, 102]. The tests most often performed by pediatric endocrinologists are the insulin tolerance test (ITT), arginine tolerance test (ATT), and the levodopa or L-Dopa, glucagon, and clonidine tests. Since only two stimulatory tests usually are necessary for the diagnosis of GH deficiency, these tests are performed sequentially on the same morning, i.e., the arginine–insulin tolerance test (AITT) or the arginine–L-dopa tolerance test [101, 102, 104]. A GH concentration in serum or plasma that exceeds the lower limit of normal for the laboratory, usually 7 to 10 ng/mL, is inter-

preted as a normal GH response. These tests are performed by the intravenous (insulin and arginine) or oral (L-dopa and clonidine) subcutaneous or intramuscular (glucagon) administration of the medication after two baseline specimens are obtained, and specimens are collected thereafter every 15 to 20 minutes for at least one hour (table 5-4).

The quantitation of IGF-I/Sm-C in a single blood specimen has limited value in the diagnosis of GH deficiency. Although the concentrations do not change appreciably throughout a 24-hour interval, the values vary considerably with age and sex, and may be low in the absence of GH deficiency in various disorders, particularly in delayed puberty and impaired nutritional states. Therefore, if the value is normal for age, it is very likely that the patient does not have GH deficiency, since there are only a few

TABLE 5-4. Tests of growth hormone secretion

Test	Procedure	Peak response
<i>PHYSIOLOGIC</i>		
Exercise	Vigorous exercise for 20 minutes (exercise bicycle; run up and down stairs); specimens before exercise and at +20 and +40 minutes after exercise	+20 or +40 minutes
24-hour sampling	Blood collections (< 1 mL) every 20 minutes for 24 hours during normal hospital activity, food intake, and sleep	Peak GH level during sleep; Quantitate the 24-hour secretion
<i>PHARMACOLOGIC</i>		
AITT	L-arginine monochloride 0.5 gm/kg infused IV in normal saline for 30 minutes; then at +60 minutes after starting arginine, Regular insulin 0.05–0.075 units/kg IV bolus; sample every 15 minutes for two hours; patient should be supine during the test	30–60 minutes after arginine 20–45 minutes after insulin; blood glucose must fall by > 50% of basal
L-dopa	0.5 gm/1.73 M ² orally; sample every 30 minutes for two hours; patient should be supine during the test	0.5–2 hours
Clonidine	4 µg/kg orally; sample every 30 minutes for two hours; patient should be supine during the test	1–2 hours
Glucagon	30 µg/kg IM or SC (1 mg maximum dose); sample every 30 minutes for two hours; the test is preferable for infants who have a tendency to develop hypoglycemia	0.5–1 hour

Notes: GH = growth hormone; AITT = arginine–insulin tolerance; L-dopa = levodopa; M² = meter square of body surface area.

cases of GH deficiency with normal concentrations of IGF-I/Sm-C. This observation justifies the determination of IGF-I/Sm-C as a screening test for GH deficiency during the initial evaluation of the patient. However, if the value is low, no definitive interpretation is possible, since low results are reported in malnutrition, particularly in acute and chronic illnesses with recurrent vomiting and reduced caloric intake, as occurs in patients with tumors involving the hypothalamic-pituitary region.

Ideally the tests for GH secretion should be performed prior to surgical or radiation therapy to determine the status of GH secretion prior to therapeutic intervention. However, when the clinical status of the patient does not permit an assessment of GH secretion before therapy, tests for ACTH, TSH, and AVP secretion are of greater clinical importance in the immediate management of the patient. Approximately 3 to 6 months after primary therapy, the patient should have an assessment of hypothalamic-pituitary function that includes an evaluation of GH secretion. Thereafter, GH secretory tests should be performed only if growth deceleration is observed.

Clinical diseases in which there is an acceleration of growth velocity caused by excessive GH secretion are very rare. The secretion of GH by a chromophobe or eosinophilic adenoma causes gigantism during childhood [105], and the secretion of GRF or GRF-like peptides by pancreatic tumors has been reported [106, 107]. The measurement of IGF-I/Sm-C provides a very useful initial screening test for diseases in which the primary defect results in excessive GH secretion [108]. The evaluation of the child with growth acceleration also should include an oral glucose tolerance test (1.75 g glucose/kg body weight not to exceed a total dose of 100 g), an accurate neuroradiologic examination of the pituitary fossa, and tests to exclude causes of growth acceleration that are not mediated by GH [99]. In normal children and adults, but not neonates, the ingestion of glucose causes a prompt suppression of GH to undetectable

values during the first two hours. In patients with excessive GH secretion by a pituitary adenoma or by a GRF-secreting pancreatic tumor, there is no suppression of GH and often a paradoxical rise in GH values after a glucose load.

ABNORMALITIES OF TRH AND TSH SECRETION

Pathophysiology of TRH and TSH Deficiency.

The hypothalamic-pituitary control of the secretion of TSH is mediated by the intrapituitary concentrations of T_4 and T_3 derived both from the circulation and from the intrapituitary conversion of T_4 to T_3 [109]. When the levels of T_4 and T_3 decrease, TSH is secreted by the thyrotroph in response to TRH stimulation. TRH is synthesized by hypothalamic neurons and secreted into the hypothalamic-pituitary portal circulation to the pituitary gland, where it stimulates the release and later the synthesis of TSH. These effects are inhibited when T_4 and T_3 concentrations increase to normal [110]. When there is destruction of the hypothalamus or portal circulation, there is no stimulus for the release of preformed TSH from the pituitary. In response to low circulating levels of T_4 and T_3 , there is an increase in TSH synthesis, and the pituitary content of TSH increases. Although small amounts of TSH are released into the circulation in the absence of TRH, the biological potency of TSH is reduced, since TRH is necessary for glycosylation of the alpha- and beta- subunits of TSH that are required for biological activity. Therefore, patients with TRH deficiency have low circulating levels of total and free T_4 and T_3 and usually normal or on rare occasions even slightly elevated levels of TSH as measured by competitive binding assays. When exogenous TRH is administered, TSH is released into the circulation either normally or with an exaggerated and delayed response [111] (figure 5-3). Children with TRH deficiency, also known as tertiary or hypothalamic hypothyroidism, usually have

mild hypothyroidism with minimal symptoms, and the total T_4 values are found in the 3–5 $\mu\text{g/dL}$ (39–64 pmol/L) range. Deceleration of growth velocity occurs even in the absence of other symptoms of hypothyroidism.

When there is destruction of the pituitary gland, basal TSH values are low or nondetectable, and there is no TSH rise after the administration of exogenous TRH [111]. In these patients with TSH deficiency, also known as secondary or pituitary hypothyroidism, the circulating levels of thyroid hormones usually are very low, with total T_4 values less than 3 $\mu\text{g/dL}$ (39 pmol/L) and total T_3 values below 60 ng/dL (0.9 nmol/L). In addition, the patient often has symptoms and signs of hypothyroidism, and deceleration of growth velocity invariably develops in untreated or inadequately treated patients in a manner similar to primary hypothyroidism. The TRH test, therefore, will differentiate hypothalamic and pituitary hypothyroidism in patients with hypothalamic-pituitary disease [111].

Radiation thyroiditis with primary hypothyroidism may develop in patients in whom radiation therapy for head and neck cancer is directed toward the thyroid gland, particularly when a high dose is required for treatment of the very young child. The TSH value in children with primary hypothyroidism usually exceeds 20 mU/L [112], whereas in hypothalamic hypothyroidism the TSH value is less than 12 mU/L [113] and usually within the normal range. Thyroid antibodies may be detected in serum at low titers in children with radiation thyroiditis.

In the evaluation and management of children with brain tumors, there are specific non-thyroidal conditions that are associated with abnormalities of thyroid function tests even though the patient is euthyroid and does not require thyroxin therapy. In these disorders it is very important that the free T_4 levels are measured either by equilibrium dialysis or by one of the reliable solid-phase free T_4 methods [114]. Certain drugs, usually anticonvulsants, interfere with thyroid hormone binding to

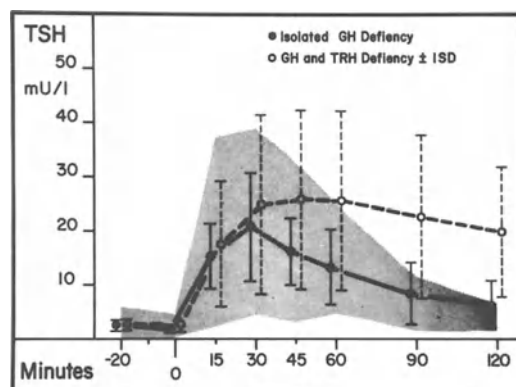


FIGURE 5-3. TSH response to TRH stimulation, showing an increased and prolonged response in TRH- and GH-deficient individuals in comparison with individuals with GH deficiency only.

serum proteins and intracellular transport, and accelerate the metabolism of T_4 [115]. These changes may result in serum thyroid hormone values that are very similar to the values seen in hypothalamic hypothyroidism, and the effects are especially complex with therapeutic levels of the diphenylhydantoins. The total and usually the free T_4 values are low, as are the reverse T_3 values. However, the concentrations of TSH and total and free T_3 are normal, although the effects on T_3 values remain controversial [109]. Phenobarbital may increase the metabolic clearance rate and fecal excretion of T_4 in some patients and cause a decrease in concentrations of T_4 , free T_4 , and T_3 .

Whenever the values for total T_4 and T_3 are low, the serum proteins that bind thyroid hormones should be measured, either by an indirect method (resin uptake test) or, preferably, by a direct assay of thyroid-binding globulin (TBG). Only by these determinations and an accurate measurement of the free T_4 is it possible to avoid unnecessary thyroxin or anti-thyroid therapy in patients with disorders of deficient or excessive thyroxin-binding proteins.

Patients with severe catabolic illnesses may have abnormalities of thyroid function tests that

resemble hypothalamic hypothyroidism. In nonthyroidal illness (NTI), the total T_4 value is normal or low, the free T_4 value is normal, the total T_3 value is low, and the TSH value is normal [116]. In contrast to hypothyroidism, the value for the biologically inactive stereoisomer of T_3 , called reverse T_3 , usually is elevated. The normal free T_4 and elevated reverse T_3 values are helpful to differentiate NTI and hypothalamic hypothyroidism; however, the free T_4 must be measured by a direct method that is valid for patients with NTI [114, 117].

Hyperthyroidism secondary to TSH-secreting pituitary adenoma. There are a few case reports in the literature of patients with a pituitary adenoma that secretes TSH and causes clinical thyrotoxicosis [117]. This disease must be differentiated from juvenile graves' disease (JGD) and the rare syndromes of isolated pituitary resistance to thyroid hormone (IPRTH) [118] and familial hyperthyroidism [119] unless the patient has an adenoma detected by neuroradiologic methods. The serum concentration of the alpha-subunit of TSH is elevated in patients with TSH-secreting pituitary adenomas but normal in IPRTH and JGD. Since familial hyperthyroidism and IPRTH are familial diseases, members of the family would be expected to have evidence of the same disease. The levels of TSH and alpha-subunit are normal before and after TRH in IPRTH, whereas they are low or absent without a response to TRH in familial hyperthyroidism and JGD [118, 119]. TSH-receptor antibodies are present in the serum of greater than 95% of patients with JGD prior to therapy [120], and are not present in patients with TSH-secreting pituitary adenomas, IPRTH, and familial hyperthyroidism. The latter three diseases are extremely rare in children.

ABNORMALITIES IN THE SECRETION OF PROLACTIN

The secretion of prolactin by the pituitary gland is controlled by the inhibitory effect of dopa-

mine secreted by hypothalamic neurons into the pituitary portal circulation. Prolactin release may be stimulated by the exogenous administration of TRH [121], although it remains uncertain whether TRH is an important regulator of the physiologic release of prolactin in man [122]. Elevated basal levels of prolactin are seen in patients with hypothalamic disease, primary hypothyroidism, postcontraceptive amenorrhea, prolactin-secreting pituitary adenomas (prolactinomas), and during therapy with certain drugs. The serum prolactin values are generally higher (greater than 100 ng/mL) in patients with prolactinomas when compared with the other disorders associated with hyperprolactinemia; however, overlap of the values certainly occurs. Stimulation of prolactin release with TRH and suppression with chlorpromazine and bromocriptine also may be helpful in the differential diagnosis.

ABNORMALITIES OF ACTH SECRETION

CNS tumors can cause abnormalities of ACTH secretion through abnormal secretion of corticotropin-releasing hormone (CRH) in the hypothalamus or through dysfunction of the pituitary. Dysfunction resulting in hypersecretion of ACTH causes hypercortisolism (Cushing's disease). Hypofunction results in inadequate ACTH stimulation and hypocortisolism. When hyperfunction of the adrenal glands resulting from excessive ACTH secretion is associated with CNS tumors, pituitary adenomas or microadenomas may be demonstrated as part of the diagnostic evaluation for Cushing's syndrome [123, 124]. In such instances, pituitary adenomas are demonstrated by CT scan, magnetic resonance imaging (MRI), or surgery. The etiology of such tumors is unclear but is probably related to excessive CRH stimulation. The presenting clinical signs and symptoms are those of Cushing's syndrome rather than those of a space-occupying intracranial lesion. The diagnosis of Cushing's disease is made when increased autonomous secretion of pituitary ACTH is present. This is demonstrated by

TABLE 5-5. Normal values for ACTH and cortisol

Plasma ACTH	20–100 pg/ml at 8 AM 3–60 pg/ml at 8 PM
Plasma cortisol	8–25 ug/dl at 8 AM 5–15 ug/dl at 8 PM
Urinary free cortisol	20–80 mg/M ² /day Approx 3–9 ug/day (40 ± 25 mg/M ² /day) age 4–10 years
Urinary 17-hydroxycorticoids	3 ± 1 mg/M ² /day Approx 3–6 mg/day age 3–6 years 6–8 mg/day age 6–10 years

elevated ACTH levels (especially in comparison with concomitant cortisol levels), elevated levels of urinary-free cortisol and 17-hydroxycortisol excretion (table 5-5), and a predominance of elevated plasma cortisol levels [125]. There is a lack of suppression of cortisol on overnight or low-dosage dexamethasone-suppression testing [126, 127]. Abnormal response to CRH [128], computerized radiographic scans, and selective pituitary venous drainage sampling for ACTH levels [129] may or may not be of diagnostic value.

In contrast to the adenomas related to Cushing's disease, most CNS tumors in children that affect adrenal function cause decreased cortisol secretion by destroying or decreasing the normal secretion of CRH and ACTH [130]. ACTH deficiency may occur concomitantly with other pituitary hormone deficiencies. It generally does not occur as an isolated deficiency. After treatment, it is less frequent than GH and TSH deficiency (figure 5-4) and usually is not present unless both of those deficiencies coexist. This destruction of the ability of the hypothalamus and pituitary to secrete adequate CRH and ACTH is usually not accompanied by the profound and progressive symptomatology that is classic for Addison's disease. By history, symptoms are mild, and stressful situations are often tolerated and resolved without glucocorticoid coverage. Hypoglycemia, which is usually

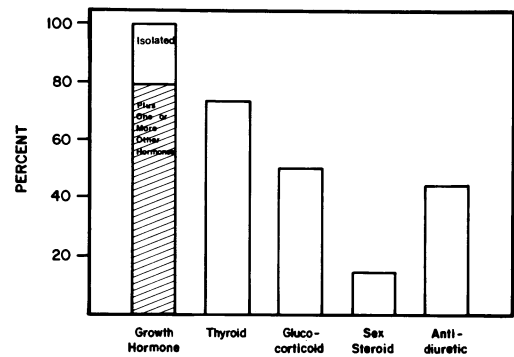


FIGURE 5-4. Endocrine therapy in 259 children with hypothalamic-pituitary deficiencies who had brain tumors including craniopharyngiomas (sex steroid percentage is from the 95 individuals who were Tanner 2 or greater). GH, TSH, ACTH, LH and FSH, and ADH deficiencies are presumed to be indicated by therapy with growth hormone, thyroid hormone, glucocorticoid, sex steroid, and anti-diuretic hormone, respectively. (Data from Genentech, Inc. National Cooperative Growth Study, 1987, used by permission.)

asymptomatic, may be present. A decreased ability to secrete a water load may be present but unapparent until glucocorticoid replacement is given; at that time, DI may be unmasked.

Since mineralocorticoid secretion is primarily under the control of the renin-angiotensin system, normal ACTH secretion is not obligatory for normal aldosterone secretion. Patients with hypoadrenocorticism due to insufficient ACTH are not expected to have electrolyte abnormalities. Therefore, one would not expect to find the classical hyponatremia and hyperkalemia of Addison's disease.

Baseline laboratory evaluation of ACTH and cortisol function [131] includes an 8 AM plasma cortisol level and 24-hour urinary levels of free cortisol or total 17-hydroxycorticoids (table 5-5) [131]. Low values suggest ACTH deficiency. Undetectable plasma ACTH levels concomitantly with low cortisol values, particularly in the early morning, suggest ACTH deficiency

and are evidence against primary adrenal failure. A common procedure to assess pituitary ACTH reserve as part of the assessment of hypopituitarism with concomitant GH evaluation is insulin-induced hypoglycemia [132]. A normal cortisol response to hypoglycemia (plasma glucose less than 40 mg/dL) is greater than 20 ug/dL.

The combination of normal cortisol levels from early morning, random or periodic 24-hour plasma sampling, normal urinary free-cortisol levels for body mass, and a normal cortisol response to insulin-induced hypoglycemia presents strong evidence for normal ACTH pituitary physiology. If levels are low or borderline, further diagnostic testing is indicated. Possible tests include metapyrone testing, ACTH stimulation, CRH stimulation, and vasopressin or pitressin stimulation.

Metapyrone testing evaluates feedback inhibition upon ACTH release by cortisol by blocking the 11-hydroxylase conversion at the final step of the glucocorticoid synthetic pathway. By blocking the conversion of 11-desoxycortisol to cortisol, there is less circulating cortisol, and if the ACTH feedback mechanisms and secretion are normal, a rise of ACTH results. The increased ACTH secretion stimulates the glucocorticoid pathway as far as the 11-hydroxylase block by metapyrone. Therefore, 11-desoxycortisol levels rise markedly in the normal individual.

Initially, a single-dosage overnight metapyrone test [133] should be done and may be adequate if consistent with other parameters indicating normal or subnormal cortisol secretion. This test is administered at a time when in the normal patient it would be superimposed upon the diurnal phase of increased ACTH secretion. A single dose of metapyrone, 30 mg/kg, is given at 11 PM. a blood sample is obtained at 8 AM for desoxycortisol and ACTH. Elevated levels of those hormones indicate a normal test response. Normal or minimally elevated desoxycortisol (compound S) levels and low ACTH level indicates ACTH deficiency.

If results are equivocal, the classical [131] or intravenous [134] metapyrone testing may be done. The classical test involves 24-hour urine collections before, during, and after the day of metapyrone administration. A normal response is a rise of urinary free cortisol or 17-hydroxycorticoids to greater than three times baseline. However, most hypopituitary individuals, even with other evidence of ACTH deficiency, show such a response unless the pituitary gland has been destroyed. This prolonged test and a IV infusion metapyrone test [134] are seldom indicated because they are cumbersome and expensive and may not resolve the clinical dilemma of whether or not to treat the patient with cortisol.

If there is no response to metapyrone testing, this may be due to ACTH deficiency but also to a suppressed or destroyed adrenal cortex. Therefore, unless other information is available to indicate that the defect is at the level of the hypothalamus and pituitary rather than the adrenal, ACTH testing may be done to differentiate the site of the abnormality. A rapid IV ACTH test using 0.25 mg of Cortrosyn® and a 30-minute post-injection cortisol and aldosterone response should be done first [135, 136]. Adrenal cortical failure is associated with a lack of rise of both cortisol and aldosterone, while patients with ACTH deficiency have a subnormal cortisol rise but a clear aldosterone incremental change. If there is no response and if adrenal suppression by exogenous glucocorticoids or chronic ACTH deficiency is a possibility, a prolonged IM ACTH stimulation test is indicated.

Corticotropin-releasing hormone stimulation testing is expected to become a useful clinical tool in differentiating the hypothalamic, pituitary, or adrenal causes of hypoadrenocorticism [137, 138]. A rise of ACTH would be expected in the former two but not in the latter. Such a response should be consistent with that occurring after insulin-induced hypoglycemia or lysine vasopressin, both thought to act primarily on the hypothalamus.

INTEGRITY OF POSTERIOR PITUITARY HORMONE SECRETION

Osmotic homeostasis in man is regulated by the secretion of ADH, AVP, the intake of water as controlled by thirst, and the excretory function of the kidneys [139]. There is a narrow range of normal for serum osmolality and sodium in each individual. A 2% increase in extracellular fluid osmolality causes shrinkage of the osmoreceptor that is located in the anteroventral aspect of the third ventricle outside the blood–brain barrier [140, 141]. This stimulatory response is mediated to the supraoptic and paraventricular nuclei, where AVP is synthesized, and then transported along the neuron to the posterior pituitary, where AVP is released into the circulation [139]. Renin and angiotensin II also increase plasma ADH levels [142]. Antidiuresis results from the stimulatory effect of AVP on the renal tubule, and the net effect is water conservation with a reduction of extracellular fluid osmolality to normal. This effect on the osmoreceptor also causes an increased thirst sensation and water ingestion. This response may be stimulated by angiotensin II [139].

When there is a 3% to 10% decrease in circulating volume, the baroreceptor is stimulated and mediates its response along cranial nerves IX and X to stimulate AVP release [139, 143]. In addition, the baroreceptor stimulates thirst [144]. The osmotic threshold for AVP release is 280 mOsm/kg. When the serum osmolality is less than 280 mOsm/kg, there is a

basal secretion of AVP with circulating levels between 0.5 and 1.5 pg/mL; as the serum osmolality increases above 280 mOsm/kg, there is a progressive increase of AVP secretion. The increment in AVP concentrations in serum can be calculated to be 0.38 (serum osmolality: 280 mOsm/kg) [145, 146]. When an acute, severe volume contraction occurs, the volume-mediated stimulus for AVP release overrides the osmotic-regulatory mechanisms, and AVP is secreted. Furthermore, the magnitude of the AVP response to volume depletion is several-fold greater than the response to osmotic stimuli.

The Effect of Drugs on AVP Release and Peripheral Response. There are certain pharmacologic effects on water metabolism that are mediated by AVP release [139]. These effects on AVP release are summarized in table 5-6.

These agents can interfere with normal osmotic homeostasis and may aggravate existing conditions of antidiuresis or diuresis, particularly during the early postoperative period. Furthermore, clofibrate and carbamazepine are effective in the treatment of some children with partial DI [147] and mask the clinical expression of the disease.

PITUITARY DIABETES INSIPIDUS (PDI). Lesions that damage the supra optic nucleus (SON), paraventricular nucleus (PVN), supraopticohypophyseal tract, or the posterior pituitary may

TABLE 5-6. Pharmacologic effects on AVP release

Enhance	Potentiate	Suppress
Anesthetic agents	Chlorpropamide	β-Adrenergic agents
Cholinergic agents		Alcohol
Barbiturates		Narcotic antagonists
Carbamazepine		Phenytoin
Clofibrate		
Cyclophosphamide		
Hypercapnia and hypoxia		
Morphine and narcotic analogues		
Nicotine		
Vincristine		

cause impairment of AVP synthesis and release and the development of partial or complete diabetes insipidus. However, removal of the posterior pituitary alone does not necessarily cause PDI, since intact neurons of the supraopticohypophyseal tract will continue to secrete AVP [148–151]. The usual symptoms and signs are polydipsia and polyuria with preference for cool water. Children who were previously toilet trained may develop nocturia and enuresis as the early symptoms of PDI. Other symptomatology depends upon the severity of the PDI, because the presence of acute or chronic dehydration will cause increased thirst, constipation, dry skin and mucous membranes, fever, lethargy, and, as the dehydration progresses, decreasing levels of consciousness. PDI alone is sufficient evidence to search for an intracranial lesion, because the diagnosis of idiopathic PDI requires that every appropriate test to identify an intracranial lesion is normal.

Partial PDI and “masked” PDI are the most difficult clinical disorders of water metabolism to identify and accurately diagnose. The presence of glucocorticoid deficiency, either as primary adrenal insufficiency (Addison’s disease) or more likely as ACTH deficiency, prevents or limits the full clinical expression of PDI, since glucocorticoids are required for the secretion of a normal water load. In glucocorticoid deficiency, there is a reduced intravascular volume with water shift to the extravascular compartments and a reduced glomerular filtration rate such that the patient cannot promptly excrete a water load and will not experience polydipsia and polyuria. However, the excretion of water often is delayed until the patient assumes the supine position at night, and he will complain of nocturia or enuresis. When replacement therapy with glucocorticoids are initiated, there is a prompt diuresis and the development of the classic signs of PDI. The clinician must be aware of this clinical disorder, for the initiation of glucocorticoid therapy just prior to intracranial surgery may render the patient at an increased risk for intraoperative dehydration

unless this entity is recognized and appropriately treated. Less often, the presence of moderate to severe hypothyroidism also may mask the development of the clinical symptoms and signs of PDI.

The patient with an intracranial lesion may have related psychiatric symptoms that in the presence of partial PDI are misdiagnosed as psychogenic polydipsia. The delay in diagnosis can be avoided by proper diagnostic procedures to identify space-occupying lesions and partial PDI. Often the patient also has evidence for abnormal anterior pituitary function, as discussed herein, and intracranial disease.

The adequacy of AVP secretion in most instances can be determined by an accurate history of fluid intake and output in conjunction with selective laboratory tests. On occasion the water deprivation test is necessary to differentiate between partial PDI and primary polydipsia [139]. The typical findings in PDI include persistent hyposthenuria in the presence of high normal to elevated serum osmolality and an elevated serum sodium concentration [140, 141, 142]. The urine specific gravity is consistently less than 1.006, the urine osmolality is less than 200 mOsm/kg H₂O, the plasma osmolality exceeds the normal value of 287 mOsm/kg H₂O, and the plasma AVP concentrations is inappropriately low (less than 2 pg/mL) for the elevated plasma osmolality [140, 141]. In patients with an obvious lesion in the hypothalamic–pituitary region and a history of polyuria and polydipsia, further diagnostic tests of posterior pituitary function usually are not necessary.

The initial evaluation of the child with a suspected brain tumor in the absence of symptoms of PDI should include the collection of simultaneous plasma and urine specimens following an overnight fast and deprivation of water intake. Urine and plasma osmolality, urine specific gravity, serum electrolytes, BUN, creatinine, and plasma AVP will provide an accurate assessment for the presence of subclinical partial PDI. However, an overnight

urine specific gravity value exceeding 1.015 in the absence of abnormal quantities of urinary solutes that raise the specific gravity suggests normal AVP secretion, and if serum electrolytes and simultaneous urine and plasma osmolality are normal, no further tests are needed. The plasma determination of AVP by a reliable laboratory provides a very accurate diagnostic capability since it correlates very well with the indirect tests of AVP release [143]. If these tests are abnormal, the child may require the water restriction-ADH simulation test [140, 141] to accurately assess the integrity of the secretion of AVP, particularly the child who is not subjected to surgery in the hypothalamic-pituitary region. Hypertonic saline infusions and the nonosmotic stimulation of AVP release by nicotine do not provide additional diagnostic information and are not longer indicated in the evaluation of children with suspected PDI.

On occasions polyuria may be caused by other disorders that could be present in children with brain tumors, particularly during the management of their primary disease. These include causes of solute diuresis from glucose, mannitol, and urea, and impaired renal concentrating ability from hypercalcemia, hypokalemia, and renal diseases with reduced glomerular filtration rate.

SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH). Since SIADH may develop in children during the postoperative period following intracranial procedures, the early recognition and proper diagnosis of the disorder is essential. By definition there is an inappropriate and sustained release of the antidiuretic hormone, AVP, in the absence of either the osmotic or nonosmotic stimuli for AVP release [139]. Therefore, the diagnosis requires the presence of hyponatremia, the absence of salt depletion, and no reduction in the effective circulating volume. In the presence of persistent AVP secretion there is hypotonicity, expanded volume, and an increase in body weight by 5% to 10%. SIADH also may develop at times other than the early postoperative period, and should be con-

sidered when the symptoms and signs of water intoxication and hyponatremia occur. SIADH in children is likely to develop during intracranial infections, radiation therapy, or other trauma to the brain, and during treatment with the drugs that augment the release and action of AVP (table 5-6). The clinical symptoms of SIADH are confusion and deterioration in the level of consciousness from somnolence to coma and seizures. Patients with SIADH retain water either from oral intake or intravenous fluid administration, develop hyponatremia, are moderately fluid-expanded, and experience an increase in body weight by 5% to 10%. Therefore, the diagnosis should be suspected when there is an unexplained change in the clinical status of the child, and the serum sodium should be monitored frequently in those children at an increased risk to develop SIADH. In children receiving antidiuretic therapy such as desmopressin acetate, there is a clinical picture very similar to SIADH. It may develop if excessive fluids are infused or ingested even though children taking desmopressin acetate are resistant to the development of water intoxication after the oral intake of a water load of 20 mL/kg of body weight [152].

The diagnosis of SIADH is suspected when hyponatremia and serum hypotonicity occur in the presence of urinary hypertonicity and volume expansion as evident by an increase in body weight. When plasma AVP levels are quantitated at the time of hypotonicity and expanded extracellular fluid volume, four types of AVP responses to stimuli have been reported to occur [139], as follows:

1. There are wide fluctuations of plasma AVP that are independent of the osmotic or nonosmotic control (37%);
2. There is a low osmotic threshold for AVP release, but the AVP and osmolal increments at higher osmolalities correlate normally (33%);
3. Below a serum osmolality of 278 mOsm/L, there is a sustained AVP release, even

though AVP release to osmotic stimuli is normal (16%); and

4. Even in the absence of any detectable abnormality in AVP release, there is a failure to maximally dilute the urine for unknown reasons (14%).

The diagnosis is confirmed by the simultaneous measurements of serum osmolality and sodium (both low, or hypotonic), urine osmolality and sodium (hypertonic), an increase in body weight, and evidence for unrestricted fluid intake. Hypouricemia is present because the urinary loss of uric acid varies directly with the rates of sodium excretion and effective circulating volume, and provides additional support for the diagnosis of SIADH. In the hospitalized patient who is maintained on daily intake and output measurements, the fluid balance calculations will favor progressive fluid retention with the parallel increase in body weight.

ABNORMALITIES OF GONADOTROPIN SECRETION

Excessive gonadotropin secretion during childhood or inadequate secretion during adolescent years may occur as a consequence of CNS tumors.

Sexual precocity, due to premature activation of the hypothalamic luteinizing-hormone-releasing hormone (LHRH)–pituitary gonadotropin secretion, may occur in association with a variety of brain tumors as already discussed. Pubertal gonadotropin secretion should be documented to be physiologically normal although chronologically early. Testing includes basal hormonal levels, LHRH testing [153], nocturnal periodic gonadotropin sampling [154], and skeletal-age X rays.

The more common effect of these CNS tumors or their treatment is the destruction of the potential for normal secretion of hypothalamic LHRH or pituitary gonadotropins. The diagnosis of gonadotropin deficiency, due to either abnormal hypothalamic-LHRH or pituitary LH and FSH secretion, is unlikely if

there is no other pituitary malfunction (figure 5-4). In fact, gonadotropin-secreting potential is often preserved even when several other pituitary hormones are deficient.

However, there is no sure way to make the diagnosis of hypogonadotropism before an individual has reached biologic maturity appropriate for the onset of puberty. While pubertal onset cannot be considered to be delayed until after age 13 in females and age 14 in males, biological maturity needs to be gauged by skeletal age rather than chronologic age, especially if there has been other untreated hormone deficiency such as GH deficiency.

The problem of diagnosing hypogonadotropism before the point when pubertal maturity ought to have occurred is that the prepubertal state is, by definition and physiologic function, hypogonadotropic. In both the prepubertal child and most hypogonadotropic adults, one expects low levels of LH and FSH in circulation and some response when stimulated with LHRH [155]. The hypogonadotropic state that may be present with CNS tumors or following their treatment may be complete or partial. With complete deficiency, the prepubertal child does not begin pubertal development, while the child with partial deficiency may have the onset of pubertal changes. Thus not only the onset of puberty but also the normal progression and completion of pubertal development should be documented.

In the male patient, in addition to clinical evidence, hormonal documentation of the onset of puberty is verified simply by a testosterone value within the pubertal and above the prepubertal range (table 5-7). Evidence of puberty in females should include clinical evidence of breast budding, estrogenized vaginal mucosa, and blood gonadotropin and estradiol levels within the pubertal range. A pubertal LH and FSH response to LHRH stimulation is often required to document a pubertal gonadotropin status [153, 156]. Because LH and FSH levels fluctuate and because there is considerable overlap between the normal range for prepubertal

TABLE 5-7. Normal gonadotropin* and sex steroid values

		Blood		
		Perpubertal	Pubertal	Adult
Female	LH (ng/ml)	< 4.9–2.5	< 4.9–91	15–99
	FSH (ng/ml)	< 20–123	< 20–250	135–355
	Estradiol	< 9–20	< 9–85	30–300
Male	LH (ng/ml)	< 4.9–21.5	< 4.9–46	11–86
	FSH (ng/ml)	< 20–174	38–270	54–324
	Testosterone (ng/dl)	< 10–22	20–650	285–980

* LER—907 standard.

and pubertal values for a single sample [157], a random LH and FSH determination is often not helpful (table 5-7).

However, extensive hormonal documentation may be unnecessary, because once puberty has occurred spontaneously, clinical findings make it obvious that there is at least early pubertal-type gonadotropin secretion. The presence of Tanner 2 breast development in females is clinical evidence of gonadotropin-stimulated estrogen secretion. In males, testicular size of 3 cc or a longitudinal testicular axis of greater than 2.5 cm is indicative of FSH stimulation.

To verify that gonadotropin secretion is adequate, full maturation needs to be observed as having occurred and as being maintained. In females, full physical development plus the onset of menses and reasonably regular menstruation should occur within four years from onset [158]. Males should reach full physical development with attainment of adult testicular and prostate size within 3.5 to 4.5 years [158].

Hormonal assessment of gonadotropin status is indicated if there is no pubertal development, minimal development such as some pubic hair in males or barely palpable breast tissue in females, or lack of progression of development. Minimal pubic hair development may be a reflection of increased adrenal androgen secretion or minimal gonadotropin secretion. Assessment of pubertal gonadotropin status may be by periodic blood sampling, especially during sleep, LHRH stimulation, several random

serum samples, and nocturnal or 24-hour urinary LH and FSH determinations [159].

Sampling of LH and FSH during sleep (nocturnal) may be continuous [160] or with a frequency of every 10 or every 20 minutes [154]. Normal early pubertal gonadotropin secretion is characterized by the episodic release of LH with a marked and abrupt rise occurring one to several times during the sleep period. Mean levels of gonadotropin during sleep can be compared with wakefulness. If clearly greater, this suggests a pubertal pattern [154, 160]. If a difference is not found, however, this does not necessarily mean hypogonadotropism. The sampling or sleep cycle may be inadequate. If episodic release and increased secretion in relation to sleep are both obvious, this is clear evidence of maturation with pubertal-type gonadotropin secretion.

LHRH stimulation testing does not necessarily differentiate gonadotropin deficiency from an immature response (figure 5-5). Most individuals, even with hypothalamic dysfunction, still have an LH and FSH response to LHRH stimulation unless the pituitary gonadotropin-producing cells are destroyed. Therefore, the response in the prepubertal individual is likely to be low and not different between the individual who simply has a delay in development and the one who lacks the potential for pubertal gonadotropin secretion. The eventual endogenous secretion of pubertal levels of hormones differentiates the former from the latter. Hypo-

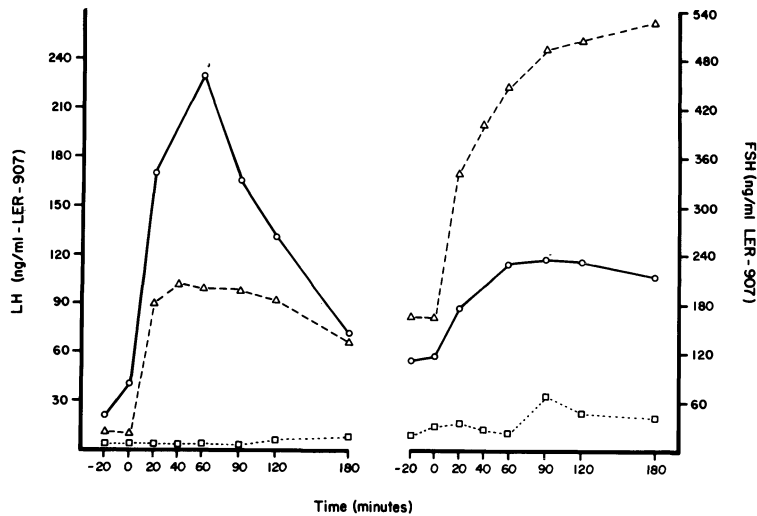


FIGURE 5-5. LHRH stimulation tests (response to 100 ug LHRH at time 0 min) in three patients with brain tumors: (○)—A two-year-old male with sexual precocity due to a hypothalamic hamartoma. Adult basal and response LH and FSH levels are comparable to a mature adult hypothalamic-pituitary axis. (△)—A four-year-old male with sexual precocity, neurofibromatosis, and an optic glioma. LH response is mature while FSH basal and response levels are greater than the usual adult response. (□)—A 15-year-old female with lack of pubertal development and craniopharyngioma. There is minimal to negligible gonadotropin basal and response levels, indicative of a hypogonadotropic state and suggestive of little potential for increased gonadotropin secretion.

gonadotropism is implied after LHRH testing in the rare instances in which there is no rise of LH and FSH indicating no pituitary gonadotropin-secreting cells. A low response of LH and FSH in individuals who are old enough and biologically mature enough so that a mature gonadotropin response should be occurring indicates hypogonadotropism.

Repetitive LHRH stimulation with an increased response of gonadotropins is not differentiating, since this can be expected to occur in both the immature and permanently deficient individual [161, 162].

The rise of LH from baseline to peak levels after an acute LHRH stimulation in most prepubertal and hypogonadotropic individuals is generally about fivefold. In the adult, there is approximately a ten fold rise. FSH changes are not as dramatic with sexual maturity. In the prepubertal female, there is a relatively dramatic FSH response and with puberty the rise may not be discernably different. Among males, FSH increments, which are often not differentiating, are a rise of 1.5 for prepubertal individuals and of 2.0 in the pubertal or postpubertal state.

Urinary gonadotropin measurements of either overnight sampling (first morning void) or 24-hour collections can be used to indicate prepubertal versus pubertal levels, providing that normal ranges are available [159].

The above-mentioned evaluations using either gonadotropin sampling or LHRH stimulation are not helpful and thus not indicated until the patient reaches pubertal age and approaches appropriate biologic maturity. For example, a GH-deficient male patient who is 14 years old but has a bone age of 10 years would not be expected to have pubertal gonadotropin secretion even if he were potentially capable of it.

Management

DISORDERS OF GROWTH HORMONE SECRETION

Replacement therapy with human growth hormone (hGH) is indicated for those patients who have documented growth deceleration and failure to secrete GH in response to a minimum of two stimulatory tests. After surgical therapy for hypothalamic–pituitary tumors, some children have normal linear growth postoperatively, even when there is no GH release to the usual GH stimulatory tests [163]. These children usually have normal IGF-I/Sm-C and prolactin values [164, 165]. The reason for this discrepancy is unknown, although hyperinsulinemia has been hypothesized as the growth factor in some children with obesity [165]. Because normal linear growth may occur after surgery, it is important that patients be measured sequentially for a minimum of six months prior to the initiation of GH therapy. Patients who fulfill the criteria for hGH therapy should be eating a normal caloric diet and not have a persistent chronic illness or be in a catabolic or cachectic state, since GH does not stimulate linear growth in patients with malnutrition or chronic illness [99]. Preparations of hGH synthesized by recombinant DNA technology now are available by prescription. A hGH dose of 0.1 mg/kg of body weight parenterally three evenings each week should be effective in stimulating linear growth in GH-deficient children [166]; in fact, those children who had growth deceleration prior to diagnosis may experience growth acceleration, or “catch-up” growth, during the initial year of therapy. In those patients with a poor growth response to hGH, there should be a careful investigation for adequacy of caloric intake, hypothyroidism, excessive glucocorticoid therapy, and adequacy of the technique for the injection of hGH.

In those cases with excessive secretion of GH, the patient can be monitored most effectively by serial measurements of linear growth and serum or plasma IGF-I/Sm-C. When these parameters

are abnormal, the patient should be investigated for persistent or recurrent disease in a manner similar to the initial investigation.

DISORDERS OF THYROTROPIN SECRETION

Hypothyroidism, either hypothalamic (tertiary) or pituitary (secondary), may be present at diagnosis or may develop at any time after therapy for the primary disease. To avoid any confusion in the differential diagnosis between hypothyroidism and the euthyroid sick syndrome that may be present during the catabolic posttherapeutic phase of the disease, a free thyroxine determination should be performed prior to the initiation of replacement therapy with L-thyroxine [114]. At this time a TRH test should be performed to differentiate hypothalamic versus pituitary hypothyroidism [111], because this distinction is useful for future therapy with the specific releasing hormones for other pituitary hormones.

If CNS surgery is performed and the pretreatment thyroid function tests are normal, there is no need to repeat the tests before one week after surgery. It is important to remember that thyroid function tests may be altered during both severe illness and reduced caloric intake, as previously discussed. Subsequently at 3- to 6-month intervals following surgical or radiation therapy, and particularly after the initiation of hGH therapy, thyroid function tests should be determined.

The thyroid preparation that is most effective in maintaining euthyroidism and in monitoring the response to therapy in children is L-thyroxine [167]. A single daily dose is prescribed, preferably one half hour or more prior to food intake. The dose varies with age and body size, and children with hypothalamic or pituitary hypothyroidism often require less L-thyroxine than children with primary hypothyroidism. The dose for age and weight (table 5-8) may serve as an initial guide to replacement therapy for patients with hypothalamic or pituitary hypothyroidism.

The thyroid-function, tests to monitor dur-

TABLE 5-8. L-thyroxine dosage guide

Age	Dose per kg body weight	Dose range
< 6 months	7–10 µg/kg	25–50 µg/day
6–12 months	5–8 µg/kg	37.5–75 µg/day
1–5 years	4–6 µg/kg	50–100 µg/day
6–12 years	3–5 µg/kg	50–125 µg/day
> 12 years	2–3 µg/kg	100–150 µg/day

ing the initiation of therapy are the total and free T_4 and T_3 . There is no reason to measure TSH levels during L-thyroxine therapy in patients with hypothalamic or pituitary disease; however, if the patient has primary hypothyroidism secondary to radiation thyroiditis following cervical radiation therapy, the TSH should be measured to assure adequacy to L-thyroxine therapy. Once the dose has been established to maintain euthyroidism and normal thyroid function tests, further tests of thyroid function should not be required any more often than once every 1–2 years.

DISORDERS OF ACTH SECRETION

Excessive ACTH secretion resulting in Cushing's disease caused by microadenomas or adenomas of the pituitary are treated ideally with resection [168]. In the situations in which adenomectomy is not possible, traditional procedures such as bilateral adrenalectomy are used [169]. Cyproheptadine has been used to temporarily suppress ACTH secretion but is not a recommended long-term treatment [124]. Stereotactic pituitary irradiation may have significant therapeutic potential [170].

Although the adrenal cortex secretes glucocorticoid (primarily hydrocortisone), mineralocorticoid, and androgens in response to ACTH stimulation, if ACTH secretion is subnormal usually replacement of only glucocorticoid is necessary. Mineralocorticoid secretion can be expected to be maintained because it is primarily under the control of the renin-angiotension system. Adrenal sex steroids, normally secreted in significant quantities after pubertal age, apparently have a negligible physiologic

function, and replacement is very rarely, if ever, needed.

Replacement therapy with ACTH or CRH is impractical because either would have to be administered frequently and parenterally. Thus, treatment of ACTH hyposecretion, whether it is due to CRH–hypothalamic defect or a pituitary malfunction, involves replacement of glucocorticoid. The prescribed glucocorticoid can then be the same as in adrenal insufficiency due to any cause, although the guideline for dosage may differ, particularly in the child who has not yet completed growth and has other anterior pituitary hormone deficiencies. This is because of the clinical observation that panhypopituitary patients treated with full calculated replacement dosages of glucocorticoid grow less well than those treated with one half to three quarters of that dosage. Acute adrenal crises without a precipitating stress are not likely to occur among hypopituitary patients, so full replacement is also unneeded. The commonly recommended glucocorticoid for treatment during childhood, whether for CRH, ACTH, or primary adrenal cortical insufficiency, is cortisol (hydrocortisone). This steroid, the primary glucocorticoid secreted by the human adrenal, has a relatively low potency when compared with other glucocorticoid drugs (table 5-9). This makes appropriate dosaging easier, since precision is important during childhood to allow normal growth. Greater-than-physiologic replacement suppresses normal growth and development. In fact, as noted above, it is also a common clinical observation that full calculated replacement dosage of glucocorticoid for surface area is correlated with slower growth than

TABLE 5-9. Comparison of glucocorticoid preparations

Glucocorticoid	Trade names	Relative glucocorticoid potency	Mean oral dosage (mg/m ² /day)		Mean IM or IV dosage (mg/m ² /day)	Daily administration frequency
			Deficiency			
			Adrenal	ACTH		
Hydrocortisone (cortisol)	Cortef Solu-cortef Hydrocortone	1	15–20	10–20	10–12.5	3X
Cortisone	Cortone	0.8	25–30	15–25	12.5–15	3X
Prednisone*	Deltasone	4–5	5–6	–	–	2–3X
Dexamethasone*	Decadron	25–30	.5–.75	–	–	1X

* Not recommended for replacement therapy during childhood.

smaller dosages. Therefore, the recommended dosage for hypopituitary patients should be begun at approximately half the calculated replacement.

When calculating replacement, total daily dosage and frequency of administration should be based on the pharmacology of the drug, and intervals of supraphysiologic and subphysiologic replacement should be avoided. Because cortisol has such a short half-life and is readily absorbed, administration once or twice a day results in high levels for a few hours and subnormal levels subsequently.

The criteria for replacement of glucocorticoid, as well as for determining subnormal endogenous secretion, are based on the daily secretion of cortisol in normal individuals. Except in the early neonatal period, secretion is not age-related. Secretion of glucocorticoids correlates best with body mass, so surface area (square meters, M²) is used to calculate replacement dosage. Normal secretion of cortisol is 12.5 ± 3 mg/M²/24 hours (mean ± SD) [130,171]. Full replacement or maintenance therapy of cortisol given parenterally (IV or IM) then is calculated to give this amount daily per meter square. Full oral replacement therapy is based on 1.5–2 times the physiological secretion rate (15 to 25 mg/M²/day). Replacement among ACTH-deficient patients is one half to

three quarters this amount, i.e., 10 to 15 mg/M²/day orally.

Oral cortisol should be given at least every eight hours because of its short half-life. The dosage may be divided in thirds or a larger dosage may be given in the morning to simulate endogenous diurnal variation. Adequacy of cortisol replacement may be ascertained by evidence from history, physical exam, normal growth in the child, and appropriate urinary free-cortisol excretion for surface area (table 5-5). The drug of choice is hydrocortisone. Prednisone and dexamethasone are not recommended because of their potency and growth-retarding effect in childhood.

If deficiency of ACTH is only partial (see diagnosis section), glucocorticoid therapy may be needed only in times of stress using the guidelines outlined below.

If parenteral replacement therapy is necessary due to surgery, illness, trauma, or other stress, dosages should be three times the usual daily amount or calculated at three times full maintenance therapy. If given IV, replacement should be by continuous infusion; the short half-life of cortisol makes bolus injections ineffective. Intramuscular replacement should be given every 6 to 8 hours; the total daily dosage should be divided equally. The most effective means of rapid coverage is intravenous cortisol (e.g.,

cortisol hemisuccinate, SoluCortef®). Initial dosage ranges from 50 to 100 mg. It may be given half as a bolus.

To be assured that increased levels of glucocorticoid persist, depot injections of cortisone acetate can be given. Stress replacement is in the range of 45 mg/M²/day. Because cortisone acetate is absorbed slowly after intramuscular administration, adequate coverage is not present until 18 to 24 hours after administration. Daily injections of three times maintenance are indicated as long as stress persists. Coverage is present from 2 to 3 days after the last injection.

After stress dosages of steroids, therapy in ACTH-deficient patients can be immediately reduced to previous replacement levels if not otherwise contraindicated.

Mineralocorticoid replacement is not indicated in patients with only hypothalamic–pituitary dysfunction because aldosterone secretion is adequate and fluid and electrolyte normalcy is maintained without therapy. Androgen replacement is virtually never indicated in ACTH-deficient individuals. The only rare indication might be the post-pubertal female who is gonadotropin-deficient and desires sexual hair development.

DISORDERS OF POSTERIOR PITUITARY HORMONE SECRETION

The management of fluids, electrolytes, and antidiuretic therapy when needed in children during the perioperative and postoperative periods may be one of the greatest challenges in medicine. To avoid cerebral edema, neurosurgeons often maintain mild intravascular dehydration and use high doses of glucocorticoids, and in those patients with uncertain requirements for ADH and variable fluid losses there is a need for continual surveillance of fluid intake and output, serum chemistries and osmolality, body weight whenever possible, and routine vital signs. Ideally, these parameters should be maintained in a flow sheet at the bedside to permit prompt review by the responsible

medical personnel. Furthermore, the laboratory should provide results of electrolytes, glucose, and osmolality within 30 minutes of specimen collection during the early postoperative period to assure proper therapy.

There often is a three-phase response of ADH and urinary volume during and following hypothalamic–pituitary surgery [139]. During the initial or acute phase at the time of surgery, impaired AVP secretion and diuresis occur in response to the injury-related neuronal shock to the distal supraopticohypophyseal tract and the posterior pituitary. Treatment includes additional free-water intake and low doses of short-acting (AVP) or long-acting (desmopressin acetate) administered parenterally. However, within 2 to 4 days postoperatively, the interphase of antidiuresis appears as a result of the leak of AVP from degenerative neurons. At this time, the classic presentation of SIADH may occur, and therapy must be adjusted accordingly. Any ADH therapy, including those drugs that enhance AVP release and effect, should be discontinued and a strict control of fluid intake instituted. This interval may continue for an additional 4 to 8 days, after which permanent DI develops. Whenever ADH therapy is prescribed, the minimal effective dose is optimal in order to avoid an excessive duration of response. If antidiuresis is not evident within an hour, a second dose should be given. The parenteral dose of desmopressin acetate is approximately 10% of the intranasal dose, since the direct intravenous administration circumvents inactivation and degradation of the drug. Until the patient is conscious and drinking fluids in response to thirst, no ADH therapy should be given until there is evidence of “breakthrough” diuresis. One must avoid any cumulative effect of the longer-acting ADH preparations to prevent the induction of water intoxication, although children are quite tolerant of the ingestion of a water load during therapy with desmopressin acetate [152]. As soon as the patient can tolerate the intranasal administration of desmopressin acetate, the

parenteral route of the therapy should be discontinued.

Changes in total body water and free-water clearance are best monitored by sequential measurements of serum osmolality, sodium, potassium, total protein, BUN, uric acid, and glucose. In addition to accurate records of fluid intake volume and composition, the urine volume and osmolality and fluid losses should be quantitated on an hourly basis until stabilization. To prevent an osmotic diuresis, the patient, particularly if hypothermic, should not be given large quantities of glucose-containing solutions, for glucosuria will develop if glucose is administered more rapidly than it can be metabolized. Furthermore, extremely high doses of glucocorticoids should be avoided, and the dose of glucocorticoids should be tapered gradually during the first three days postoperatively and reduced to the physiologic replacement dose or less by one week after surgery.

DISORDERS OF GONADOTROPIN SECRETION

Treatment of sexual precocity associated with brain tumors involves appropriate surgery and radiation therapy for the underlying lesion; if possible, surgical removal of small hypothalamic hamartomas may cure the sexual precocity [45]. LHRH analogue suppression of gonadotropin secretion [172] is the treatment of choice if sexual precocity persists after appropriate tumor therapy.

Therapy for gonadotropin deficiency is by providing the appropriate sex steroid stimulation to cause physical pubertal development. Therapy is the same for patients with delay in onset of gonadotropin secretion (which may occur if biological age lags behind chronologic age) and for patients with constitutional delay of growth and development, severe illness, or other hormonal deficiency. With such stimulation, physical pubertal development in terms of clinical pubertal characteristics can become complete and adult, except that in males testicular size remains small. Females should be

treated so that eventually regular withdrawal uterine bleeding occurs. Potential for full sexual function is present and can be realized at an appropriate time.

If physical pubertal development is considered to be desirable once a patient has reached pubertal age for physical, emotional, social, or psychosexual indications, hormonal therapy can be given to begin pubertal changes, and diagnostic testing can be deferred to a later date. Before sex steroid therapy is given, however, appropriate consideration must be given to the growth- and maturation-promoting effects of sex steroids. Sex steroids, particularly in large quantities such as adult replacement dosages, can markedly advance skeletal age. Such treatment can accelerate bone age faster than comparable growth rate and thereby compromise final adult height. In patients with GH deficiency, GH as well as sex steroid can be given concomitantly, provided such treatment is also given after ultimate height will not be expected to be compromised.

For females, treatment can begin with estrogen stimulation or may be started using low-dosage estrogen–progesterone combination contraceptive pills. It is appropriate to begin pubertal development in females using the lowest readily available standardized estrogen preparation (currently estinyl estradiol 0.02 mg tablets). This dosage is given daily for as long as six months unless vaginal bleeding or spotting occurs. If bleeding occurs, or after six months of regular estrogen therapy, cyclic medication with the addition of a progestational agent should begin. Such a regimen can involve ethinyl estradiol given daily for three weeks. The dosage may range from 0.02 to 0.05 mg daily. If physical development is progressing too slowly, increased dosage to 2 to 3 times this amount can be given for limited time periods to stimulate full pubertal development. Such stimulation, however, should be avoided if the patient is very short for her age with considerable delay of skeletal maturation. High dosage of estrogen stimulation can disproportionally advance ske-

letal maturation in relation to statural growth and height and thus will diminish the ultimate adult height. Lower dosages are adequate to begin and usually cause appropriate progression of pubertal development.

A regimen that is easy to remember is based on the calendar month. Estrogen can be taken from the 1st to the 21st and progesterone from the 12th to the 21st. From the 22nd to the end of the month, regardless of the length of the month, no medications should be taken. Long-term unopposed estrogen therapy should never be given. Progesterone should be added to the cyclic regimen during the second half of the three-week estrogen cycle. Examples are Provera® at a daily dosage of 5–10 mg or Norlutin® at 5 mg. Either can be given for the last ten days.

After several months of sex steroid treatment, it is expected that withdrawal bleeding will begin within two days of stopping medications and that it will last from 3 to 5 days. However, regardless of whether menstruation occurs, how long it lasts, or how many days are in the calendar month, estrogen medication should begin again on the first of the month.

If the higher dosages of estrogen are used either as a separate medication or in a combination pill, once physical pubertal development is full, the dosage should be lowered to that which will maintain regular cycling with a reasonable flow and duration of withdrawal bleeding [173]. This will prevent excessive endometrial stimulation and pathologic changes. Usually adequate medication is provided by using either 0.02 mg of ethinyl estradiol plus progesterone for the last ten days, Lo-Ovral® (0.03 mg ethinyl estradiol and 0.3 mg of norgesterol) or Ortho-Novum® 7-7-7 (0.035 ethinyl estradiol and three successively greater concentrations of norethindrone: 0.50, 0.75, and 1.0 mg). Regular gynecologic examination should begin by the time puberty is complete. If the diagnosis of hypogonadotropism has not been clearly verified, after adequate stimulation for appropriate pubertal development for age, medication should be

discontinued at the end of the cycle for several months to document gonadotropin status. If pubertal development was already midpubertal or beyond before the onset of disease, initial therapy can be full adult cyclic therapy.

In males, when the time for pubertal development is appropriate, testosterone therapy should be given by intramuscular injection. Such treatment may be begun before it is possible to confirm the diagnosis of gonadotropin deficiency if biologic and skeletal age are considerably delayed in relation to chronologic age. The effect upon adult height must always be considered. If such treatment is begun, it should be subsequently stopped long enough to verify or rule out the diagnosis.

Oral or sublingual forms of testosterone are inadequate and hepatotoxic. Synthetic androgens are also not adequately potent. Thus, the only option for full androgen administration is parenteral therapy [174]. The depot oil-based injections that are indicated are testosterone enanthate, cyprionate, or propionate. The full replacement dosage is 100 mg/week given at 2- to 3-week intervals.

Dosage for initial therapy depends upon the rapidity of pubertal development desired and the remaining statural growth potential. Large dosages are more potent in stimulating skeletal maturation and hence would tend to diminish ultimate height to a greater degree.

Physical pubertal change can be initiated using 50 to 100 mg every four weeks. Initial therapy ranges from that level up to 250 mg every four weeks. Dosages can be titrated upward and administered more frequently such as every 2 to 3 weeks until full physical postpubertal genital development is attained. Usual full replacement dosages would be 200 mg every two weeks or 300 per three weeks. If full dosages are given to a prepubertal boy, dramatic stimulation to the genital area and priapism may occur. However, if pubertal development was considerable before tumor presentation, full replacement may be started as initial therapy.

With treatment in the prepubertal gonado-

tropin-deficient individual, testes can be expected to grow minimally or remain small. Indeed, if dramatic testicular growth occurs, that is suggestive of endogenous gonadotropin secretion.

If the diagnosis of gonadotropin deficiency needs to be confirmed, testosterone therapy should be discontinued for two months or more and a baseline testosterone value obtained. A low level of testosterone (< 100 ng/dL) confirms this diagnosis. A value in the adult range (> 375) indicates normal LH secretion. Values between these indicate that further assessment is required until adult levels are documented or deficiency ascertained.

Obviously, sex steroid replacement therapy only stimulates the development of the physical characteristics of puberty and does not cause gametogenesis. Individuals with congenital hypogonadotropism are unlikely to have adequately differentiated or developed gonads, so gametogenesis is unlikely even with gonadotropin stimulation. The likelihood of stimulating spermatogenesis or ovulation in patients with acquired disease because of CNS tumors is greater with older age at time of onset. Such stimulation is appropriate only when spermatogenesis or ovulation is desired and judged to be reasonable. If individuals were already pubertal or postpubertal at the onset of disease, resumption of gametogenesis is relatively easy.

When reproduction is to be attempted, further stimulation is required. This may be via LHRH or LH and FSH therapy. Both, however, must be given intermittently, and there is currently no good regimen because frequent parenteral injections or infusions are required. In most instances, the pituitary is intact and responsive to LHRH stimulation [175]. Gonadotropin administration involves injections of hCG for LH properties and of human menopausal gonadotropin (hMG) primarily for FSH properties [176]. Such treatment regimens are long, expensive, and arduous, differ for males and females, and belong to

adult, not pediatric, replacement regimens for gonadotropin deficiency.

Gonadotropin stimulation will also cause testicular growth. In the majority of instances currently, gonadotropin treatment is not given and testes remain small. Testicular prostheses should be offered. Most males elect to receive them unless anticipating gonadotropin treatment. If prostheses are placed, there is usually an option concerning removal of very small testes. A good general recommendation is that the prostheses not be placed until full adult-sized ones can be easily accommodated within the scrotum. Although testicular prostheses are available in graded sizes, repeated procedures are seldom warranted because of the increased risk of several surgeries.

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6. SURGERY

A. Leland Albright

The neurosurgical care of children with brain tumors has changed considerably in the past decade. The tumors are localized by computed tomography (CT) and magnetic resonance imaging (MRI) scans far more accurately, and with minimal morbidity, than by angiograms or ventriculograms. The operations are more frequently performed by pediatric neurosurgeons. The tumors are more likely to be biopsied stereotactically. Tumor removals are done with ultrasonic aspirators and lasers, more completely and with less trauma to surrounding brain than with forceps and scissors. Postoperative morbidity and mortality have declined. Children are more likely to be treated postoperatively in randomized clinical protocols.

Protocols are needed to answer many fundamental surgical questions about pediatric brain tumors: 1) Should children with totally resected low-grade gliomas be given radiotherapy? 2) Does the extent of removal of supratentorial low-grade gliomas influence duration of survival? 3) Are craniopharyngiomas treated as effectively by subtotal resection plus irradiation as by total resection? Questions such as these remain because brain tumors are uncommon in children; each year, approximately 1500 children in the United States develop one of the nine common brain tumors. There are approximately 4500 neurosurgeons in the U.S., so most individual practitioners will see few cases. There are several reasons why children with brain tumors should be treated in pediatric neurosurgical centers: 1) experience: the major pediatric neurosurgical centers each treat 25–50 children with brain tumors per year; how-

ever, the majority of children with brain tumors are not treated in such centers, 2) equipment: diagnosis and treatment require CT, MRI, microscopes, lasers, ultrasonic tumor aspirators, evoked potentials, and stereotactic frames, equipment that is less frequently available in small hospitals, and 3) accurate neuropathologic diagnosis and adjunctive radiotherapy and chemotherapy, as well as clinical protocols, are not as accessible outside such centers.

A neurosurgeon's goal in dealing with a child with a brain tumor is to give that child the best care possible; that usually involves treatment, either operative or adjunctive, but not always. Infants with large teratomas that virtually replace their hemispheres are probably best cared for by no operation (the tumors are clinically or histologically malignant, and infants die within a few months). Good care requires determining the tumor type either by inference from CT or MRI scans, or by biopsy, and may involve removal of some or all of the tumor. At the Children's Hospital of Pittsburgh, approximately 90% of children are operated on by craniotomy and 10% stereotactically.

This chapter will review the preoperative, operative, and postoperative neurosurgical aspects of care for children with brain tumors. A neurosurgeon's role is clearly not limited to operative aspects of the child's care; parents develop a unique bond with the physician who "has been in their child's head," and neurosurgeons are the appropriate physicians to coordinate the child's preoperative and postoperative care, because after irradiation and perhaps chemotherapy are completed, children need

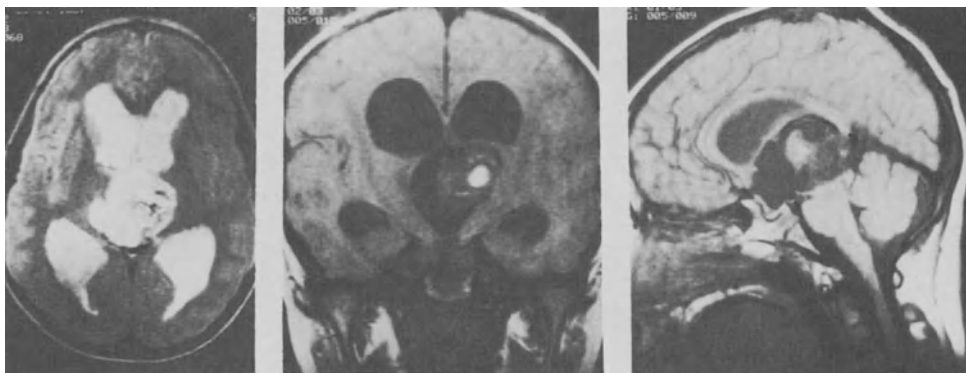


FIGURE 6-1. Axial T2-weighted, coronal and sagittal T1-weighted images of an intraventricular teratoma.

Careful coordinated follow-up to detect both tumor recurrences and the sequelae of treatment.

Preoperative Considerations

DIAGNOSTIC STUDIES

Most children with brain tumors are now referred to neurosurgeons after a CT scan in the local hospital. Good-quality CT scans may be the only radiographic study needed before an operation. Skull X rays occasionally show tumor calcifications or signs of increased intracranial pressure (ICP) but are generally unhelpful. CT is now augmented by MRI scans, which often define the extent of tumor in three planes (figure 6-1) more accurately than CT, and show tumor vessels and displacement of surrounding vessels. The differentiation between tumor periphery and adjacent edema can be difficult on T2-weighted MRI scans. That differentiation has been helped by MRI enhancement with gadolinium.

Angiograms are infrequently performed now, but are still helpful in choroid plexus papillomas to identify feeding arteries and in vascular tumors, e.g., hemangioblastomas. Tumors with large arterial feeders can be embolized by neuroradiologists, substantially reducing intraoperative bleeding (figure 6-2).

Children with brain tumors often require

sedation to obtain good-quality diagnostic studies. Children who are lethargic because of increased ICP associated with a brain tumor should not be sedated without meticulous monitoring of their respiratory status. Children less than two years old can usually be adequately sedated with chloral hydrate, 50 mg/kg orally. Older children may need meperidine (1 mg/kg) plus secobarbital (2 mg/kg). Pupil-dilating drugs are not contraindicated, but their use must be documented in the medical chart to prevent a false diagnosis of uncal herniation. Mannitol is infrequently needed preoperatively.

CLINICAL ASPECTS

The two primary preoperative clinical considerations are increased ICP and seizures. ICP is increased at the time of diagnosis in 60% of children with brain tumors because of hydrocephalus, peritumoral edema, and mass effect. Hydrocephalus is present in the majority of midline and intra-axial tumors, whether supratentorial or infratentorial, and is associated with deep hemispheric tumors that distort the aqueduct. Hydrocephalus causes headaches, vomiting, papilledema, and diplopia, and can be treated either before or at the time of craniotomy by an external cerebrospinal fluid (CSF) shunt (external ventricular drain (EVD) if the neurosurgeon anticipates that tumor removal is

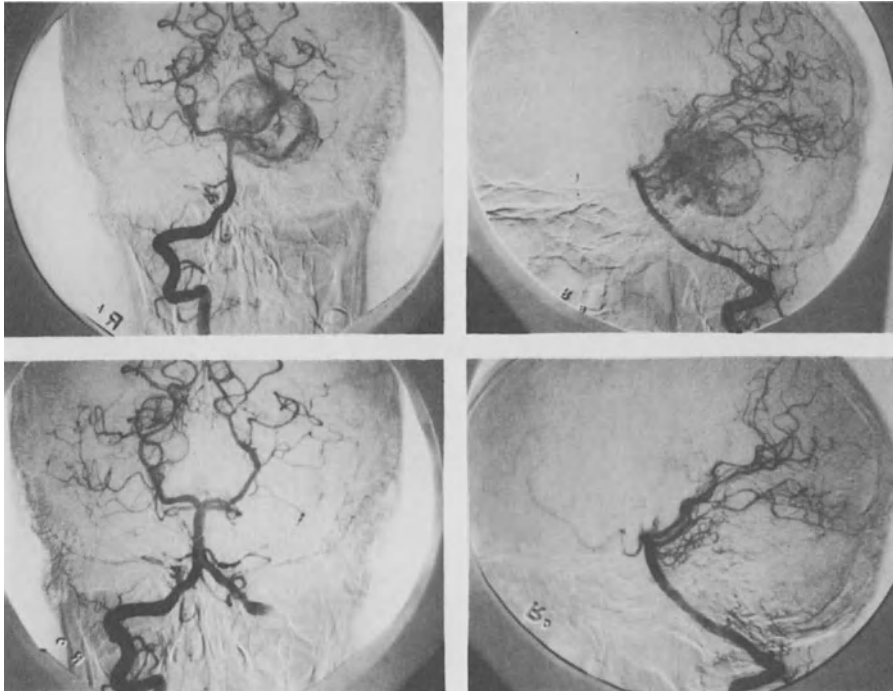


FIGURE 6-2. Vertebral angiogram preembolization (top row) and postembolization (bottom row) of a hemangioblastoma. The left superior cerebellar artery supplied the 4–5 cm tumor and was embolized with 200–300 polyvinyl alcohol particles suspended in contrast material.

likely to open CSF pathways, which is usually the case, or by an internal CSF shunt if tumor removal is unlikely to open those pathways [1]. Hydrocephalus can be treated before craniotomy if it causes obtundation, since a child's condition at the time of craniotomy correlates with the condition afterward. ICP becomes normal within 24 hours after insertion of an EVD and lethargy clears within 2 to 3 days. EVDs can be left in place for one week with a low (less than 5%) risk of infection. They should be drawn several centimeters subcutaneously before exiting the scalp, a technique to reduce infection that is analogous to the one pediatric surgeons use in inserting Broviac catheters. The proportion of children treated with precraniotomy internal shunts has decreased in the past decade because hydro-

cephalus in the majority of children can be effectively treated by tumor removal, with or without an EVD, so that postoperative internal shunts are needed now in less than 30% of children after posterior fossa craniotomies.

Upward herniation has been reported in children with posterior fossa tumors when hydrocephalus is treated by either EVDs or internal shunts. That herniation occurs in approximately 3% of such children, generally those with large midline posterior fossa tumors insinuated up into the tentorial incisura, especially those whose CT scan shows deformity of the posterior third ventricle. The upward herniation compresses the brainstem, and children become obtunded within 12 hours of shunt insertion. The risk of upward herniation can be lessened in children with rostral posterior fossa tumors by inserting EVDs, rather than shunts, so that CSF outflow can be carefully regulated on an hourly basis. If the syndrome develops in a child after insertion of an

internal shunt, the shunt is occluded and unless the child rapidly improves, emergency tumor removal is indicated.

Peritumoral edema is present in many pediatric brain tumors, especially supratentorial ones, and can be reduced by corticosteroids. Dexamethasone, (0.5–1 mg/kg bolus then 0.25–0.5 mg/kg/day divided every six hours) or methylprednisolone (15–30 mg/kg initially and every 4–6 hours) are the steroids given most frequently. Neurologic symptoms and signs improve within 24–48 hours after corticosteroids are begun, although the mechanism of their action on peritumoral edema is unknown. ICP is elevated by tumor mass effect, especially in supratentorial hemispheric tumors, but that effect cannot be reduced prior to craniotomy.

Seizures are associated with 35% of supratentorial, superficial hemispheric tumors, and are more frequently focal than generalized. Children should be started on anticonvulsants if their tumor has caused seizures or if the craniotomy is likely to cause seizures either by increasing peritumoral edema, or because of retracting normal epileptogenic cortex (e.g., temporal, posterior frontal, or anterior parietal). Although carbamazepine (Tegretol®) is the drug of choice for focal seizures, it is not yet available for intravenous injection; if children are treated with carbamazepine, they are switched intraoperatively to phenytoin or phenobarbital, which can be given intravenously.

The hormonal status needs to be evaluated in children whose tumors alter the hypothalamic–pituitary axis, suprasellar tumors such as craniopharyngiomas, germinomas, or astrocytomas, and any intrasellar tumor. If testing reveals hypothyroidism, thyroid replacement should be given for two weeks preoperatively if possible, to avoid the increased risk of general anesthesia on the hypothyroid myocardium.

A decision to operate is based on several factors: the value of making a histologic diagnosis, the need to remove mass effect, and the effect of tumor removal on survival. Operations

are usually needed to make a diagnosis, although there are a few instances where a diagnosis may not alter therapy—optic chiasm astrocytomas, and brainstem gliomas—but note that each of these is a precise histologic diagnosis. CT-guided stereotactic biopsies are ideal for many deep tumors (diencephalon, midbrain, pons) where extensive resections are often precluded by high risks (figure 6-3). Such biopsies can obtain tissue within 1 mm of the desired target, can sample sequentially deeper levels of the tumor, beginning with peritumoral “edema”, then sampling the enhancing tumor ring, and lastly the tumor core [2] (figure 6-4). In order to fit into and be rigidly fixed by the stereotactic frame, a child must be approximately four years old.

Operative Considerations

Virtually all operations for pediatric brain tumors require general anesthesia. Only stereotactic biopsies in older adolescents can be accomplished under local anesthesia plus sedation. The choice of anesthetic agent varies from center to center, but many centers avoid inhalation agents, such as halothane, because they cause vasodilatation, which may increase ICP unless the patient is hyperventilated, and because they abolish the cortical wave form, so evoked potentials cannot be monitored intraoperatively.

Anesthesia is induced with thiopental if intravenous access is available with a minimum of struggling and crying, and then is continued with a mixture of fentanyl, nitrous oxide, and muscle relaxant, or an inhalation agent plus a muscle relaxant. Central venous and arterial catheters are usually inserted before craniotomies. Many neurosurgical operations are long, and children must be positioned to avoid pressure points. For supratentorial craniotomies, children are usually positioned in the supine or lateral position. For infratentorial tumors, the prone or lateral positions are used more often, because of concern for venous air embolism, than the upright position, which is often used in

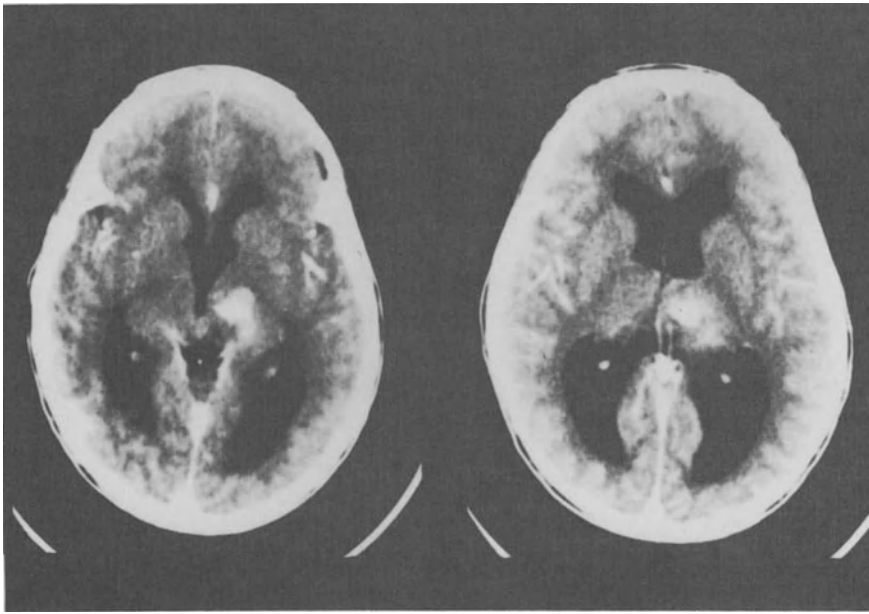


FIGURE 6-3. Contrast-enhanced axial CT scan of a partially calcified left thalamic tumor in a neurologically normal six-year-old with headaches. Stereotactic biopsy diagnosed a low-grade astrocytoma.

adults. The child's head may need to be stabilized in a three-pin head holder. Since the pins can penetrate the skull of a young child and cause a depressed skull fracture, infants' heads are usually supported by foam pads or rings.

The use of prophylactic antibiotics is debated. The risk of craniotomy infection is 2.5% or less without antibiotics, but many neurosurgeons use them because of the report of Malis, who found no infections in 1732 patients operated on with one intraoperative dose of vancomycin and tobramycin, with streptomycin in the irrigating solution [3]. Phenytoin or phenobarbital are given intravenously intraoperatively if the child has seizures preoperatively or if the operation is thought likely to cause postoperative seizures. Corticosteroids are given as a bolus at the onset of operation and repeated every six hours if the operation continues that long.

If the child's ICP is increased, it is usually lowered intraoperatively by mannitol, 0.25–1

gm/kg, and by CSF drainage via an EVD, inserted after the institution of general anesthesia but before craniotomy. Minimizing blood loss is more important in infants and small children because of their small blood volumes and low cardiovascular reserves. Blood loss is minimized by injection of epinephrine solutions along the scalp incision, compression of scalp vessels until scalp clips are applied, waxing bone margins carefully, and meticulous hemostasis.

Intraoperative monitoring of visual, brainstem, and somatosensory evoked potentials (EPs) probably lowers the morbidity of tumor resections near those pathways. If the latency of the EP increases or the waveform deteriorates, the likelihood of neurological deficit is increased, and the neurosurgeon generally waits a few minutes until the waveform recovers and then approaches the tumor from a different angle. The appropriate pathways must be monitored; normal somatosensory EPs during resection near the corticospinal pathways do not mean that the patient will not awaken with a hemiparesis.

The operative approach to a tumor depends on its location, and on minimizing cortical

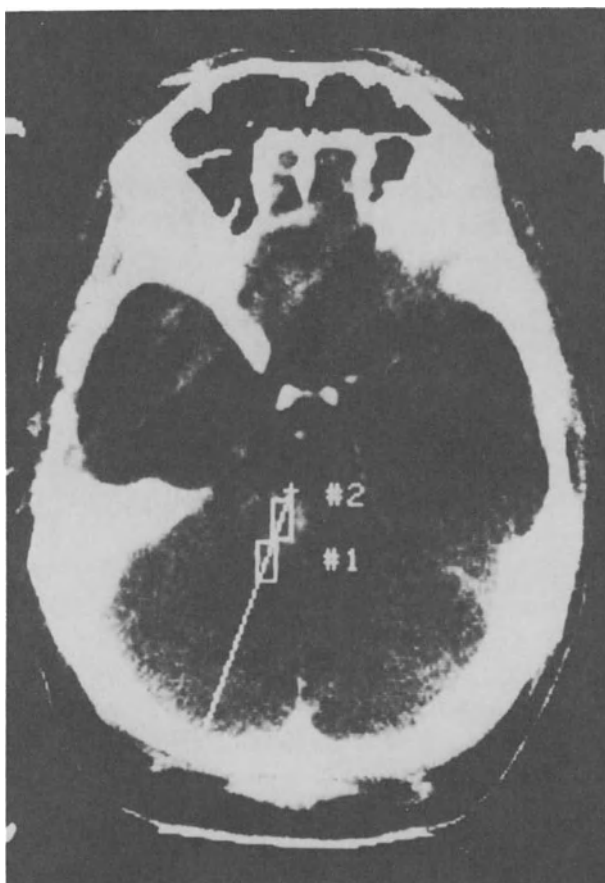


FIGURE 6-4. Intraoperative CT scan of a patient with a brainstem anaplastic astrocytoma undergoing CT-guided stereotactic biopsies. The straight line indicates the trajectory of the biopsy needle; #1 and #2 indicates biopsy sites.

damage and brain retraction. Tumors that present at the cortical surface are approached through a local craniotomy. Deep tumors whose associated cysts extend near the cortex are approached through the cyst. Diencephalic tumors are often approached through the anterior corpus callosum, a route that causes little, if any, neurologic deficit. Choroid plexus and other ventricular neoplasms are approached through the dilated ventricles. If the location of deep or small tumors is uncertain, they can be located intraoperatively by ultrasound. If the location of the central sulcus is in question, cortical mapping of the somatosensory EPs reveals mirror-image waveforms on opposite sides of the central sulcus; in the motor cortex, the major positive and negative peaks occur at 20 and 30 msec after stimulation,

whereas the sensory cortex has the major negative and positive peaks occur at 20 and 30 msec, respectively [4].

Nearly all supratentorial tumors are approached via craniotomies, removing a segment of skull before tumor removal but replacing it afterward. Many neurosurgeons approach posterior fossa tumors via a craniectomy, permanently removing the suboccipital bone, partly because of tradition and partly because of a fear that replacing the bone will increase postoperative pressure within the posterior fossa and increase the likelihood of apnea/bradycardia. That risk, in the experience of this author, is

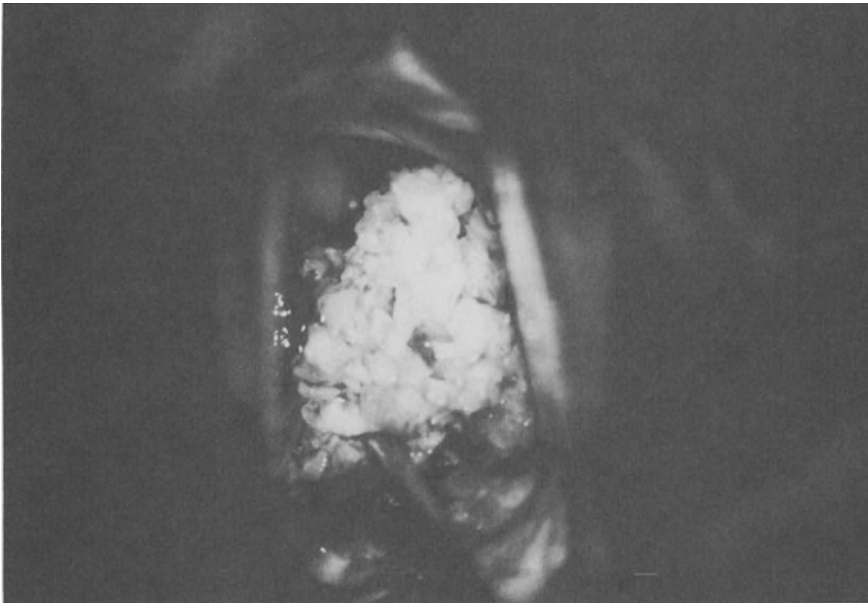


FIGURE 6-5. View through the operating microscope of an intraventricular teratoma approached via the corpus callosum.

negligible if posterior fossa tumors are adequately removed and hydrocephalus is effectively treated.

The goal of most operations is to both biopsy the tumor and to remove as much of it as can be removed without causing or increasing neurologic deficit. There are few circumscribed, well-encapsulated tumors that can be removed in toto. Most gliomas have margins that blend imperceptibly into adjacent normal parenchyma, precluding complete resection. In such cases, removal begins within the nidus of tumor and proceeds toward its periphery, stopping when the differentiation between tumor and brain is indistinct. There is no definite correlation between the "focalness" of a tumor on CT or MRI and its appearance at operation, and the decision as to how much tumor can be removed cannot be made until the tumor is seen.

The operating microscope is an invaluable surgical adjunct. Its illumination and magnification permit surgeons to distinguish tumor margins from adjacent structures with precision

(figure 6-5). It is nearly always used in operations where exposure is limited, as with deep hemispheric tumors, intraventricular tumors, and tumors near the skull base. Microsurgical forceps, scissors, and dissectors are narrow, elongated instruments that permit delicate manipulation of structures at a depth of several centimeters. Because of the fineness of their movement, they are not well suited for intratumoral decompressions of medium or large tumors. Such decompressions are accomplished by the ultrasonic surgical aspirator or the laser, both of which remove tumors with far less trauma to surrounding brain than conventional forceps and scissors. The ultrasonic aspirator has a 1×5 mm tip that vibrates at 22,200 Hz, breaking off microfragments of tumor (figure 6-6). The tip is surrounded by two concentric channels, one dispensing saline to solubilize the fragments and another to suction away that suspension. The most commonly used laser is the CO₂ laser, which emits a narrow beam of light that vaporizes tumors at its focal point. Although lasers have captured the public interest, the ultrasonic aspirator is more frequently useful; it removes tumors more efficiently and



FIGURE 6-6. Handpiece of the Cavitron ultrasonic surgical aspirator. The instrument removes brain tumors with less trauma to adjacent neural structures than traditional instruments.

with less risk to adjacent structures than the laser.

There is debate as to whether the extent of resection correlates with improved survival in pediatric brain tumors. In medulloblastomas and malignant astrocytomas, there appears to be an association between total or near-total resection and longer survival [5]. However, this relationship is less certain in low-grade gliomas, which make up the largest proportion of pediatric tumors. The issue is of importance because of the risks of extensive removals but will probably never be answered definitively. A definitive answer could come only from a protocol in which extent of resection was randomized; neurosurgeons feel strongly, with some basis, that the maximal feasible resection

should be done, and few would participate in a trial randomizing extent of resection.

Infants with brain tumors present different problems [6]. Because infant brains and skulls are pliable, tumors are often very large before they are detected. Few operations are done with infants in the sitting position; their skulls are too thin for pins needed to hold the head upright, and their large dural veins predispose to air embolism. Their skulls are often so thinned by chronically increased ICP that they can be opened with scissors. Their (normally) small major vessels are attenuated even further by the tumor, and major normal vessels may

be mistaken for tumor vessels. Infant tumors are often associated with marked distension of the ventricles. Ventricular collapse must be minimized during and after tumor removal to prevent postoperative refractory seizures and subdural hematomas. Lastly, the extent of tumor removal is more important in infants because the risks of postoperative adjunctive therapy, especially radiotherapy, are substantially higher.

Hemostasis in the tumor bed is obtained primarily by bipolar coagulation but may be augmented by adjuncts such as gelfoam or Surgicel. These materials may alter the appearance of postoperative scans and mimic residual tumor (although they do not enhance after contrast agents are administered). The dura is usually closed primarily, both to prevent CSF leaks and pseudomeningoceles and perhaps to lessen the small chance of spread of malignant tumors such as medulloblastomas. The incidence of postoperative aseptic meningitis is thought to be lower if the dura is closed, whether primarily or with a graft.

Postoperative Care

Postoperative vital signs and neurologic signs are examined frequently for the first 24–48 hours. Fever (37.5–38.5°C) develops in many, if not most, children after craniotomy, and is attributed to atelectasis, intracranial air, and most importantly, to blood and debris in the CSF. After posterior fossa craniotomies, children may develop a syndrome of aseptic meningitis (fever, photophobia, mild nuchal rigidity, irritability, and anorexia). CSF samples from EVDs or shunts will exclude bacterial infection; lumbar punctures in these children are generally avoided because of the risk of tonsillar herniation.

Nearly all postoperative wound infections are epidural. Infections are infrequent (< 2.5%) and present 3–7 days postoperatively with persistent fever spikes, wound erythema and edema, and leukocytosis. Purulent infections

are not confined to the scalp but involve all of the structures in the epidural space, including the bone flap, and are treated by removal of the bone flap, debridement of subcutaneous tissue, and intravenous antibiotics.

Postoperative hematomas usually develop within 24 hours. They occur in approximately 5% of patients either subdurally within the resection cavity or epidurally, but require removal because of lethargy or other neurologic deficits attributable to the hematoma in only 1%. Posterior fossa hematomas have greater risk of apnea/bradycardia and are more likely to be removed than a supratentorial hematoma. Postoperative epidural hematomas occur less frequently in children than in adults, partly because epidural veins are smaller.

Postoperative pain is usually not severe and is treated by acetaminophen and codeine. Postoperative edema may transiently increase neurologic deficits or seizures, and is reduced by the use of corticosteroids, which are maintained for 3–5 days and then tapered off over 3–14 days. The rate of tapering varies depending on the clinical appearance of the child and on the likelihood that edema is contributing to postoperative neurologic deficits or hydrocephalus. Anticonvulsants are continued postoperatively for varying lengths of time, depending on the estimated likelihood of postoperative seizures, and are usually maintained for 6–12 months before being slowly discontinued.

Postoperative CT scans obtained within 48–72 hours have fewer postoperative changes that mimic residual tumor than scans obtained at 3–14 days.

Postoperative complications are lessening and are dependent on several factors: the experience of the operating surgeon, the preoperative condition of the child, the tumor location, and the extent and gentleness of tumor removal. In general, mortality after a craniotomy for pediatric brain tumors is less than 1%. The current morbidity in polar gliomas and cerebellar astrocytomas is 5%–10% and for nuclear tumors is from 20–30%. The likelihood of neurologic

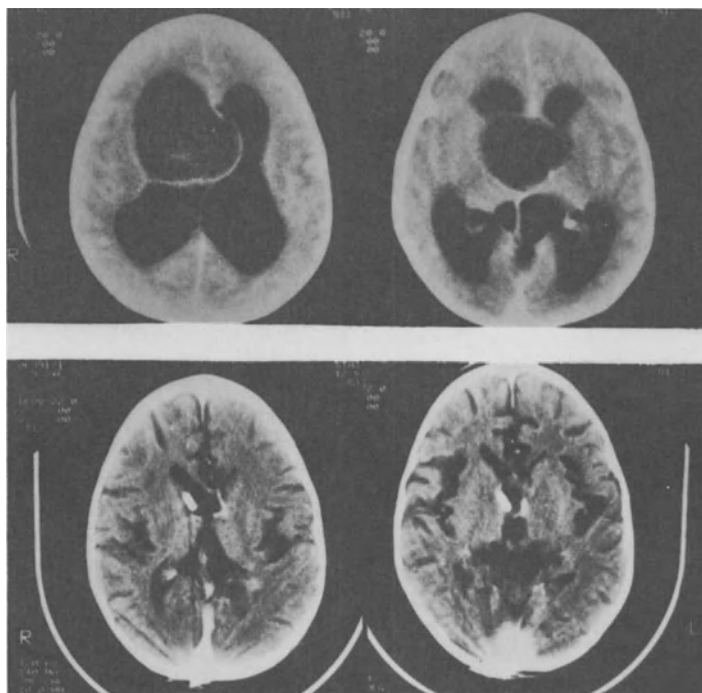


FIGURE 6-7. Axial contrast-enhanced CT scan of a three-year-old boy with a cystic craniopharyngioma before (top row) and 2½ months after (bottom row) intratumoral stereotactic injection with ^{32}P .

deficits recovering depends on whether they resulted from tumor compression and edema, or from tumor infiltration and destruction of normal tissues. Operative morbidity for the various tumors will be discussed in the appropriate chapters.

The likelihood that a new postoperative neurologic deficit will recover depends primarily on one factor, its severity. Although neurologic recovery in children is far better than in adults, a child who awakens from anesthesia with a flaccid hemiplegia is unlikely to regain normal use of those extremities. Neurological deficits that persist for one year rarely resolve later. The usual duration of hospital stay after an uncomplicated craniotomy is 5–7 days. After stereotactic biopsies, children are usually discharged in 1–2 days. Physical and occupational therapy are useful to normalize the child's activities and functions postoperatively.

Craniotomy incisions must be healing well before children begin radiotherapy. Children resume their usual activity level within 2–3 weeks but must avoid physical activities that

have any risk of head trauma until the craniotomy bone flap is well healed, usually by eight weeks. Activities thereafter will depend on the neurologic and hematologic condition of the child and must be individualized. Children with posterior fossa craniectomies have no bony protection for the posterior fossa and should probably avoid contact sports permanently unless a cranioplasty is inserted. Although CSF shunts are rarely damaged during contact sports or by diving, decisions about allowing a child with a shunt to participate in contact sports must be made by that child's neurosurgeon and parents. The frequency of follow-up visits is dependent on the neurologic conditions of the child, the need for additional therapy, and the likelihood of tumor recurrence. Follow-up scans are usually obtained every 3–6 months for 2–3 years for most tumors, then yearly until five years after operation.

Neurosurgeons are increasingly collaborating with radiotherapists to treat solid residual tumors in children by using interstitial radioactive "seeds," usually ^{125}I , to supplement external beam radiotherapy. High activity (40–50 mCi) seeds deliver 30–100 cGy per hour at the tumor periphery and in pilot studies have effectively treated recurrent anaplastic astrocytomas. Some cystic brain tumors (craniopharyngiomas, astrocytomas) can be treated with ^{32}P in colloidal suspension (figure 6-7).

Recurrent brain tumors are usually not operated on, although reoperations are indicated for recurrent juvenile pilocystic astrocytomas in the posterior fossa and occasionally for recurrent gliomas, papillomas, and craniopharyngiomas. If the child is in good preoperative condition and the surgery (with or without adjunctive therapy) has the potential for offering a reasonable quality or quantity of life, the risks of such operations are generally comparable to those of the initial operation [7]. Stereotactic biopsies are occasionally needed to distinguish tumor recurrence from radionecrosis.

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7. RADIOTHERAPY

Melvin Deutsch

On November 8, 1895, Wilhelm Conrad Roentgen, while experimenting with a Hittorf–Crookes vacuum tube, noted fluorescence of a piece of barium-platinocyanide-painted paper and realized that he was dealing with a hitherto undescribed type of radiation. Over the next several weeks, he experimented with this new radiation and noted that wire in the path of the rays projected a shadow on fluorescent paper, but wood, paper, and rubber did not. He discovered that the intensity of fluorescence or the intensity of the radiation was inversely proportional to the square of the distance from the tube. On December 22, 1895, he exposed his wife's hand to these rays and, using photographic plates, produced the first clinical roentgenogram. Roentgen called this new kind of radiation *X-rays*. His discovery became public on January 5, 1896 [1].

Within weeks, Antoine Henri Becquerel reported that the phosphorescence phenomenon of uranium was similar to X-ray and was capable of fogging photographic plates shielded by aluminum. Shortly thereafter, thorium was found to have similar activity and then, in 1898, Pierre and Marie Curie discovered and named polonium and then radium [2].

Several weeks after Roentgen's discovery, Emil Grubbe, a medical student and manufacturer of Crookes tubes, had developed a dermatitis on his left hand from repeated exposure to X-rays produced by his tubes. After showing this reaction to his professors, it was suggested that such a reaction might be therapeutic for skin afflictions. On January 29, 1896, Grubbe exposed a patient's breast cancer

to one hour of X-ray treatment. This represented the first patient ever therapeutically irradiated [3]. Becquerel, Pierre and Marie Curie, and many other early workers also noted skin changes induced by X-ray and radium exposure and within a decade, radiation-induced skin cancers became apparent.

Early in the 1900s, several investigators found that irradiation of the testes of laboratory animals would cause sterility. In 1906, Regaud reported that the mitotic phase of the cellular cycle seemed to be the most sensitive to radiation. Also in 1906, Bergonie and Tribondeau stated that the effects of irradiation were more intense the greater the reproductive activity and the longer the mitotic phase. They also reported that less well-differentiated cells seemed more sensitive [4].

Becelere, in 1909, began using radiation to treat pituitary tumors, and by 1914, Pancoast was treating gliomas with external radiotherapy and/or radium implantations [5,6]. The first therapy machines generated X-rays with a maximum energy of about 100 kilovolts (KV). In 1913, Coolidge developed an improved X-ray tube allowing the generation of 200 KV X-rays [7]. This improvement in penetrability was responsible for 200 KV therapy being called *deep therapy*.

Another early form of radiotherapy for intracranial tumors was the use of radium packs. Multiple radium sources were placed on the skull in order to irradiate intracranial tumors. It is unlikely that tumoricidal doses of radiation could have been delivered to intracranial tumors without causing severe skin reactions. Early

attempts at interstitial implants for brain and pituitary tumors involved the insertion of radium needles into tumors [8, 9]. Early workers realized the hazard to normal tissue from radium and emphasized that the needles should be placed into the tumor and not in the normal brain adjacent to tumor.

Until the Roentgen unit was agreed upon in 1928, there were no systematical, universally accepted means of measuring radiation dose. Early investigators spoke of skin erythema doses, the amount of radiation which in a single administration would cause subsequent erythema of the skin. Radiation treatments in the first quarter of this century were often administered in single large fractions at weekly or monthly intervals. Often treatments were carried out for many months thereafter. An alternative method was to give a series of daily treatments over a period of about one week and then repeat the series at monthly intervals. Some of the single administered doses must have been rather high, and there are reports of acute neurological deterioration occurring within hours following a single dose of radiation to the brain [10].

By the 1920s, some authors were suggesting radiotherapy alone or postoperatively in all cases of glioma. James Ewing typified this enthusiasm when he wrote in 1921, "... I know of no tumor which on a priori grounds ought to yield more readily to moderate radiation than the average glioma" [11].

By 1928, Bailey et al. had treated 456 brain tumor patients with radiation in the eight preceding years [10]. Their technique utilized 130–140 KV X-rays administered via a single portal. Radiation was administered once every three weeks for 4–8 such treatments. Four more treatments were then repeated after an interval of 3–6 months. The single field was placed directly over the tumor. Occasionally bilateral portals were used. The authors noted the responsiveness of rapidly growing gliomas such as medulloblastoma and spongioblastoma multiforme, but they did not believe that

radiotherapy actually cured patients with brain tumors.

Until the early 1950s, practically all external radiotherapy was accomplished with 100–250 KV equipment. The relatively poor penetration of the X-ray beam made it extremely difficult to deliver tumoricidal doses to deep tissues without causing an intense skin reaction. As far back as 1912, attempts were made to use radium as a teletherapy source. The rarity of radium limited the amount available for these units. Outputs were relatively low because of the low specific activity, and the radium source had to be relatively close to the skin, usually 10 cm. In the 1930s and 1940s, several high-energy X-ray machines in the range up to one megavolt were produced. In the late 1940s, the potential of cobalt-60 (1.25 million electron volt or MeV gamma) became apparent. High specific activities of cobalt-60 (1000–3000 curies) could be obtained, making gamma teletherapy practical. The widespread availability of cobalt-60 for therapy in the 1950s and the subsequent development of linear accelerators and betatrons producing megavoltage X-ray and electron beams made possible the delivery of high doses to deeply situated tumors with relative sparing of overlying skin. There is no longer any justification for using less than megavoltage beams for external radiotherapy of brain tumors.

Physics of Radiotherapy

The radiations used in radiotherapy are *ionizing* by virtue of the fact that they ionize atoms. Ionizing radiation may be either electromagnetic or particulate. However, not all electromagnetic or particle radiations are ionizing (table 7-1).

X-rays and gamma rays are part of the broad spectrum of electromagnetic radiation that includes radio waves and infrared, visible, and ultraviolet light. Electromagnetic radiation can be considered as waves of oscillating electric and magnetic fields at right angles to each other.

TABLE 7-1. Ionizing radiation

I. Electromagnetic
A. X-ray
1. Superficial 50–150 KeV
2. Orthovoltage 180–300 KeV
3. Megavoltage or supervoltage ≥ 1 MeV
B. Gamma
II. Particles
A. Beta (electrons)
B. Pi-mesons (pions)
C. Protons
D. Fast neutrons
E. Alpha (He^{++})
F. Heavy charged nuclei (C, Si, Ar)

The term *photon* is used for electromagnetic radiation and is considered as a *packet of energy*. The energy of the photon increases as the wavelength decreases according to the equation:

$$E = 12.4/\lambda.$$

E is energy in kilo-electron volts (KeV) and λ is wavelength in angstroms. Thus, the shorter the wavelength, the greater the energy of the electromagnetic radiation.

X-rays are photons produced by the interaction of high-energy electrons with a suitable target. Gamma rays are photons emitted by atoms during a nuclear transition from an excited to a stable state. *Radioactive* is the term commonly applied to an excited-state atom. Radioactive decay refers to the nuclear transition from an unstable to a stable state. As radioactive decay takes place, gamma rays may be emitted. Different radioactive elements decay by different mechanisms. Some decay with emission of alpha particles having a discrete energy. Other radioactive elements decay with emission of beta particles (electrons or positrons) having a continuous spectrum up to a maximum energy. Gamma rays are emitted in those situations where alpha or beta emission has resulted in the nucleus being in an excited state. The half-life ($T_{1/2}$) is the time period during which one half of a given number of radioactive atoms has decayed. Cobalt-60 has a $T_{1/2}$ of 5.3 years.

Thus, a cobalt-60 source used in a teletherapy unit will have a specific activity one half of its original at the end of 5.3 years. The output (dose/minute) will be one half the original value at the end of 5.3 years.

The methods of administering radiotherapy can be divided into two broad categories: teletherapy (external radiotherapy) and brachytherapy (close or short-range therapy) (table 7-2).

External Radiotherapy

By far the most common mode of administering radiation is teletherapy or external therapy. A source of radiation is at a distance from the patient, usually at least 80 cm for cobalt-60.

TABLE 7-2. Methods of radiotherapy

I. Teletherapy (external)
A. Gamma teletherapy
Co-60, 1.25 MeV
Cs-137, 0.662 MeV
B. Superficial and kilovoltage X-ray machines
50–300 KeV
C. Linear accelerators and betatrons
Electrons and X-rays, 4–40 MeV
D. Deuterium–tritium neutron generators
Fast neutrons
E. Cyclotrons, very large accelerators
Neutrons, pi-mesons, protons, He^{++} , heavy charged nuclei
II. Brachytherapy (short-range): Encapsulated gamma sources
A. Interstitial: Sources in seeds, needles, wires inserted directly into tumor
B. Intracavitary: Sources in ovoids, tandems, capsules inserted into body cavity containing tumor
C. Molds: Sources on appliance attached to tumor.
III. Unencapsulated sources: Gamma- or beta-emitters
A. Intracystic, intrathecal, intraperitoneal, intrapleural
B. Systemic administration of tumor-seeking molecules with radioactive isotope

The source of radiation and the patient are positioned so that the tumor is irradiated from one or more directions. Collimation and blocking between the source and the patient define the size and shape of the radiation beam. The external source may be a radioactive nuclide such as cobalt-60 or cesium-137 that continuously emits gamma rays or else a linear accelerator or betatron that produces X-rays and electron beams.

For external radiotherapy, X-rays and gamma rays are used most often. Electrons are the most common particles used for external radiotherapy. X-rays are described by the maximum energy of the photons in the beam. For superficial X-ray, the maximum energy is in the 50–150 KV range, and for orthovoltage, the maximum energy is 200–300 KV. Megavoltage or supervoltage radiation beams have a maximum energy over one million eV (1 MeV). In the X-ray beam, there is a continuous spectrum of photon energies up to the maximum. However, lower-energy photons are filtered out by the X-ray tube. For superficial or orthovoltage beams, filters of aluminum or copper are inserted into the beam to absorb the lower-energy photons and thus “harden” the beam.

The greater the maximum and also the average energy of the photon beam are, the greater will be the penetration of the beam in matter (figure 7-1).

For less than megavoltage X-rays, the maximum dose is at the surface. For megavoltage X-rays and gamma rays, the maximum absorbed dose is below the surface. This is the skin-sparing effect that is so important in radiotherapy. The depth of the maximum dose ($D_{\max}$) varies with the energy of the X-ray or gamma ray. For cobalt-60, the $D_{\max}$ is 0.5 cm below the surface. For 8 MV X-ray, the $D_{\max}$ is 2.0 cm below the surface and accordingly, the actual dose at the surface will be less than with cobalt-60. The greater the photon energy, the greater will be the depth of the $D_{\max}$ (figure 7-2).

The only radioactive isotope used in tele-

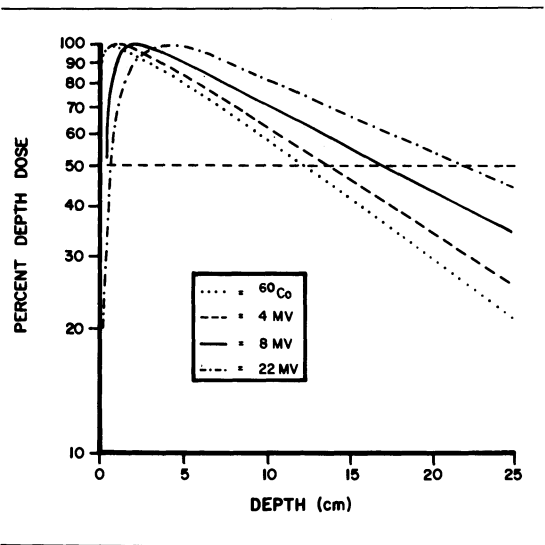


FIGURE 7-1. Beam energy versus penetration in tissue. $10 \times 10 \text{ cm}^2$ field size. Note that 50% of the cobalt-60 (1.25 MV) beam is attenuated by about 12 cm, whereas for the 22 MV beam, it takes approximately 22 cm of tissue to attenuate 50% of the beam.

therapy today is cobalt-60, which is produced in a nuclear reactor by bombardment of cobalt-59 with neutrons. Cobalt-60 emits two gamma rays, 1.17 and 1.32 MeV monoenergetic beams, as it converts to nickel-59. Cobalt-60 can be produced with a specific activity, 2000–5000 curies, high enough to provide a dose rate of 100–150 rads at 80 cm from the source.

For electromagnetic radiation, the source-to-skin distance (SSD) is important in defining the depth-dose isodose curves. The depth-dose penetration will be greater at longer SSDs. For cobalt-60, $10 \times 10 \text{ cm}$ field, the 50% isodose line is at 11.1 cm with an SSD of 70 cm. If the SSD is increased to 100 cm, the 50% isodose line is at 12.1 cm from the surface. However, as the SSD increases, the dose rate at the surface will decrease.

Electron beams in the 5–20 MeV range produced by accelerators are the most common particle beams used in teletherapy. The penetration of an electron beam through matter is dependent upon its energy, with a rapid falloff

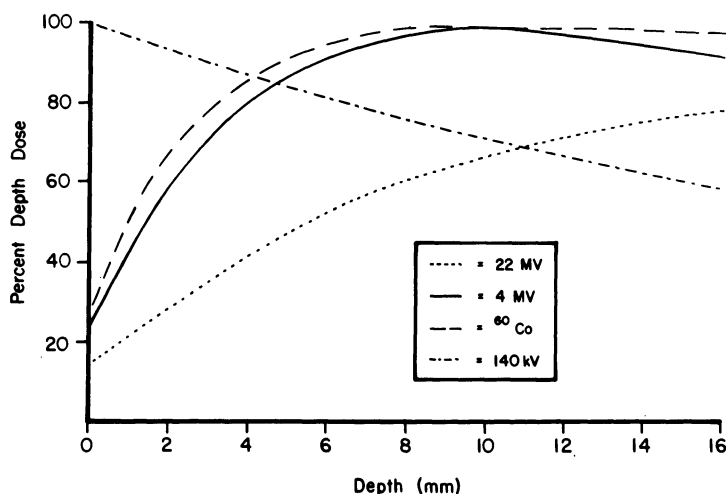


FIGURE 7-2. $D_{\max}$ versus energy. With 140 KV, the 100% dose line is right at the surface, whereas for supravoltage radiation, the dose right at the surface is much less. The higher the energy of the beam, the greater the distance from the surface will be the $D_{\max}$.

in dose beyond a certain depth (figure 7-3). As with megavoltage X-rays, there is some skin-sparing effect with megavoltage electrons, but this is very slight. Unlike megavoltage X-rays, the higher the electron energy, the less will be the skin-sparing affect. The rapid dropoff in dose can be advantageous in treating tumors near the surface that are overlying deeper vital structures.

Brachytherapy

Brachytherapy is the use of encapsulated radioactive sources placed within or in contact with the tumor. Radioactive nuclides used in brachytherapy are listed in table 7-3. Interstitial implants are the commonest form of brachytherapy used in the treatment of brain tumors. Implants can be either temporary or permanent. For permanent implants, seeds are placed directly into the tumor. However, in order to prevent migration of the seeds, techniques have

been developed that use radioactive seeds in plastic catheters. These may be left in place indefinitely. For permanent implants, low-intensity iodine-125 (I-125) seeds have been used. For temporary implants, high-activity I-125, gold-198 (Au-198), or iridium-192 (Ir-192) seeds in catheters are most frequently used.

Most temporary implants are done by first inserting plastic tubes into the tumor in the desired location. Once the position of the tubes is verified, the radioactive sources in narrower tubing are then afterloaded into the original tubes. By choosing the appropriate specific activity of the seeds, and with accurate placement using stereotactic guidance, it is possible to deliver high doses to a well-defined volume.

The naturally occurring radionuclides, radium and radon, that were the mainstay of brachytherapy until the 1950s are no longer used in many departments. Since radon is a gas, there was always the potential for a serious contamination problem in the event of damage to a radium source. Radium and radon have been largely replaced by the numerous nuclear-reactor-produced radionuclides, such as cobalt-60, gold-198, cesium-137, iridium-192, and iodine-125, which offer the radiation oncologist

TABLE 7-3. Properties of selected radionuclides useful for therapy

Nuclide	Half-life	Useful radiation
<i>Encapsulated sources</i>		
Ra-226	1604 years	0.83 MeV gamma
Rn-222	3.82 days	0.83 MeV gamma
Co-60	5.26 years	1.25 MeV gamma
Cs-137	30 years	0.662 MeV gamma
I-125	60.25 days	0.028 MeV gamma
Ir-192	74.2 days	0.38 MeV gamma
Au-198	2.7 days	0.416 MeV gamma
Cf-252	2.6 years	2.1 MeV neutrons 6.1 MeV alpha 0.5–1 MeV gamma
<i>Unencapsulated sources</i>		
P-32	14.3 days	1.7 MeV beta
Au-198	2.7 days	0.416 MeV gamma 0.97 MeV beta
I-131	8.05 days	0.61 MeV beta 0.284–0.637 MeV gamma
I-125	60.25 days	0.028 MeV gamma
S-25	88 days	0.17 MeV beta
Y-90	65 hours	2.24 MeV beta

a wide selection of specific activities, half-lives, and gamma energies (table 7-3). This allows for greater flexibility in designing interstitial implants.

In 1910, the curie, a unit of radioactivity, was defined as the activity of the amount of radon gas in equilibrium with 1 gram of radon-226. At equilibrium, radon is being formed from radium at the same rate that it is decaying to polonium-218. This equilibrium quantity of radon has an activity of about 3.7×10^{10} degenerations per second (DPS). In 1954, the curie was defined as that amount of any radioactive nuclide undergoing 3.7×10^{10} DPS.

Unencapsulated radioactive sources in the form of radioactive isotopes incorporated into compounds also have a role in radiation therapy. Colloidal solutions of chromic phosphate (P-32) or radiogold (Au-198) have been injected into the pleura, pericardium, and peritoneum for the control of malignant effusions. Table 7-3 shows that the beta (electrons) energies of these isotopes range from 0.96–2.2 MeV. For radio-

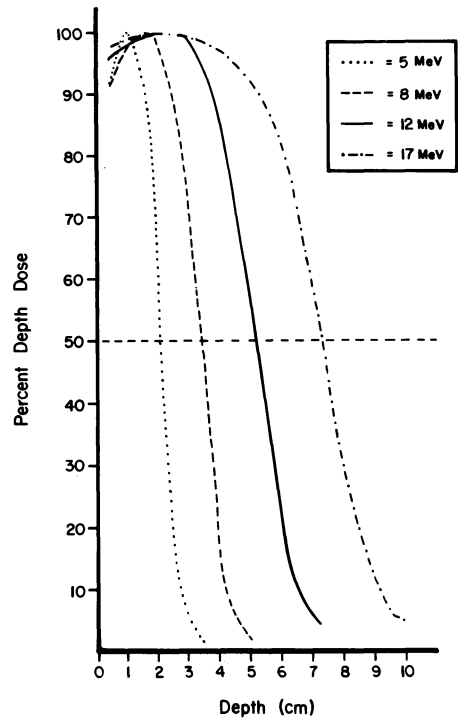


FIGURE 7-3. Electron energies versus depth dose.

active solutions, the beta rays with relatively short ranges are the important feature. It is postulated that the radioactive solutions exert beneficial effects by the direct action of electrons on free cells in the effusions and on seedlings on the serosal surfaces. There may also be a direct effect on the serosal surface, causing fibrosis that limits fluid production.

The use of radioactive solutions for treatment of malignant effusions is less frequent today than in the past. Chemical sclerosing agents and chemotherapeutic drugs injected directly into these body cavities are often just as efficacious.

Radioactive solutions of beta-emitters such as chromic phosphate (P-32) and yttrium silicate (Y-90) have been used to treat primary or recurrent craniopharyngioma cysts [12–14]. The radioactive solution is injected into the cyst using a stereotactic method. Using Y-90 silicate solution, Strauss et al. calculated the dose to the cyst wall to be about 20,000 rad [13].

Colloidal radioactive gold (Au-198) instilled intrathecally was used in the past as a method of irradiating the cerebral spinal fluid pathways in patients with medulloblastoma [15, 16]. It was thought that the Au-198, by emitting short-range electrons, would effectively irradiate the leptomeninges. The occasional occurrence of severe complications, difficulties in determining dose distribution, and lack of proven benefit have accounted for the lack of use of this modality.

Molecules containing radioactive isotopes offer the possibility of selectively irradiating tumor cells if such molecules would be incorporated in or bound to tumor cells preferentially. Isotopes producing low-energy beta rays or alpha rays would have advantages for such type of therapy. The radionuclide would be limited to the tumor-bearing tissues.

In 1952 it was demonstrated that sodium sulphate (Na_2SO_4) injected intravenously was selectively taken up by chondrosarcoma [17]. Subsequently, preferential uptake in chordoma was demonstrated [18]. Using sulphate (S-35), attempts have been made to treat chordoma and chondrosarcoma. Mayer et al. treated six chondrosarcomas and had one good response [19]. Seven chordomas were treated, but only one showed some response and two of the chordoma patients developed terminal leukemia. All patients showed severe pancytopenia. Obviously, the preferential concentration of the radioactive sulfur in tumor was not sufficient to provide therapeutic benefit.

The most successful use of a radioactive compound for therapy purposes is the use of radioactive sodium iodide (I-131) for the treatment of hyperthyroidism and well-differentiated thyroid carcinoma. Iodide is selectively taken up by the thyroid and also by some well-differentiated thyroid carcinomas.

Unlike this situation with thyroid cancer and its preferential uptake of iodine, there are no other tumors which demonstrate such a therapeutically advantageous preferential uptake of an element or compound.

Absorption of Radiation

As gamma rays and X-rays pass through matter, they are absorbed or scattered (attenuated) mainly by photoelectric effect, Compton scattering, or pair production. The method of attenuation depends upon the energy of the photon and to a lesser extent on the matter through which it is passing.

Photoelectric absorption is the main process of attenuation for photons with energies up to 40 KeV. Photoelectric absorption involves a photon interacting with a bound electron, causing it to be ejected from orbit with the energy of the photon minus the binding energy of the electron. Photoelectric absorption varies directly with Z^3 (Z = atomic number). Thus, low-energy photons are absorbed to a greater degree by high- Z materials such as bone (calcium) and contrast material (iodine) than by low- Z elements and compounds such as soft tissue, water, and air (carbon, hydrogen, oxygen). Photoelectric absorption is the principle by which diagnostic radiographs are obtained. With photoelectric absorption, bone attenuates the beam much more efficiently than soft tissue or air. With the use of low-energy radiation for radiotherapy, the absorbed dose in bone may be several times higher than in surrounding soft tissue.

Compton scattering is the primary method of absorption of photons in the 40 KeV–30 MeV range. Part of the energy of the photon is transferred to a loosely bound electron in an outer orbit, and the scattered photon thus has a lower energy than the incident photon. Compton scattering depends upon electron density, and for most living matter, electron densities are similar. Therefore there is very little difference seen between bone and soft tissue on a roentgenogram taken with high-energy photons. Likewise there is only slight preferential absorption by bone with high-energy photons.

Pair production takes place only if the energy of the incident photon is greater than 1.022 MeV. The photon is absorbed by the nucleus

and a positron–electron pair is emitted. Energy in excess of 1.022 MeV is carried off as kinetic energy by the two particles. The positron rapidly combines with a free electron in an annihilation reaction whereby the positron and electron are converted into two photons, each with 0.511 MeV.

Basically, the above three processes produce fast electrons that ionize many atoms before coming to rest. X-rays and gamma rays are referred to as *indirectly ionizing radiation*. They cause the production of electrons that produce the ionizations. Beams of particles with mass and charge such as electrons, protons, and alpha particles are referred to as *directly ionizing radiation*. It is the ionization of atoms that results in the chemical reactions that ultimately lead to biological effects.

As a charged particle transverses matter, it deposits energy along its path in the form of ionization and excitation. Linear energy transfer (LET) refers to the energy deposited per unit length of track of an ionizing particle. This is expressed in KeV/micron. The amount of energy deposited by a charged particle or the rate of loss of energy by the particle will be related inversely to its velocity and directly to its charge. A highly charged, slow-moving particle will have a higher LET value than a faster-moving particle with a lesser charge. As a charged particle moves through matter, its velocity will decrease, and as the velocity decreases the LET will increase. Just before the particle comes to rest there will be a marked increase in the deposition of energy in the form of ionization. This peak in energy deposition is called the *Bragg peak* (figure 7-4).

As electrons slow down in the course of traversing matter, there are multiple changes in direction that completely obscure the Bragg peak. Thus, a Bragg peak type of dose distribution is not seen with high-energy electrons. Heavy charged particles maintain their forward direction in matter, and all show a Bragg peak. The supervoltage electrons and those electrons produced by gamma radiation, X-rays, or su-

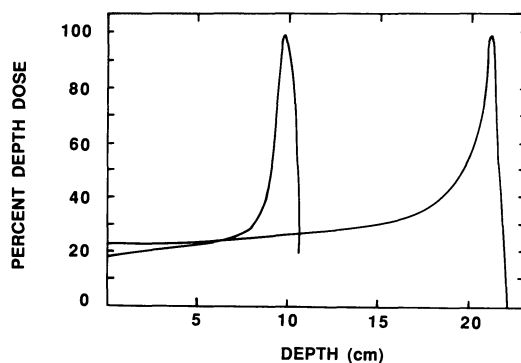


FIGURE 7-4. Depth dose curves for 52 MeV pionson beam (left) and 180 MeV proton beam (right). (Redrawn from Andrews JR: *The Radiobiology of Human Cancer Radiotherapy*. Baltimore: University Park Press, 1978, p 266.)

pervoltage X-rays have a low LET, and these radiations are called low LET radiation.

Neutrons do not have a charge and therefore do not show a Bragg peak dose distribution common to the heavy charged particle beams. For a neutron beam with a mean energy of 8 MeV, the penetration in tissue is similar to cobalt-60.

Neutrons can interact with tissue in one of three ways:

1. Recoiling protons as the neutrons hit hydrogen atoms
2. Recoiling heavy nuclei from other atoms in tissue such as carbon, nitrogen, and oxygen
3. Nuclear disintegrations with emission of helium atoms, deuterons, and other nuclear fragments

The recoiling nuclei of atoms other than hydrogen have a very high LET, but their range is extremely short. Therefore, fast neutron beams are considered high LET radiation.

Dose

Prior to the 1970s, various terms and symbols such as *roentgen*, *R*, and *r*, were used without

specifying whether or not these were absorbed doses. Frequently, the *dose in air* was quoted — an exposure dose — and the reader then had to try to determine the actual absorbed dose, which would depend upon factors such as beam energy, amount of filtration, field size, source to skin distance, etc. The rad is the unit of absorbed dose in tissue (100 erg/gm). In 1980, the gray (Gy) was proposed as the unit of absorbed dose (one gray equals 100 rads, 1 cGy equal 1 rad).

For the reader who encounters the use of absorbed or tumor dose in roentgen (R or small letter r) in the older literature, the roentgen was equal to almost one rad especially for supervoltage radiation. For doses expressed as Roentgen in air, the absorbed dose in rads at the surface may be 20%–30% higher.

The dose for a course of external radiotherapy should always be expressed as total dose/number of fractions/elapsed time. Most centers still treat patients daily, five days per week, and often a stated dose of 6000 cGy/30 fractions implies six weeks of elapsed treatment. Likewise, 6000 cGy in six weeks implies 30 fractions of 200 cGy administered five times per week.

For brachytherapy, the dose should be expressed as total dose in cGy over elapsed time or as a dose/hour. There should be specification of the volume wherein the dose is being administered. The dose around an implant will vary greatly. Tissue adjacent to a source will receive a higher dose than tissue further away. The radiation oncologist must ensure that the desired isodose line covers the tumor volume. Sometimes the expression mg-hrs was used to specify dose; this referred to the amount in milligrams of radium or radium-equivalent isotope left in place multiplied by the number of hours.

Radiobiology

In radiotherapy, the important biological endpoint is cell death or loss of reproductive cap-

ability. In the dose ranges used for clinical therapy, it is believed that damage to DNA is the responsible event leading to cell death.

Damage to DNA may result from the direct action of charged particles or more likely by the indirect action of free radicals produced by the ionization of water. It is believed that the ionization of water with the subsequent production of free radicals is the predominant mechanism leading to alteration of DNA. The free radicals are a highly reactive species with an extremely short half-life (figure 7-5).

The damage caused by radiation may be of three types: sublethal, potentially lethal, and lethal.

Sublethal damage is damage that can be repaired by the cell. Within a certain dose range, most of the damage induced is sublethal repairable damage. Mechanisms of repair are complicated but can be affected by factors such as oxygenation and LET of the radiation. Repair of sublethal damage occurs within four hours of a given dose.

Potentially lethal damage is damage that may be lethal depending upon the postradiation environment. Potentially lethal damage can be demonstrated by irradiating identical cells with the same dose and then varying the postradiation media and obtaining different surviving fractions. Factors that inhibit cell proliferation and delay mitosis will promote recovery from potentially lethal damage.

Lethal damage is irreparable damage that prevents the unlimited proliferation of the cell. The lethally damaged cell may appear viable until such time as it attempts to divide. It is then that the damage becomes manifest as the cell fails to survive replication. The cell even may go through one or more apparently normal divisions before the daughter cells actually die.

Puck and Marcus in 1956 first described the process whereby mammalian cells could be counted and plated in much the same way as bacteria [20]. Using these methods, cell survival can be plotted versus dose curves (figure 7-6). The D_0 describes the slope of the linear

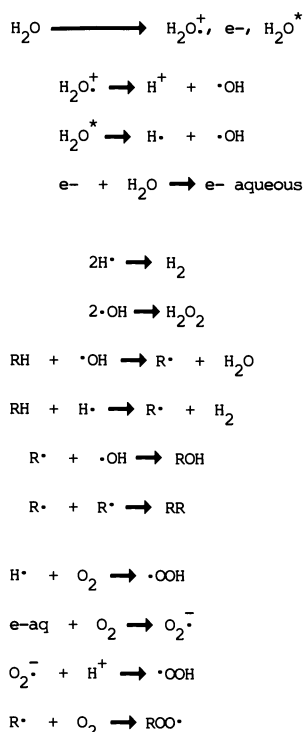


FIGURE 7-5. Possible chemical reaction resulting from ionization of water by radiation.

portion of the curve and is the dose required to reduce the cell survival to 0.37 its initial value along this portion of the curve. The D_0 is the dose required to produce an average of one lethal lesion per cell. Because of the random deposition of radiation, the surviving fraction along the exponential portion of the curve is reduced to e^{-1} (about 37%). Mathematically, the surviving fraction of cells with a simple exponential survival curve (straight line) is $\text{SF} = e^{-D/D_0}$, where D = total dose. The extrapolation number (n) corresponds to the size of the shoulder curve and is found by extrapolation of the straight line of the curve back to the vertical axis. This value is thought to correlate with the number of critical targets that must be hit in order to cause death of the cell. The size of the shoulder is thought to reflect sublethal damage and can also be represented

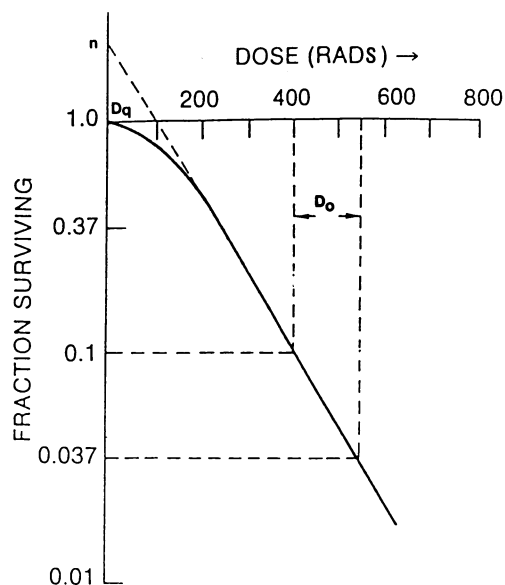


FIGURE 7-6. Typical cell survival curve for mammalian cells. In this example, $D_0 = 150$ rads and $D_q = 100$ rads.

by the term *quasi-threshold dose* (D_q). This is found by extrapolating the straight line of the curve back to the point of 100% survival. The survival curve depicted in figure 7-6 is typical of mammalian cells irradiated with low LET radiation (X-rays, gamma, electrons).

For most mammalian cells, the cell survival curves are remarkably similar. This is true for both normal and malignant cells. The D_0 is usually between 100 and 200 rads, and the extrapolation number (n) is usually between 1.5 and 10.

The sensitivity of a cell to low LET radiation varies with the cell cycle phase. Cells are most sensitive during mitosis and tend to be the most resistant in the S phase. However, between different cell lines there can be variation in the relative sensitivity within the G1, G2, and early S phases.

In 1953, Gray et al. published a series of experimental studies which demonstrated that mammalian tumor cells in vitro and in vivo

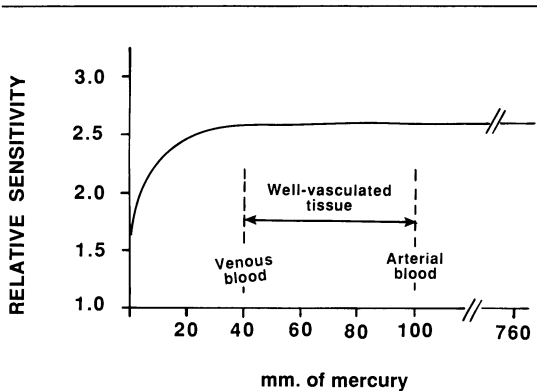


FIGURE 7-7. Sensitivity to low LET radiation as a function of oxygen tension in tissue. Oxygen tension in normal tissues is sufficient to provide maximum radiosensitization.

were about three times more sensitive when irradiated under well-oxygenated as opposed to anoxic conditions [21]. Prior to this time, there had been some reports of the protective effects of anoxia in plants and insects exposed to radiation. Some data in animals had indicated that tissues with a decreased blood supply were more resistant to radiation [22].

The radiosensitivity dependence on oxygen increases as the oxygen concentration is raised from zero to PO_2 levels seen in normally oxygenated tissues (figure 7-7). Further increases in the oxygen concentration beyond normal levels do not produce a corresponding further increase in sensitivity. Also, oxygen administered post-radiotherapy has no effect on sensitivity. Typical cell survival curves for irradiation under anoxia versus well-oxygenated conditions are shown in figure 7-8. The oxygen enhancement ratio (OER) is the ratio of dose in anoxia to dose in air required to give a similar endpoint. For low LET radiation, the OER varies between 2.5 and 3. It is believed that oxygen reacts with free radicals and thus prevents restoration of stable molecules. Furthermore, some of the free radicals produced by combination with oxygen may react with target molecules.

In 1955, Thomlinson and Gray, using lung

tumor nodules, histologically demonstrated that tumors tended to grow in solid masses or in cords not penetrated by capillaries [23]. Tumor cords over 200 microns in radius always contained central necrosis, whereas tumor cords less than 160 microns in radius did not. Thus, necrosis and hypoxia seemed to be related to distance from a capillary. Subsequent animal tumor studies demonstrated that larger tumors have a higher number of hypoxic cells; the percentage of hypoxic cells in a tumor may be as high as 50% [24–26].

Oxygen tension levels in tumor may be affected by conditions other than distance from a capillary. Edema, hemorrhage, and inflammation from infection may lead to capillary congestion with impairment of blood flow and oxygen delivery to tumor cells.

With high LET radiation, the shoulder of the cell survival curve is smaller, the extrapolation number (n) is lower, and the slope of the exponential portion of the curve is steeper (D_0 lower) than with low LET radiation (figure 7-8). High LET radiation, by producing an intense path of ionization, is biologically more effective for inactivating target molecules and producing cell death. The radiobiological effectiveness (RBE) is the ratio of a dose with 250 KV or some other standard radiation versus the dose with another radiation that produces the same end effect in identical test situations. As the LET of a radiation increases, the RBE increases up to a point. Beyond an LET of about 200 KeV/micron there is an overkill phenomenon or wasted energy, and the RBE begins to decrease. With very high LET radiation, the cell survival curve becomes exponential, without a shoulder, and with $n = 1$.

As LET increases, the OER decreases until at very high LET values, the OER is very close to one. With high LET radiation there is minimal sublethal damage — practically all damage is lethal. Thus, there is little recovery between fractions of radiation. Also, there is little variability in radiosensitivity with different phases of the cell cycle.

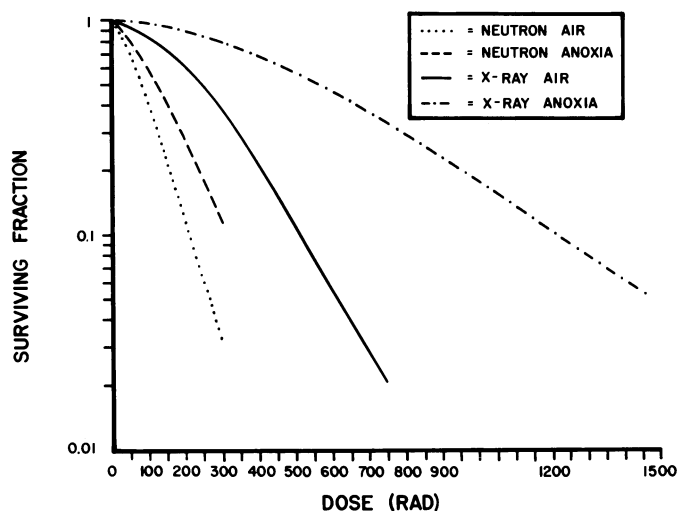


FIGURE 7-8. Effects of anoxia on survival curves for low LET radiation (the two curves on the right) and high LET neutron radiation (the two curves on the left). Note that for high LET radiation, there is a very small shoulder (D_q), and the OER is less than two. As LET increases, the OER becomes closer to one.

The RBE for a high LET type of radiation can vary according to energy, dose, dose rate, and position within the beam (Bragg peak versus plateau). The LET is highest in the Bragg peak, and the RBE tends to be higher in the peak portion of the beam as compared to the plateau. The RBE also depends on the system being tested, and it is important that the RBE of a particular type of radiation be qualified by such factors as endpoint being observed, dose delivered, dose rate, and portion of the beam tested. For example, with californium-252, a neutron- and gamma-emitter, the RBE increases at low dose rates. For cell kill, the RBE is about 6–8. For cataract induction or carcinogenesis, it may be as high as 50 [27].

Cobalt-60, gamma rays, X-rays, and super-voltage electrons are all low LET radiation, and RBE values are close to one when compared to 250 KeV X-rays. Actually, the RBE is slightly less. Fast neutrons and pi-mesons are high LET radiations, as are the heavy nuclei particle beams made up of the nuclei, without orbital electrons, of neon, argon, silicon, carbon, etc., and have a higher RBE than the low LET radiations. Protons and helium particle beams have a high LET in the Bragg peak, but radio-

biologically are characteristic of low LET radiation; their RBE is about 1.1–1.4. Even the heavy charged particle beams may have a low RBE in the plateau portion of the beam.

The terms *radiosensitive*, *radioresponsive*, and *radiocurable* are often used incorrectly and interchangeably. Very few human tumors are indeed radiosensitive, responsive, and also highly curable, such as seminoma. The term *radiosensitive* is best applied in the context of the cell survival curve. Cells that have a low D_0 are radiosensitive. An agent that lowers the D_0 acts as a radiosensitizer. Responsiveness to radiation signifies the rate at which a tumor mass regresses in size during or following radiation. This rate of regression can depend upon proliferation kinetics of the tumor, architectural structure, and location of the tumor mass. Tumors that are rapidly proliferating may respond with dramatic regression in size, but these same tumors, if not completely sterilized,

can regrow rapidly. On the other hand, a slowly proliferating tumor may respond slowly over a period of weeks or months. The curability of a tumor by radiation is not necessarily related to the rate at which it regresses.

Fractionation

The experimental studies by Regaud on ram's testicle showed that fractionated radiation sterilized the testicle without causing necrosis of overlying skin, whereas a large single dose would cause necrosis of the skin without permanent sterilization. Coutard, and later Baclesse, applied this concept in the clinical practice of radiotherapy [4]. Patients were treated with daily doses over a protracted uninterrupted period (fractionation). A greater total dose could be administered resulting in improved clinical results without an increase in adverse sequelae.

The possible advantages of administering radiotherapy in daily treatments over many weeks (fractionation) instead of one or two large doses include the following:

1. *Repair of sublethal damage.* It is believed that normal cells have a greater capacity than tumor cells to repair sublethal damage. Most sublethal damage is repaired within four hours of a dose.
2. *Reoxygenation.* As well-oxygenated tumor cells are destroyed during therapy, there will be increased oxygen delivery to previous hypoxic tumor cells, rendering them more radiosensitive.
3. *Regeneration.* Between fractions of radiotherapy there will be some repopulation of cells. Fractionation will be advantageous if normal cells repopulate to a greater degree than tumor cells.
4. *Redistribution.* A dose of radiation will preferentially kill cells that are in the most sensitive phase. Immediately after the dose of radiation, there will be a partial synchrony of the residual population. Cells

will then redistribute into the sensitive phases of the cycle. Previously resistant cells may redistribute into more sensitive phases by the time of the next treatment. It is difficult to extrapolate the redistribution concept to human radiotherapy.

The appearance in time of radiation effects in normal tissues are related to the rate of cell turnover. Tissues with a rapid turnover of cells, such as the oral mucosa, intestinal mucosa, and skin, manifest a rapid response to radiation and will recover rapidly. Tissues with slowly proliferating cells will show a delayed or late response to radiation. Clinical experience has demonstrated that larger but fewer fractions with total doses adjusted to give equivalent acute effects will produce more severe late effects.

Clinical radiotherapy developed empirically to the point that radiotherapy courses for curative intent are usually given in a series of continuous daily treatments administered five days per week for up to seven weeks, usually at 180–200 cGy/day. However, it frequently happens that such a continuous course cannot be completed for a variety of reasons. Intercurrent illness, deteriorating clinical condition, and socioeconomic factors may necessitate interruption in therapy lasting several weeks or more. Sometimes daily treatments may be impractical and may cause extreme hardship for patients living at a great distance from a center. In an attempt to equate different fractionation-dose schemes and to correct for interruptions, Ellis proposed the Nominal Standard Dose (NSD) concept [28].

$$NSD = Total\ Dose / N^{0.24} \times T^{0.11}$$

Total dose is expressed in rads. N is the number of fractions, and T is overall time in days. NSD is expressed in ret. This concept is based on iso-effects on skin and normal connective tissue. Regimens with the same NSD may have varying effects on tumor and other normal tissues. A

minimum of four treatments is necessary for using this formula. Orton and Ellis further simplified this concept with the time-dose-fractionation (TDF) value [29]. One can get TDF values from tables and use the TDF to equate different therapy regimens. The same constraints apply to TDF as to the NSD concept.

From the NSD and TDF concepts it becomes apparent that a small number of large fractions may be equivalent biologically to a large number of smaller doses.

It is important to treat all fields daily. If a midline lesion is being irradiated with alternating lateral fields, each delivering 200 cGy at the tumor, there will be variation in the dose at the lateral aspects of the irradiated volume. With the 200 cGy doses being delivered by one of the lateral portals, the entrance-side $D_{\max}$ may be 300 cGy or more, whereas on the opposite side, the exit dose will be much less than 200 cGy. Thus, there will be alternating high and low doses at the entrance and exit regions. The biological effect of alternating high and low doses may be much greater than if the daily entrance and exit doses are unchanged and similar to the midline tumor dose, as would be the situation where bilateral opposed portals are used to treat a midline volume. Mathematically, the NSD is higher for alternating high-low doses than for the same daily intermediate dose schedule. The greater the separation between the entrance and exit fields and the lower the energy of the treating beam, the greater will be the differences between the midline and lateral doses, and thus the greater will be the biological effects on normal tissue by treating alternate fields daily.

Therapy Planning

Obviously, the most important aspect of treatment planning is to define the tumor volume accurately. Prior to the advent of computerized tomography (CT), tumor localization and subsequent portal arrangements were determined

by angiography, pneumoencephalography, nucleotide scanning, plain skull films and neurologic signs. With CT and magnetic resonance imaging (MRI), intracranial tumors can be much more accurately localized.

The volumes irradiated in the treatment of childhood brain tumors vary from just a few cm^3 , as in the treatment of a pituitary adenoma, to the entire craniospinal axis, as for medulloblastoma. Once the volume to be irradiated (tumor plus margin) has been determined, the optimum portal arrangement, beam energy, and method of dose delivery must be ascertained in order to irradiate the target volume as homogeneously as possible and minimize the dose delivered to normal tissues.

Figure 7-9 shows a plan for irradiation of a midline suprasella tumor by a single lateral field using 8 MV X-ray. If a minimum tumor dose of 5000 cGy is intended, then the portion of brain between the right edge of tumor and the skin surface would be irradiated to a dose 10%–20% higher. With a single lateral cobalt-60 beam, the excess dose to normal brain would be even higher. Also, the distribution across the tumor volume is rather inhomogeneous using a single lateral field. By using two lateral fields, a more homogeneous distribution across the tumor volume is achieved. However, with a bilateral field arrangement, there is still a higher dose at the entrance and exit sites of the beam, and the brain lateral to the tumor receives a higher dose than the tumor. The excess dose can be minimized by using higher energy beams.

A four-field technique further limits the high dose volume to just the region of the tumor volume. A three-field arrangement (two lateral and one anterior) could be used, but then wedges or compensators have to be placed in the lateral beams to attenuate the anterior portion of the beams.

Some childhood brain tumors require irradiation of the craniospinal axis because of the high likelihood of dissemination via the CSF pathways. Usually, the entire brain is irradiated via two large lateral portals and the entire spinal

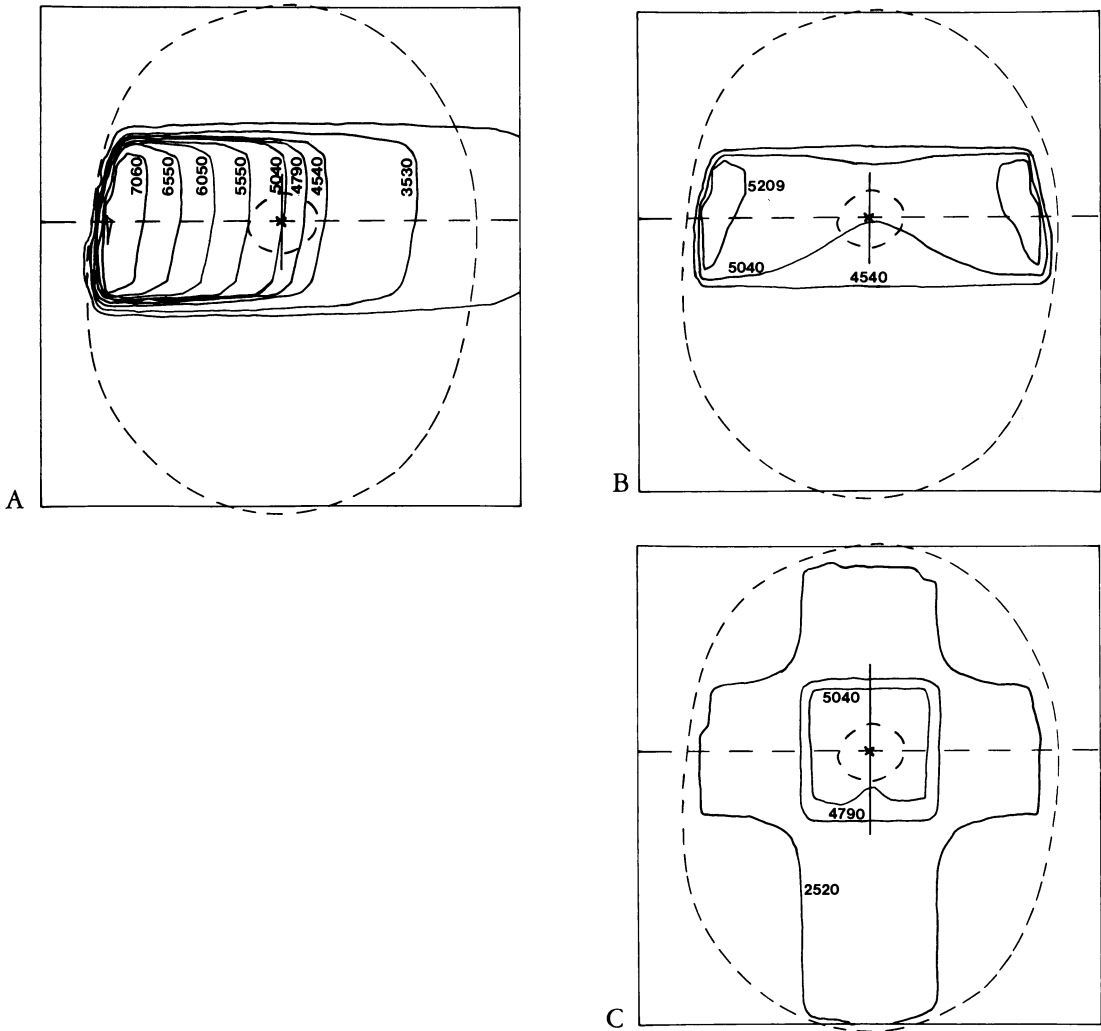


FIGURE 7-9. Three different treatment plans for treating a midline tumor with 8 MV X-ray. In all cases, the intended minimum total dose to the tumor is 5040 cGy. A. The entire dose is administered via a single lateral field. There is inhomogeneity of dose across the actual tumor, and the dose to normal tissue between the tumor and the surface through which the beam enters is much higher than at the tumor. This is an unacceptable method for treating the tumor. B. The midline tumor is treated using two lateral portals. The dose distribution across the tumor is homogeneous. However, there is still a higher dose to the normal tissues lateral to the tumor. This dose discrepancy between the midline and the adjacent normal tissues in the beam can be minimized by using a higher-energy beam. C. A four-field arrangement, two laterals and anterior–posterior, provides a much better dose distribution. This method limits the high dose volume to the midline. Normal tissues near the exit and entry points of the beams receive a much lower dose.

cord by a single posterior field. The patient must be in the same position for treatment of all fields. It is especially important that the borders between the brain fields and spinal field be positioned precisely in order to avoid overdosing or underdosing a portion of the upper cervical cord. Methods have been described by Van Dyke et al. [30] and Bukowitz et al. [31] that allow for correct positioning of the two lateral brain portals with the posterior spinal portal. Maor et al. have described a technique for craniospinal-axis irradiation using 6 MV X-rays for the two lateral brain portals and high-energy electrons for the posterior spinal portal [32]. For craniospinal irradiation, accuracy is easier to achieve if the patient can be kept immobilized in the prone position. However, for young children requiring sedation and for those in poor clinical condition, it may be necessary to have the patient lying supine. Tokars et al. have described a method of administering craniospinal irradiation by using a single large field including the entire brain and the entire spinal cord [33]. The patient lies prone with the head turned 90° to the right and left side on alternate days. This method eliminates the need for having a junction between the cranial and spinal fields.

Treatment planning is done on a simulator X-ray machine whereby the portals are drawn on the patient's scalp. By using CT and/or MRI, a three-dimensional tumor volume is related to the patient's skull [34]. Appropriate shielding can be added. The simulator is a diagnostic X-ray machine that simulates an actual treatment by a therapy machine by using the same field sizes and distances from the source to the skin. A film from the simulator with the field outlined is a representation of the actual area to be irradiated by the therapy machine. Film detail on the diagnostic-type simulator machine is much clearer than radiographs taken on the actual treatment machine (figure 7-10). Most centers have the computer capability to generate treatment plans and isodoses. Using the computer, a great variety of

field arrangements can be planned and evaluated in a short period of time.

For most therapy machines, the output (rads/minute at 80 cm or 100 cm) is high enough so that the treatment of each portal takes only about 1–5 minutes. Obviously, the patient has to remain immobilized for the duration of the treatment. Bite blocks, plastic molds, and other immobilization devices are used to keep the patient steady during the treatment. For infants and uncooperative toddlers, the author has been using general anesthesia, usually Ketamine®. Sometimes, prior to trying Ketamine®, sedative agents, such as phenobarbital, Demerol®, and Thorazine® are tried alone or in combination.

Therapy is usually administered in a continuous course of daily treatments, five days per week, over 5–7 weeks. Daily and total doses are determined in part by such factors as tumor histology, tumor size, location, age of the patient, and concomitant other therapy.

Acute Sequelae

The acute side effects of radiotherapy for brain tumors are rarely life-threatening and usually resolve within weeks after completion of treatment. Hair loss begins after about 3–4 weeks of daily treatments at 180–200 cGy per day. Obviously, alopecia will be limited to those portions of the scalp through which the radiation beam enters or exits. Regrowth of hair usually begins within several months following completion of radiotherapy if the dose to the scalp has been in the range of 4500–5000 cGy over 5–6 weeks. Portions of the scalp receiving higher doses may show less than full regrowth of hair. Whenever possible, multiple fields should be used so that no area of the scalp receives more than 3500–4000 cGy over 5–6 weeks.

Sometimes erythema is seen on the treated portion of the scalp; this may be severe in the posterior auricular region due to loss of the skin-sparing effect because of the overlying

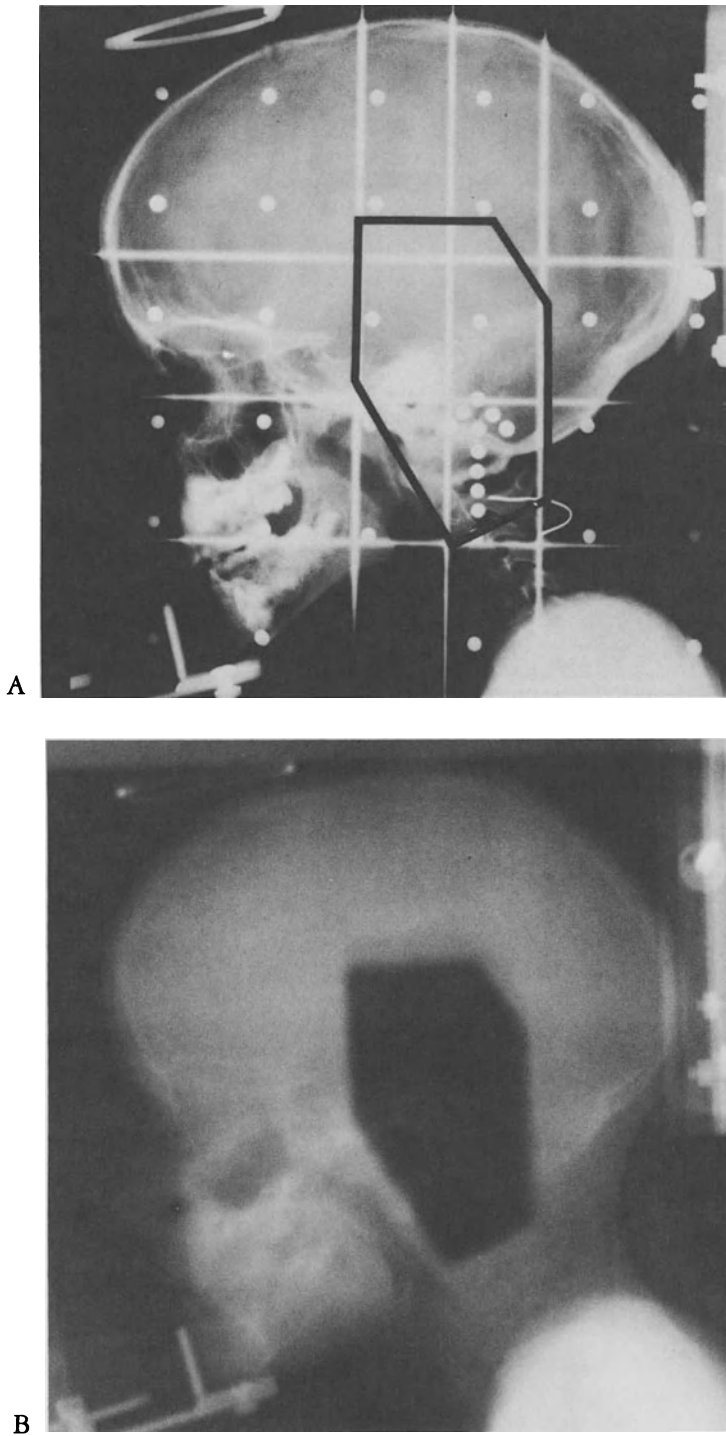


FIGURE 7-10. A. Simulation film on the left taken with a diagnostic X-ray beam shows the field outline for irradiation of a brainstem glioma. B. Portal film taken on the actual treatment unit (8 MV) shows much less detail, since with megavoltage X-ray there is very little preferential absorption of the beam in bone.

ear. However, with the use of megavoltage radiation, the skin reaction is rarely severe enough to warrant interruption of therapy.

Craniospinal irradiation, as for medulloblastoma, is associated with additional acute sequelae due to the long spinal field that overlies the pharynx, esophagus, and part of the stomach and intestines. Thus, mild to moderate pharyngoesophagitis and nausea may occur but usually resolve within a few weeks after completion of treatment. Hematopoietic depression occurs with craniospinal irradiation but is seldom severe enough to necessitate interruption of therapy. However, concomitant chemotherapy may aggravate hematopoietic depression. With irradiation of just a portion of the brain, the amount of bone marrow included in the beam is not enough to cause hematopoietic depression.

Otitis-media-type symptoms may occur during the course of radiotherapy if the middle ear is included in the high dose volume.

Tolerance of normal brain to radiation is dependent on the total dose, individual fraction size, type of radiation (high LET versus low LET), volume irradiated, age of the patient, and the use of concomitant chemotherapy. Radiation oncologists have often described tolerance in terms of doses that would cause a particular incidence of brain necrosis or severe damage. However, even much lower doses can be associated with late sequelae that can affect quality of survival (chapters 22, 23).

Approaches to Improving Radiotherapy

Conventional radiotherapy is still the most effective modality for the treatment of malignant gliomas, the primitive neuroepithelial tumors (PNET, medulloblastoma), and also the histologically benign tumors unresectable by location, such as optic chiasm glioma and the midline intra-axial tumors. However, for many tumors, long-term control by radiotherapy is infrequent.

Various means have been explored to improve the effectiveness of radiotherapy (table

TABLE 7-4. Approaches to improving radiotherapy

-
I.	Improved Dose distribution
A.	Brachytherapy—interstitial
B.	Heavy charged particle beams
C.	Intraoperative external radiotherapy
D.	Stereotactic radiosurgery—Gamma Knife
II.	Overcoming hypoxic cell resistance
A.	Hyperbaric oxygen
B.	Hypoxic cell sensitizers
C.	High LET radiation—fast neutrons
D.	Hyperthermia
III.	Exploitation of biological differences between tumor and normal tissue
A.	Alterations in fractionation schedules
B.	Radioprotector chemicals
C.	Boron neutron capture therapy
D.	Halogenated pyrimidine analogues as radiosensitizers
E.	Tumor-seeking radioactive molecules
-

7-4). These methods can be divided into three main approaches:

1. Improved dose distribution
2. Overcoming hypoxic cell resistance
3. Exploitation of biological differences between tumor and normal tissues

One of the major limitations of radiotherapy in terms of dose delivery is normal tissue tolerance. If conventional external radiotherapy is used there is always some dose delivered to normal tissues. CT and MRI have greatly simplified the task of defining the main tumor volume. However, gliomas and other malignant tumors are infiltrative by nature, and a margin of normal-appearing tissue should be included in the irradiated volume in order to ensure irradiation of all tumor cells. With better definition of tumor volumes, the margin of normal surrounding brain could be decreased. Computer planning is useful for demonstrating field arrangements that deliver homogeneous high doses to the tumor volume while at the same time limiting the amount of normal tissues in the high dose volume. Among the various available radiation modalities that

are predicated on the delivery of a high dose to the tumor volume and a much lower dose to the surrounding normal tissue are heavy charged particle beam irradiation, intraoperative radiotherapy, interstitial radiotherapy, and stereotactic radiosurgery.

The presence of hypoxic but viable cells in tumor and their increased resistance to radiotherapy is considered to be a major reason for failure to control large tumors. Attempts to overcome the inherent resistance of hypoxic cells include hyperbaric oxygen, chemical hypoxic cell sensitizers, high LET radiotherapy, and hyperthermia.

Biological differences between tumor and normal tissues offer another possibility for improving the effectiveness of radiotherapy. Normal intracranial tissue such as neurons, glial cells, and vascular tissue have a much lower mitotic index or proliferation rate than malignant gliomas. The blood-brain barrier may be disrupted in the presence of the tumor but not in normal areas of the brain, thus limiting access of drugs to normal cells. Attempts to exploit these biological differences involve changes in fractionation schedules, boron neutron capture therapy, radioprotectors, and the use of halogenated pyrimidine analogues as radiosensitizers. In addition, one can consider the use of tumor-seeking radioactive tagged molecules as a method of exploiting biological or immunological differences between tumor and normal cells.

Interstitial Radiation

There has been a recent resurgence of interest in using interstitial radioactive sources for the treatment of brain tumors. I-125 and Ir-192 are probably the most commonly used nuclides for brachytherapy of brain tumors. I-125 is a convenient isotope for interstitial implantation of brain tumors, since seeds can be obtained ranging in activity from 0.5 mCi up to 50 mCi. I-125 emits low-energy photons (under 35 KeV) that pose little radiation hazard to medical

personnel, and shielding is much easier than for the high-energy gamma-producing sources such as Au-198 or Ir-192. A very thin layer of lead placed on the scalp is extremely effective in attenuating radiation emitted by the implanted I-125 seeds. The low-energy electrons emitted during radioactive decay of I-125 are effectively shielded by the metal casing used to encapsulate the sources.

The dose rate around the radioactive source falls off rapidly. Thus the dose rate at 2 cm from a source is 25% of the dose rate at 1 cm. By properly placing radioactive sources within a tumor, a high dose can be administered to a restricted volume and the dose to surrounding normal tissues can be kept low. Obviously, the tumor volume must be accurately defined and the placement of the sources must be precise. CT and MRI allow for accurate definition of the tumor volume. Seeds placed in hollow plastic catheters can be inserted under stereotactic guidance to assure proper placement. Computer planning is available for accurate dosimetry. Most implants in the brain are temporary and the catheters are removed after 1–7 days. However, with low-activity sources, catheters have been left in situ permanently [35].

Eddy et al. have described the dosimetry planning and permanent implantation of I-125 for recurrent malignant gliomas [35]. The tumor volume is accurately determined by summation of the volume on 5 mm CT scan slices. The margin of the enhancing rim is used for calculating the volume. Up to 100 different seed sources within ten different lexan tubes have been inserted into a tumor via an open craniotomy. Total doses greater than 20,000 cGy are delivered to the tumor edge as determined by the enhancing border over the effective lifetime of the implant (> 1 year). Most of the dose is delivered within the first two half-lives (120 days).

Mundinger and his colleagues probably have the largest experience with brachytherapy for intracranial tumors [36–38]. He has developed a Gamma Med iridium-192 contact-irradiation

device whereby Ir-192 is afterloaded into a stereotactically positioned cannula. A total dose of several thousand rads is administered in several minutes and the source is withdrawn. He calls this *brachy-curie therapy*. Curie therapy is the term he applied to permanent implants. Prior to 1979, 492 Ir-192 implants were performed. Since 1979, I-125 has been used. Temporary I-125 implants have also been used as an alternative to the high-dose Ir-192 Gamma Med.

For some tumors, external radiotherapy was added to curie therapy or brachy-curie therapy. In addition, the halogenated pyrimidine analogue, 5-bromo-2-deoxyuridine, (BUDR) was administered to most patients receiving brachy-curie therapy.

For low-grade tumors, Mundinger recommends curie therapy (permanent implant) alone. For anaplastic grade II–III, he recommends curie therapy and external radiotherapy. For grade III–IV gliomas, he recommends brachy-curie therapy and external radiotherapy.

His extensive experience with implants in over 1200 patients with many different tumor types proves the safety and feasibility of the technique. However, from published reports, it is not clear that the results obtained with the use of permanent or temporary implants are better than with the use of just external radiotherapy. Likewise, the apparent nonrandomized use of BUDR as a radiosensitizer with brachy-curie therapy precludes comment as to its value.

Leibel and Gutin have implanted radioactive sources in 141 patients with recurrent primary or metastatic intracranial tumors [39]. In 115 patients, 118 temporary implants using high-activity I-125 seeds have been accomplished stereotactically. The majority of patients had malignant glioma. One to 4 catheters, each containing 1 to 3 high-activity I-125 sources, were implanted to deliver a minimum dose of 8000 cGy for recurrent glioma. Forty-two (42) patients treated for recurrent malignant glioma had a subsequent median survival of 18

months. The authors emphasize the difficulty in differentiating radiation necrosis from tumor progression following implant and suggest reoperation with resection of necrotic tumor in cases with clinical deterioration and CT scan findings of a mass following implantation. The finding of mainly necrotic tissue at reoperation was associated with a good prognosis. Resection of the necrotic material frequently led to clinical improvement.

Lunsford et al. have also used high-activity I-125 sources to implant malignant gliomas [40]. Ten patients with malignant glioma were treated with 6000 cGy external radiotherapy and 5000–7000 cGy administered by interstitial implants. Six of seven glioblastoma multiforme patients were still alive 40–60 weeks from diagnosis. Usually 1–3 catheters, each with 2 or 3 sources, were implanted.

Salcman et al. have described the use of stereotactically implanted Ir-192 for the treatment of malignant gliomas [41]. Two to 4 catheters, each containing 3 to 6 high-intensity Ir-192 seeds, were left in place for 50 hours to deliver 5000 cGy to the entire tumor. Interestingly, two patients developed increased somnolence 48–72 hours after implantation. Follow-up intervals were too short for evaluation of therapeutic success.

There is no definite answer as to which form of implant, high or low dose rate, is preferable radiobiologically for various tumors. Possibly, high-dose-rate implants may be more efficacious for rapidly dividing tumors, whereas low-dose-rate implants may be more beneficial for slowly proliferating tumors.

At present, interstitial implants with I-125 seem to be a good way of administering a boost dose to the tumor mass. The Brain Tumor Cooperative Group (BTCG) is carrying out a two-arm study in adults with malignant cerebral glioma (anaplastic astrocytoma and glioblastoma multiforme); both groups receive the same external radiotherapy, 6000 cGy/35 treatments, but one arm includes an interstitial I-125 implant designed to administer 6000 cGy

in six days to the edge of the tumor as defined by the enhancement edge on CT.

As diagnostic imaging modalities improve, it should be possible to identify very accurately the tumor volume and to differentiate it from surrounding edema and noninvolved brain. Improvements in computer dosimetry and the availability of three-dimensional planning, together with stereotactic implantation of sources, may make brachytherapy a valuable modality in the future.

Interstitial implants at present are contraindicated in patients with very large tumors, tumors involving vital structures such as the brainstem, and in situations where the tumor boundaries are not clearly defined.

Heavy Charged Particle Beams

Heavy charged particle beams may be of benefit in clinical radiotherapy for two reasons:

1. Improved dose distribution
2. Increased RBE, low OER

The well-defined width of the Bragg peak, the low ratio of plateau-to-peak dose distribution, and the negligible dose distribution beyond the peak are the potential beneficial aspects of charged particle beam therapy in terms of dose delivery. By using appropriate filters in the beam, the width of the Bragg peak can be increased in order to conform to the dimensions of the tumor target. However, increasing the width of the Bragg peak causes dilution of the high LET component and diminution in RBE. In order to exploit the dose distribution characteristics of charged particle beams, target volumes must be precisely defined and localized. Tissue homogeneity must be taken into account and corrections made.

At present, there are less than two dozen heavy charged particle facilities throughout the world that are administering radiotherapy [42]. Of the heavy charged particle beams, proton beams have been most extensively evaluated.

The huge cost, extensive size of such facilities, and the amount of expertise required effectively limit their proliferation.

Austin-Seymour et al. at the Harvard Cyclotron Laboratory have reported an extensive experience using a 160 MeV proton beam with a range of 15.9 cm in tissue to treat uveal melanomas and intracranial and base-of-skull tumors [43]. Using in vitro and in vivo assays, the calculated RBE value of this proton beam compared to cobalt ranges from 1–1.42. For clinical proton-beam radiotherapy, they have used an RBE value of 1.1. All intracranial and paracranial tumors were treated with conventional fractionation schemes using daily doses of 1.8–2.1 CGE (cobalt gray equivalent. physical dose in gray $\times 1.1 =$ CGE).

The majority of their experience using the proton beam has been for the treatment of uveal melanoma. However, seven patients with malignant glioma were treated with proton-beam radiotherapy after large-field photon (X-ray or gamma ray) irradiation. The median total dose (photon and proton) was 73.1 CGE. Only one patient was alive at 68 months from therapy, but he had resection of tumor at seven months posttherapy. Eight patients were treated for craniopharyngioma postoperatively with 54.6–63.6 CGE. With a very short follow-up of 5 to 46 months, seven were considered stable and free of disease. Six patients were treated following subtotal resection of meningioma. The follow-up was extremely short.

Saunders et al. reported results of radiotherapy in 19 patients (10 chordomas, 5 low-grade chondrosarcomas, 4 meningiomas) treated with 934 MeV helium ions from the 184-inch synchrocyclotron at the Lawrence Berkeley Laboratory in San Francisco, California [44]. The calculated RBE of the helium ion beam compared to cobalt was 1.2–1.4 depending upon the amount of spread of the Bragg peak and the position in the Bragg peak. With a short follow-up, 14 patients were considered free of disease.

Pi-mesons have the improved dose distribution characteristics of heavy charged particles and biological advantages of high LET radiation. The RBE of the spread-out peak varies from 1.2–1.7 and the OER is around 2 [45–47].

At the Los Alamos Meson Production Facility, pi-mesons have been used to treat 29 patients with grade III and grade IV malignant gliomas [48]. A variety of fractionation schemes was used, with minimum doses of 2200 cGy in 24 fractions up to about 3800 cGy in 31 fractions. Most patients received between 2700–3700 cGy in 33–38 fractions administered on a daily basis. Only two patients, both with grade III astrocytoma, were alive with apparent local control at 36 and 47 months, respectively. One additional patient with grade III astrocytoma died at 15 months without evidence of tumor but with evidence of radiation necrosis. All other patients have died.

At the Swiss Institute for Nuclear Research in Villigen, Switzerland, 20 glioma patients were treated with pi-mesons [48]. Administered tumor doses were 2700–3000 cGy in 16–18 fractions over four weeks. Thirteen of 20 patients were alive and well more than six months but only one of 15 patients was alive apparently free of disease more than nine months.

Goodman et al. have used pi-mesons at the Tri-University Meson Facility in Vancouver, British Columbia, to treat 32 patients with malignant glioma [49]. Most patients received whole-brain photon irradiation followed by pi-meson irradiation of a restricted volume. One hundred and twenty five (125) to 220 cGy fraction sizes were used to total doses up to 3300 cGy. There was a tendency towards improved survival in patients receiving larger daily fractions, but the median survival was less than one year regardless of the fractionation scheme used.

Castro et al. have reported using heavy charged particles to treat 33 patients with previously unirradiated glioma and six patients with recurrent glioma after previous photon irradiation [50]. The Lawrence Berkley Labor-

atory Facility in Berkley, California, can produce helium ions and heavy nuclei such as neon, carbon, and silicon. For helium ions, they calculate the RBE as compared to cobalt to be 1.2–1.4. For neon ions, the RBE is 2.3–3. Of the untreated patients, 17 had glioblastoma multiforme, 11 had anaplastic astrocytoma, and five had either grade II astrocytoma or unbiopsied tumors with clinical and radiographic evidence suggesting low-grade astrocytoma. Ten of the 33 patients were treated just with neon beam irradiation administering 1600 cGy in 16 fractions over 28 days. With an RBE of about 3, they consider this to be equivalent to 4800 cGy administered with cobalt-60. One patient with glioblastoma was treated just with helium-ion irradiation and the remainder of the patients had low LET radiation (photons) administered to the entire brain to a dose of 4500–5000 cGy at 180–200 cGy per day. Then, an additional 1500–2000 rad equivalent (rad equivalent = physical dose $\times$ RBE) was administered with heavy charged particles, either helium, carbon, or neon, to bring the total dose to the tumor to 6000–7200 rad equivalent. The patients with recurrent glioma after previous low LET irradiation were treated with an average dose of 4200 rad equivalent using heavy charged particles at daily doses of 200–300 rad equivalent. Of the 17 patients with glioblastoma, only one was alive and apparently free of disease at 15 months. Fifteen patients died, 13 with definite tumor recurrence. Two patients died without definite evidence of tumor at 2.5 months and 11 months posttherapy. Of the 11 patients with anaplastic astrocytoma, one was alive and well at 39 months and one was alive with disease at 67 months. Nine patients died with tumor. The five patients with grade II astrocytoma or no biopsy had a median survival of 24 months with three alive at 24, 34, and 50 months posttherapy. The six patients treated for recurrent glioma all died with persistent tumor, with a median survival of five months. The results in this phase I–II study were certainly not better

than those achieved with low LET radiotherapy.

There has not been much investigation into the use of heavy charged particle beams in the treatment of childhood intracranial tumors. So far, this modality has not provided any significant advantage in the treatment of adult malignant gliomas. With further improvements in imaging, the localization of tumor boundaries may become precise enough to warrant further evaluation of the dose-distribution characteristics of heavy charged particle beams. Further investigation is necessary to determine the optimum regimens of fractionation and combination with photons for the treatment of intracranial tumors.

Stereotactic Radiosurgery (Gamma Knife)

Stereotactic radiosurgery is the term used to describe the process whereby a target within the brain is positioned precisely at the convergence of multiple beams of radiation. Initial attempts used 250 KeV irradiation, and then, by the 1960s, proton beams were used. By 1968, the first stereotactic gamma unit using cobalt-60 was installed at the Sophia Hemmet Hospital in Sweden. This *gamma knife* was specifically designed for functional neurosurgery. It was used to section white matter fiber tracks or create small lesions in the brain primarily for the treatment of pain, movement disorders, and behavior disorders. The lesions were disc-shaped. In 1974, a second gamma knife, designed to irradiate spherical volumes, was installed at the Karolinska Hospital in Stockholm [51]. Subsequently, units were installed in Buenos Aires and Sheffield, England. The fifth it is at the University of Pittsburgh.

The gamma knife is an apparatus with multiple sources of cobalt-60 arranged in a hemispherical shell (figure 7-11). The Pittsburgh unit contains 201 Co-60 sources. Through a collimator system, the beams from the sources are directed to a small volume. By altering the collimation, the volume encompassed by the

convergence of the beams can be varied from a diameter of 4 mm to about 2 cm (figure 7-12). After stereotactic localization of the lesion with the patient's head in a Leksell frame, the patient's head is then inserted into the spherical shell where it is attached by the frame. A single dose of several thousand rads is administered in less than one hour. This is the main advantage of the gamma knife, namely, that a single high dose of over several thousand cGy can be administered to a localized volume in a single treatment. Such a large dose should be extremely effective in destroying any tumor. The amount of radiation delivered beyond the target volume is only several hundred rads. The disadvantage is that for a tumor to be irradiated adequately, the volume has to be under about 3 cm [3]. Slightly larger volumes can be irradiated by using two treatment sessions.

The major experience with this modality comes from Sweden, where the gamma knife was developed. Worldwide, over 2000 patients have been treated in the past 20 years [52]. The majority of patients and arteriovenous malformations, pituitary tumors, acoustic neuroma, or craniopharyngioma. Relatively few patients have been treated for malignant glioma. For small gliomas, the gamma knife may be an alternative to an implant boost without the need for operation or hospitalization. As a primary modality, it may be an alternative to surgery and/or external radiotherapy for tumors whose boundaries can be very accurately localized, such as craniopharyngioma, pituitary adenoma, and acoustic neuroma.

The gamma knife has not been used extensively in children. In 1981, Steiner summarized the experience of the Karolinska Hospital, Stockholm, Sweden in the use of the gamma knife to treat children [53]. Five tumors in the pineal region were irradiated with single doses of 2000–5000 cGy. Three patients with pineocytoma were alive and well 4–12 years later. One patient with grade II astrocytoma was alive at one year, with complete disappearance of the tumor on CT. The remaining child with

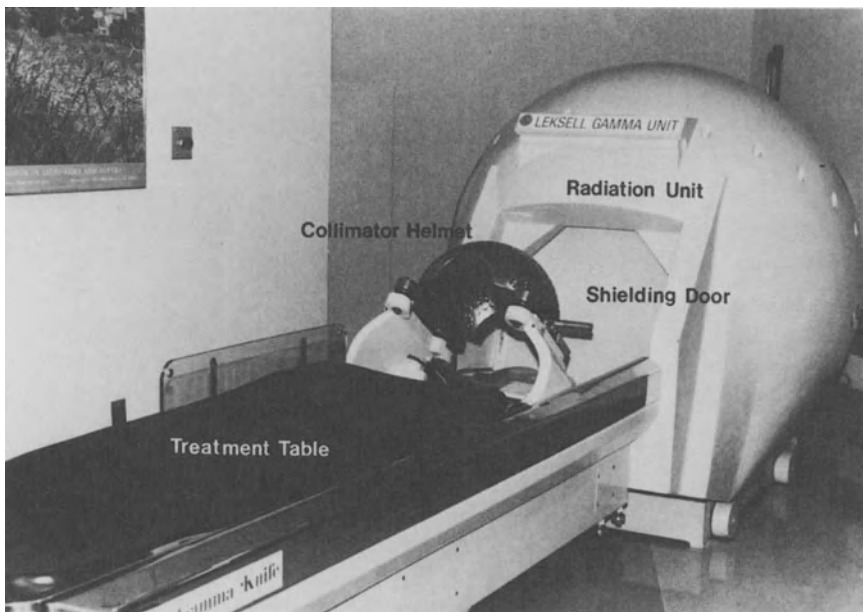


FIGURE 7-11. The Leksell Gamma Unit (gamma knife) in Presbyterian University Hospital, University of Pittsburgh, Pittsburgh, PA. This unit contains 201 separate cobalt sources in the radiation unit. The collimator helmet focuses the beam to the desired isodose. Helmets are available with openings of four different sizes. (Reprinted with permission from Maitz et al., Shielding requirements on-site loading and acceptance testing of the Leksell gamma knife: The Pittsburgh experience. *Int J Radiat Oncol* 18:469–476, 1990.)

medulloblastoma of the pineal region died at two years.

Four children with craniopharyngioma treated with the gamma knife were alive and well after single doses of 2000–5000 cGy. Length of follow-up was not stated. Five children have had gamma-knife irradiation for Cushing's disease, with a good result in all with up to 3½ years of follow-up. Fifteen children have been treated for arteriovenous malformation.

Kjellberg and Abe reported using the Bragg peak portion of the 160 MeV proton beam to treat 1025 patients with pituitary adenomas, 777 patients with vascular malformations, 59 patients with histologically benign tumors, and 33 patients with malignant tumors [54]. The patient is positioned in a stereotactic frame and up to 12 different portals varying in size from 7–50 mm are used to administer a single dose of radiotherapy. The selected dose depends upon size of the treatment beam and type of tumor. Larger doses are given for smaller targets. The majority of patients with functioning pituitary tumors had a beneficial response, but that response often took many years to occur. Overall, therapy appeared to be relatively safe.

A visual field disturbance occurred in only 1.57% of 551 treated acromegalic patients. Hypopituitarism occurred in about 10% of patients with pituitary tumors. Recurrence of hyperfunction was extremely rare.

Linear accelerators can be adapted to stereotactic systems, and large single doses to a restricted volume can be administered by rotating the source along an arc. Combinations of arcs and field sizes can be used to cover the intended volume. There is much less experience using accelerators for stereotactic radiosurgery than there is for using the gamma knife apparatus. The widespread availability of linear accelerators and CT scanners may some day make the stereotactic radiosurgery technique widely avail-

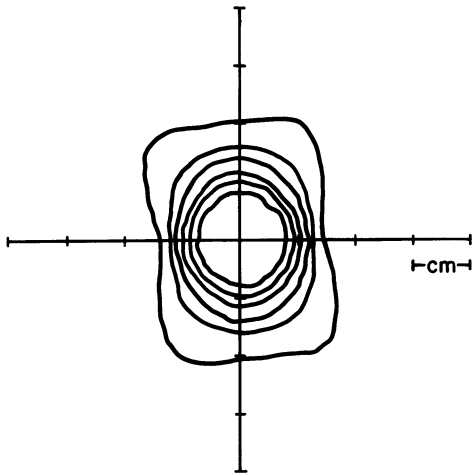


FIGURE 7-12. Cross section of dose distribution using the gamma knife with the 1.8 cm collimator. Isodose line from inside outward are 90%, 70%, 50%, 30%, 20%, and 10% of dose at midpoint.

able. The various adaptations and experiences using the linear accelerator for stereotactic radiosurgery have been summarized by Patil [55].

Intraoperative Radiation Therapy

A novel approach to administering radiotherapy is intraoperative external-beam radiation therapy. A single large dose of radiation is administered after surgical exposure of the neoplasm. The benefits of intraoperative radiotherapy are that the tumor may be directly visualized, thus allowing very accurate delineation of the tumor volume to be irradiated, and normal sensitive structures may be retracted out of the path of radiation or else appropriately shielded. Thus, it may be possible to deliver a single high dose just to the tumor with minimal exposure of normal tissues.

In 1937, Elsberg et al. reported their experience with 18 patients treated with intraoperative radiotherapy for intracranial tumors [56]. They used a 200 KV X-ray machine stationed in the operating room. They treated 18 patients with

unresectable or partially resectable brain tumors, including five children, four with medulloblastoma and one with a pineal tumor. Adults with supratentorial tumors were treated with single doses of 3000 r units. The medulloblastomas were treated with 2000–2500 r units, and the pineal tumor was treated with an estimated dose of 2230 r units. Five of the 18 patients died between $\frac{1}{2}$ and 11 days after the surgery, but the authors believed that their deaths were unrelated to the radiation treatment. Four patients had wound complications. Two of the children with medulloblastomas died in the postoperative period. At the time this report was written, follow-up intervals were rather short. Two of the authors, Dyke and Davidoff, in their book *Roentgen Treatment of Disease of the Nervous System* published in 1942, mentioned these 18 cases, but did not give any further information as to whether or not additional patients were so treated [57].

In 1971, Abe et al. published their experience with intraoperative radiotherapy using either cobalt or electrons for abdominal and cerebral tumors [58]. Two patients were treated with electron beam therapy for recurrent intracranial tumors that had initially been treated with partial resection and postoperative radiotherapy. They received single doses of 3500 and 4000 rads, respectively. Both were dead within six months. In 1980, the same group reported an additional two patients treated with radiotherapy for recurrent gliomas [59].

Goldson et al. in 1984, reported 12 patients treated with intraoperative radiotherapy and then postoperative conventional radiotherapy for intracranial tumor [60]. All patients received an intraoperative dose of 1500 rads using 9–12 MeV. Electron energies were selected so that the 90% isodose line was at least 1 cm beyond the deepest margin of the tumor as demonstrated by CT scan or direct surgical exposure. Field diameters were selected to give a 1–2 cm margin of normal tissue. At the time of their report, four patients with malignant

glioma were still alive free of disease for periods ranging up to 15 months. Two patients with meningioma were alive and well 33 and 42 months following intraoperative treatment.

The concept of intraoperative radiotherapy is extremely attractive. Since the most common cause of therapeutic failure of intracranial tumors is persistent or progressive primary tumor, it seems logical that additional radiation to the tumor, or tumor bed following resection, should improve local control rates and survival. With radiographic studies and direct visualization of the tumor area, a relatively precise determination of the extent of the intracranial tumor can be made, allowing for the selection of the appropriate electron energy and field size.

At the present time, there is more enthusiasm within the United States for using intraoperative radiotherapy to treat advanced intra-abdominal and pelvic malignancies [61]. In such cases, it may be relatively easy to retract the normal bowel and to shield normal tissues. With intracranial tumors, it is difficult to expose the entire tumor bed adequately by retracting normal brain. Limitation of the high dose to just the volume of the tumor with avoidance of adjacent normal structures can be extremely difficult in the brain where adjacent sensitive normal structures such as the brainstem or hypothalamus may be only several mm from the edge of the tumor.

Intraoperative radiotherapy can be a cumbersome and time-consuming process. Unless there is a treatment machine within the operating room, the patient must then be transported to the radiation facility. Ideally, a specialized operating suite with a self-contained radiotherapy unit or else an operating suite immediately adjacent to a radiotherapy facility is required.

Due to the complexities of intraoperative radiotherapy for intracranial tumors, it is not likely that this modality will be widely adopted for the treatment of intracranial pediatric tumors unless further pilot data become available that demonstrate definite benefit.

Hyperbaric Oxygen

The reasons for believing that hyperbaric oxygen used with X-irradiation would provide higher control rates than radiation alone are:

1. All tumors of a size sufficient to be clinically detectable, especially large tumors, are likely to contain hypoxic but viable cells
2. Hypoxic cells are resistant to radiation by a factor of 2–3 (OER)
3. Breathing oxygen at 3–4 atmospheres should increase the PO_2 in the vicinity of hypoxic cells, making them more sensitive to radiation
4. Hyperbaric oxygen should not increase the sensitivity of well-oxygenated normal tissues

Most investigators involved with hyperbaric oxygen used three atmospheres of pressure as follows. After the patient was placed in the chamber, the pressure was slowly increased to the desired level over 15 minutes and the patient remained at the full pressure for about 15–25 minutes. After treatment, the patient was decompressed over several minutes.

Four tumor types have been the subject of intense investigation in human clinical trials: advanced carcinoma of the uterine cervix, carcinoma of the urinary bladder, carcinoma of the lung, and carcinoma of the head and neck. A variety of fractionation schemes were used, and although some trials indicated a benefit from hyperbaric oxygen, very few trials produced results that were statistically significant. The reader is referred to Glassburn et al. [22] for a detailed analysis of hyperbaric oxygen trials.

Relatively few patients with brain tumors have been treated with hyperbaric oxygen and radiotherapy. Overall, results have been unimpressive. Churchill-Davidson treated eight glioma patients with 3500–3750 rads/6 fractions over 18 days (two fractions/week), and all were dead by three years [62]. Watson and Banarjee treated 30 glioma patients with radiation and hyperbaric oxygen [63]. The one-year survival was 43% compared to a 51.5%

one-year survival for a historical control group treated with the same dose–fractionation scheme.

Chang et al. treated glioblastomas with 400 rads three times per week to 3600 rads; one group also had hyperbaric oxygen [64]. At six months, the results seemed slightly better in the hyperbaric oxygen group.

Hyperbaric oxygen has been reported to increase radiation effects on some normal tissues. van den Brenk et al. noted an 8.8% incidence of radiation myelitis among 239 patients who survived at least nine months following radiation and hyperbaric oxygen for carcinoma of the upper respiratory tract [65]. They believed this incidence to be higher than expected with radiation in air. Coy and Dolan reported radiation myelitis in 3 of 17 patients (18%) surviving at least nine months following radiation with hyperbaric oxygen for carcinoma of the lung [66]. Patients received 3600 cGy in eight fractions over four weeks. They stated that this dose in air was not associated with radiation myelitis.

There is theoretical reason to speculate and experimental data to indicate that hyperbaric oxygen would be of greater value if used with larger X-ray fractions than the usual 180–200 cGy/day, since OER increases as the dose is increased [67].

The lack of convincing data demonstrating benefit for hyperbaric oxygen and radiotherapy except possibly for upper respiratory tract carcinoma and carcinoma of the cervix has dampened enthusiasm for this modality as an adjunct to radiation. The time involved in preparing the patient for treatment makes it difficult to treat large numbers in a typical department. In order to improve the effectiveness of hyperbaric oxygen, more research would be required to define optimum total dose, fraction size, and interval between fractions.

With the advent of chemical hypoxic sensitizers, it was hoped that there would be an easier way to circumvent the influence of hypoxia-associated radioresistance.

Hypoxic Cell Sensitizers

The feasibility of developing chemical agents that, like oxygen, would sensitize hypoxic but not well-oxygenated cells was first demonstrated in 1960 by Bridges, who showed that N-ethylmaleimide (NEM) sensitized anoxic but not well-oxygenated bacteria to X-ray [68]. Subsequent investigators showed the relation between the electron affinity of a compound and its ability to sensitize anoxic cells [69, 70].

The two drugs that have been evaluated most extensively in vitro and in vivo as radiosensitizers of hypoxic cells are the nitroimidazoles, metronidazole and misonidazole, which did prove to be effective sensitizers in various experimental animal models [71–75]. Studies in humans have been less rewarding.

Usually, conventional fractionation schemes of 180–200 cGy/day over 5–7 weeks are used to treat brain tumors. Daily permissible doses of misonidazole would probably be too low to afford significant sensitization. Therefore, fewer but larger fractions of radiotherapy in conjunction with misonidazole have been used, or else fewer than daily doses of misonidazole.

A study by Urtasun et al. randomized patients with glioblastoma multiforme to radiotherapy alone or radiotherapy with metronidazole [76]. Each arm received 300 cGy/9 fractions over three weeks. This fractionation scheme was chosen in order to be able to limit the number of drug doses and avoid toxicity. The median survival was increased from 15 weeks in the control group to 26 weeks in the radiotherapy plus metronidazole group. There were only 15 patients in the control group and 16 patients in the group that received metronidazole. This is the only published randomized trial indicating a possible benefit for a hypoxic cell sensitizer in the treatment of malignant glioma. However, this improved survival was still not better than results commonly achieved with radiotherapy alone using conventional fractionation regimens.

Misonidazole was evaluated in a Brain Tumor Study Group (BTSG) study [77]. Six hundred

TABLE 7-5. Brain Tumor Study
Group (BTSG) 77 02 protocol

1. XRT 6000/30–35 + BCNU
2. XRT 6000/30–35 + streptozotocin
3. XRT 6000/30–35 + misonidazole + BCNU*
4. XRT 6600/60 (2 × daily) + BCNU

Notes:
BCNU: 80 mg I.V/m²/day × 3 q 8 weeks;
Streptozotocin: 1.25 g/m²/week × 6 q 8 weeks;
Misonidazole: 1.5 g/m² 2x/week during XRT;
XRT: Whole-brain irradiation.
* In arm 3, BCNU started after completion of XRT.

and three (603) patients with supratentorial malignant glioma were randomized to four different arms, one of which included misonidazole and radiotherapy (table 7-5). There was no benefit associated with the addition of misonidazole. For the 557 patients in the valid study group, the median survival ranged from 9.2–10.4 months. Nonglioblastoma patients had a worse survival on the misonidazole arm than on the other three arms of the study. For glioblastoma patients, survival was similar on all four arms of this study.

The poorer survival for anaplastic astrocytoma patients treated with misonidazole was also noted in a Radiation Therapy Oncology Group (RTOG; study [78]. The RTOG evaluated misonidazole administered with radiotherapy using the following schedule [78, 79]: On Mondays, 400 cGy was administered. On Tuesdays, Thursdays, and Fridays, 150 cGy was administered. Misonidazole, 2.5 gm/M² was administered orally four hours preceding the 400 cGy weekly dose. During the seventh week, the radiation dose was 180 cGy per day for five days. The control arm was treated with 6000 cGy delivered daily at 170–200 cGy per day five days per week. In both arms of the study, patients received BCNU, 80 mg/M² for three days every eight weeks. Two hundred and eighty-five (285) patients were randomized. The median survival for the radiation plus BCNU arm was 55 weeks. For the arm containing misonidazole, the median survival was 46 weeks. For the subgroup of 50 patients

with anaplastic astrocytoma, survival with radiation plus BCNU was significantly longer than for radiation, BCNU, and misonidazole: 132 weeks versus 57.5 weeks.

Three smaller randomized studies from Europe have also failed to demonstrate a benefit for misonidazole in the treatment of malignant gliomas in adult patients [80–82].

Wara et al. reported a series of 29 pediatric patients treated with radiotherapy and misonidazole for recurrent intracranial tumor [83]. All patients had completed radiotherapy after their initial diagnosis, and 22 patients also received chemotherapy. At relapse, patients were treated with whole-brain irradiation to 3000 cGy/10 fractions. Misonidazole, 1.5 gm/M², was administered orally 4–6 hours before radiotherapy on alternate days for a total dose of 9 gm/M². Time to progression ranged from 0–48 months, and survival from time of retreatment ranged from 3–52 months (median 13 months). Patients with recurrent medulloblastoma survived slightly longer than other patients. The authors believed that their results were similar to those obtained with salvage chemotherapy for recurrent pediatric brain tumors.

Misonidazole causes neurotoxicity manifested as peripheral neuropathy and ototoxicity. The use of corticosteroids appears to confer some protection against peripheral neuropathy [84]. In the BTSG Study, there was no association between development of peripheral neuropathy and age, number of doses of misonidazole, use of phenytoin or barbiturates, and total dose of misonidazole [77, 84, 85]. The analysis of dose is confounded by the fact that misonidazole administration was discontinued upon development of peripheral neuropathy.

For a hypoxic cell sensitizer to be clinically beneficial, it would have to be more effective and/or less toxic than misonidazole. It is possible that the efficacy, but not the toxicity, of misonidazole could be enhanced by agents that deplete radioprotective intracellular sulfhydryl compounds. There may be an ideal way to use

corticosteroids so as to decrease the neurotoxicity of misonidazole and yet still provide benefit in terms of reducing cerebral edema. Another approach would be the development of better fractionation schemes.

In relation to this last point, it may be possible to develop fractionation schemes which initially use large fractions of radiotherapy with misonidazole. Early in a course of radiotherapy, one would expect that there would be more hypoxic cells present. Then, after the maximum total dose of misonidazole has been administered, a more conventional fractionation scheme could be used to complete the course of radiotherapy.

The combination of brachytherapy and misonidazole has not been thoroughly evaluated for brain tumors. It is possible that during a course of brachytherapy that lasts up to seven days, effective high concentrations of misonidazole could be maintained that would not be toxic.

Fast Neutrons

In the late 1930s, fast neutrons were first used to treat patients [86]. Patients selected for treatment had very advanced tumors, and many had received previous surgery or radiotherapy. Disappointing results in terms of survival and severe complications dampened enthusiasm for this modality until the 1960s. The results of this early trial were subsequently reevaluated by Sheline et al. [87]. They determined that the severe sequelae of neutron irradiation in this group of patients were due to overdosage.

The benefits of fast neutron beam radiation are due to the high LET characteristics. Unlike heavy charged particle beams, there are no advantages in terms of dose distribution. Skin-sparing and penetration in tissue are comparable to cobalt-60 gamma rays for a neutron beam produced by 30 MeV deuterons on a beryllium target.

The potential benefits of high LET radiation such as fast neutrons and heavy ion beams at the cellular level are:

1. Low OER, which theoretically should prove beneficial in the treatment of malignant gliomas containing large areas of necrosis with hypoxic cells
2. Less repair of sublethal and potentially lethal damage
3. Less variability of cell sensitivity according to phase in the cycle

Parker et al. in 1976 reported treatment of 21 patients with grade III (7) and grade IV (14) gliomas using 8 MeV mean energy neutrons produced by 21 MeV deuterons on a beryllium target [88]. The depth dose is similar to cobalt-60. The entire brain was irradiated with doses of 1550 cGy/10 fractions to 1850 cGy/17 fractions over 43 days with radiation administered two or three times weekly. Six patients were alive for 6–17 months, but overall, the results were no better in terms of survival or neurologic improvement than for patients treated with conventional radiotherapy. In seven patients, at autopsy, a mass of coagulative necrosis was seen with few tumor cells.

Later on, Laramore et al. in 1978 reported treatment of 37 patients with malignant glioma, 15 grade III and 22 grade IV, using neutrons alone or in combination with photons [89]. This included the above patients of Parker et al. Among 15 autopsied patients, there was apparent tumor eradication in 14. There was coagulation necrosis in the region of the tumor with diffuse gliosis and white-matter demyelination in other areas of the brain. The authors believed that there was no survival advantage compared to historical controls treated without neutrons. Only one patient was alive, and he had received a 450 rad neutron boost after a 5000 rad whole-brain irradiation with photons.

Catterall et al. treated 30 patients with malignant glioma using fast neutrons with a mean energy of 7.5 MeV [90]. Eighteen patients received 1560 cGy, 11 patients received 1300 rads, and one patient received 1400 cGy. All patients were treated with 12 fractions, three

fractions per week, over 26–33 days. There was no difference in survival compared to that of 33 patients treated with conventional radiation during the same time period. In fact, three patients treated with conventional radiotherapy were alive at two years, whereas none of the patients treated with neutrons were alive at two years. Of 16 patients treated by neutrons who then had either second-look craniotomy or autopsy, there was no gross tumor in 11.

The RTOG compared neutron irradiation in combination with photons (cobalt-60 or X-ray) to irradiation with photons alone [91]. All patients received 5000 cGy at 180–200 rads per day using photons. Then patients were randomized to a boost with photons or with neutrons. The photon dose was 1500 cGy, and for neutrons the dose was equivalent to 1500 cGy assuming an RBE of 3–3.5 depending upon beam energy. One hundred and fifty-eight (158) patients were analyzed. The median survival was 9.7 months in the neutron boost group versus 8.5 months in the photon boost group. There were no differences in outcome between neutrons and photons for any subgroup according to prognostic variables. The two-, three-, and four-year survival was slightly better for the photon boost group compared to the neutron boost group. At four years, survival was 11% in the photon boost group versus 3% in the neutron boost group. Autopsies were performed on 12 patients treated with the neutron boost; in nine, there was significant necrosis of tumor, with only sparsely scattered bizarre cells present. In 12 patients treated with just photons, autopsy showed infiltrating proliferative tumor.

Neutrons seem to be an effective modality for destroying malignant glioma, but with the reported fractionation schedules, the amount of damage to brain is prohibitive. It is still necessary to define the optimum dose fractionation scheme for high LET radiations and the optimum combination with photon beams. Further studies will be necessary in adult patients with malignant glioma before high LET

radiations are tried in the pediatric population. Also, convincing data as to the superiority of high LET radiation as compared to photon beams with or without other experimental modalities will be necessary before there is widespread use of this expensive modality.

Californium-252

Californium (Cf-252) is a man-made radioisotope that emits neutrons and gamma rays. The half-life is 2.65 years. With Cf-252 one can combine the advantages of interstitial therapy with neutron-beam radiotherapy. The dose from Cf-252 is partly made up by gamma rays. At low total dose rates (< 20 rads per hour), the OER for cells in vitro varies from 1.3–1.9. The RBE for cell killing is about six or seven [27].

Cf-252 has been used together with whole-brain cobalt-60 irradiation for the treatment of malignant glioma at the University of Kentucky Medical Center [92,93]. The Cf-252 implant was done about two weeks after surgery. The sources were left in place for 7–8 hours; the authors assumed an RBE of six. Following the implant removal, patients were treated with external radiotherapy. Children were not included in the reported experience.

The number of treated patients is small, and it is difficult to make any definite statement as to the amount of improvement, if any, due to the use of Cf-252 implants.

Hyperthermia

Hyperthermia as an anticancer modality involves heating a tumor several degrees above normal, usually to at least 41°C. It is not the use of an extremely hot metal or cautery to ablate tissue.

Curves of survival versus time at an elevated temperature resemble the survival curves for radiation (figure 7-13). For a given temperature, the longer the exposure to heat, the greater will be the amount of cell kill. For a given endpoint in survival, the exposure time at tempera-

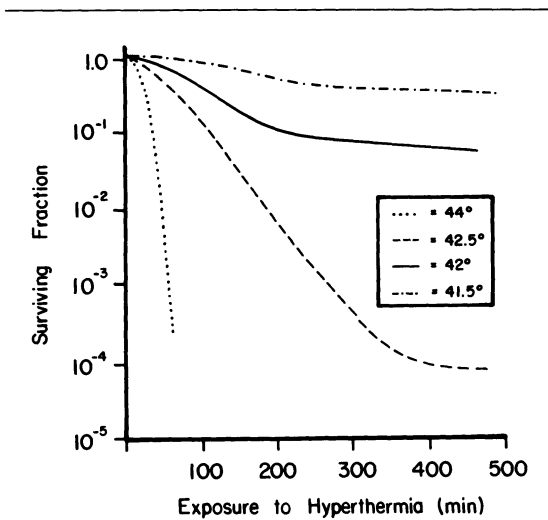


FIGURE 7-13. Typical cell survival curves at different temperatures.

tures above 43° can be halved for each increase in one degree temperature [94]. Thus, the higher the temperature, the less the exposure time necessary to achieve a particular endpoint in cell survival.

Malignant and normal cell lines can vary markedly in heat sensitivity [94,95]. Factors increasing the sensitivity to heat include low

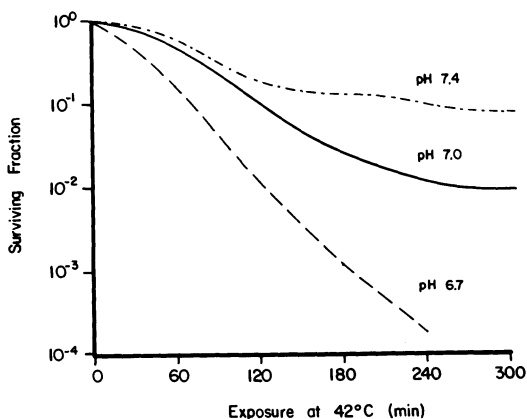


FIGURE 7-14. Cell survival at 42°C as a function of pH.

pH and a nutritionally deficient environment, conditions often seen in hypoxic areas of tumors [96]. Hypoxic cells maintained at normal nutrition and pH are less preferentially sensitized by heat (figure 7-14). Cells in the late S phase may be more sensitive to heat, and it is precisely these cells that are more resistant to radiation. Thus, hyperthermia may complement radiotherapy by having its maximal effect on those cells that are most likely to be radioresistant.

Exposure of cells to heat for a period of time that is less than required to kill the cells makes the cells temporarily resistant to further heat. Thermotolerance reaches a maximum within 24 hours and then disappears slowly, but may last for as long as seven days. Obviously, this phenomenon has important implications in the use of heat together with daily radiation therapy.

Blood flow in tumors is considered to be more sluggish than in normal tissues. Blood flow is one method by which heat is dissipated and thus, once heated, a tumor may reach a higher temperature and retain heat longer than normal tissues, thereby producing a greater effect on tumor as opposed to normal tissues.

The relationship between therapeutic gain and the temporal sequencing of heat and radiation is very complex. Not only the sequence order and time intervals between heat and radiation, but also the length of heating, temperature, radiation dose, and tumor type influence the therapeutic benefit obtainable [96–98]. Heat immediately before or after radiation may give equivalent sensitization of normal tissue and tumor, thus producing no therapeutic gain.

There are three main methods for local hyperthermia. Microwave applicators, radiofrequency applicators, and ultrasound applicators can be used to treat tumors near the surface or even in deep-seated regions by positioning multiple applicators around the patient. These three methods of hyperthermia have been adapted also for interstitial and intracavitary heating.

Regional perfusion with warmed blood can be used to achieve hyperthermia in an extre-

mity. Similarly, warm saline can be perfused across a mucosal surface for the treatment of superficial mucosal tumors.

Finally, there is systemic hyperthermia, or whole-body hyperthermia, where the entire patient is heated by warming blankets, heat boxes, warm baths, etc.

One significant problem with the use of hyperthermia is the determination of the actual temperatures achieved throughout the tumor and also in normal tissues. Unfortunately, there are no simple isotherm plots available that would be analogous to the isodose distributions available for ionizing radiation. Thus, during the course of hyperthermia, it is necessary to insert temperature probes directly into tissue. Obviously, there are limitations to how many probes one can place within a desired volume, and therefore one can obtain only a relatively rough idea as to the distribution of heat within the tumor and adjacent normal tissues.

Oleson et al., reporting their experience with hyperthermia in 163 patients, noted difficulty in achieving minimum temperatures above 41°C within the tumor [99]. This suggests that significant portions of a tumor may be relatively unaffected by administered heat treatments.

Clinically, heat has been combined with radiotherapy mainly in the treatment of superficial or accessible tumors that can be easily heated and that can be relatively easily implanted with temperature probes. Obviously, there are greater problems in trying to deliver adequate heat safely to deep structures. One has to make allowances for inhomogeneity of tissue such as bone and air cavities, especially when using ultrasound.

There is some interest in combining interstitial hyperthermia with interstitial radiotherapy for the treatment of malignant glioma [100]. Plastic tubes inserted into a tumor can be used first to insert antennae for heating; immediately afterwards, the radioactive isotope is placed into the same catheters.

There is very little experience using hyper-

thermia either alone or as an adjuvant to radiation therapy in the treatment of brain tumors. The brain is sensitive to heat; in fact, the brain and liver are the limiting organs for systemic hyperthermia. It is hard to imagine the safe use of hyperthermia in the treatment of an intracranial neoplasm unless the tumor were directly on the surface. There may be a role for interstitial hyperthermia combined with interstitial radiotherapy as a very localized treatment for intracranial tumors.

More data are necessary to determine possible sequelae of combined hyperthermia-radiotherapy on the central nervous system. Douglas et al. reported three cases of myelopathy following whole-body hyperthermia administered to patients after thoracic irradiation that included the spinal cord [101]. The report suggests that hyperthermia may precipitate myelopathy in the previously irradiated spinal cord. This troublesome finding suggests that care must be taken in the administration of hyperthermia with cranial irradiation.

Further technical improvements in heat delivery and the thermometry of heat distribution within tissue will be necessary before hyperthermia becomes a widespread modality, especially in the treatment of brain tumors. In addition, further biological data are needed to determine the optimum sequencing of hyperthermia and radiotherapy. It will also be necessary to determine whether different tumors will respond differently to hyperthermia in the same way that tumors vary in their responsiveness to radiation according to histology, size, location, etc.

Currently, practically all hyperthermia research is being done on adult patients, and the possible application of hyperthermia for the treatment of pediatric intracranial tumors is still in the distant future.

Alteration in Fractionation Schedules

In an attempt to improve the therapeutic index in clinical radiotherapy, radiotherapists have

tried fractionation schemes other than one treatment per day in a continuous course.

Hyperfractionation. The individual fraction size is reduced and two or more fractions are administered per day. The total dose will be higher than for conventional fractionation schemes, but the total duration will be about the same. By reducing the individual fraction size, there should be less late radiation damage than for conventional daily fraction doses. However, the individual fraction size has to be sufficiently large so that the entire course is not excessively prolonged. The interval between fractions should be at least three hours in order to allow for repair of sublethal injury. Most clinical trials of hyperfractionation for brain tumors have used individual doses of 80–120 cGy [77, 79, 102–104].

Accelerated fractionation. The individual fraction size is about the same or slightly less than for conventional fractionation. The same total dose as for conventional fractionated radiotherapy is administered over a shorter period of time. Two or three fractions are administered daily at least 3–4 hours apart. This type of regimen is likely to be associated with an increased incidence of acute sequelae. It should be considered for tumors with a rapid repopulation capability and in situations where a rapid response is necessary. There is very little experience with this type of fractionation scheme for the treatment of brain tumors. The RTOG is currently evaluating 160 cGy twice daily to total doses of 4800 cGy/30 fractions/15 days and 5440 cGy/34 fractions/17 days for supratentorial malignant glioma.

Hypofractionation. Instead of daily treatments, large individual doses are administered at intervals of several days or more. Depending upon the interval between fractions, the total dose may be the same or less than for a conventional course. As noted above, large individual fractions are associated with a greater incidence of late effects. In the past, hypofractionation has been used mainly for convenience. It has been used with hyperbaric oxygen, radiosensitizers,

and high LET radiation in situations where daily treatments would be rather inconvenient. At the present time, hypofractionation alone for the treatment of brain tumors is not recommended.

Rapid fractionation. Daily doses of greater than 250 cGy are administered for 2–3 weeks. Total doses are kept relatively low. Rapid fractionation schemes are used mainly for palliation. In such situations one hopes to get a quick response that will last for at least several months.

Split course. A planned interruption in therapy after one, two, or three weeks is usually followed several weeks later by resuming the course of radiotherapy until completion. The purposes of interrupting therapy are to avoid or lessen acute sequelae. Theoretically, an interruption in therapy may allow for better reoxygenation of residual tumor cells and repopulation of normal cells. However, interrupting therapy also allows for repopulation by tumor cells. There are no convincing studies to indicate that a split course of radiotherapy provides a better therapeutic result than a continuous course.

Two large cooperative groups have evaluated hyperfractionation in adult patients with malignant glioma. The BTSG administered 110 cGy twice daily to a total dose of 6600 cGy/60 fractions over six weeks [77]. The other three arms in the study received conventional fractionated radiotherapy to 6000 rads in seven weeks. One arm received misonidazole during radiotherapy and then BCNU afterwards. The control arm received BCNU along with radiotherapy, as did the hyperfractionated arm. The fourth arm evaluated streptozotocin and conventional radiotherapy. There was no difference in median survival between any of the four arms. In the hyperfractionated arm, the total dose was increased by only 10%, which may be too low to provide an increased benefit over conventional fractionation.

The RTOG evaluated hyperfractionation at 120 cGy twice daily to total doses of 6460

rads, 7200 cGy and 7680 cGy [79]. There was no significant difference in survival between the treatment arms and no apparent difference in toxicity. The RTOG is currently evaluating 8160 cGy administered at 120 cGy twice daily.

Smaller single institutional studies have produced variable results. Simpson and Platts randomized 134 patients to treatments at 24-hour intervals (daily) or at eight-hour intervals (three fractions/day) to total doses of 3000 cGy or 4000 cGy [102]. Individual fractions varied from 48–191 cGy. There were no differences in survival between the accelerated fractionation schemes and conventional fractionation. Douglas and Worth reported improved survival in patients treated with 100 cGy fractions twice daily to 4500 cGy, 5400 cGy, or 6000 cGy total doses, as compared to a control group treated with 4000 cGy/22 fractions to 5000 cGy/20 fractions [103]. However, the survival of patients treated with hyperfractionated radiotherapy was not much different than survival of patients in the BTSG study who received conventional radiotherapy. Fulton et al. compared conventional fractionation (5800 cGy/30 fractions) with hyperfractionation (89 cGy three times daily) to 6141 cGy/69 fractions with and without misonidazole [104]. Survival was significantly improved for patients treated with hyperfractionation. Misonidazole did not produce any further improvement in survival. However, patients in the control arm had a median survival of only 29 weeks, which is much worse than that seen in the BTSG study. Again, the median survival for patients receiving hyperfractionated radiotherapy was not much different from survival of the BTSG patients.

Pilot nonrandomized studies have evaluated hyperfractionated radiotherapy in the treatment of pediatric brainstem gliomas. Packer et al. evaluated 6480 cGy administered at 120 rads twice daily [105]. Thirteen of 16 (81%) patients developed progressive or recurrent disease at a median of seven months from diagnosis. Three patients remained in remission at 8,

12, and 15 months following diagnosis. Thus, there did not seem to be any apparent improvement compared to conventional fractionation schemes. A second pilot study in which 7200 cGy is administered at the rate of 100 rads twice daily is under way, and preliminary data indicate that there may be an improvement in survival compared to historical controls but with no increase in sequelae [106].

Optimum fractionation schemes are likely to vary according to tumor size, histology, location, and proliferation kinetics of the tumor. Perhaps variations in individual dose size during a course of radiotherapy would be most advantageous.

Radioprotective Drugs

As an alternative to selectively sensitizing tumor to radiation, the use of radioprotective drugs offers the potential of selectively increasing the resistance of normal cells, thereby reducing morbidity and allowing the administration of higher doses to the tumor. A radioprotective drug is an agent that increases the resistance of cells to radiation. A drug that preferentially protects normal tissue vis-a-vis tumor would have potential therapeutic value by allowing higher doses to be administered to a tumor while at the same time decreasing morbidity. The criteria necessary for a radioprotective agent to be useful in clinical radiotherapy are:

1. Low toxicity
2. Preferential protection of normal tissues
3. Protection against early and late radiation changes
4. Protection with single and fractionated radiation

In 1949, Patt et al. demonstrated that cysteine administered IV to rats prior to total body irradiation conferred significant protection [107]. Cysteine, 875 mg/kg intravenously administered five minutes or one hour before whole-body irradiation with 800 roentgens (250

KV) resulted in four-week survivals of 87% and 80%, respectively, compared to 13%–20% for controls. The same dose of cysteine administered five minutes following radiation had no protective ability. Other sulfhydryl agents were soon developed for evaluation.

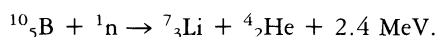
The U.S. Army Medical Research and Development Command, in an attempt to develop radioprotective agents for military use, produced a number of compounds, the most important of which was WR-2721. This is probably the most extensively studied protector in clinical trials. In animal models, WR-2721 conferred protection upon various nontumor tissues by a dose reduction factor (DRF) of 1.2 up to 2.7, whereas tumor tissue was only slightly if at all protected (DRF = 1.00–1.3) [108, 109]. The DRF is calculated as the dose necessary to obtain an endpoint in the presence of the protector divided by the dose without use of a protector. Yuhas has suggested that the selective protection of normal tissue is accounted for by a lower concentration of the drug in tumor because of decreased blood flow and by a decreased effectiveness of the drug in tumor because of hypoxia [108]. However, central nervous system tissue is not significantly protected. Following intravenous administration of WR-2721, levels of the drug in brain tissue are very low compared to other normal tissues, perhaps because of the blood–brain barrier [110].

Boron Neutron Capture Therapy

Boron neutron capture therapy (BNCT) involves the selective concentration of boron-10 in a tumor and then the exposure of the tumor to slow-moving (thermal) neutrons. Thermal neutrons move with a speed of 2200 m/second and with an energy of 0.025 eV, which is too low to cause ionization. Thus, thermal neutron beams are nonionizing. Boron-10 has a large neutron-capture cross section (3837 barns) compared to other elements in tissues such as hydrogen (0.33 barns), carbon

(0.0034 barns), and oxygen (0.0027 barns).

When captured by boron-10, the slow neutrons lead to fission, with the resulting fragments sharing an energy of 2.4 MeV:



The heavy particles formed have a very short range in tissue of less than 10 μ , and thus the radiation effect is limited to a single cell and its immediate environment.

In Japan, boron-10 neutron-capture therapy was begun in 1968 [111]. The boron compound currently used is mercaptoundecahydro-dodecaborate ($\text{Na}_2\text{B}_{12}\text{H}_{11}\text{SH}$). A nuclear reactor is necessary for obtaining the high flux of thermal neutrons. Treatment of deep tumors, beyond 6 cm from surface, may be impractical with the currently available reactors because of the low neutron flux at this depth.

The boron compound in a dose of 30–80 mg boron/kg body weight is infused intra-arterially over 1–2 hours on the evening prior to neutron irradiation. Prior to exposure to the thermal neutron beam, the scalp is reflected and shielded. Depending upon the neutron flux of the particular reactor, the exposure may take up to several hours. Studies show that the average boron concentration is 26 micrograms of boron-10 per gram of brain tumor at 16 hours after the boron infusion, whereas the normal brain takes up very little of the compound. The tumor-to-blood ratio of boron-10 is between 1.6 and 2.4. The compound may not penetrate the blood–brain barrier, thus explaining the selective concentration within the tumor. Several examples of low-grade astrocytoma contained very low concentrations of boron as compared to high-grade tumors. The investigators believe that disruption of the blood–brain barrier is more likely to occur in the vicinity of high-grade gliomas, whereas it may be relatively intact adjacent to low-grade gliomas, thereby leading to preferential uptake by high-grade malignant gliomas [111].

Thirty-eight (38) patients with grade III–

IV malignant glioma have been treated with BCNT [112]. Results were compared with a group of 46 patients treated by a combination of surgery, external radiotherapy, and chemotherapy and/or immunotherapy. The five- and ten-year actuarial survivals of the 38 patients treated by BNCT were 19.3% and 9.6%, respectively, compared to 4.6% and 0% in the conventionally treated group. Eight of 38 patients were alive. In the conventionally treated group, only 1 of 46 patients was alive. Greater improvement in the Karnofsky score of patients was noted in those treated by BNCT versus conventional therapy.

Hatanaka et al. have treated five children with brainstem glioma using BCNT [112]. The survival of this group was not significantly prolonged compared to a conventionally treated control group.

Currently, the applicability of BCNT for the treatment of brain tumors is limited by the availability of atomic reactors producing a sufficient neutron flux. In Japan, the best results have been with tumors close to the surface of the cortex. The necessity for reflecting the scalp to avoid a skin reaction can be at least a minor inconvenience. On the other hand, precise localization of the tumor boundaries is not necessary as long as the neutron beam dimensions are large enough to ensure exposure of the tumor. Because of the presence of boron-10 in the blood at the time of exposure to the thermal neutrons, there can be damage to the vasculature. Hatanaka et al. claim that massive doses of cortical steroids can prevent vascular wall damage during BNCT [112].

Halogenated Pyrimidine Analogues

In the late 1950s, Szybalski and colleagues were studying mechanisms of mutagenesis in bacteria and human cells [113]. In the course of using radiation and also 5-bromo-2-deoxyuridine (BUDR) and 5-iodo-2-deoxyuridine (IUDR) as comutagens and also as density labels for DNA, they discovered that replacement of thymidine

by either halogenated analogue rendered cells more sensitive to X-irradiation and ultraviolet.

Djordjivic and Szybalski showed that some cell lines could be cultured indefinitely in media containing 3×10^{-5} M BUDR without loss of viability [114]. Up to 45% of the thymidine in DNA could be replaced. Subsequent studies by Erikson and Szybalski indicated that IUDR was less effectively incorporated than BUDR [115]. For the same degree of thymidine replacement, BUDR was a better sensitizer to ultraviolet, but IUDR was a better sensitizer to X-irradiation. Only cells in the S phase at time of exposure to the halogenated pyrimidine analogue will incorporate the drug into DNA. These authors noted that they could obtain 42% replacement of thymidine by exposure to 5-bromo-2-deoxycytidine (BCDR). BCDR is deaminated in vivo to BUDR. This amount of replacement provided a 2.6-fold increase in sensitivity to X-irradiation.

Miller et al. noted about equal uptake of IUDR or BUDR with in vitro exposure to equal amounts of the drug [116]. There was no difference noted in sensitization between the two analogues when cells were exposed to 15 MeV X-rays.

Berry and Andrews, using a mouse lymphocytic leukemia model, demonstrated in vivo sensitization by IUDR [117]. The amount of radiation sensitization was proportional to the dose of IUDR administered. As little as 2% replacement of thymidine by IUDR produced significant enhancement of radiation-induced tumor-cell kill.

Studies by Kriss et al. suggested that parentally administered BUDR was rapidly degraded in vivo [118]. IUDR seemed to be cleared more quickly than BUDR, prompting the authors to suggest that "greater clinical emphasis" be given to the latter.

Goffinet et al. used BUDR intra-arterially with radiotherapy in a mouse glioma model and showed prolonged survival with the combination [119]. They believed that the intra-arterial route was necessary because of dehalo-

genation of the analogue by the liver. The reason for the prolonged infusion was predicated upon the need to expose as many cells as possible while in the S phase.

In 1965, investigators at the University of Tokyo in Japan began using BUDR as a radiosensitizer in the treatment of brain tumors [120]. Malignant glioma seemed a good clinical model to evaluate intra-arterial BUDR for the following reasons:

1. The arterial blood supply could be determined and catheterized, and a large drug dose could be administered continuously.
2. Malignant gliomas should have a high mitotic index and therefore should incorporate BUDR, whereas the normal neural tissue and intracranial connective tissue should have a very low mitotic rate and incorporate very little if any BUDR. Thus, there should be preferential sensitization of the rapidly proliferating brain tumor cells compared to normal intracranial tissues.
3. The blood-brain barrier should further restrict access of BUDR to neural tissue.

Hoshino and Sano in 1969 reported that glioma cells in vitro incorporated BUDR [120]. The uptake of BUDR by the tumor cells could be increased by adding small amounts of an antimetabolite such as methotrexate or 5-FU to the media. The antimetabolite, by blocking the *de novo* synthesis of thymidine, increased the uptake of the halogenated analogue. BUDR alone, without radiotherapy, did not exert an inhibitory effect on tumor cells in vitro. Uptake of BUDR was proportional to the amount of drug in the media. By 1969 Hoshino and Sano had treated 30 intracranial tumors with intra-arterial infusions of BUDR administered at the rate of 600–1000 mg per day together with small amounts of methotrexate, 1–5 mg per day, or 5-FU, 3–5 mg per day. Radiotherapy was initiated 7–14 days after the start of the continuous BUDR infusion and the infusions were continued for 3–6 weeks. The authors

postulated that infusion times should be lengthened for slow-growing tumors with longer cell-cycle times in order to allow for a greater number of cells to pass through the S phase. Radiotherapy was administered to a total dose of 5000–6000 rads. Hoshino and Sano claim that therapy was well tolerated, but they did describe some increased skin reaction on the catheterized side of the skull, and brittleness of the nails was noted 2–3 months after completion of therapy. By 1972, these investigators had treated 107 patients with BUDR infusion plus antimetabolite and radiotherapy [121]. Fifteen patients (14%) did not complete the full course of therapy. The authors believed that their results for the group, which they called highly malignant glioma, were improved, but this group also included patients with medulloblastoma and ependymoblastoma. By 1976, the authors had treated a total of 177 patients [122]. Because of the large number of histological types treated and lack of concomitant controls, it is difficult to state whether or not BUDR afforded any significant improvement in survival rates.

There are technical problems associated with maintaining an intra-arterial catheter for long periods of time. The investigators reported 28 catheter-associated complications in 177 patients [122].

Goffinet and Brown in 1977 evaluated BCDR as a radiosensitizer in mice with EMT-6 carcinoma and noted that sensitization was about the same for equal amounts of the drug administered either intravenously or intra-arterially [123]. Their studies indicate that liver degradation is not a limiting factor in the intravenous administration of the analogue. However, hematopoietic toxicity limited the amount of drug that could be administered intravenously, and they suggested that the intra-arterial route would give higher local concentrations of the analogue.

Kinsella et al. in 1984 reported preliminary results using intravenous BUDR and radiotherapy to treat 14 patients with glioblastoma

multiforme and seven patients with other extensive malignancies [124]. BUDR (350–850 mg/M²/12 hours) was administered intravenously daily over a 14-day period. Radiotherapy was started 4–6 days after the start of the infusion. Glioblastoma patients were treated with whole-brain irradiation to 4000–4500 cGy at 180–200 cGy/day. Then the involved volume as determined by CT scan was treated with an additional 2200–2400 cGy at 200 cGy/day. Most patients received a second 14-day infusion of BUDR 10–14 days after the first course and while still receiving radiotherapy. At the time of their report, three patients were alive at 4, 4, and 9 months, respectively, from diagnosis. The other 11 patients had died by 14 months. With the above regimens and BUDR doses above 750 mg/M²/12 hours, leukopenia and thrombocytopenia consistently occurred with levels < 1000/mm³ and < 50,000/mm³, respectively, by day 10–14 of the infusion. Treatment with < 600 mg/M²/12-hour infusion caused little hematopoietic suppression. With infusions > 600 mg/M²/12 hours, most patients developed dry desquamation and scaling of the palms and soles of the feet and also a brittleness of the nails. Several patients developed a widespread rash.

In 1987, the same group of investigators reported updated results using either BUDR or IUDR on 60 patients with malignant glioma [125]. Patients received either 12-hour or 24-hour infusions for two-week periods as described above. All the BUDR patients received conventional radiotherapy at 180–200 cGy per day to total doses of 6500–7000 cGy. Patients receiving IUDR were treated with hyperfractionated and split-course radiotherapy. The IUDR patients were treated with 150 rads twice daily to 4500 cGy over three weeks with large fields. After a two-week break, an additional 2500 cGy was administered to a cone-down boost volume at 125 cGy twice daily.

There were no differences in survival between IUDR versus BUDR, 12-hour versus 24-hour infusions, extent of surgical resection, or sex.

For the entire group, the median survival was 13 months, and the 18-month survival was 24%. This is similar to the results obtained in the BTSG phase III Studies [77].

Using bone marrow aspirate cells from four patients taken immediately prior to and then following a 14-day infusion, the extent of BUDR-enhanced radiosensitivity of normal proliferating cells was assessed [124]. In all four patients, D_0 was lower following infusion of BUDR. Enhancement ratios (pre-BUDR D_0 /post-BUDR D_0) of 1.2–2 were noted. This demonstrated that at least normal proliferating cells could be sensitized in vivo by BUDR infusions.

Fairchild et al. have suggested that IUDR replacement of thymidine can be exploited by using 33–70 KeV radiation [126]. They postulate that low-energy photons in this range, as opposed to megavoltage X-rays, would be absorbed preferentially by the iodine atom. The absorption of lower-energy X-rays leads to emission of Auger electrons—mainly with energies < 3 KeV, but with a high LET and very short range. The emission of these electrons caused by the absorption of low-energy photons in the iodine atom should cause a very high dose to be absorbed mainly within the cell nucleus because of the short range of the electrons. They call this process *photon activation therapy* (PAT).

By a complicated set of equations and assumptions, Fairchild et al. postulate that IUDR would be the most effective of the halogenated pyrimidine analogues for PAT. Their calculations indicate that a 5% replacement of tumor DNA thymidine by IUDR would increase the effectiveness of radiation (in the 33–70 KeV range) by a factor of at least 3 and perhaps as much as 5.5.

As far back as 1963, Erikson and Szybalski showed that the radiosensitivity effect of BUDR was not dependent on the incident X-ray energy [115]. Over a range of X-ray energies from 25 KeV up to 450 KeV, there was no difference in the radiosensitivity afforded by BUDR in cells

that had been exposed for four days to a concentration of 2×10^{-5} M BUDR. Regardless of the X-ray energy used, there was about a 1.9-fold increase in sensitivity.

Miller et al. demonstrated a 16% replacement of thymidine DNA in Chinese hamster V 79 cells with a 17-hour exposure in vitro to either 10^{-5} M IUDR or BUDR [116]. They compared the amount of radiosensitization of BUDR- or IUDR-exposed cells irradiated by either 15 MV photons or an orthovoltage machine (peak 100 KeV) with 55% of the photons in the 33–60% KeV range. There was a very slight increase in cell killing with the lower energy photons, but only by a factor of 1.07 when compared with the higher energy photons. This is much lower than the amount of enhancement predicted by the PAT concept. As expected, the presence of additional IUDR in the extracellular media did not further increase sensitivity.

On the other hand, Nath et al., using Chinese hamster lung cells, showed increased radiosensitivity of IUDR-exposed cells to 250 KV X-ray as compared to 4 MV X-rays with a factor of about 1.5 [127]. In experiments with low dose rates (55.5–58.7 rads/hour), IUDR sensitization was increased by a factor of 1.5–2 when cells were irradiated by americium-241 (60 KeV) as opposed to radium-226 (860 MeV).

There are theoretical problems associated with the use of halogenated pyrimidine analogues as radiosensitizers. For the drug to affect radiosensitivity, it must be incorporated into the DNA molecule during the S phase. Therefore, cells in G0 or G1–G2 phases of the cell cycle would not show a change in radiosensitivity regardless of the amount of exposure to the halogenated pyrimidine analogue. Thus, cells that do not enter S phase during the infusion of the drug would not be affected. Even with rapidly growing tumors such as glioblastoma and medulloblastoma, not all cells are in the proliferating phase. Tumors are likely to contain large numbers of viable but slowly proli-

ferating or nonproliferating cells that may not enter the S phase during the several-week period of exposure.

If indeed radiosensitization by IUDR could be significantly improved by using low KeV radiation, the only possible way to deliver an adequate dose to a brain tumor would be by intraoperative external low KV radiotherapy or interstitial sources such as americium-241.

Using a rat brain tumor model with the clinical and pathological features of dissemination via the CSF pathways, Deutsch et al. demonstrated that IUDR administered into the CSF, together with craniospinal axis irradiation, provided a significant survival advantage over radiotherapy alone [128]. IUDR alone did not provide any advantage over control (no treatment). It is possible that halogenated pyrimidine analogues administered into the CSF would be beneficial as radiosensitizers in those clinical situations such as medulloblastoma where radiotherapy is administered to the craniospinal axis for the treatment of cells and small implants in the CSF pathways.

Radioactive Molecules

Another interesting approach for treating malignancies with radioactive isotopes is the use of I-125-labeled IUDR. Bloomer and Adelstein demonstrated the efficacy of the compound in the treatment of an ascites malignancy in mice [129, 130]. The I-125 produces electrons mainly in the 0.8–3.7 KeV range. These electrons have a range in tissue of only 0.05–0.4 microns, and thus IUDR has the potential for being used not only as a radiosensitizer but also as an internal emitter of beta rays when incorporated into cells. Obviously, the problems with using such a compound for the treatment of brain tumors are:

1. Only the proliferating cells will take up the IUDR
2. If there is impairment of blood flow to portions of the tumor, many cells will not

take up the compound

3. Getting the compound to the cells is problematic—if one uses the systemic circulation, then proliferating cells outside of the CNS will be exposed to the radioactive compound

One promising solution to the problem of selectively attaching a radioactive isotope to tumor cells is to attach radioactive isotopes to an antibody directed against the particular tumor cells. I-125 can be attached to antibody molecules. Obviously, for such a scheme to be effective, the antibody must be specific for tumor antigen and not be cross-reactive with antigens on normal cell surfaces. The antibody must localize on the tumor and there should be rapid clearance of nonbound antibody. Preferably, the radioactive moiety should have a short half-life, thus providing less chance for free isotopes to affect other tissues. The wide application of this technique awaits the production of highly specific antibodies that would be specific for all cells of a particular tumor and yet would not react with nontumor cells.

Conclusions

Over the next several years, it is likely that there will be further improvements in the radiotherapy of pediatric intracranial tumors. Better tumor localization by improved imaging methods together with better dose localization is one very likely avenue of improvement. Optimization of fractionation schemes with or without hypoxic cell sensitizers and/or radioprotectors may provide the same benefits as high LET radiation. Improvements in the use of intraoperative radiotherapy and interstitial implants, again combined with hypoxic cell sensitizers and/or radioprotectors, may increase therapeutic gain and limit injury to normal tissue. In addition, further advances in chemotherapy for pediatric brain tumors may allow radiation dose reductions, which would possibly decrease the incidence of late sequelae.

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8. PATHOPHYSIOLOGIC BASIS FOR BRAIN TUMOR CHEMOTHERAPY

Jeffrey A. Stephenson, Jonathon L. Finlay

Systems Unique to the Brain and Brain Tumors

ANATOMIC CONSIDERATIONS

In order to understand the rationale underlying brain tumor chemotherapy, it is important to review the unique properties of brain tumors. Unlike most carcinomas and sarcomas that are malignant because of their propensity to metastasize, brain tumors generally remain confined to the central nervous system. Histologically, they span a spectrum from slow-growing, low-grade astrocytomas to the aggressive glioblastoma multiforme, a tumor with the capacity to double in size every six days [1]. Unfortunately, brain tumors may be of very small size and low histologic grade, such as a brainstem astrocytoma, but can nevertheless rapidly kill the patient if untreated. In systemic tumors, it is generally felt that one kilogram (10^{12} cells) of tumor burden is lethal to the patient. In the setting of a brain tumor, 100 grams or less can be lethal. Surgical excision or debulking maximizes the chance of cure for the patient with a primary brain tumor [2]. Increases in survival have resulted from radiation therapy and chemotherapy; however, both work best in the context of minimal residual disease [3].

CEREBRAL EDEMA

An understanding of peritumoral edema is relevant to the therapeutic approach towards the patient with a brain tumor for several reasons.

Edema compounds the mass effect of the tumor, and it exacerbates, both locally and globally, the neurological deficits caused by the tumor as a result of generalized increased intracranial pressure. There are three types of brain edema that have been described; vasogenic, cytotoxic, and interstitial [4, 5].

Vasogenic edema is the most common type of edema associated with brain tumors. Ultrastructural studies on brain tumors have demonstrated defects in the walls of tumor capillaries; normal brain capillaries have no defects and thus serve as a barrier between the blood and the brain [6]. It is felt that the angiogenesis of the tumor blood supply differs from that of normal brain, accounting for these defects in the endothelial lining of the capillaries. Protein, electrolytes, and water are able to leak out through these defects and primarily enter the white matter and nerve tracts of the brain. Once this fluid enters the brain substance, there are no lymphatic channels for the fluid to follow; likewise, there is negligible uptake by the astrocytes and axons. Since there is no interstitial compartment, the fluid must flow extracellularly into the cerebrospinal fluid (CSF) [7]. Studies have shown that this peritumoral edema fluid spreads throughout brain parenchyma at a rate of 10 mm per week. This rate is slower than what would be expected from passive diffusion alone, and reflects the rate at which fluid is leaking out of the peritumoral capillaries [8].

Cytotoxic edema is the result of direct injury

to the cells associated with disruption of the ATPase-controlled sodium–potassium pump, leading to membrane instability, with consequent intracellular swelling. Studies have shown that membrane permeability characteristics are normally intact in the peritumoral regions [9]. Positron emission tomography (PET) using ^{82}Rb ($^{82}\text{Rb}^+$) has allowed qualitative and quantitative analysis of membrane-permeability characteristics, since $^{82}\text{Rb}^+$ behaves similarly to potassium in terms of being transported into the cell via the sodium–potassium–ATPase pump. Injury to this pump prevents the influx of $^{82}\text{Rb}^{+10}$. Yen et al. showed that in conditions of edema and increased intracranial pressure there was uptake of $^{82}\text{Rb}^+$ by brain tumors due to intracellular damage. This damage and membrane instability results in cytotoxic edema as a component of vasogenic edema [11].

Interstitial (or transependymal) edema is defined as that seen in raised intracranial pressure resulting from increased cerebrospinal fluid (CSF) pressure gradient from the ventricles into the white matter, with an increase in water and sodium content of the white matter, and is thus only seen when there is obstruction to CSF flow by tumor [5].

THE ROLE OF CORTICOSTEROIDS, DIURETICS, AND HYPEROSMOLAR AGENTS

The majority of patients with brain tumors will receive glucocorticoids at some point in their management, and many will require long-term therapy. Using electron microscopy, Long et al. were able to demonstrate the presence of vasogenic and cytotoxic edema, and they correlated improvement in clinical status with resolution of edema following therapy [12]. Laboratory studies by Shapiro et al. defined the role of corticosteroids in correcting the flux of sodium, potassium, and water out of the cell resulting from hydrostatic pressure [13]. They were able to demonstrate increased membrane stability and decreased vascular permeability with the use of corticosteroids. Corticosteroids,

specifically glucocorticoids, are generally in the forms of dexamethasone, methylprednisolone, hydrocortisone, or prednisone. Bracken et al. and the National Acute Spinal Cord Injury Study have extensively studied methylprednisolone intravenously in acute spinal trauma and have found a 100 mg bolus with 100 mg daily for ten days to be effective in adults. Higher doses did not appear to confirm an advantage [14, 15]. To date, no studies have demonstrated a clear-cut advantage of one glucocorticoid over another in patients with brain tumors, although intravenous administration would act more rapidly in the symptomatic patient. Balis et al. found that higher free plasma levels were obtained with oral dexamethasone compared to prednisone, resulting in higher CSF levels of dexamethasone compared to prednisone, probably conferring a therapeutic advantage in central nervous system (CNS) prophylaxis in leukemia [16]. By increasing vascular membrane stability, an improvement in blood flow and increased oxygenation results in decreased CSF pressure.

There is also some evidence that glucocorticoids may have a systemic diuretic effect by decreasing the secretion of aldosterone, thereby increasing renal tubular secretion of sodium [17]. In addition, Weiss and Nulsen examined the effect on canine CSF production and found it to be lowered by as much as half with the administration of glucocorticoids [18]. Determination of CSF production in human is difficult to quantitate but intracranial pressure monitoring of patients receiving corticosteroids shows a reduction of CSF pressure that correlates with initiation of corticosteroid therapy [19, 20].

Both furosemide and ethacrynic acid block sodium transport in the renal tubules and lower CSF production by inhibiting carbonic anhydrase. In 1973, Schurmann et al. found a greater effect on reducing edema with a combination of dexamethasone and diuretic than with either agent alone [21]. A clinical trial by Meinig et al. confirmed the beneficial

effect of combining furosemide and dexamethasone treatment in patients with brain tumors. They also saw decreased water, sodium, and chloride in the peritumoral region of edema [22].

Hyperosmolar agents, such as urea and mannitol, exert their effect by osmotic force, with draws fluid from the extracellular space and induces diuresis. In 1961, Javid reported the results of urea in the treatment of 700 patients with increased intracranial pressure and found a sustained fall in pressure in virtually all patients [23]. Two major side effects associated with urea, hemoglobinuria and generalized sloughing of the skin, have made mannitol a more popular hypertonic agent. In 1962, Wise and Chater reported on the effective use of mannitol in lowering CSF pressure and decreasing mass effect in a series of neurosurgical patients [24]. Clinical trials have demonstrated the effectiveness of mannitol at reducing intracranial pressure; as a general rule, the higher the initial CSF pressure, the briefer will be the response to mannitol [25]. Fishman cautions that the effects of hyperosmolar agents are short-lived, and there is the potential of rebound edema developing as the brain strives to balance intracellular osmolality with plasma osmolality by increased uptake of sodium and potassium [5].

Corticosteroids may exert either a positive or negative tumoricidal effect on the treatment of brain tumors. Mealey et al. have demonstrated a positive tumoricidal effect by in vitro inhibition of glioma cell lines by dexamethasone [26]. Sherbert et al. suggest in vivo inhibition of growth of human gliomas by dexamethasone [27]. A recent study using methylprednisolone therapy in patients with brain tumors did not show a survival advantage using methylprednisolone alone but did note a high incidence of infections [3].

In contrast, Zager et al. warn that the membrane stabilization seen with the use of corticosteroids may actually decrease the permeability of the blood-brain barrier and inhibit the

entry of methotrexate and other water-soluble chemotherapeutic drugs into the tumor [28].

THE BLOOD-BRAIN BARRIER

The term *blood-brain barrier* describes a physiologic phenomenon whereby certain chemical compounds are not able to cross from the vascular space into the brain parenchyma. Ultrastructural studies have shown that the cerebral capillaries are composed of endothelial cells, a basement membrane, and astrocytic foot processes. The endothelial cell itself is felt to be primarily responsible for protein exclusion from the brain [29]. The cerebral endothelial cells are attached to one another by a continuous series of tight junctions or zonulae occludentes. In addition, microscopic examination of the endothelial cells shows the absence of pinocytic vesicles, which are a major method of active transport across other cells. The experience with childhood leukemia patients has clearly demonstrated that the CNS has a barrier that prevents systemic chemotherapy reaching the neuraxis in tumoricidal concentrations. Rall and Zubrod in their classic article in 1962 stated that the characteristics that most favored the passage of a drug across the blood-brain barrier were high lipid solubility, minimal charge, lack of protein binding, and small molecular size [30]. The results of single-agent clinical trials have shown this to be true of the nitrosoureas, small lipid-soluble compounds, whose "member" drugs are the most active single agents against CNS neoplasms [31].

THE BLOOD-BRAIN TUMOR BARRIER

The idea of a permeable blood-tumor "barrier" was introduced as it became clear that brain tumors selectively enhanced with intravenously administered radiocontrast materials. This physiologic phenomenon was referred to as a blood-tumor barrier. A series of laboratory reports began to qualify this phenomenon using both induced and transplantable brain tumor models. A major criticism of all studies utilizing transplantable brain tumors is that the development

of their blood vessels in this contrived situation may not be reflective of the blood supply developed in the face of endogenous brain tumors. Brightman et al. used a virally induced rat astrocytoma model to show that a high-molecular-weight compound, horseradishperoxidase, did cross the vascular wall and enter brain tumors [32]. Ausman et al. demonstrated the passage of albumin and inulin into implanted choriocarcinoma in the monkey brain [33]. Efforts were then aimed at determining the ability of water-soluble chemotherapeutic agents, which generally do not cross the blood-brain barrier, to cross the blood-tumor barrier. Levin et al. demonstrated in vivo that systemic radiolabeled 5-fluorouracil (5-FU) would selectively accumulate in intracerebrally implanted Ep murine glioma with a concentration that was 11 times that of the normal mouse brain [34]. Methotrexate, another drug which generally is not considered to cross an intact blood-brain barrier, was also found to concentrate in the intracerebral Ep murine glioma [35] and ependymoblastoma [36].

Recently PET scanning using ^{11}C -labeled methylalbumin has demonstrated that the uptake of this macromolecule appears to be confined to the tumor, with virtually no uptake by surrounding edematous tissue [37]. Histologically, the reason for this uptake of compound by the brain tumor is the angiogenesis of an aberrant network of tumor blood vessels [38]. Brain tumor capillaries show thinning of the endothelial cells, aberrations in the basement membrane, increased surface area between vascular space and parenchyma, and frank openings between endothelial cells [39, 40]. To further understand the ability of chemotherapeutic agents to cross the blood-tumor barrier, Shapiro and Ausman tested a series of agents against four different transplantable murine ependymoblastomas. The results showed CCNU, BCNU, and cyclophosphamide to have the greatest therapeutic activity as measured by prolonged survival of the animals in these models [41, 42]. Of significance was the

observation that while 5-FU and methotrexate had minimal therapeutic efficacy, they did accumulate in these tumors, suggesting that other factors may account for their lack of therapeutic effect [36, 43]. Furthermore, combinations of drugs such as nitrosoureas plus procarbazine or dianhydrogalactitol were more effective than either agent alone; in fact, some of the mice with the transplantable tumor achieved a normal lifespan [44]. Based on these experimental data, clinical trials with chemotherapeutic agents began in the late 1960s in patients with a variety of different malignant brain tumors. Drugs with minimal to moderate activity included vincristine, cyclophosphamide, cisplatin, the epipodophylotoxins (VP-16 and VM-26), aziridinylbenzoquinone (AZQ), thiotepea, methotrexate, hydroxyurea, cytosine arabinoside, dacarbazine, and nitrogen mustard. The single most active agents have been the nitrosoureas, BCNU, CCNU, and Methyl-CCNU, and to a lesser extent procarbazine [31], the results of these clinical trials confirmed the importance of small molecular size and lipid solubility in active drugs in the treatment of brain tumors.

To explain why large-molecular-weight and water-soluble compounds performed so poorly in single-agent clinical trials, investigators began to study the properties of the blood-tumor barrier. Using a rat brain tumor model, Levin et al. discovered that the rapidly growing periphery of the tumor displayed decreased areas of capillary permeability similar to an intact blood-brain barrier [9]. Tator, using a transplantable mouse glioma, demonstrated heterogeneous uptake of labeled methotrexate by the tumor, suggesting regional variations in the blood-tumor barrier [35]. The development of PET scanning using ^{68}Ga -labeled EDTA (^{68}Ga -EDTA) has allowed mapping of a particular tumor with reference to quantitative breakdown of the blood-brain barrier in brain tumors [45]. Using this and laboratory measurements of capillary permeability, it may be possible to select specific agents to

treat an individual brain tumor based on known permeability characteristics and regional variations as seen on PET [46].

BLOOD FLOW AND BLOOD-TO-TISSUE TRANSPORT

As experimental evidence began to confirm the presence of a blood–tumor barrier, Blasberg et al. in 1981 reported on the use of quantitative autoradiography (QAR) to measure local blood flow and blood-to-tissue transport in a variety of brain tumor models. QAR is a technique where animals bearing experimental brain tumors are given timed infusions of radiolabeled compounds. The animals are then sacrificed, and autoradiographs are performed in 20-micron-thick sections of brain tissue that can then be mapped by a computer to quantitate the permeability of a region as small as 50 microns [47]. Measurements were made to define blood flow using five different experimental rat brain tumor models, either induced by the avian sarcoma virus [48], by transplacental exposure of rats to ethylnitrosourea [49], or by intracerebral injection of RG-2 and RT-9 brain tumor cells [50,51], as well as a metastatic model produced by intracarotid injection of Walker-256 cancer cells.⁵² Blood flow was measured using ¹⁴carbon-labeled iodoantipyrine (¹⁴C-IAP), a compound that rapidly enters normal brain tissue with a rate of entry directly proportional to the blood flow. The results in each of the systems were similar in that they all showed that overall the rate of tumor blood flow was fairly high, being similar to normal white-matter blood flow. Unfortunately, there were regional variations in tumor blood flow with the lowest rates of flow in the central necrotic regions of the brain tumors [53]. This could explain the failure of nitrosoureas to make an impact on survival in single-agent clinical trials, since the concentrations of nitrosourea in the tumor is proportional to blood flow and independent of the permeability of the blood–brain barrier.

The question of regional variations in per-

meability and the rate of blood-to-tissue transport were also investigated in these five rat brain tumor models. ¹⁴Carbon-labeled alpha-aminoisobutyric acid (AIB) is taken up by most cells using an active transport system for the uptake of amino acids. AIB does not cross an intact blood–brain barrier but will cross the blood–tumor barrier. Once AIB is in the CNS tissue, it is taken up by both tumor and normal cells, where it can be quantified and used to calculate a blood-to-tissue transfer constant for a given region of the tumor. Molnar et al. showed that there was marked variation of this blood-to-tissue transfer constant (*K*) within the avian sarcoma virus-induced rat brain tumors, and that the central region of the tumor could have extreme transport or virtually none at all; further, this variation in transport could not be correlated with any distinctive histological features [54]. Blasberg et al. demonstrated that there was virtually no change in transport of AIB between the ethylnitrosourea-induced rat glioma and the normal brain [55]. Groothuis et al. reported on the transplantable RG-2 rat brain tumor model and demonstrated that transport was much greater in the tumor than in the surrounding brain and that the rate of transport was homogeneous throughout the tumor [56]. Molnar et al. demonstrated that transport increased dramatically as tumor size increased in the rat transplantable brain tumor RT-9, so the small tumors did not differ from normal brain in terms of transport from the blood to tissue [57]. Blasberg et al. found the Walker-256 metastatic tumors to behave similarly to the RT-9 transplantable model: small-sized tumors did not disrupt the blood–brain barrier enough to show increased transport across the capillaries, while invasion of the vascular meninges or choroid plexus did result in higher transport of AIB [58]. The overall conclusion that can be drawn from these data on transport of small, uncharged, amino acids is that the transfer constant of a given tumor can range from 1 to 100 times the transfer across an intact

blood–brain barrier. Therefore, generalizations or models cannot be constructed on the basis of tumor size, location, histology, or the amount of tumor necrosis. Generally speaking, the delivery of water-soluble chemotherapeutic agents will be dependent upon the permeability characteristics of a regional capillary bed, not on blood flow [53]. Small, lipid-soluble compounds such as the nitrosoureas are able to work independent of these variations in permeability, and the effectiveness of nitrosoureas becomes a function of blood flow and delivery to the tumor [59].

QAR is a laboratory technique that cannot be applied to in vivo human systems. It is clear that with variable rates of transport into a tumor, the development of an in vivo assay for human brain tumors would permit tailored drug regimens depending on the blood flow and transport characteristics of an individual tumor. Recent investigations have utilized PET scanning with ^{11}C -carbon-labeled 3-O-methylglucose, ^{68}Ga -EDTA, and $^{82}\text{Rb}^+$ to help evaluate regional blood flow and permeability characteristics of a given tumor [60, 61, 62]. While QAR has the capability of detecting subtle variations that are only 50 microns apart (100–200 tumor cells), PET has a resolution of only 0.6 to 1.0 cm. Yamamoto et al. have investigated the kinetics of uptake of ^{11}C -carbon- and ^{13}N -nitrogen-labeled BCNU into gliomas by PET. They demonstrated that initial uptake of BCNU was dependent upon blood flow characteristics of the tumor, and that by disruption the blood–brain barrier with mannitol intravenously, an increased uptake of BCNU was observed in the tumor [63]. As PET scanning techniques improve, accurate determinations of blood flow and permeability will allow precise determinations of the efficacy of chemotherapeutic regimens in patients with brain tumors. Manipulations such as hyperosmolar agents may be an effective way of increasing blood flow by decreasing edema and increasing capillary permeability to boost the efficacy of brain tumor chemotherapy. A detailed discussion of clinical

trials using hyperosmolar agents will follow later in this chapter.

Maximizing the Therapeutic Ratio

EFFECTS OF IRRADIATION— IMPLICATIONS FOR CHEMOTHERAPY

A central hypothesis in understanding the effects of irradiation is that radiation damage is preceded by and is a function of radiation effects on the vascular system [64]. Hopewell, in 1974, reported on the late vascular effects of irradiation in the brain and showed occlusive endothelial changes histologically. After giving a dose of 2000 cGy to a hamster, focal occlusive changes are seen in the capillaries, and a reduction of vascular volume is seen within 2 to 3 months [65]. Young demonstrated the histologic presence of arterioles totally or partially occluded by endothelial cells at 10 to 12 weeks after irradiation of pig skin [66]. Moustafa gave 2000 cGy to the rat brain and at three months observed reduction in cerebral blood flow using extraction of iodoantipyrine, and did not find blood flow to return to normal with time [67]. Price has described a form of delayed neuropathy, known as mineralizing microangiopathy, seen in children with CNS leukemia who receive craniospinal irradiation and intrathecal methotrexate [68]. This condition has also been seen in patients who receive radiation therapy for primary brain tumors [69]. Radiation-induced changes in the endothelium and vascular wall will eventually lead to mineralizing destructive and occlusive lesions of the vessels, accompanied by dystrophic calcification of surrounding tissue [70]. McIntosh et al. have suggested that intrathecal chemotherapy may cause progression of these lesions [71]. These studies stress the importance of the spatial relationship between radiation therapy and chemotherapy. If chemotherapy is to have the greatest benefit from blood flow characteristics, then it should be delivered before the vascular changes compromise blood flow to the tumor.

This may explain why preirradiation chemotherapy may be effective not only by shrinking tumor mass but also by increasing oxygenation of the tumor cells and thereby rendering them radiosensitive. In 1978, Poisson et al. described 46 patients with high-grade astrocytomas treated by surgical excision, followed by six cycles of VM-26 and CCNU over six months; following this, an average dose of 5800 cGy external radiotherapy was delivered to the region of involvement. Of 34 patients who survived to six months, 50% were alive at two years. Overall survival using this regimen was 35% at two years, considerably better than the nitrosourea and surgery only control group [72]. In 1982, Allen et al. reported on 14 children with a variety of brain tumors considered of poor prognosis. They were treated with two cycles of cyclophosphamide prior to radiation therapy. Five patients also received intrathecal cytosine arabinoside and oral hydroxyurea; objective responses were seen in eight patients (57%) and no child progressed prior to radiation therapy [73].

Other experimental systems show that a synergistic relationship occurs when chemotherapy and radiotherapy are used together in certain spatial relationships. Simultaneous chemotherapy and radiotherapy may facilitate the passage of drug into the brain. Griffin et al. demonstrated that mice given intraperitoneal methotrexate had no detectable CSF level of methotrexate at 24 hours. If these mice were given 2000 cGy to the brain over ten minutes followed by intraperitoneal methotrexate, the CSF concentration of methotrexate was higher than the plasma level at 24 hours. This effect reached its peak at 1 to 2 days after irradiation and persisted for at least six days [74]. Bleyer and Griffin caution that simultaneous administration was associated with increased toxicity and that any gain in therapeutic effect may make this unacceptable [75]. Phillips reviewed the mouse solid tumor studies, which compared the spatial relationship of chemotherapy to radiotherapy. Actinomycin was found to be synergis-

tic with irradiation if given six hours before irradiation in the EMT6/St model. BCNU was synergistic if given before irradiation in the KHT system and after irradiation in the EMT6/SF models. Cyclophosphamide was synergistic in the EMT6/SF and RIF-1 models if given after irradiation. Cisplatin if given 24 hours before irradiation was synergistic in the RIF-1 model [76]. Synergism between cisplatin and irradiation was confirmed by Bartelink et al. using the RIF-1 tumor in mice; they noticed a synergistic effect when cisplatin was given once a week, 24 hours before the daily fraction of irradiation [77].

Synergy between chemotherapy and radiotherapy has also been studied in primary brain tumors. The interaction of BCNU and irradiation was examined in the 1970s by Wheeler. It was shown that BCNU could modify the shape of the cell survival curve in cultured rat 9L brain tumor cells. Ten irradiation fractions were delivered over two weeks to a total dose of 2600 cGy, with BCNU being administered at variable time intervals before each dose of radiation. The results showed that BCNU given 16 hours before irradiation gave the highest rate of cell kill [78]. This led to a pilot study for the Eastern Cooperative Oncology Group (ECOG) consisting of weekly pulses of BCNU 16 hours before irradiation treatment to a total dose of 7000 cGy in 35 fractions over seven weeks for patients with malignant gliomas. The results did not show an advantage to the addition of BCNU, but there is some concern that the dose of BCNU may not have been high enough to see a synergistic effect [79]. Other investigations have shown that levels of cisplatin as low as 1 mg per ml are radiopotentiating [80, 81]. In a study of patients with primary and metastatic brain tumors, Stewart et al. were able to demonstrate that this concentration could be achieved without appreciable toxicity, but were unable to see a therapeutic effect [82]. Mulne et al. have shown that a combination of eight drugs—vincristine, hydroxyurea, procarbazine, CCNU, cisplatin, cytosine arabinoside,

methyl prednisolone, and either cyclophosphamide or dacarbazine, (the *8-in-1* regimen)—is more effective *in vitro* against human brain tumors when used before irradiation than when it is used with or after irradiation. The LD₅₀ (the dose of irradiation required to kill 50% of the tumor cells) was less than 500 cGy when the tumor cells were exposed to the eight drugs in combination, administered one hour before irradiation. This compares with 950 cGy when the drugs were given one hour after irradiation and 1350 cGy when no drugs were given [83]. Furthermore, the group found the effects of eight drugs in combination, each at a lower dose, to be more consistently effective than any one drug alone at standard higher doses against 16 human brain tumor cultures [84]. Results in primary brain tumor patients treated with two cycles of *8-in-1* chemotherapy before irradiation have shown a 50% reduction of tumor bulk by CT scan evaluation in half the patients. Theoretically this allows for enhanced oxygenation and radiosensitivity with a greater probability of cell kill within the curative range [85]. As increasing knowledge about drug–radiation interactions accumulate, clinical trials that exploit this knowledge may allow us to maximize the therapeutic potential of chemotherapy and radiotherapy for primary CNS malignancies.

EFFECTS OF HYPERTHERMIA — IMPLICATIONS FOR CHEMOTHERAPY

Hyperthermia is being investigated both as a single therapeutic modality and in combination with irradiation and chemotherapy in the treatment of malignant brain tumors. There are several reasons why primary brain tumors are ideally suited to localized hyperthermia treatment. Brain tumors rarely spread outside the brain and are potentially cured by controlling local disease. In addition, with new imaging techniques, there is an enhanced capacity for precise tumor localization. The brain is a relatively homogeneous region that does not present the challenges of dose perturbations that are seen in other regions of the body [86].

Hyperthermia works by direct cell kill and sensitization of the remaining cells to chemotherapy and radiotherapy. Another advantage of hyperthermia is that it selectively kills cells that are resistant to irradiation, cells that are in the synthesis (S) phase, and radioresistant hypoxic cells. Hyperthermia can prevent recovery of the cancer cell from sublethal damage, and if delivered in the correct spatial relationship to chemotherapy and radiotherapy, may increase the therapeutic ratio [87]. Clinical trials in human malignancies suggest that hyperthermia is synergistic with irradiation in the treatment of neck node metastases [88] and advanced local carcinomas [89–91]. This synergistic effect is also seen when hyperthermia is combined with chemotherapy *in vitro* [92, 93] and is synergistic between hyperthermia and adriamycin or bleomycin [94]. *In vivo* data using hyperthermia and nitrosoureas show a synergistic effect in a murine ependyoblastoma model [95]. A clinical trial of hyperthermia and chemotherapy for patients with extremity melanomas has shown synergistic effect [96]. Storm et al. demonstrated 15% tumor regression and 56% stabilization of disease using combined hyperthermia and chemotherapy in advanced cancer patients [97]. In a study of patients with either anaplastic astrocytoma or glioblastoma multiforme who had already received surgery, radiation, and nitrosourea therapy, Salzman and Samaras utilized an interstitial implant with a flexible microwave radiator. Of six patients, four were alive at 18 months, two were without evidence of disease on CT, and none had neurologic sequelae as a result of treatment. The group is currently initiating a phase I/II trial to evaluate combined interstitial radiotherapy and interstitial hyperthermia in newly diagnosed patients with glioblastoma multiforme [98]. Silberman et al. have reported on a phase I trial combining hyperthermia and intravenous chemotherapy in ten patients with both primary and metastatic brain tumors. They found no mortality or increased chemotherapy toxicity from the treatments, but did observe three

transient neurological complications [99]. Sutton et al. reported on five patients treated with an interstitially placed heat probe and intravenous 5-FU for malignant gliomas. In an additional nine patients, they used a combined heating source and catheter to deliver methotrexate to the tumor tissue in combination with intravenous cyclophosphamide [100]. They were able to achieve enhanced tumor kill and minimal toxicity in both a mouse laboratory model and humans [100, 101]. As our understanding of hyperthermia improves, future clinical trials will be concerned with testing new modalities such as focused ultrasound [102], and better defining the therapeutic efficacy of hyperthermia in combination with chemotherapy and radiotherapy.

HEMATOPORPHYRINS AND A NEW MODALITY, PHOTORADIATION THERAPY

Photoradiation therapy is a technique that exploits a property of acidified hematoporphyrin in producing cytotoxic effects on surrounding tissue when exposed to intense photic energy. Hematoporphyrin does not readily cross the blood-brain barrier, but does preferentially accumulate in brain tumors, regions of trauma, and the pituitary stalk [99]. In the early 1970s, investigations by Diamond et al. and Granelli et al. of glioma cells grown in culture or implanted into rats demonstrated that sensitization of the cells with hematoporphyrin derivative and exposure to light produced a cytotoxic effect, similar to the effect of ionizing radiation, with formation of free radicals and cell killing [104, 105]. In 1978, Dougherty et al. reported on the successful treatment of a variety of cutaneous and subcutaneous malignancies with photoradiation therapy [106]. Perria et al. and Laws et al. have reported on the preliminary results of photoradiation treatment in patients with malignant gliomas and have achieved tumor regression without appreciable toxicity [107, 108]. Two recent laboratory investigations by Wharen et al. and Cheng et al. in rat brain tumor models warn of damage to

normal brain tissues, which is a function of the interaction of high hematoporphyrin concentrations and intense photic energy [109, 110]. Research directed at time-dose relationships, toxicity, and delivery systems should expand upon the application of this new modality for the treatment of patients with primary brain tumors.

Heterogeneity, Oncogenes, and Chemotherapy Resistance

The idea of malignant tumors arising from a single cell that undergoes mutation and begins to divide uncontrollably has dominated our understanding of cancer for decades. In recent years, it has become clear that malignant transformation involves a number of steps and a multitude of tumor-versus-host interactions that determine whether a cancer cell lives or dies within a host. Tumor heterogeneity describes a Darwinian process of natural selection whereby certain subsets of cells survive changing environmental pressures [111]. These environmental pressures include change in oxygen tension, nutritional status, ionizing radiation, cytotoxic chemicals, and the host immune response. Cells respond to these pressures by gene expression, in which oncogenes appear to be a crucial factor.

The number of oncogenes in the genome appears to be small and remarkably conserved through the course of evolution. Activation of these oncogenes causes the cell to break away from its normal course of differentiation and directs it towards unregulated growth and malignant transformation. Techniques used in the study of gene transfer and retroviruses have unlocked many of the secrets behind this gene expression. Two concepts, the mutation hypothesis and the gene dosage hypothesis, have been proposed to explain the activation of oncogenes [112]. In addition, multiple chromosomal abnormalities are known to exist in cancer cells. Translocations, deletions, and duplications or ploidy have all been associated

with oncogene expression [113]. Cellular transformation appears to be a multistage event, with both initiation and promotion; oncogene activation is one of two or more crucial steps in this pathway [114].

Specific studies examining human gliomas have shown extensive heterogeneity not only between adjacent regions of brain tumors but also between adjacent cells [115]. Heterogeneity can be seen on the microscopic level by differences in cell size, nuclear and cytoplasmic morphology, and cell biological, biochemical, and immunological marker studies [116]. Shapiro has performed karyotyping studies on human gliomas and found relatively homogeneous diploid chromosomes in the low-grade astrocytomas but noticed a striking increase in structural chromosome rearrangements in the high-grade astrocytomas. Specific chromosome aberrations that have been observed include 45 chromosomes with either a missing X or Y chromosome, overrepresentation of chromosome 7, and underrepresentation of chromosome 22 [117]. The oncogene *c-erb-B* has been mapped to chromosome 7 and encodes for 3 of the 4 domains of the epidermoid growth factor (EGF) receptor [118]. The *c-sis* oncogene has been mapped to chromosome 22 and encodes for one of the polypeptides of platelet-derived growth factor (PDGF) [119]. Growth factors are felt to circulate in the blood and bind to surface membrane receptors that activate cell growth. Of interest is the observation that overrepresentation of chromosome 22 was associated with the production of a compound similar to PDGF and the development of BCNU resistance in human glioma cells [120]. It appears that compounds that allow communication between cells are produced by tumor cells; intrinsic drug resistance may result from this communication. Therapeutic efforts aimed at blocking these receptor sites or the elimination of these growth factors would be expected to have a significant impact on tumor growth.

Cell culture techniques have been used to examine the heterogeneity of chemosensitivity at doses encountered in human brain tumor

patients [122]. Using BCNU and cisplatin, a wide range of LD₅₀ response values were seen for human glioma cell cultures. More important is the emergence of resistant cell populations if a tumoricidal dose is unable to be achieved [123]. It appears that inherent variable chemosensitivity within a population of glioma cells may lead to the later development of a refractory tumor [121].

Administration of beta-receptor-agonists may increase differentiation of glioma cells. Studies in rats implanted with the C6 glioma have shown that administration of isoproterenol, a beta-agonist, increases the level of cyclic AMP by stimulation of the adenyl cyclase system. Using this model, suppression of tumor growth and increased differentiation of the tumor was seen in sacrificed specimens [124].

Chemotherapeutic Principles

THE CELL CYCLE

Modern chemotherapy is based on the interaction of cytotoxic drugs with a rapidly proliferating cancer cell population. A knowledge of cell cycle kinetics has provided a rational basis for the design of chemotherapy protocols. The cell cycle is defined as the interval from one mitosis to the next [125]. The proliferating cell undergoes four phases before dividing into two daughter cells. The first phase is known as a gap (G1); during this stage many of the enzymatic and ribonucleic acid (RNA) synthetic pathways are active. From G1 the cell may go into either G0, a resting phase where the metabolic and synthetic pathways of the cell are dormant, or the synthesis phase (S), where the cell doubles the amount of deoxyribonucleic acid (DNA) in preparation for mitosis. The second gap (G2) follows when the cell completes the final steps in preparation for mitosis (M) [126] (see figure 8-1).

CELL CYCLE SPECIFICITY

Cytotoxic chemotherapy is able to exert two primary effects upon rapidly dividing cancer

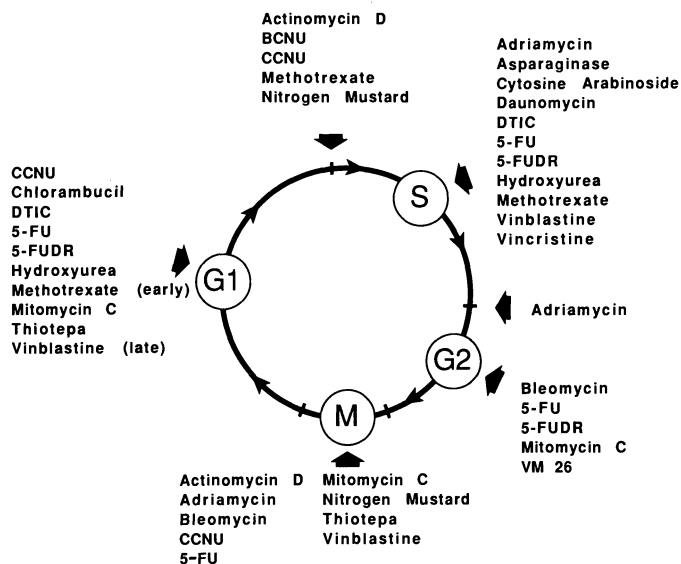


FIGURE 8-1. (modified from Hill and Baserga [129]). The phases of the cell cycle where antitumor drugs exert their lethal effects.

cells. First is a lethal effect that occurs maximally at a specific phase of the cell cycle. Second is the ability to manipulate the progression of cancer cells through the cell cycle by blocking cells at a certain point in the cell cycle. This blocking effect is often reversed as the drug is cleared, but recruitment of noncycling cells into a sensitive phase may have occurred [127]. Generally speaking, low concentrations of a drug are more likely to halt progression through the cell cycle, while larger concentrations are more likely to achieve cell kill [128]. Hill and Baserga have catalogued the phases of the cell cycle where chemotherapeutic drugs exert their lethal effect (figure 8-1, from Hill and Baserga [129]). They suggest that the concept of a drug being purely “phase specific” is rarely seen, since most chemotherapeutic drugs exert some effect on multiple sites in the cell cycle [129]. Cell cycle considerations can also be used to reduce toxicity from chemotherapy. Goldie et al. have demonstrated with single-agent treatment using methotrexate that a 40- to 100-times greater dose could be safely given

over 24 hours compared with the total dose over a five-day period, with equal marrow toxicity [130]. Using combinations of drugs, Price and Goldie demonstrated significant lessening in marrow toxicity if cyclophosphamide, methotrexate, vincristine, and 5-FU were given over 24 hours; this has come to be known as the Price–Goldie–Hill hypothesis for the administration of therapy over a short period of time to minimize toxicity [131].

CELL KINETICS AND CHEMOTHERAPY

Skipper et al. first demonstrated that chemotherapeutic drugs killed cancer cells by first-order kinetics. A constant percentage of cells are killed at each administration of drug rather than killing an absolute number of cells at each administration [132]. By first-order kinetics, for a large bulky tumor mass (for example, 10^{12} or 1 kilogram tumor size), if a drug kills 90% of the cancer cells at each administration, then after four cycles of the drug a theoretical 99.99% reduction in number has occurred, but 10^8 or a .5 cm mass will remain viable. The significance of this kinetic analysis is that if chemotherapy is given in the adjuvant setting, at the time of minimal residual disease

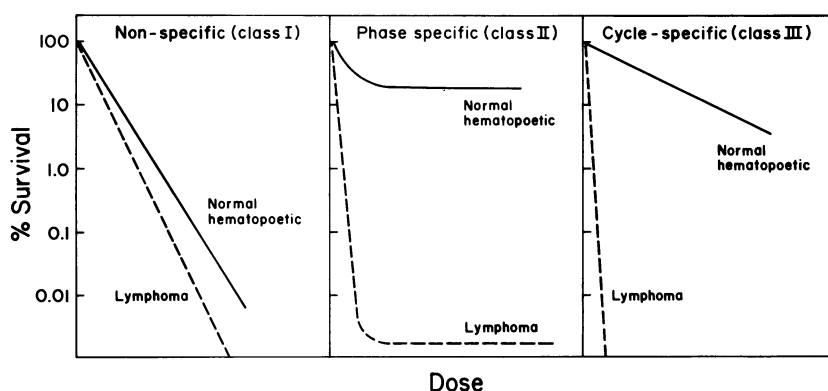


FIGURE 8-2. (from Bruce et al. [134] and Hill and Baserga [129]). Dose-survival curves for both normal hematopoietic and transplanted lymphoma colony-forming units. Normal or tumor-bearing mice were given different doses of a given agent and their femoral marrows were assayed 24 hours later for their content of colony-forming units. Three different patterns of cell killing were observed.

or microscopic disease, a much greater probability of cure is theoretically and clinically possible [133].

Bruce et al. utilized a spleen cell culture system to compare normal mouse hematopoietic cells with transplanted malignant lymphoma cells and demonstrated cell-kinetic differences [134]. By exploiting these differences, they were able to design curative chemotherapeutic regimens with a high degree of specificity for the cancer cells. In fact, for certain regimens, a 10,000-fold difference was seen in the killing of lymphoma cells over normal hematopoietic cells [134]. Three different mechanisms were proposed to explain where in the cell cycle a drug had its effect. In class I (see figure 8-2, from Bruce et al. [134]), there was no difference in cytotoxicity of normal hematopoietic stem cells and lymphoma-colony-forming cells. Class I agents kill in all phases of the cell cycle and are not dependent upon the proliferative capacity of the cells. Agents such as ionizing radiation have a class I mechanism of action because all cells, tumor or otherwise, are affected equally. The next group of agents, class II, are called phase-specific because proliferating cells are preferentially killed in a specific phase of the cell cycle. A plateau is quickly reached with this mode of cell kill because noncycling cells are spared; furthermore, normal cells have a smaller subpopulation of actively divid-

ing cells than do the cancer cells and are thus protected. The third class of agents, class III, are termed cycle-specific because these agents exert their action throughout the entire cell cycle so that both proliferating and resting cells are affected; however, the cancer cells are preferentially killed, since the drug has a greater specificity for cancer cells compared with normal cells [135]. Hill and Baserga have summarized the results of multiple investigators and catalogued a kinetic classification of anti-tumor drugs [129] (figure 8-3, from Hill and Baserga [129]).

KINETICS OF COMBINATION CHEMOTHERAPY

In 1943, Luria and Delbruck described the selection of a resistant population of *E. coli* cells following infection by a bacteriophage [136]. The next year streptomycin was introduced for the treatment of tuberculosis, and soon afterwards resistant populations of myobacteria emerged. It became clear that prokaryotes possessed a means by which they could develop

Phase specific (class II)	Cycle specific (class III)
Cytosine arabinoside Hydroxyurea 6-Mercaptopurine Methotrexate Procarbazine Vinblastine Vincristine VM 26 VP-16	Actinomycin D BCNU CCNU Carboplatin Cisplatin Cyclophosphamide Daunomycin DTIC 5-Fluorouracil Methyl-CCNU Nitrogen mustard Thiotepe

FIGURE 8-3. (modified from Hill and Baserga [129].) Kinetic classification of antitumor drugs with respect to activity on the cell cycle.

resistance to both infectious and cytotoxic agents; likewise it became clear that combinations of drugs could prevent the emergence of resistance in a given cell population [137]. In 1951, Potter discovered that the inhibition of two separate enzymes in a biosynthetic pathway, known as sequential blockade, could be employed clinically to prevent cancer resistance to chemotherapy [138]. A second strategy proposed by Elion et al. in 1954 involves simultaneous inhibition of parallel metabolic pathways, such as blocking with purine and pyrimidine synthesis in deoxyribonucleic acid production; this is termed concurrent blockade [139]. Finally, complimentary inhibition, as described by Sartorelli, involves the interaction of two different intracellular mechanisms that together have the same end result [140]. An example would be direct damage to DNA by radiation coupled with an antimetabolite to inhibit DNA synthesis and repair (see figure 8-4, from Sartorelli [140]).

RESISTANCE TO CHEMOTHERAPY; GOLDIE-COLDMAN HYPOTHESIS

In 1979, Goldie and Coldman proposed a mathematical model that related curability of

a malignancy to the appearance of singly or doubly resistant cell lines. Furthermore, drug-resistant phenotypes arise spontaneously and with a definite frequency that is independent of the selecting agent. The probability that there are no resistant cells in a given population is represented by an equation¹ that predicts that smaller tumors are more likely to have no resistant cells. This also means that a 1 to 2 log doubling of tumor size increases the likelihood of spontaneous mutation to a resistant clone. They postulate that the expectation of curing a neoplasm is a function of both the spontaneous mutation rate towards resistance, the intrinsic properties of the tumor, and the size the tumor has reached before intervention; the probability of curing a neoplasm may change from likely to impossible in a matter of days to weeks [141]. The mutation to resistance hypothesis also predicts that the probability of a tumor being resistant to multiple agents administered simultaneously will be less than the probability of its being resistant to individual agents. The clinical result has been to develop treatment strategies utilizing the most active agents in the highest tolerable doses as soon as possible after diagnosis [142]. In 1983, Goldie and Coldman expanded on this concept by calculating a "probability of cure" curve that suggests that markedly heterogeneous tumors will have a

period early in their growth history when a chemotherapeutic cure is possible. In practical terms, this means that chemotherapy, when used in the adjuvant setting, has a curative role, and that single-agent trials against widespread and extensive disease may not accurately predict the effectiveness of a drug in the adjuvant setting [143].

PLEIOTROPIC DRUG RESISTANCE

Pleiotropic drug resistance (PDR) is a phenomenon whereby tumor cells in culture or animal models are exposed to a single chemotherapeutic agent with the consequent emergence of resistance to a broad range of structurally unrelated chemotherapeutic agents [144]. Specifically, in vitro and in vivo exposure of cells to vincristine results in mutant cells resistant not only to vincristine but also to adriamycin, actinomycin-D, and VP-16. Exposure of these cells to adriamycin will result in resistance to adriamycin, vincristine, actinomycin-D, and VP-16 [145]. The current hypothesis to explain PDR is found by examining epithelial cells, which possess a protective capacity in terms of responding to environmental toxins by either excluding them from the cell or modifying them into an inert form [146]. The mediator of this protection appears to be the P170 glycoprotein. Indirect evidence to support this is the presence of P170 glycoprotein on the membrane fractions of the ovarian tumor human CEM cell line. In vivo human data by Ling et al. show that untreated patients without P170 membrane glycoprotein, demonstrated by western blot analysis with specific radiolabeled antibodies, subsequently express the P170 membrane protein after treatment of the tumor cells [147]. Recently Paston et al. have demonstrated that iodine-131 radiolabeled vinblastine binds to a 170-molecular-weight protein that appears to be the P170 glycoprotein [147]. Identification of P170 membrane proteins has been found in patients with ovarian carcinomas and soft tissue sarcomas. P170 membrane proteins are also present in normal adrenal, renal epithelial,

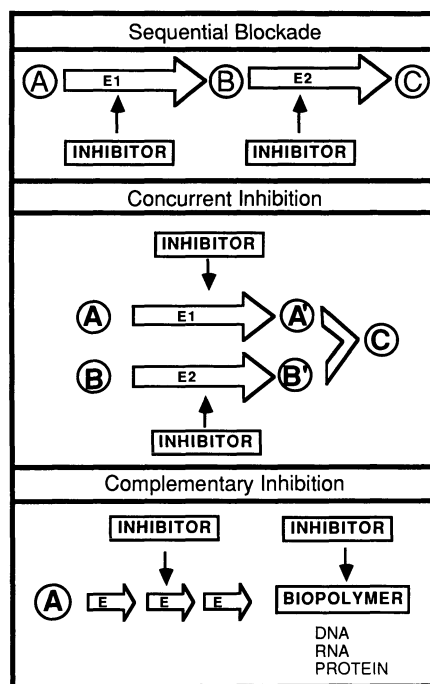


FIGURE 8-4. (from Sartorelli [140]). Use of combination drugs to produce metabolic blockade at multiple sites.

pulmonary parenchymal, and to a lesser extent gastrointestinal tissues. Amplification of this membrane protein by drug-resistant cells probably confers a survival advantage and is merely the amplification of an existing cellular mechanism of excluding toxic substances.

Of interest is the apparent reversal of pleiotropic drug resistance by the administration of calcium channel blockers in experimental systems. Suzuki et al. demonstrated a 40% increase in lifespan in rats given an intraperitoneal injection of GA-1 glioblastoma cells when treated with the calmodulin antagonist W-7 [148]. Unfortunately, the cardiac side effects of calcium channel blockers limit their usefulness in man [149]. Recently, at the National Cancer Institute (NCI), vindoline, an inactive vincristine analogue, has been added to drug-resistant cells in culture and appears to revert these cells into a sensitive form [147].

INDIVIDUAL AGENTS

Nitrosoureas. The nitrosoureas, BCNU, CCNU, and Methyl-CCNU, are alkylating, cell-cycle-specific agents and therefore affect tumor cells at all phases of the cell cycle. Nitrosoureas are small, highly lipid-soluble molecules of low ionization at blood pH and are not plasma-protein-bound. As a family of compounds, the nitrosoureas possess the features outlined previously in the chapter for passage across the blood–brain barrier. Nitrosoureas and their breakdown products alkylate DNA in the same manner as nitrogen mustards [150].

Nitrosoureas work independent of variations in permeability, and the effectiveness of nitrosoureas reflects a function of blood flow and delivery to the tumor [54]. In vivo studies have shown the emergence of resistant cells to BCNU with a plateau for the 9L glioma at 3 to 4 log cell kill [152]. Experimental evidence suggests that nitrosoureas may be synergistic with irradiation [78]. In a randomized prospective phase III study, Walker et al. of the Brain Tumor Study Group (BTSG) treated 303 patients with high-grade astrocytomas. The valid study group consisted of 222 patients. Median survival times for patients treated with radiotherapy alone compared with patients treated with the combination of BCNU and radiotherapy were not statistically different. In another arm of the study comparing the combination of Methyl-CCNU and radiotherapy with the combination of BCNU and radiotherapy, median survival was 34.6 weeks versus 50.3 weeks, respectively. The BCNU and radiotherapy treatment was statistically significantly superior when compared with the radiotherapy only control (50.3 weeks versus 37.5 weeks median survival) [151].

Vincristine. The vinca alkaloids, vincristine and vinblastine, are derived from the ornamental shrub, *Vinca rosea*. By binding to tubulin, the vinca alkaloids inhibit the assembly of microtubules and lead to the dissolution of

the mitotic spindle [153]. Vinca alkaloids bind to tubulin during the S phase; they are phase-specific and water-soluble drugs that cause metaphase arrest. Rosenstock et al. treated 17 children with recurrent brain tumors in 1976. Eight of 16 (50%) who received four weeks of treatment with vincristine demonstrated either stabilization or improvement of signs or symptoms for a median of greater than 29 months [154]. In vivo data suggest that, if given 12 to 24 hours before cyclophosphamide, vincristine may be synergistic [155]. Vincristine is generally administered weekly by intravenous bolus. The dose-limiting toxicity is neuropathy; due to its minimal myelosuppressiveness, it is commonly seen in combinations with other drugs.

Cisplatin and Carboplatin. Cisplatin (cisdiamminedichloroplatinum, CDDP) and a newer analogue, carboplatin, are water-soluble inorganic compounds. They act through interstand and intrastand cross-linking of DNA, primarily of the guanine base, resulting in changes in DNA conformation and inhibition of DNA synthesis [156]. These two platinum analogues are cell-cycle-specific rather than phase-specific agents, although cells seem most sensitive if exposed during the G1 phase [157]. Ototoxicity and nephrotoxicity are the dose-limiting toxicities; the latter can be minimized by vigorous hydration with mannitol and slow administration as a continuous infusion. Khan et al. demonstrated a favorable response in 11 of 22 (50%) recurrent and advanced childhood brain tumors with cisplatin as a single agent [158]. Sexauer et al. reported on the Pediatric Oncology Group experience with single-agent cisplatin in children with primary recurrent brain tumors resistant to standard therapy. Complete and partial responses were seen in 4 of 10 children with medulloblastoma, and 3 of 15 with ependymoma, with minimal activity in astrocytic tumors [159]. Allen et al. have recently evaluated carboplatin in 36 patients with recurrent primary brain tumors. They

found an overall response rate (complete and partial response) of 9 of 36 (25%) patients with a 43% response rate in patients with medulloblastoma [160]. Cytosine arabinoside, if given 2 to 4 hours after cisplatin, has been shown to have a synergistic lethal effect on human carcinoma cell lines in culture [161]. Of special interest is the apparent synergism of combined cisplatin and radiotherapy for malignant brain tumors [82].

Epipodophyllotoxins (VP-16 and VM-26). The epipodophyllotoxins, VP-16 and VM-26, are drugs derived from the mandrake plant. Their mechanism of action is similar to vincristine in that they bind to tubulin during the S phase and inhibit microtubule assembly, making them phase-specific drugs [162]. Both drugs penetrate the CSF poorly even though they are highly lipid-soluble; they are primarily excreted by the liver. Dose-limiting toxicity is myelosuppression and nausea. Skylanski et al. in 1974 reported on 5 of 13 patients with inoperable or subtotally resected recurrent malignant intracranial tumors, who exhibited improvement on VM-26 sustained for at least three months [163]. Kessinger et al. reported on VM-26 as a salvage therapy for patients with high-grade astrocytomas who had failed radiotherapy and BCNU, and demonstrated a 48% objective response rate [164].

Aziridinylbenzoquinone (AZQ). Aziridinylbenzoquinone (AZQ) is a synthetic, lipid-soluble drug with low ionization at physiologic pH. AZQ is known to cross-link DNA in a similar manner to alkylating agents, and demonstrates excellent penetration into the CSF [165]. While CSF penetration does not necessarily reflect brain parenchymal (normal or tumor) penetration, nevertheless, this drug was considered a logical compound to test against brain tumors. When AZQ was tested against mice with intracranially implanted ependymoblastoma, the resulting life-span of the tumor-bearing mice increased by more than 200%, and some cures

were observed [166]. Savaraj et al. have reported on preoperative administration of AZQ to five patients with brain tumors with subsequent radiochemical and chromatographic analysis of plasma, CSF, edematous brain, and tumor specimens. They found that tumor and normal brain concentrations of AZQ ranged from 47.5% to 85.0% of plasma concentrations, suggesting that AZQ does, in fact, readily penetrate into both normal brain and brain tumor tissue [167]. Haid et al. in 1985 summarized six recent phase II trials with AZQ for primary CNS astrocytomas. Of 119 total patients treated, 13 patients (10.9%) experienced objective responses [168].

Thiotepa. Thiotepa is a cell-cycle-specific alkylating agent. It is an aziridine derivative and has been used against a variety of solid tumors either intravenously or by intracavitary instillation. In 1977, Gutin et al. reported the successful use of intrathecal thiotepa in treating meningeal leukemia [169]. Levin et al. reported on 36 children with recurrent medulloblastoma who had failed craniospinal irradiation and were treated with an aggressive multidrug regimen tailored to the individual, but including intrathecal and intraventricular cytosine arabinoside, methotrexate and thiotepa in conjunction with systemic CCNU, procarbazine, vincristine, and VP-16; further radiation was also used in select cases. Of the patients so treated, 50% survived two years, with 25% surviving at 2.9 years [170]. Edwards et al. in 1979 treated 12 patients with malignant gliomas using intravenous thiotepa in a phase II trial. As a single agent, systemic thiotepa at low dose did not demonstrate appreciable activity against high-grade astrocytomas [171].

Cyclophosphamide. Cyclophosphamide is a cell-cycle-specific agent, with a wide range of activity, that requires in vivo activation by the liver. Gerosa et al. have reported on 16 patients with medulloblastoma treated by surgery, radiotherapy, and adjuvant biweekly cyclophospha-

mide and vincristine with an overall survival of 31% and 38-month mean actuarial survival [172]. McIntosh et al. treated a similar group with surgery, radiotherapy, and weekly alternating cyclophosphamide and vincristine and found a six-year disease-free survival of 81% [173]. Allen et al. used high-dose cyclophosphamide in 18 children with recurrent brain tumors. Overall partial and complete responses were 89% for a mean duration of seven months; 8 of 8 patients (100%) with medulloblastoma improved [174]. Vincristine, if given 12 to 24 hours before cyclophosphamide, has been shown to be synergistic in vivo [155].

Methotrexate. Methotrexate is a folic acid antagonist that preferentially competes with folic acid for binding with dihydrofolate reductase. Methotrexate is phase-specific, exerting its effects during the synthetic (S) phase of the cell cycle. Conversion of dihydrofolate to tetrahydrofolate is inhibited; this prevents formation of the coenzyme that moves one-carbon fragments in the synthesis of DNA. Leucovorin (citrovorum factor) is activated to 5-methyltetrahydrofolate and bypasses the methotrexate block allowing protein synthesis in normal cells rather than tumor cells. Leucovorin prevents the acute complications of high-dose methotrexate, such as mucositis, nephrotoxicity, and neutropenia, by preferentially rescuing normal cells, yet allows the administration of higher doses of methotrexate, resulting in better penetration into solid tumors and a greater concentration gradient to facilitate crossing the blood–brain barrier [175]. Djerassi et al. treated seven children with cerebral astrocytomas using escalating intravenous doses of methotrexate and added leucovorin when toxicity was observed. Six of seven children had objective neurological improvement [176]. A follow-up report in 1985 showed an accrual of 11 patients, six of them less than 18 years old, two with grade II, four with grade III, and four with grade IV astrocytomas. Responses were reported in 8 of 11 patients; 4 of 11 are alive [177]. Shapiro treated

six adults with high-grade astrocytomas using high-dose methotrexate and leucovorin; 5 of 6 had progression of disease [178].

Hydroxyurea. Hydroxyurea is a small, lipid-soluble compound that crosses the blood–brain barrier and is excreted by the urine [179]. The drug is phase-specific by acting during the S phase and inhibiting the production of ribonucleoside diphosphate reductase, an enzyme involved in DNA synthesis [180]. Of particular importance is a synergistic effect seen when hydroxyurea is combined with irradiation. Piver et al. combined hydroxyurea with irradiation and demonstrated a dramatic increase in effectiveness against the C3H mouse mammary tumor in vitro [181]. Irwin et al. in 1975 reported on a group of 29 patients with high-grade astrocytomas; 14 patients received radiotherapy at 4800 cGy alone and survived a median of eight months, 15 patients received 4800 cGy plus daily hydroxyurea and survived a median of 12 months [182]. Levin et al. in 1979 reported a randomized phase III trial comparing BCNU and radiotherapy in combination with BCNU, hydroxyurea, and radiotherapy. When the results were stratified by histology, the patients with glioblastoma multiforme who received radiotherapy, BCNU, and hydroxyurea had a significantly longer median time to progression compared with those patients in the group who did not receive hydroxyurea (42 weeks versus 32 weeks) [183]. A report by Walsh et al. demonstrated that pretreatment with hydroxyurea increased the radiomimetic effects of both alkylating agents and cytosine arabinoside against L-1210 leukemia cells in vitro [184].

Procarbazine. Procarbazine as a chemotherapeutic agent is water-soluble, cell-cycle-phase-specific and rapidly crosses the blood–brain barrier. Its cytotoxic mechanism is not completely understood, but it appears that after undergoing microsomal activation, the active compound methylates and/or alkylates nucleic

acids, thereby inhibiting synthesis and damaging DNA directly [185]. In 1974, Kumar reported on a group of patients with primary and secondary brain tumors of mixed histologies treated in a phase II protocol with procarbazine. Of 29 patients, 48% experienced either objective improvement or stabilization of disease. Three of four children with medulloblastoma had a sustained response to therapy [186]. Walker et al. in 1980 reported on the Brain Tumor Study Group (BTSG) experience with procarbazine and radiotherapy; they found its activity in patients with brain tumors to be equivalent to the combination of BCNU and radiotherapy [187].

Cytosine Arabinoside (Ara-C). Cytosine arabinoside is a pyrimidine analogue; it is metabolized in vivo to arabinofuranosylcytosine triphosphate (ara-CTP), which is the active metabolite. Ara-CTP interferes with DNA synthesis by inhibiting DNA polymerase and by direct incorporation into the DNA chain. It is phase-specific and exerts its effect on the S phase. Cytosine arabinoside has been used primarily in the treatment of leukemia and lymphoma. The use of high-dose cytosine arabinoside is known to be toxic to the central nervous system, and it appears that at high concentrations the drug crosses the blood-brain barrier [188]. Basler et al. demonstrated an in vivo response to cytosine arabinoside in mice with intracranially implanted GL-261 murine ependyoblastoma [189]. In vitro cell culture sensitivity suggests that cytosine arabinoside may be active against astrocytomas [190]. Stewart et al., using cisplatin and cytosine arabinoside in 21 adults with high-grade astrocytomas, demonstrated a 10% complete response rate and a 30% partial response rate, with 24% of the patients maintaining stable disease [191]. Two recent reports suggest that cytosine arabinoside and cisplatin are synergistic and cytotoxic to human carcinoma cell lines grown in nude mice [161, 192].

Dacarbazine (DTIC). Dacarbazine was initially synthesized to be an antimetabolite in the purine synthesis pathway. After the drug enters the circulation, it is metabolized to a compound that behaves similarly to an alkylating agent. It appears to inhibit ribonucleic acid and protein synthesis in addition to acting on other parts of the cell cycle [193]. Dacarbazine is commonly used in the treatment of malignant melanoma, neuroblastoma, and Hodgkin's disease. In 1975, Levin et al. reported a phase II trial of dacarbazine in 24 patients with primary and secondary brain tumors. Response was based on both neurological and radionuclide brain-scan improvement. In patients who had received no prior chemotherapy, a 25% response rate was seen; in those patients who had failed prior chemotherapy, a 33% response rate was observed; a 21% response rate was observed in patients with high-grade astrocytomas [194].

COMBINATION AGENTS

MOPP. Mechlorethamine, vincristine, prednisone, and procarbazine (MOPP) was first described by DeVita et al. in the treatment of advanced Hodgkin's disease [195]. In 1976, Frias-Monserrate et al. treated eight children with recurrent brain tumors with MOPP according to the Hodgkin's disease schedule. All patients had end-stage disease, and 62% demonstrated objective improvement after therapy [196]. A second encouraging report by Cangir et al. demonstrated a 73% response rate in children with medulloblastoma [197]. In 1979 the Pediatric Oncology Group initiated a randomized phase III cooperative trial to investigate the use of MOPP as an adjuvant to surgery and radiotherapy for medulloblastoma. Van Eys has recently summarized the Pediatric Oncology Group and M.D. Anderson Hospital experience with MOPP in pediatric brain tumor patients [198]. At present there is a trend in patients with medulloblastomas that the addi-

tion of MOPP to radiation therapy may confer an advantage over the use of radiation therapy alone. As salvage therapy for a wide range of recurrent brain tumors, MOPP was compared with OPP. The highest activity was seen in patients with medulloblastoma; 4 of 9 (45%) response rate (CR + PR) was seen with MOPP, and 3 of 12 (25%) response rate was seen with OPP, the numbers being too small to be significant. However, in patients with recurrent astrocytomas, the addition of nitrogen mustard did seem to make a dramatic difference. Three of eight (38%) response rate (CR + PR) was seen in recurrent astrocytoma patients treated with MOPP, versus 0 of 10 (0%) response rate with OPP. Finally, as primary therapy in children less than two years of age, in whom radiation therapy is preferably postponed due to the high incidence of growth deformities and intellectual impairment, 17 children have been treated at M.D. Anderson Hospital with MOPP for a wide variety of tumors but predominantly medulloblastoma and astrocytoma. Of a total of 17 children so treated, 15 responded (88%); furthermore, six (35%) are in continuous complete remission with a median duration of 28.9 months [198].

Three Drug Regimens Containing CCNU and Vincristine. In 1972, Gutin et al. reported on a series of patients with high-grade astrocytomas, medulloblastoma, and unbiopsied deep cerebral masses of whom 44% improved with procarbazine, CCNU, and vincristine therapy [199]. Hildebrand reported similar results using CCNU and vincristine but substituting systemic methotrexate for procarbazine in both metastatic and primary brain tumors [200].

In the mid-1970s the Childrens Cancer Study Group (CCSG) and the Internal Society of Pediatric Oncology (SIOP) embarked upon several studies to determine the efficacy of CCNU and vincristine plus or minus prednisone for medulloblastoma, cerebral high-grade astrocytomas,

and brainstem tumors [201]. A trial for newly diagnosed children with medulloblastoma was opened by the CCSG in 1976. The study compared conventional craniospinal irradiation and one year of therapy with CCNU, vincristine, and prednisone (CVP). Two hundred and thirty-three patients were accrued, and a trend for improved survival was achieved by the addition of CVP to irradiation. When this population was stratified by tumor stage, children with small (T1–T2) tumors who had no evidence of CSF seeding (M0), had a five-year event-free survival of 65%–70% in both groups. Patients who had large tumors (T3–T4) or evidence of CSF spread (M1–M3) (two thirds of all children with medulloblastoma) were found to have a statistically significant improvement in event-free survival by the addition of chemotherapy [202]. A similar trial conducted by the SIOP in Europe accumulated 276 children with newly diagnosed medulloblastoma. A statistically significant improvement in 54-month disease-free survival was seen by the combination of irradiation with CCNU and vincristine (CV) chemotherapy (55%) compared to irradiation alone (43%) [203].

A trial for newly diagnosed children with high-grade astrocytomas was also opened by the CCSG in 1976. Patients aged 2 to 21 years of age and biopsy of proof of high-grade astrocytoma (Kernohan grade III or IV) were eligible, and children were randomized to receive conventional irradiation alone following surgery or combined irradiation and CVP chemotherapy following surgery. Only 58 children were accrued by 1981. The results of the study demonstrated statistically significant improvement in five-year disease-free survival for those children who received combined chemotherapy and irradiation following surgery (45%) compared to children treated with irradiation only following surgery (13%). This advantage for combining chemotherapy with irradiation continued to be statistically significant when prognostic variables were taken into account and represents the

best five-year disease-free survival results that have been achieved in either adults or children with high-grade astrocytomas [204].

A trial for newly diagnosed children with brainstem tumors was initiated by CCSG in 1977. Due to risks of brainstem biopsy, the diagnosis was made by clinical or radiographic criteria. This randomized trials compared the combination of CVP chemotherapy and irradiation to irradiation alone. Sixty-nine children were accrued and no benefit was seen by adding chemotherapy to primary irradiation. Overall two-year survival was 29% for combined irradiation and chemotherapy and 22% for irradiation alone [205].

Eight Drugs in One Day, The "8-in-1" Regimen. By exploiting the known properties of brain tumors, such as blood–brain barrier, blood–tumor barrier, blood-to-tissue transport, tumor heterogeneity, cell-cycle considerations, mutation to resistance, scheduling of chemotherapy regimens, known synergistic effects of certain drug combinations, and preradiation chemotherapy, the 1980s have seen changing strategies in the chemotherapy of brain tumors [206]. Bleyer in 1983 reported a complex regimen of eight drugs given in one day, known as the 8-in-1 regimen. The agents used in this regimen include vincristine, hydroxyurea, procarbazine, CCNU, cisplatin, cytosine arabinoside, methylprednisone, and either cyclophosphamide or dacarbazine, administered within 12 hours and repeated at 2- to 3-week intervals [207]. Rozental et al. reported 50% reduction in tumor size in half the patients with both recurrent and newly diagnosed high-grade astrocytomas and medulloblastomas in both children and adults, and increased survival in adults with glioblastoma multiforme [85]. Prendergrass et al. administered 330 courses to 107 children with recurrent or incompletely resected primary brain tumors, and report a 15.5% complete response rate and 35% partial response rate, making a 50% overall objective response rate [208]. Zeltzer et al. have reported

five children with medulloblastoma, considered high-risk by virtue of young age (2–4 years of age), and large primary tumor or seeding of the neuroaxis. Treatment was with two cycles of 8-in-1 followed by craniospinal axis irradiation, followed by a further eight cycles of 8-in-1 at six-week intervals. With a follow-up from 12 to 28 months, they have experienced no recurrences [209]. Sieverts et al. have treated 22 children with relapsed brain tumors using 8-in-1 chemotherapy; 77% had objective improvement in symptoms. Based on CT scan measurements, 27% had a complete response and 32% had a partial response [210]. Based on these exciting results, the CCSG is currently undertaking two trials that will evaluate vincristine, CCNU, and prednisone in combination with radiation therapy versus 8-in-1 preirradiation and postirradiation therapy for high-grade astrocytoma (CCG-945; opened April, 1985), and for “unfavorable” medulloblastoma (CCG-921; opened June, 1986).

Delivery of Chemotherapy

HYPEROSMOLAR AGENTS AND BLOOD–BRAIN BARRIER DISRUPTION

The delivery of chemotherapeutic agents to brain tumors is dependent on capillary permeability and blood flow properties of brain tumors. As previously discussed in the section on blood flow and tumor permeability, Blasberg et al. have utilized quantitative autoradiography to study the impact of capillary permeability and blood flow on the delivery of drugs to brain tumors [211]. They have shown marked variability in a number of in vivo brain tumor systems — not only variability of blood–brain barrier permeability in brain tumors but also marked decreases in blood flow in and around many brain tumors [212]. To enhance drug entry into brain tumors, attempts have been made to transiently open the blood–brain barrier with hyperosmolar agents. In 1978, Rapoport et al. reported a 20-fold increase in

cerebrovascular permeability to ^{14}C -labeled sucrose in the gray matter of rat brains after the administration of intracarotid hyperosmolar arabinose [213]. Neuwelt et al. demonstrated enhanced delivery of a water-soluble drug, methotrexate, into in vivo rat gliomas induced by the avian sarcoma virus [214]. These observations form the basis of human brain tumor therapy trials, which utilize intra-arterial chemotherapy infusion with reversible blood-brain barrier modification. Neuwelt and colleagues were able to show statistically significant prolongation of survival and increased efficacy of multiagent chemotherapy in patients with glioblastoma multiforme when utilizing blood-brain barrier modification [215]. Even more encouraging are the results in patients with primary CNS lymphoma treated with combined chemotherapy and osmotic blood-brain barrier modification. The results show a response rate and overall survival rate that is as effective as primary radiotherapy [216]. Despite these encouraging preliminary results, Hiesiger et al. warn that in the C6 glioma tumor induced in rats, considered indicative of a primary CNS tumor, quantitative autoradiography using ^{14}C -labeled methotrexate demonstrates an advantage for intracarotid infusion in terms of tumor uptake of drug but that hyperosmolar disruption of the blood-brain barrier simply puts more drug in normal brain tissue where it is not needed [217]. Shapiro warns that the potential benefits of greater tumor cell kill must be weighed against the effects of exposing normal brain to higher concentrations of potentially lethal drugs [218].

ROUTES OF DELIVERY: ORAL, INTRAVENOUS, INTRA-ARTERIAL, INTRAVENTRICULAR

As brain tumors grow, the distance from tumor capillary to tumor cell becomes greater. As this occurs, the likelihood that adequate drug concentrations will reach a tumor cell decreases. The reasons for this include a wide concentration gradient, limits to the diffusion of a given

drug, and biotransformation of a drug before it reaches a tumor cell [219]. Furthermore, there is evidence that if a reduced concentration of drug reaches the tumor cell, it may only serve to induce resistance and not achieve cytotoxicity [142, 144]. The importance of route of delivery is characterized by comparing CCNU, an oral nitrosourea, with BCNU, a parenterally administered nitrosourea. Most clinical trials testing CCNU in high-grade astrocytomas found little advantage of combined radiotherapy and CCNU over radiotherapy alone. Radiotherapy plus BCNU is found in most studies to be more effective than CCNU plus radiotherapy [220]. Only one study, that of Solero et al., demonstrated a seven-week survival advantage for CCNU and radiotherapy over BCNU plus radiotherapy (45 versus 52 weeks). This difference was not statistically significant [221]. The systemic intravenous dose of BCNU that is most often used in patients with malignant astrocytomas is limited to 200–250 mg/ M^2 every 6 to 8 weeks, and is limited by delayed and sustained myelosuppression [222]. In 1967, Bruce et al. demonstrated a steep in vivo dose-response curve for BCNU in a murine lymphoma system [223]. Further investigation by Rosenblum et al. found a similar steep exponential dose response curve for BCNU in the 9L gliosarcoma model in both in vitro clonogenic cell assays and in vivo treatment of rats [224].

Intra-arterial. It is appropriate that experimental evidence has led to clinical trials in patients with malignant brain tumors utilizing intra-arterial administrations of BCNU to achieve improved cytotoxicity and survival by high-dose loco-regional therapy. Intra-arterial chemotherapy increased the response rate of colorectal adenocarcinoma metastatic to the liver from 21% administering intravenous 5-FU [225] to 55% with intra-arterial 5-FU, which includes 75% of 293 patients having failed systemic 5-FU prior to entry [226]. With the transfemoral artery approach, a catheter can be selectively placed

in the internal carotid artery. The tumor is supplied by the distribution of the internal carotid artery, and angiography can qualitatively evaluate tumor blood supply and blood-brain barrier permeability [227]. High-grade astrocytomas are localized malignancies that kill by local invasion. Intra-arterial infusion of BCNU maximizes the dose of drug to the tumor yet minimizes the systemic dose-limiting myelosuppression. Crafts et al. and Levin et al. using ^{14}C -labeled BCNU in rhesus and squirrel monkeys, have demonstrated four times greater concentration of BCNU following carotid artery infusion than with intravenous administration, but did not show increased efficacy resulting from increased concentration [228, 229]. Bullard et al. in 1985 were able to show statistically better survival in 1 of 2 trials using intracarotid BCNU in the 9L gliosarcoma rat brain tumor model over controls. No differences in survival were seen between controls and intravenous-BCNU-treated 9L gliosarcoma rats [230].

The first clinical trials of intra-arterial therapy utilized intra-arterial BCNU in the treatment of patients with brain metastases. West et al. in 1979 and Greenberg et al. in 1981 demonstrated that the technique could be safely performed [231, 232]. Magajewicz et al. performed a phase II study of intra-arterial BCNU (100 mg/M^2) for lung cancer and melanoma metastatic to the brain. Of 25 evaluable patients with metastatic lung cancer, 12 patients (48%) had a complete or partial response lasting from 1 to 14 months [233]. Hochberg et al. in 1985 reported the results of intra-arterial BCNU in 79 patients with high-grade astrocytomas. Patients treated with intra-arterial BCNU after radiation survived 64 weeks with infraophthalmic carotid artery infusion and 49.5 weeks with supraophthalmic carotid artery infusion. Twenty percent of patients developed white-matter changes on CT scan. The authors found that intra-arterial BCNU (400 mg every four weeks) before radiation appears to be associated with less toxicity [234]. Using intra-

arterial BCNU combined with systemic cycles of Methyl-CCNU, vincristine, and procarbazine, West et al. found a median survival of 12.7 months in 25 adult patients with high-grade astrocytomas [235]. Yamashita et al. reported a nonrandomized comparison of intravenous ACNU (a nitrosourea) in eight patients with glioblastoma multiforme who survived a median of 9.0 months compared with nine patients with glioblastoma multiforme treated with intra-arterial ACNU who survived 12.5 months. While not statistically significant, there was a survival trend in favor of intra-arterial ACNU administration [236].

At the University of Wisconsin, we have reported on a ten-year-old girl, originally diagnosed with posterior-fossa medulloblastoma and treated with conventional craniospinal irradiation. She recurred in the lumbar spine region with massive retroperitoneal extension (13 cm). We treated her with combined continuous infusion, intra-arterial actinomycin-D (2 mg/kg/day) and irradiation, 2000 cGy to the previously treated spine and 4500 cGy to the retroperitoneal soft tissue mass. She had complete reversal of her neurological defects. She is normal and asymptomatic 13 years after therapy without evidence of disease [237].

Recent trials have utilized combinations of drugs intra-arterially to determine if a synergistic combination could be found. Mughal et al. reported on the combination of BCNU and FUDR with negligible systemic toxicity [238]. Stewart et al. used intra-arterial BCNU, cisplatin, and VM-26 against primary and metastatic brain tumors. Retinal and neurologic toxicity were dose-limiting, and responses were seen in 13 of 19 (68%) evaluable primary brain tumors [239]. Vance and Kapp have reported on 13 patients with high-grade astrocytomas treated with multiple infusions of cisplatin 150 to 200 mg and BCNU 300 mg via supraophthalmic artery catheterization. There was an 83% response rate, but with 23% permanent neurologic deficits after infusion. Reducing the dose of cisplatin to 110 mg resulted in a

radiographic response rate of only 25% [240]. Mahaley et al. report neurotoxicity in 5 of 16 patients who received intra-arterial BCNU (200 mg/M²). Coagulative necrosis similar to delayed radiation vasculitis was seen in one patient. These observations stress the importance of careful clinical observation and regular catheter placement checks to minimize toxicity in trials utilizing intra-arterial drugs [241].

Intraventricular Therapy. First described by Ommaya in 1963, the CSF reservoir has since become an important tool for neuro-oncologists [242]. The Ommaya or Rickham reservoir allows for both the instillation and monitoring of drug levels in the CSF. The reservoir also facilitates the drainage of cystic tumors and lateral ventricles, as well as the instillation of morphine and antibiotics into the CSF. As patients with primary CNS malignancies live longer from advances in loco-regional control, the frequency of CSF seeding from primary CNS malignancies appears to be increasing [243]. In addition, medulloblastoma, malignant ependymoma, and pineal germ cell tumors are primary brain tumors in the pediatric population with a predisposition to seed the craniospinal axis. Just as intrathecal chemotherapy has replaced craniospinal irradiation in the management of many children with leukemia, so too might intrathecal chemotherapy replace craniospinal irradiation in certain patients with medulloblastoma, ependymoma, and pineal germ-cell tumors. This would be desirable, since growth retardation, intellectual deterioration, and pituitary deficiencies are known side effects of high-dose extended-field radiotherapy. The search for drugs with minimal toxicity and yet the same therapeutic efficacy as irradiation, if such can be found, would make a significant impact on the quality of life. Currently, methotrexate and cytosine arabinoside are the most extensively studied drugs pharmacokinetically due to their widespread application in the treatment of leukemia. In addition, Blasberg has described

the CSF perfusion characteristics of hydroxyurea, BCNU, and thiotepe after ventriculocisternal perfusion in the rhesus monkey [244]. Fulton et al. have studied intrathecal cytosine arabinoside in the treatment of meningeal metastases from both malignant brain tumors and systemic tumors. A total of 32 patients were treated. All four symptomatic patients improved, with malignant cells eradicated from the CSF in 6 of 12 patients with positive cytology [243]. Currently, intraventricular therapy is being integrated into a number of clinical trials in an effort to maximize the response rate and minimize the likelihood of tumor seeding by primary CNS neoplasms.

HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS MARROW RESCUE

The use of marrow-ablative doses of chemotherapeutic agents, followed by "rescue" of the patient with autologous bone marrow, has been investigated in patients with a variety of solid tumors. The rationale for such as sledgehammer approach to patients with primary brain tumors resides in the attempt to overcome drug resistance at a number of levels. First, certain drugs have dose-response curves that indicate that activity against brain tumors might be optimally attained at such marrow-ablative levels; this was the rationale for the original evaluations of the nitrosourea, BCNU, in high-grade astrocytomas in this setting. A number of experimental studies had demonstrated a particularly steep exponential dose-response curve for BCNU [224]. Second, higher doses may permit penetration into brain tumor tissue of drugs that cannot adequately penetrate brain tumor tissue at lower, more conventional doses. Brain tumors would seem a reasonable group of tumors to consider for this therapeutic strategy, since the tumor cells rarely if ever involve the bone marrow—a prerequisite for autologous bone marrow transplantation.

Much experience has already accrued in the application of a wide variety of chemotherapeutic regimens at marrow-ablative doses followed

by autologous bone marrow “rescue”, in adults with the more common solid tumors, such as lung, breast and melanoma. The results in these studies were fairly predictable; patients with significant bulk disease who had failed multiple chemotherapeutic strategies could hardly be expected to achieve more than a transient response to such an aggressive approach. Nevertheless, responses have been impressive enough to justify evaluation of autologous bone marrow transplantation strategies in select newly diagnosed patients following surgical debulking, in such conventionally resistant tumors as malignant melanoma and lung cancer [245].

For the majority of patients with malignant brain tumors who have failed surgery, radiotherapy, and front-line chemotherapy regimens, this therapeutic approach is most unlikely to achieve a cure with presented available chemotherapeutic agents, used either singly or in combination. Nevertheless, select patients with recurrent brain tumors—those with minimal residual tumor following surgical debulking and with good neurologic function—may achieve significant and prolonged palliation, even cure, from such an aggressive multimodality approach. Treatment would include initial surgical debulking of recurrent tumor, additional irradiation if feasible, and marrow-ablative chemotherapy followed by autologous marrow rescue.

At this time, there have been no more than a dozen reported studies of autologous bone marrow transplantation for patients with brain tumors. The earliest study, reported in 1980, used CCNU at nonablative doses (390 mg/M^2), but did determine that at this dose, CCNU caused early myelosuppression. No responses were seen in seven patients so treated [246]. Since that time, there have been seven reports using BCNU at high-dose in conjunction with autologous bone marrow rescue. Of approximately 75 patients with recurrent high-grade astrocytomas, the response rate overall was about 50%. However, about 15% of patients

expired from nonhematologic toxicities, mainly neurologic or pulmonary [245–255]. One of the prerequisites of high-dose chemotherapy in the transplantation setting should be that the predominant toxicity of the drugs used is myelosuppression; the finding of significant irreversible, even fatal, nonhematologic toxicity in these studies is a major disappointment, and prompts a need to seek other agents that may be more useful in this setting by virtue of a paucity of nonhematologic toxicity. One agent so studied has been VP-16 [251]; Wolff reported four partial responses in eight adults with recurrent glioblastoma multiforme. Another agent is thiotepa; Herzig has reported a partial response of greater than nine months duration in 1 of 2 patients with glioblastoma [245].

At the University of Wisconsin, we have developed a protocol for children and adults with recurrent brain tumors, utilizing high-dose thiotepa (300 mg/M^2 daily for three days delivered as an intravenous infusion over three hours), intraventricular thiotepa, and intravenous high-dose VP-16 (1500 mg/M^2 as a continuous infusion over 15 hours), followed by bone marrow rescue. Select patients who could tolerate further involved-field irradiation then receive radiotherapy in the weeks following chemotherapy, during the period of marrow reconstitution. Only patients with minimal residual tumor are permitted on this study; thus, patients with tumor recurrence must undergo surgical debulking procedures prior to study entry. Of the first four brain tumor patients treated with this regimen, all four achieved an objective partial tumor response, and the degree of toxicity due to chemotherapy was considered acceptable. One patient treated on this study had had three recurrences of a beta-HCG- (human chorionic gonadotropin) secreting pineal germ-cell tumor, and achieved a partial response. Also, one patient with a recurrent glioblastoma multiforme following 13 courses of 8-in-1 therapy remained without evidence of active disease until nine months posttransplantation [256].

The rational basis for using this combination of drugs is as follows: 1) neither thiotepa nor VP-16 is used in current protocols for newly diagnosed children with brain tumors; 2) both thiotepa and VP-16 have activity against brain tumors; 3) both thiotepa and VP-16 have been used individually in adult autologous marrow rescue regimens for patients with various adult tumors, including brain tumors, so that their individual toxicities at high-dose have been well described [245]; 4) thiotepa is a cycle-specific alkylating-type agent without cross-resistance with cyclophosphamide, and in keeping with alkylating agents in general, the higher the dose employed, the more effectively is low-dose resistance overcome; and finally, 5) studies conducted in dogs have indicated that thiotepa has excellent penetration of both the CSF and brain parenchyma following continuous intravenous infusion [257].

The feasibility of this approach to patients with resistant brain tumors should become apparent within the next few years, since this study will shortly be opened as a CCSG study among five pediatric transplant centers. It may well be that this approach will prove applicable to certain high-risk brain tumor patients at the time of diagnosis, such as those with rapidly growing but inoperable high-grade astrocytomas of the deep cerebral hemispheres and the brainstem.

Immunotherapy

INTERFERONS

The development of recombinant DNA technology in the 1970s has generated biologic compounds in sufficient quantity to permit clinical evaluation. The most extensively studied of these biological response modifiers are the interferons. Of the hundreds available in nature, three, namely alpha, beta, and gamma, are currently available for clinical trials. Generally speaking, interferons have been shown to exert an antiproliferative effect on both animal and

human cancers both in vivo and in vitro [258]. This activity may be the result of a direct toxic effect on the malignant cells or possibly activation of immune mechanisms such as natural killer lymphocytes or macrophages. In 1981, Lundblad and Lundgren demonstrated that interferon could inhibit the proliferation of the human glioma cell line V-251MG in culture by preventing DNA synthesis in the S phase [259]. Korosue et al. using KNS-42 human glioma cells in culture confirmed that been-interferon inhibits DNA synthesis and induces specific differentiated proteins and morphologic alterations in the tumor cells [260].

A number of clinical trials have been undertaken to try to determine if the in vitro effects of interferons on glioma cell lines could be duplicated in patients with high-grade astrocytomas, Mahaley et al. reported on a group of nine patients with high-grade astrocytomas who received a three-week course of alpha-interferon after surgery and before irradiation. Using retrospective analysis, they compared these patients with a control population of 18 patients treated with surgery, BCNU, and radiotherapy. Median survival in the group that received interferon was 534 days versus 455 days for the control group [261]. A follow-up report in 1985 evaluated alpha-interferon as a phase II agent in recurrent gliomas; 7 of 17 patients (41%) were responders to interferon therapy based on CT scan; those patients who responded demonstrated a survival advantage of 511 days as compared with the nonresponders, who had a 147-day mean survival [262]. Duff et al. reported on 12 patients with recurrent glioblastoma multiforme treated with combined intravenous and intralesional beta-interferon; none had a sustained response based on CT scanning and no survival advantage was seen [263]. A report of seven patients by Obbens et al. at M.D. Anderson Hospital, using alpha-interferon given by intralesional or intraventricular administration, demonstrated that 1 of 3 patients (33%) with high-grade astrocytoma achieved a sustained response on CT following

intralesional interferon, and 4 of 4 (100%) patients with leptomeningeal metastases achieved CSF free of malignant cells for up to ten weeks following intraventricular interferon. Although the patient numbers are small, the results of intraventricular therapy for leptomeningeal metastases are encouraging [264].

INTERLEUKIN-2 ACTIVATED KILLER CELLS

In 1982, Grimm et al. reported on the ability to activate peripheral blood lymphocytes *in vitro* to a tumoricidal state by incubating the lymphocytes with interleukin-2 for a minimum of 48 hours [265]. In 1986, Jacobs et al. described *in vitro* killing of human glioblastoma cells in culture by the patient's own peripheral blood lymphocytes when cultured with interleukin-2 [266]. The authors subsequently followed up with experience on nine patients with malignant glioma treated with interleukin-2-activated killer cells. Using a microcytotoxicity assay, they demonstrated *in vitro* ability of the activated killer cells to lyse glioma cells but not normal cells [267]. Jacques et al. have recently reported on injection of interleukin-2-activated autologous lymphocytes into malignant brain tumors; they documented safe administration, and preliminary results are encouraging [268]. Recently McLeary and Tubergen have collaborated on a group of 24 patients who received injections of lymphokine-activated killer cells into malignant brain tumors; the median survival of these patients has already passed historical controls (L. McLeary and M.D. Tubergen, personal communication, 1986). Based on the encouraging initial results with systemic administration of lymphokine-activated killer cells (LAK) and interleukin-2, the CCSG is considering testing these approaches for children with recurrent brain tumors.

MONOCLONAL ANTIBODIES

The availability of monoclonal antibodies has had a profound impact upon the future direction of brain tumor research and on the development of clinical trials for patients with brain tumors. The concept of using antibodies for

treating cancer began to emerge as early immunologists unlocked the mysteries surrounding antibody-mediated immunity. In 1895, Hercoult and Richert injected an antibody preparation into cancer patients. In 1906, Ehrlich further suggested that antibodies could be tagged with chemotherapeutic agents to selectively target cancer cells [269]. In 1965, Mahaley and Day reported on heterologous (rabbit) antiglioma antibodies that were radio-labeled with iodine-125 for tracer studies in patients with brain tumors [270]. A report in 1975 by Kohler and Milstein found that an antibody producing B-lymphocyte can be fused with a cultured myeloma cell resulting in a hybridoma that secretes a specific monoclonal antibody [271]. Since 1975, investigators have had unlimited capability of producing monospecific antibodies to antigens that are difficult to isolate by conventional means. This can be applied to brain tumor cells, which may express either antigens in excess of those seen on normal brain cells or possibly unique antigens not seen on normal cells.

Once the tumor-specific antibody is synthesized, there are two possible strategies for the construction of a chemotherapy-antibody conjugate. One approach is to covalently link the drug to the antibody or antibody fragment. In this way the drug works at the surface of the targeted cell or may be able to be internalized by the cell. The other approach is to form a weak bond between drug and antibody so that once the drug reaches the target cell it is released and is able to diffuse more homogeneously into a region of tumor involvement [272]. Embleton et al. have recently described a monoclonal antibody conjugated with the vinca alkaloid, vindesine; osteosarcoma cells in culture exposed to this conjugate demonstrated a marked decrease in cell survival [273]. Garnett et al. describe the construction of a water-soluble antibody tagged with methotrexate and attached to serum albumin; cytotoxic assays show specificity for osteosarcomas with a significant inhibition of tumor growth [274]. Dullens et al. reported on the *in vivo* effec-

tiveness of chlorambucil-antibody conjugates against two murine tumors, a lymphoma and a melanoma, and found that the melanoma growth was inhibited when transplanted into mice inoculated with the chlorambucil-antibody conjugate [275]. Finally, daunomycin and adriamycin have been successfully conjugated to a variety of antitumor antibodies. In vivo activity has been demonstrated against rat hepatoma xenografts with a daunomycin-anti-alpha-fetoprotein conjugate [276].

The most exciting clinical investigations using monoclonal antibodies in human tumors have been with radiolabeled monoclonal antibodies. Ettinger et al. have recently published the preliminary results using antiferritin antibodies labeled with ^{131}I as a component of therapy for patients with primary hepatic malignancies; an objective antitumor effect was seen in 6 of 9 evaluable patients [277]. Lashford et al. have reported on five pediatric patients with neoplastic meningitis treated with intrathecal radiolabeled monoclonal antibodies; they saw dramatic clearing of the CSF of malignant cells [278]. The Hammersmith Oncology Group has reported on three patients, one with a malignant pleural effusion, one with a pericardial effusion and gross disease, and one with malignant ascites; resolution of symptoms, clearing of malignant cells and sustained responses were seen following ^{131}I antibody therapy with negligible toxicity [279]. Perhaps one of the most exciting lines of research is the theoretical possibility of boron capture by monoclonal antibodies labelled with ^{10}B . The mechanism of boron capture is the activation of ^{10}B by slow neutrons; this results in a recoil lithium atom and an alpha particle with the generation of ionizing radiation specific to the target tissue [280].

Summary

We have described the pathophysiologic nature of brain tumors. By so doing we have attempted to clarify the rationale for many of the past brain tumor therapy trials as well as demonstrating

that the current and ongoing trials for children with brain tumors are the result of systematic and careful scientific inquiry. The good news is that the addition of chemotherapy to surgery and radiotherapy has made an impact on select groups of children with primary brain tumors. Children with high-grade astrocytomas and unfavorable-risk medulloblastomas have benefited in terms of improved survival and cure from the addition of multidrug therapy to aggressive neurosurgery and radiotherapy.

Approximately two thirds of all children with cancer are cured today; thus, children with primary brain tumors represent one of the greatest challenges to the pediatric oncologist. The child with a brain tumor must live with the neurologic sequelae of both the tumor itself and the therapy; therefore, long-term follow-up and rehabilitation of these children are critical accompaniments to continued therapeutic advances.

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Notes

1. $P = \exp \{-\alpha(N - 1)\}$, where P is the probability of cure for a tumor of size N and α is the mutation rate for cell generation.

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9. VISUAL PATHWAY GLIOMAS

Roger J. Packer

Peter J. Savino

Gary R. Diamond

Leslie N. Sutton

Probably no other intracranial tumor of childhood has been the subject of as many reports, with as many differing recommendations for treatment, as visual pathway gliomas [1–12]. In fact, some observers contend that the majority of lesions diagnosed as visual pathway gliomas are not tumors, but rather hamartomatous masses [13]. Gliomas of the visual pathway in childhood can involve one or both optic nerves, the optic chiasm, the optic tracts, and/or the occipital lobes [14]. Infiltration into intracranial structures not primarily responsible for vision, including the hypothalamus and thalamus, may also occur. Gliomas in the diencephalic region are often very large, and separation of chiasmatic lesions from hypothalamic masses is frequently arbitrary, artificial, and of no clinical importance [10].

Visual pathway gliomas constitute approximately 3% to 5% of all primary intracranial central nervous system tumors in childhood, occurring at an incidence of less than 1 per 100,000 children at risk per year [15]. In children under age two, visual pathway gliomas make up as much as 20% of all intracranial tumors (see table 9-1). Approximately two thirds of all primary optic nerve tumors in childhood are gliomas, the majority of the remaining tumors being meningiomas [15].

Over 90% of isolated optic nerve tumors occur in the first two decades of life. Seventy-

five percent of all isolated optic nerve tumors occur in the first ten years of life, with a peak of incidence between 2 and 6 years of age [1–12, 16]. Patients with intracranial tumors tend to be older than patients with isolated intraorbital masses. However, extensive intracranial masses are not uncommon in children under two years of age at the time of diagnosis. There is no clear-cut sex predilection, although some series have reported a slightly higher incidence of intraorbital gliomas in females.

The association between neurofibromatosis and visual pathway gliomas is well documented [1–12, 13, 16]. In most recent series, approximately 20% of children with intracranial visual pathway gliomas have neurofibromatosis. The association between isolated intraorbital tumors and neurofibromatosis is even stronger, since neurofibromatosis is present in up to 50% of children with intraorbital gliomas. Some authors have even suggested that an intraorbital glioma in a child under ten is diagnostic of neurofibromatosis and that children without other clinical manifestations of neurofibromatosis have a form-fruste of the disease. The reported incidence of optic gliomas in patients with neurofibromatosis is approximately 20% and as screening computed tomography (CT) scans are more commonly performed in patients with neurofibromatosis without symptoms of visual dysfunction or neurologic deficits, this

TABLE 9-1. Incidence of brain tumors in children less than two years of age at Children's Hospital of Philadelphia, 1975–1986

Tumor type	Subtotal	Total
Gliomas		30
Chiasmatic	15	
Other	15	
Primitive neuroectodermal tumors		22
Posterior fossa (medulloblastoma)	19	
Other	3	
Ependymoma		3
Choroid plexus tumors		5
Others		7
		—
Total		67

incidence will probably increase. A problem of increasing magnitude will be the management of patients with asymptomatic lesions. Some authors have suggested that the natural history of visual pathway gliomas is different in patients with neurofibromatosis than in patients without stigmata of this disease. Patients with neurofibromatosis are said to have a more favorable outcome; however, other series fail to document such an association.

Histology

Optic nerve gliomas usually enlarge the optic nerves in a fusiform or globular fashion [17]. Extension through the optic canal may give the tumor a dumbbell appearance. Optic nerve gliomas are most commonly embedded in hyperplastic arachnoidal tissue [17]. When there is intracranial extension, the chiasm tends to be diffusely enlarged. In more extensive intracranial lesions, the site of origin of the tumor is difficult to determine, and separation of neoplastic areas from uninvolved areas is impossible on gross examination.

Visual pathway gliomas are formed by thin, elongated (pilocytic), and stellate astrocytes [17]. Scattered oligodendroglial cells are commonly found, but they rarely compose a significant portion of the tumor. In some areas,

a microcystic pattern may be present and Rosenthal fibers can be found in densely fibrillated areas. Mitotic figures and areas of tumor necrosis are rarely present. In intraorbital lesions, connective tissue separation of tumor into glial bundles is commonly seen, a pattern that does not occur in intracranial masses. Otherwise, intraorbital and intracranial tumors tend to be histologically identical. The overlying dura is usually intact, but microscopically, infiltration into the overlying nerve sheet is common. Involvement of the subarachnoid space also occurs, accompanied by arachnoid hyperplasia of intermixed glial and leptomeningeal connective tissue. However, involvement of orbital soft tissue or bone does not occur.

When the gliomas are placed in tissue culture, numerous piloid astrocytes with abundant intracellular fibers develop [18]. Degenerative changes of these fiber bundles probably represents early formation of Rosenthal fibers. A distinctive feature of some optic gliomas is the ability of their long, thin cellular processes to form fiber tangles in tissue cultures.

A much more histologically malignant form of visual pathway glioma primarily occurs in adults [19]. Marked by regions of pleomorphic and mitotically active astrocytes, such tumors tend to readily invade adjacent tissues.

Clinical Presentation

The clinical symptoms and signs caused by visual pathway gliomas of childhood are dependent on the location of the tumor in the neuroaxis and the age of the patient. As stated previously, since many patients and family members of patients with neurofibromatosis are being screened by CT scanning, a subpopulation of patients who are completely asymptomatic at the time of visualization of intraorbital and/or intracranial disease is now being diagnosed.

Children with clinically symptomatic primary intraorbital gliomas usually present with unilateral or, less commonly, bilateral proptosis

and associated visual loss [11, 16, 20]. The proptosis is usually mild, rarely exceeding 3 mm, nonpulsatile and irreducible. Nasal and downward displacement of the globe may occur, and motility may be limited on a restrictive basis. On ophthalmoscopy, optic atrophy without disc elevation or other signs of papilledema is usually seen. Because of the age of the child, visual acuity may be difficult to measure, but the vast majority of patients with intraorbital disease have a significant visual loss. In one series, over 80% of patients had less than 20/200 vision at the time of diagnosis [11]. Orbital pain occurs in the minority of patients and is rarely the overriding complaint.

In contrast, less than 20% of children with primary chiasmatic lesions have significant proptosis, even with coexistent intraorbital disease [10]. Children over five years of age at diagnosis tend to have headaches and complaints of decreased vision (see table 9-2). There may be unilateral or bilateral visual loss, which, overall, tends to be less severe than in patients with isolated intraorbital masses. The pattern of visual loss is quite variable. In one series, central scotoma or measurable depression of central field occurred in 70% of the eyes studied [21]. Peripheral field defects are common, and they may be dense, quadrant, or hemianopic and result in general peripheral field contrac-

tion. At times, these peripheral field deficits are spotty. They may involve only the eye with decreased acuity, the contralateral eye (a junctional scotoma), or both eyes (usually in an incongruous fashion). Bitemporal hemianoptic visual loss occurs in less than one half of patients, and the absence of bitemporal loss cannot be used to exclude chiasmatic involvement.

Funduscopy examination in children with chiasmatic lesions most commonly discloses unilateral or bilateral optic pallor or atrophy; occasionally optic nerve hypoplasia is also present. Papilledema is uncommon. Ocular motor difficulties including abduction deficits and a rapid, find nystagmus may be present. Occasionally, hypothalamic dysfunction will be the presenting problem and may include precocious puberty or diabetes insipidus. The diencephalic syndrome, manifested by emaciation, failure to thrive, and seeming overalertness, may also be a presenting symptom, especially in children with primarily hypothalamic involvement.

Their symptoms and signs of intracranial disease in children under age five at the time of diagnosis (especially in those children under two years of age) are more variable, and there is commonly a delay of over six months between the onset of symptoms and correct diagnosis (see table 9-2). Although the majority of children under age two have significant visual loss

TABLE 9-2. Symptoms for children with chiasmatic glioma at Children's Hospital of Philadelphia, 1975–1986 (N = 34)

Symptoms	Children five years of age or less at diagnosis (N = 25)	Children five years of age or greater at diagnosis (N = 9)
Visual loss	14	6
Proptosis	4	2
Squint (strabismus)	15	1
Nystagmus	2	0
Headaches/Vomiting	2	5
Developmental delay	5	0
Motor impairment	4	1
Endocrinologic dysfunction	1	0
Increasing head circumference	3	0
Seizures	0	1

by the time of diagnosis, the most common early symptom is strabismus. Many infants undergo eye patching to treat amblyopia and even strabismus surgery before the correct diagnosis is made. The intraocular movement disorders in children with chiasmatic gliomas are variable, but most commonly a unilateral or bilateral pendular nystagmus with variable frequency and amplitude is reported [22]. A fine, rapid, almost shimmering unilateral or less commonly bilateral nystagmus with primarily a horizontal component or occasionally a vertical or rotatory component may also be present. The degree of nystagmus is usually asymmetric and most marked in the eye with the greatest degree of visual impairment.

Spasmus nutans—acquired uniocular or at times biocular nystagmus and head nodding usually occurring in children between four and eight months of age—has been reported as the presenting symptom for children with visual pathway gliomas [23, 24]. The diagnosis of spasmus nutans is a purely clinical one, and there is a great deal of variability in the pattern of nystagmus that has been reported to occur in this syndrome. Some series have considered only children with fine, rapid horizontal nystagmus as having spasmus nutans; other authors have included patients with pendular or purely vertical nystagmus in this syndrome [22–26]. It seems on the whole that children with the slower, vertical, or pendular nystagmus are more likely to harbor intracranial mass lesions. In practically, it is difficult for most physicians to completely characterize the type of nystagmus present in a young, often uncooperative child. Certainly, any child with additional symptoms or signs of neurologic dysfunction, such as a history of developmental delay, decreased visual acuity or optic pallor, who otherwise fits into the syndrome of spasmus nutans, should be radiographically evaluated for the possibility of harboring a chiasmatic glioma. The incidence of underlying neoplastic disease in children with classical spasmus nutans has not been determined, but it is our present

practice (as also recommended by others) to study all such patients radiographically before concluding that the symptoms present are not secondary to an underlying visual pathway tumor [26].

Funduscopy examination in children under five years of age commonly shows optic atrophy and, in up to one fifth of patients in our experience, optic nerve hypoplasia. Although hydrocephalus may occur, papilledema is uncommon. In this young age group, intracranial lesions may reach monstrous proportions before diagnosis, and the child may present with hemiparesis due to compression of the carotid artery by the tumor mass. Significant developmental delay may be present by the time of diagnosis in children less than two years of age at diagnosis.

Diagnosis

Prior to the mid-1970s and the development of CT, diagnosis was based primarily on appropriate visual findings, associated clinical findings (especially stigmata of neurofibromatosis), indirect radiographic evidence of intracranial or intraorbital mass lesions, and surgical biopsy. Other tests, including electroencephalograms and cerebrospinal fluid (CSF) findings, were nonspecific and usually not helpful.

In the presence of intraorbital disease, skull X-rays disclose enlargement of the optic foramina with an intact margin of cortical bone in between 50% and 80% of patients [11, 20]. The criteria most frequently used to define enlargement of the optic foramina include a diameter of 7 mm or greater or a difference of more than 1.5 mm between the two foramina. Subnormal size of the contralateral foramina due to optic nerve hypoplasia, a meningioma, or encroachment by fibrous dysplasia may cause a disparity between the size of the two foramina and falsely suggests the presence of an intraorbital glioma. Optic nerve sheath hyperplasia, which may occur in children with neurofibromatosis, can cause enlargement of the optic foramina. Enlargement of the foramina may

also be caused by infiltration of the optic nerve by sarcoma or another malignant processes or by intracranial involvement of the optic nerve sheath by neurofibroma or a meningioma. Distinction from optic gliomas is usually possible, since neurofibromas tend to irregularly enlarge the foramina and meningiomas more frequently result in irregular hyperostotic and sclerotic enlargement of canal margins. Tomography of the orbit may increase diagnostic sensitivity. Occasionally, diffuse orbital enlargement may occur in the presence of intra-orbital glioma.

Intracranial tumor is poorly demonstrated by skull films [11, 20]. Pressure of a chiasmatic tumor against the anterior clinoid process at the lateral aspect of the sphenoid bone can produce the gourd-shaped or so-called J-shaped sella. The anterior clinoid process tends to be thinned, especially inferomedially, with preservation of a well-corticated margin. This type of seller deformity is found in as high as one half of patients with intracranial lesions that involve the chiasm. In children with neurofibromatosis, a similar deformity may be present as part of a dysplasia or hypoplasia of the lesser and greater wing of the sphenoid without associated intracranial tumor [27].

Before the advent of CT scanning, pneumoencephalography was often needed to confirm the presence of intracranial masses [11, 20]. This invasive procedure did not visualize the degree of intracranial extension, nor was it useful in following the course of the disease. Similarly, arteriography could delineate the presence of large mass lesions, but was nonspecific and unhelpful in following patients.

CT scanning has eliminated the need for pneumoencephalography and arteriography in the diagnosis of children with visual pathway gliomas, independent of their location in the neuroaxis [14]. Intraorbital masses are usually well seen as fusiform, isodense masses that enhance homogeneously after intravenous contrast. Distinction between optic gliomas and other neoplastic or inflammatory orbital processes is

usually possible. Coronal views are sometimes needed to confirm the presence of primary involvement of the optic nerve. Bilateral optic nerve gliomas are well seen and may occur without evidence of chiasmatic enlargement, suggesting the presence of multicentric glioma.

Intracranial involvement on CT is shown as an isodense or less frequently as a hypodense mass, filling the suprachiasmatic cistern and often involving large proportions of the diencephalon, with variable enhancement patterns after intravenous contrast. This enhancement may be marked, even in low-grade lesions. Areas of calcification are infrequently seen. Isolated chiasmatic involvement occurs in a minority of patients. Areas of enhancement along the optic radiations, tracts, and into the occipital lobes without mass effect are also frequently seen (see figure 9-1). These areas most likely represent neoplastic tissue, although they may be alternatively dysplastic or hamartomatous areas. Extension into other diencephalic structures frequently occurs, especially in young patients.

Magnetic resonance imaging (MRI) is even more sensitive than CT in the diagnosis of visual pathway lesions [28]. Images on MRI are not obscured by surrounding bone, and with the use of a surface coil, intraorbital gliomas can be exquisitely seen. Infiltration of the chiasm is also well demonstrated. On T2-weighted images, gliomas are seen as high-signal intensity areas involving the visual pathways. Coronal and sagittal images brings out anatomic interrelationships extremely well. Often, the extent of disease as seen on MRI is far greater than that visualized on CT (see figure 9-2). It is as yet unproven, however, whether all abnormal signal intensity areas seen on MRI represent tumor.

Because of refinements in CT and MRI, children with intraorbital and intracranial tumors can be diagnosed with a high degree of reliability by imaging studies. In the majority of patients, surgical confirmation is probably unnecessary. In patients with both intraorbital and intracranial disease, especially when the

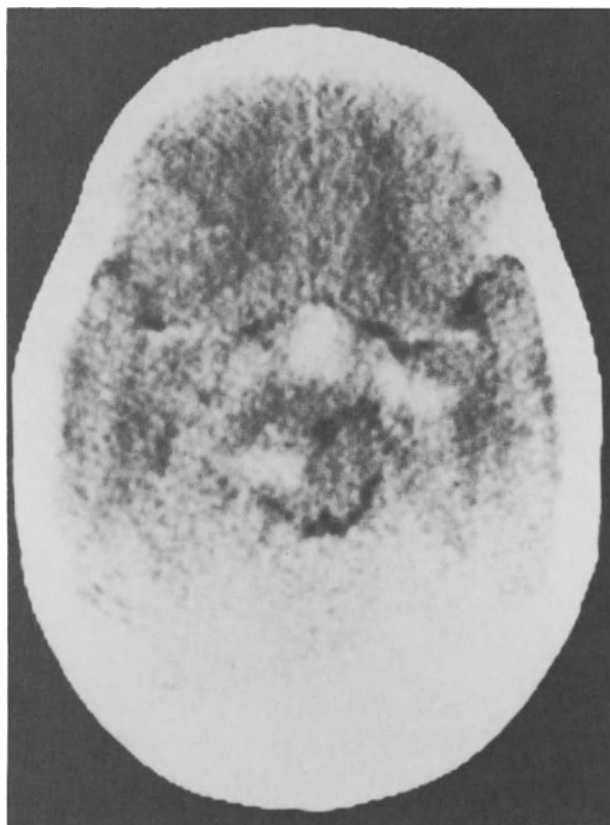


FIGURE 9-1. CT after contrast of a child with a biopsy-proven chiasmatic glioma. Streaking of the tumor from the chiasm to the optic radiations can be seen.

tumor streaks along the visual pathways or when the child has neurofibromatosis, there is essentially no differential diagnosis and no need for pathologic confirmation. Surgery in such cases has no clear-cut benefit, since it will not improve visual function or increase the chances for survival. In patients with isolated chiasmatic and hypothalamic lesions, especially with large cystic areas and mass effect, surgery is probably indicated both to confirm diagnosis and to relieve symptoms of increased intracranial pressure.

The course of illness can now be well followed by serial MRI or CT scans. Ancillary tests, such as visual evoked response, may also be of help in following the course of illness.

Treatment

As stated previously, there is no agreement on the most appropriate management of pa-

tients with visual pathway gliomas. Hoyt and Baghdassarn, in a review of 36 patients, 29 of whom had tumors that occupied the chiasm or hypothalamus, concluded that "optic gliomata during childhood are a special category among glial tumors of the brain and are congenital, non-neoplastic self limited tumors" [13]. Other reports have suggested that chiasmatic gliomas of childhood may act aggressively and that these tumors do benefit from local radiation [2, 3, 4]. Still other studies have divided visual pathway gliomas into anterior chiasmatic gliomas, involving the chiasm and/or optic nerves, and posterior gliomas that involve the chiasm with extension into the hypothalamus or optic tracts [1]. The anterior group of tumors were said to be uniformly benign and require no treat-

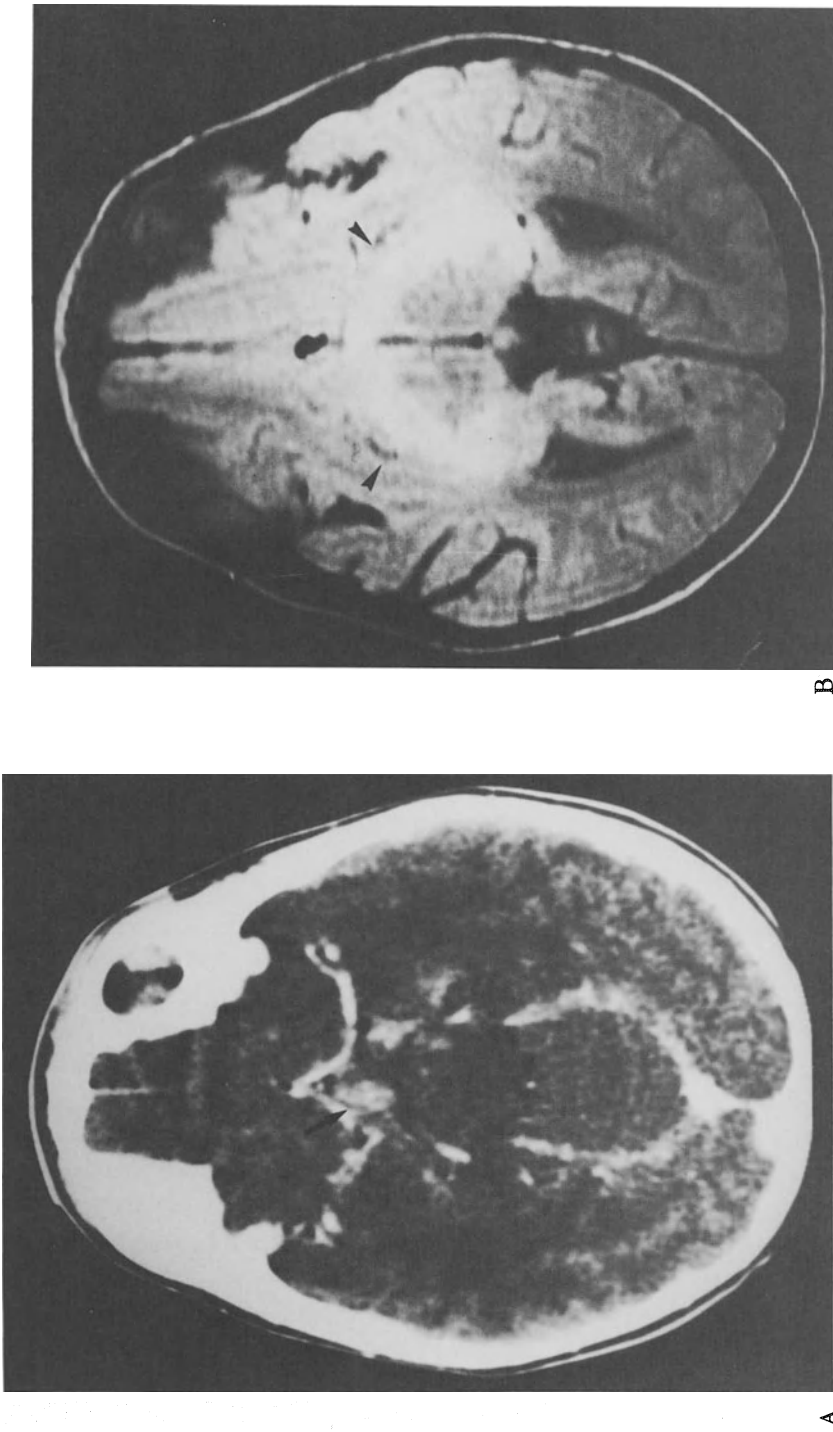


FIGURE 9-2. A. CT scan of a four-year-old with a chiasmatic glioma. Enhancing lesion (arrow) in suprasellar region is seen. B. MRI on the same patient. T2-weighted images show extensive streaking (arrowheads) of abnormal tissue along optic radiations.

ment, while the posterior lesions were believed to be potentially malignant, with a variable response to radiation. With the advent of CT and MRI, it has become clear that small intracranial lesions confined to the chiasm are relatively infrequent and that the majority of chiasmatic lesion either streak along the visual pathways or invade surrounding areas of brain. In a review of the experience of patients with histologically confirmed chiasmatic gliomas seen at our institution and reported from other institutions, it was found that chiasmatic gliomas could act aggressively, independent of their location in the visual pathway [10]. A beneficial effect of radiation on vision could not be confirmed in most patients. Progressive neurologic deterioration and visual loss occurred in both non-irradiated and irradiated patients; this tended to occur many years (a median age of seven years, in our experience) after diagnosis. Also of concern was that many survivors who had been treated with radiation therapy had moderate to severe intellectual compromise, believed in part to be due to the radiation therapy received.

It seems that with the information available, treatment of isolated intraorbital tumors should be considered separately from treatment of lesions with intracranial extension at diagnosis. Another important factor that must be kept in mind when evaluating therapy is that optic glioma are extremely slow-growing tumors, and results need to be evaluated over many years, even decades. Finally, when evaluating any form of treatment, results cannot be viewed only with regard to survival but also with regard to quality of life, including visual, endocrinologic, and intellectual function.

ISOLATED INTRAORBITAL TUMORS

In patients with isolated unilateral or bilateral optic nerve gliomas, treatment with surgery and/or radiotherapy has been instituted for differing reasons, including attempts to improve vision, to improve cosmetic appearance, to prevent the development of progressive visual loss, and to prevent life-threatening intracranial

disease [2, 3, 16]. There is no evidence that patients who are diagnosed with the present means of evaluation (CT or MRI) with isolated optic nerve gliomas, or bilateral multicentric optic glioma, whether treated or untreated, will later develop intracranial spread [1–12, 13, 14, 20]. The need for treatment to prevent the development of intracranial disease is dubious at best. On the other hand, the use of radiation to improve visual acuity in patients with isolated intraorbital disease is controversial. Some have found an increase in visual acuity in a minority of patients after radiation, while others have not been able to document this occurrence [2, 3, 13, 21]. Making interpretation of these data more difficult are reports of spontaneous improvement in vision in patients who had not received treatment [21].

The most clear-cut indication for intervention in patients with isolated orbital tumors is cosmesis for severely proptotic eyes. Severe ocular exposure in a seeing eye is also an indication for some type of decompressive procedure. A variety of surgical approaches have been successfully utilized in blind eyes. The earliest surgical approach was orbital excision of the tumor-bearing nerve; many excisions were incomplete, but few recurrences were reported [29]. When possible, the globe is spared, and the proximal 13 mm of nerve is also spared as the ophthalmic artery enters the nerve at this point. The Berke modification of the Kronlein procedure, involving posterior extension of a lateral canthotomy and excision of the lateral orbital wall, is most commonly utilized because of improved exposure and cosmesis [30]. Another frequently utilized approach, the transcranial approach involving frontal craniotomy, has the advantage of offering access to orbital apex, canal, cranial nerve, and chiasm [31]. Some surgeons prefer a two-stage procedure consisting of both the above techniques. How extensive the surgery should be is also not well documented. Recurrent disease may occur after "total surgical removal" of the tumor, and likewise long-term stable disease has been docu-

mented for years after partial resection of the tumor [11].

Radiation is an alternative means of treatment in a severely proptotic eye, especially when some vision is present. While visual improvement does occur in some irradiated patients, this improvement may occur years after radiation and is difficult to attribute to the radiation. Decreased vision has also been reported after radiation therapy, and it is usually impossible to determine whether this is due to the therapy or due to natural progression of the tumor. Survival figures after treatment with observation alone, surgery alone, or radiotherapy alone are all excellent, and in most series approach 100% at five and ten years.

INTRACRANIAL LESIONS

The natural history of intracranial visual pathway gliomas is poorly defined and erratic. Some patients have long-term stabilization with no treatment at all, while others develop progressive disease with increasing visual loss and neurologic deterioration, culminating in death. Based on available information, we believe treatment of tumors that are confined to the chiasm and/or optic nerves with evidence of minimal extension along optic tracts, without mass effect, should be delayed, as long as careful clinical observation and radiographic follow-up can be assured [10]. Specific treatment, such as radiation therapy, should not be instituted until there are signs of either clinical or radiographic disease progression. On the other hand, in patients with extensive tumors invading the hypothalamus and extending into the third ventricular region, or with massive infiltration along the optic tract, or with clear-cut evidence of rapidly progressive disease at the time of diagnosis, delay in chiasmatic gliomas treatment is not recommended, since further growth may cause severe irreversible damage to vital brain regions or acute hydrocephalus. If there are symptoms of increased intracranial pressure, especially if the tumor is composed of large cystic components, surgical intervention with

drainage of the cystic component and partial debulking of the tumor is often possible and beneficial. After surgery, local radiation therapy is then indicated.

The best long-term results have been reported with doses of between 5000 and 6000 rads delivered over 5 to 6 weeks [2–9, 16]. After treatment, patients usually experience stabilization of vision and disease control [14]. Radiologic evidence of tumor regression may occur immediately after radiation, but this does not guarantee long-term disease control. Five-year survival rates after radiotherapy range between 80% and 100% in patients with intracranial lesions; however, ten-year survival rates are probably closer to 50% [10]. As is the case with low-grade gliomas in other central nervous system sites, it is difficult to confirm improved survival at ten years in irradiated patients as compared to patients who have not received radiotherapy.

The majority of patients after treatment with radiotherapy have growth failure, as well as other endocrinologic deficits. The detrimental effects of both local and craniospinal radiotherapy on intellectual function in children is well documented, and the most severe sequelae are noted in young children. Since the median age at diagnosis in children with visual pathway gliomas is usually below five years, and since as high as 30% of patients are under two years of age at diagnosis, these patients could be expected to have a high incidence of damage after radiotherapy. In one series, 50% of children with chiasmatic glioma had significant learning problems after treatment with radiation [10].

Because of the risk of neuropsychological sequelae of radiation therapy, especially in young patients with large intracranial lesions and progressive disease, alternative means of treatment should be considered. Preliminary results suggest that in such patients chemotherapy may be of benefit [12]. In one small series treatment with actinomycin D (ACT D) and vincristine, either resulted in stabilization or regression of disease in 80% (12 of 15) of patients with pro-

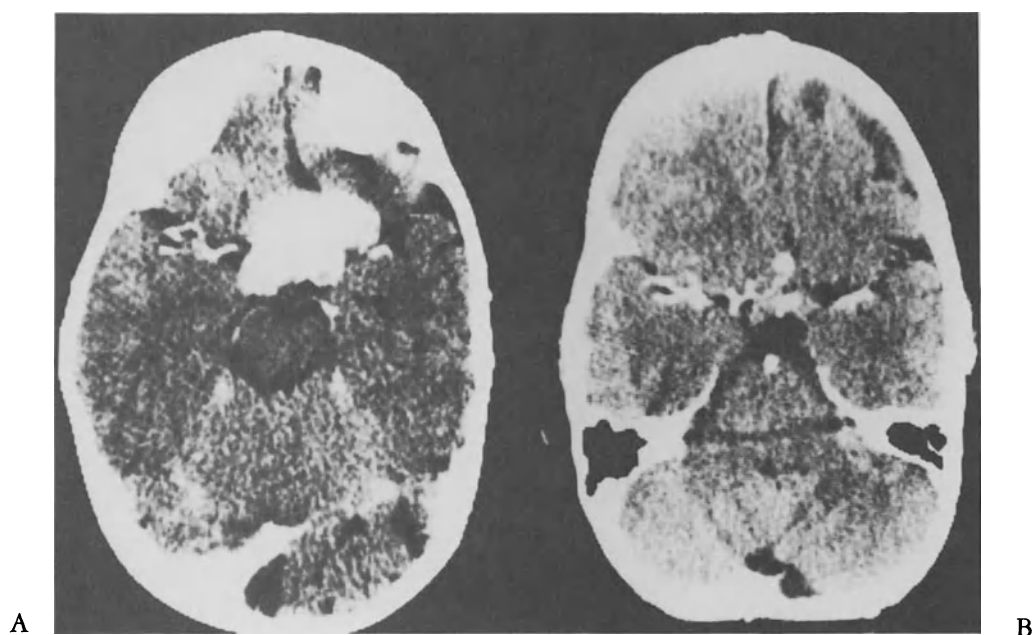


FIGURE 9-3. A. CT after contrast shows an enhancing, irregular mass filling the chiasm in this nine-month-old child. This was surgically confirmed as a chiasmatic glioma. B. CT after contrast in the same child after one cycle of chemotherapy. Marked decrease in tumor is obvious.

gressive disease; an objective response to treatment, as defined by tumor shrinkage, was seen in one half of patients [12] (see figure 9-3). The series has since been enlarged to over 20 children, with similar results. Importantly, patients treated with chemotherapy had preserved endocrinologic function and most had normal intelligence. It is unclear whether chemotherapy will result in long-term control of tumor, and as with radiation, disease may recur years after the completion of therapy. However, this type of therapy may significantly delay the need for radiation therapy, and this delay may be extremely beneficial in very young patients.

In any event, whether observation, surgery, radiotherapy, or chemotherapy is chosen as the treatment modality, children with visual pathway gliomas need to be carefully followed for long-term visual, endocrinologic, and intellectual sequelae. The optimal way to manage such patients is still not known and will require multicenter cooperative trials addressing the natural history of the illness and the impact of treatment on long-term outcome.

RECURRENT CHIASMATIC GLIOMAS

Treatment of chiasmatic gliomas that recur after therapy is problematic. Cyst formation is not infrequent at the time of recurrence, and drainage of the cyst and surgical debulking often result in relief of symptoms. The natural history of recurrent disease is as variable as the history of newly diagnosed lesions. For unclear reasons, some tumors will spontaneously stabilize after apparent growth. More frequently, once the tumor begins to grow again, it insidiously increases in size, causing headaches, increased visual loss, and other neurologic deficits. Treatment with ACT D and vincristine has seemingly halted growth for as long as seven years after recurrence [12]. Other patients have received a second course of radiotherapy with arrest of progressive symptoms. The best management of recurrent disease has yet to be determined.

Acknowledgments

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10. CRANIOPHARYNGIOMAS

Dachling Pang

This chapter reviews the current controversies surrounding the origin, natural history, and optimal therapy for craniopharyngioma. The recommended outline of treatment for this rare tumor at different stages of its lifespan must merely be regarded as the personal viewpoint of the author, and not as the undisputed answer to this complex problem. Neurosurgeons and oncologists must remain flexible enough to revise their protocols according to new revelations from the constantly changing frontiers of treatment of this tumor.

Embryologic Origin

For several decades, craniopharyngiomas were believed to arise exclusively from remnants of epithelial rests along the embryologic migration path of the anterior pituitary lobe [1–3]. At the end of the third gestational week, the ectodermal stomodeum invaginates towards the diencephalon and eventually meets the downwardly growing neurohypophyseal bud. As the sphenoid bone forms ventral to this complex, the attachment of the stomodeal cleft with the pharynx disappears, and the epithelium-lined cleft becomes a pouch (of Rathke). The anterior wall of Rathke's pouch thickens to form the anterior lobe, while the posterior wall forms the thin (in man) pars intermedia. The upper end of the pouch evaginates laterally on both sides to wrap around the anterior aspect of the infundibular stalk and forms the pars tuberalis. Any embryonic epithelial cells that fail to undergo involution later in life will therefore remain as

squamous nests along the path of the original stomodeal migration (known as the hypophyseopharyngeal duct).

In 1904, Erdheim first proposed that craniopharyngiomas arose from neoplastic transformation of these embryonic cell rests [2]. He found histologic similarities between craniopharyngiomas and adamantinomas, tumors known to arise from the embryonic lining of the buccal cavity. He and others [4–6] thought that this resemblance suggested that craniopharyngiomas were also derived from ectoblastic remnants of the hypophyseopharyngeal duct. Squamous-cell nests are most frequently found within the pars tuberalis and at its junction with the pars anterior, which are also the common sites for craniopharyngiomas [5, 7]. Also in support of the embryonic origin of these tumors are reports that craniopharyngiomas have indeed been found along the entire hypophyseopharyngeal duct from the nasopharynx to the floor of the sella [8] as well as above and within the sella [9].

Against the embryonic origin of craniopharyngioma is the fact that squamous-cell nests are rarely found in pituitary glands from persons younger than 20 years [1, 2, 7, 10–12] even though craniopharyngiomas occur with a peak incidence from age 5 to 10 years [9]. While these cell nests are present in only 3% of neonates [4], they are found with increasing frequency with each succeeding decade. Luse and Kernohan [7], for example, examined 1364 pituitary glands and found no cell nests in 78 patients younger than ten years of age, but iden-

tified them in 30% of patients between the sixth and eighth decades. These authors postulated that the squamous-cell nests from which craniopharyngiomas originate are products of metaplasia of the mature cells of the pars tuberalis and anterior lobe, and not embryonic remnants.

There is evidence to suggest that craniopharyngiomas may indeed have dual origins; that is, they may arise from squamous-cell nests that come from both embryonic and metaplastic sources. Both Kahn et al. [13] and Till [14] have described histological differences between adult and childhood craniopharyngiomas that might indicate different origins. The so-called childhood type, which occurs in all ages and appears to have a more aggressive growth pattern, contains palisading columnar cells that are reminiscent of the ameloblasts of fetal tooth buds (*adamantinomatous*). This type may be of embryonic origin. The adult type, which occurs mostly in adults and has a lower growth propensity, consists of sheets of mature stratified squamous cells. This type may be of metaplastic origin.

Pathology

The size of a craniopharyngioma found at diagnosis depends on its location and the age of the patient. An intrasellar tumor as small as 6–7 mm in diameter may declare itself clinically in a woman with secondary amenorrhea, whereas tumors in front of the chiasm may grow to 6–7 cm in size under or within the nondominant frontal lobe in a young child before near-blindness or hydrocephalus suggests a neurological abnormality.

Most craniopharyngiomas are located in the suprasellar cistern behind or below the chiasm. Approximately one third of cases are retrochiasmatic [5, 15]; the tumor displaces the infundibular stalk forwards and the chiasm and anterior cerebral arteries upwards and forwards, making the optic nerve appear falsely prefixed. The equally common subchiasmatic tumor pushes

the infundibular stalk backwards and the chiasm upwards, stretching the optic nerves. Both the subchiasmatic and retrochiasmatic lesions are frequently solid, and if large enough may reach up to and ultimately obstruct the foramen of Monro. With these large tumors, the third ventricular floor is pushed up markedly and may be so severely attenuated that computed tomography (CT) and magnetic resonance imaging (MRI) sometimes mistakenly identify these lesions as truly intraventricular. Tumors that are completely within the third ventricle have been reported but are exceedingly rare [16–18]. The less common prechiasmatic tumor displaces the chiasm posteriorly. Frequently cystic, it can burrow under and expand within the basal frontal lobes to enormous size without causing neurologic deficits [5, 9]. In contrast, the infrequent (10%–15%) [15, 19] intrasellar lesion compresses the pituitary gland early to cause endocrinopathies.

Craniopharyngiomas may be primarily solid, primarily cystic, or cystic with a large solid component that may in turn contain smaller cysts. The solid part is usually smooth, rubbery-firm, and gray or pink, resembling fish flesh. The cyst wall may be diaphanous or thickened with a shell of tumor. It contains birefringent cholesterol crystals suspended in a light-yellow-to-dark-green fluid. Either the solid part or the cyst wall, or both, may be calcified.

Microscopically, the lining of the grossly cystic parts is composed of a simple stratified squamous epithelium supported by a collagenous basement membrane that abuts against the adjacent glia or meninges. In the solid parts, Kahn et al. [13] described two distinct histologic types. The more common adamantinomatous type, found by Kahn et al. [13] and Till [14] in both children and adults, consists of epithelial sheets or trabeculae supported by a matrix of loose and scantily cellular connective tissue. These trabeculae are lined by palisading columnar cells radially arranged at the margin. The more central parts of the trabeculae are composed of round or polygonal cells that, when

well preserved, have transparent cytoplasm and intercellular bridges (prickle cells). In other foci, there are discrete rounded masses of dead cells that show whorled or laminated arrangements reminiscent of keratinization. It is this combination of peripheral palisading columnar cells and central transparent cells that reminded earlier observers of fetal tooth buds and other oral mucosal appendages.

The less common histologic type, found predominantly in adults by Kahn et al. [13] and Till [14], consists of sheets of stratified squamous epithelium embedded in a matrix of vascular connective tissue. There are no laminellae or keratinization, and calcification is seldom present.

The most common regressive change in the epithelial cells is calcium deposition within the laminated whorls of dead cells in the adamantinomatous type. This explains why microscopic calcification is found in almost all the tumors in children but only in approximately half of those in adults [9]. Small foci of calcium may become confluent to form large stones, and actual bone formation has been demonstrated [13]. The stroma often undergoes microcystic degeneration, and small cysts coalesce to form large ones [20].

The majority of craniopharyngiomas cause an intense glial reaction in the surrounding brain. In the retrochiasmatic and subchiasmatic tumors, this glial plane is between tumor and hypothalamus. While some authors feared that traction on the glial attachment may lead to hypothalamic infarction [21], this author agrees with Sweet [22, 23] that this glial sheath more likely provides a safe plane in which to dissect without injuring functional neural tissue. The more troublesome feature is the adherence of tumor to major arteries at the base of the brain. Plaques of calcified tumor adherent to the internal carotid artery had been the limiting factor for total removal in 6 of 23 children treated by Hoffman et al. [24].

As embryologic remnants of Rathke's pouch, craniopharyngiomas share the same arterial

supply as the diencephalon [5, 25, 26]. The anterior portion of the tumor thus receives perforators from the anterior communicating artery and the A₁ segments of the anterior cerebral arteries, and its lateral portion receives branches from the posterior communicating artery. If the tumor involves the sella, it will also pick up arterial twigs from the capsular arteries. It is important to realize that the tumor virtually never receives blood supply from the posterior cerebral or basilar artery, no matter how far posterior it extends [5], since these arteries normally do not irrigate the diencephalon. This fact is basic to the removal of the retrosellar portion of the tumor.

Incidence

Craniopharyngiomas constitute between 2.5% and 4% of all intracranial tumors [27, 28]. They are much more common among children, forming 9% of Matson's series of childhood tumors [29]. They also make up 54% of neoplasm in the sella-chiasmal region in children but only 20% in adults [30].

The peak incidence of craniopharyngiomas is between ages 5 and 10 years in children [9, 30, 31] and between ages 55 and 65 in adults [30, 32]. The collective study by Koos and Miller [30] even reveals a small third peak between age 20 and 25. It is therefore important to realize that craniopharyngiomas may become symptomatic at any age.

Although there is a slight male preponderance of this tumor in the older childhood series [30, 31], the two most recent series [24, 33] show equal sex distribution.

Symptoms and Signs

The clinical presentation of craniopharyngiomas differs between children and adults. Children tolerate progressive visual failure amazingly well, and they not uncommonly present with complete blindness in one eye and barely the ability to count fingers in the other [5, 9, 31].

Subtle clues of progressive visual compromise include an inexplicable deterioration in the child's school performance, and the observation that the child situates himself increasingly closer to the television.

Other symptoms of an enlarging intracranial mass are equally difficult to detect in a young child, for changes in personality, headaches, memory deficits, and even a disturbance in orientation are likely to be overlooked by parents unless they are glaringly obvious. Diagnosis is often delayed until the mass is either enormous, or until severe hydrocephalus results from obstruction of the third ventricle or foramen of Monro. This explains why severe headache and vomiting are the presenting complaints in 75% to 80% of children, whereas only 20% to 30% of children will present with visual symptoms [5, 9, 27, 31, 33].

The most frequent endocrinopathic manifestations in children are short stature and diabetes insipidus (DI) [27, 31, 33], and the most common hypothalamic dysfunction is central hyperphagia and obesity. Sleep and temperature regulations are rarely affected. An unusual disturbance of fat metabolism causing emaciation even with adequate food intake has been described by Northfield [34], and precocious puberty has been reported in four cases of craniopharyngiomas [31, 35–37], presumably because of hypothalamic compression and derepression of the arcuate nucleus luteinizing hormone releasing hormone (LHRH) pacemaker. Suppression of hypothalamic prolactin-inhibiting factor is also thought to be the mechanism of galactorrhea and hyperprolactinemia associated with this tumor [38, 39].

Neurobehavioral abnormalities occur in less than 10% of children [9, 27, 31]. Occasionally, the child shows psychomotor retardation, flattening of emotion, and loss of enthusiasm towards his environment (abulia), and has significant recent memory deficits. The amnesic syndrome has been attributed to compression of the hypothalamic component of the limbic memory circuit, such as the mamillary bodies, but the abulia probably results from compro-

mise of the dopaminergic mesolimbic pathway either within the medial forebrain bundle or at the medial septal region. This pathway has been implicated as the circuit responsible for exploratory behaviors in animals and motivation in humans [40–42].

Unlike children, most adults are very sensitive to visual disturbances, and 80% of adults in Banna's series [32] presented with various combinations of field defects, scotomas, and homonymous hemianopsia. Less than one third of adults have signs of increased intracranial pressure (ICP) [9, 27, 32]. Nevertheless, neurobehavioral syndromes unrelated to raised ICP are much more common in adults than in children [5, 9, 27]. Bartlett estimated that 31.5% of patients older than 45 years had dementia [43], and an even higher percentage had intermittent confusion and hypersomnia. Memory impairment indistinguishable from Korsakoff's syndrome was found in 30% of adult patients [44–46], and occasionally severe depression and apathy will complicate the intellectual deterioration. This combination is associated with a poor prognosis [43]. The most common endocrinopathy in adults is gonadal failure (37%) [5] presenting as secondary amenorrhea in women and loss of libido in men.

Radiographic Diagnosis

Craniopharyngioma is one of few intracranial tumors that can be accurately diagnosed with radiography. Two thirds of the adults and 95% of children with this tumor have abnormal skull X-rays [5, 32, 47]. The usual finding is erosion of the dorsum sellae and anterior clinoids, with expansion of the upper part of the sella. If the tumor has a significant intrasellar component, the entire sella may be enlarged towards the sphenoid sinus; indeed, the rare intrasellar craniopharyngioma can mimic a pituitary adenoma in causing a "ballooned" sella [19, 48]. A useful feature that distinguishes craniopharyngiomas from most other parasellar tumors is that suprasellar calcification is exceedingly common in the former, being found in approximately

85% of the childhood variety and in 40% of the adult variety [47, 49].

Until the recent advent of MRI, CT was the single most important diagnostic study. Its most important function is probably distinguishing between the primarily solid tumors and the primarily cystic ones, for their managements are different. A solid tumor has more than 70% solid component, whereas a cystic tumor has the reverse ratio of solid and fluid. Calcifications are better shown on CT than plain films. They can be curvilinear, outlining a portion of the cyst wall, or aggregates of calcium flecks [31, 50] (figure 10-1A). The CT density of the cyst fluid is usually between that of brain and cerebrospinal fluid (CSF), but is occasionally very high due to elevated protein concentration, or very low due to a high cholesterol content [51, 52]. Contrast enhancement of the solid component occurs in three fourths of children but only in one third of adults [51]. Properly angled thin coronal CT cuts (1.5 mm thickness) often demonstrate to great advantage the relationship between the tumor and the sella content, the internal carotid arteries, the hypothalamus, and the foramen of Monro (figure 10-1B).

Recently, MRI has added a new dimension to the imaging of parasellar lesions. Its sagittal imaging capabilities enable a graphic anatomical display of minute hypothalamic details in their distorted configuration (figure 10-2). Actual delineation of the lamina terminalis and other peri-third-ventricular structures allow the surgeon to select the surgical approach most likely to achieve total resection. With improving MRI technology, CT contrast cisternography has become obsolete, and angiography should only be ordered if an aneurysm is strongly suspected.

Management

PRIMARY TUMOR, PREDOMINANTLY SOLID

Treatment Options. A rational approach to the management of primary solid craniopharyngio-

mas can be derived from the results of four treatment options.

TOTAL RESECTION. In skilled and experienced hands, total resection of solid craniopharyngiomas is feasible with low mortality and morbidity. The achieved/attempted ratio for total resection, composed of the number of cases in which the surgeon is satisfied that total extirpation of tumor was accomplished versus the number of cases in which total resection was attempted, varies between 30% to 90% among experienced surgeons using modern microsurgical techniques [9, 22–24, 33, 53–55]. The best record was that of Sweet's [22] who was able to remove the entire lesion in 40 out of 42 patients, but the realistic expectation for total resection is probably around 50% to 60%. It is important that a CT is performed 2 to 3 weeks after surgery to eliminate cases of "false cure," because even experienced surgeons have been known to leave behind tumor fragments that adhere to the underside of the chiasm or the hypothalamus, or within the sella [9]. The size of the tumor appears to influence the feasibility of total resection. Both Sweet [22] and Shapiro et al. [54] found that tumors larger than 3 cm in diameter are less likely to be resectable and have high late recurrent rates.

Some surgeons are able to boast no surgical deaths [24, 33, 56–58] while others have up to 8% operative mortality [59]. The overall operative mortality is probably around 2% to 3%. Most experienced surgeons are also reporting low incidences of post-operative neurological deficits [22, 24, 33, 54].

In spite of meticulous techniques and careful postoperative radiographic screening for false cures, a number of tumors will nonetheless recur after what has been deemed "complete" resections. This is probably due to regrowth of deeply penetrated tumor pseudopods that have been broken off from the dissection plane. Recurrences are usually detected 5 to 6 years after attempted total resection [9, 22] although Carmel et al. [33] described a late recurrence after 27 years. A long-term review by Katz [53] of Matson's original series [60] reported recur-

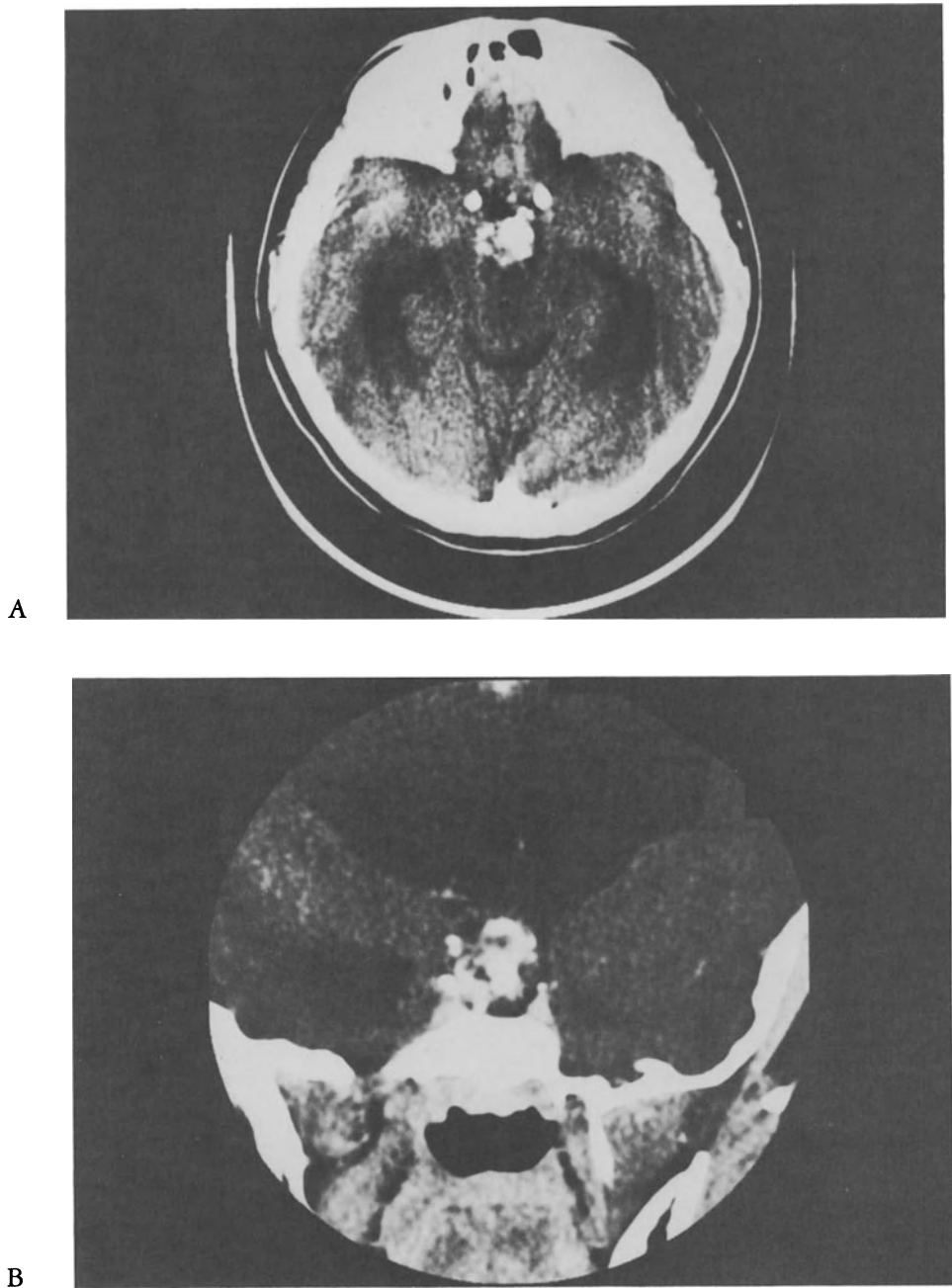


FIGURE 10-1. A. Axial CT of a calcified craniopharyngioma in a 13-year-old girl. B. Coronal view showing the relationship between tumor and the sella. The tumor reaches the level of the foramen of Monro to cause obstructive hydrocephalus.



FIGURE 10-2. Sagittal MRI of a 16-year-old boy with a large solid craniopharyngioma. Note elevation of the floor of the third ventricle, flattening of the basal hypothalamus, distortion of the mammillary bodies, and anterior displacement of the chiasm.

rences in 25% of patients after 4 to 19 years of follow-up, and most other series recorded similar late recurrence rates [22, 24, 33, 54, 55]. In spite of these recurrence rates, the ten-year survival rate of these patients are, without notable exception, well over 85%. Thus, the overall results of total resection for solid craniopharyngiomas are excellent. Obviously the associated mortality and morbidity and, to a certain extent, the recurrent rate are commensurate with the experience of the surgeon. Total excision should therefore be considered only in institutions where a large number of craniopharyngiomas are being managed.

SUBTOTAL OR PARTIAL RESECTION, WITHOUT RADIATION. In cases where only subtotal resection was performed (by choice or if total resection was abandoned because of technical difficulties) without postoperative radiotherapy

(RT), the rate of recurrence has been high. Although some long-term survivors have been reported [22, 24, 61–65] these are the exceptions rather than the rule. The combined recurrence rate for subtotal resection without RT gathered from several large series [9, 22, 24, 358, 59, 62–64, 66] is about 75%, and most recurrences occur within three years after surgery. The ten-year survival was only 25%, compared to 85% if total excision was achieved.

SUBTOTAL RESECTION, WITH POSTOPERATIVE RADIATION. In view of the difficulty and potential hazards involved in total resection, and the disappointing results with subtotal resection without RT, many surgeons are adopting a planned subtotal resection followed by postoperative radiation. This was initially suggested by Carpenter et al. [67] and later supported by the good results of earlier studies conducted by Kramer et al. [68] and Bloom [69–71]. Recent results with subtotal resection and postoperative radiation confirm beyond a doubt that this treatment option is far superior to subtotal resection alone in terms of both recurrence rate and long-term survival. For example, Manaka

et al. noted a ten-year survival of 76% with postoperative radiation versus 27% without radiation [66]. Shapiro et al. reported 80% ten-year survival and only 19% seven-year survival in the radiated and nonradiated groups, respectively [54]. Carmel also reported 87% versus 52% ten-year survival in the two groups, although he also found that 100% in the total excision group survived ten years [9]. He also found that the relapse-free survival rates were 75% after subtotal resection and RT, versus only 7% after subtotal resection alone.

External radiotherapy is usually delivered by a 3- or 4-field technique (two laterals and anterior or two laterals, anterior and posterior portals). Another common technique is to use a 180° rotation axis in the coronal plane. Both methods avoid excessive dose to normal structures lateral to the tumor. The most common field size measures 6 × 7 cm. The commonly used total adult and children dosage is 5500 to 6000 and 5000 to 5500 rads, respectively, fractionated over 6 to 7 weeks, with the daily dose not exceeding 200 rads. Even with these precautions, radiation is not without hazard. Harris and Levene [72] reported radiation-induced visual failure in five patients with craniopharyngiomas. Hypopituitarism, organic brain syndrome, dementia, and sensorimotor deficits have all been reported with radiation [23, 73–75], and Cavazutti et al. [68] recently added frontal lobe dysfunctions to the list in children with this tumor who had undergone RT. Furthermore, RT has also been etiologically implicated in mesenchymal tumors [76, 77] arising de novo within the field of treatment.

BIOPSY AND RADIATION. Most workers now believe that simple biopsy and cyst aspiration followed by RT is inferior to either total resection or subtotal resection and RT. Shapiro et al. [54] found that the five- and ten-year recurrence-free survival rates were 85% and 80%, respectively, for subtotal removal and RT, whereas those for biopsy and RT were only 62% and 50%. The figures from Sung et al. [49] and Manaka et al. [66] are comparable. Biopsy and

RT, however, still shows more promise than subtotal resection alone in controlling tumor growth [54].

The above data strongly support the conclusion that total resection is the ideal treatment for solid craniopharyngiomas if it can be accomplished with minimal morbidity. Not only does it spare the nervous system the risk of radiation necrosis, but recent long-term follow-up studies [27, 62] are beginning to show that subtotal resection even when combined with RT only delays and does not prevent eventual recurrence of the tumor, unlike cases in which the tumors had been completely removed. Thus, the surgeon should always aim for total resection at the outset, but must also be prepared to leave behind residual tumor in deference to preserving the hypothalamus or the great vessels. The patient should then receive postoperative RT. Cyst aspiration and limited resection should only be reserved for the old or the infirmed, advisably followed by postoperative RT to lengthen the recurrence-free period.

Preoperative Evaluation and Management. As soon as the diagnosis is made, the child should undergo complete endocrinological evaluation to establish a baseline against which the effect of subsequent therapy can be gauged. More importantly, preoperative testing may uncover hypoadrenalism and hypothyroidism that will contribute to intraoperative and postoperative morbidity unless promptly treated [33]. Subtle hormonal deficiencies may require challenging tests using arginine infusion, insulin-induced hypoglycemia, and thyrotropin-releasing hormone and LHRH administration [78]. An eight-hour partial water deprivation may be used to stress the pitressin axis if symptoms of DI are mild, although this information is probably only of academic value, since postoperative DI is almost universal.

Adequate thyroid replacement takes several days and should be started immediately. Steroid replacement can be done rapidly. On the night before surgery and early the next morning, the

child should be given three times the normal daily cortisol production (the mean cortisone production rate is 13 mg/m²/day for normal individuals over four months of age [79]) in the form of intramuscular cortisone acetate. During the operation, cortisol requirement can be maintained by a slow solucortef intravenous drip.

Detailed neuro-ophthalmological assessment is also important to follow the child's postoperative or postradiation visual status. Sometimes, the first sign of tumor recurrence is a decrease in visual acuity or development of a scotoma. Recently, intraoperative visual evoked-response monitoring, either with a flash component built into contact lenses or with wick electrodes directly applied to the optic nerves, has been used to minimize the incidence of intraoperative damage to the visual pathway.

Because of the recent interest in neurobehavioral syndromes following treatment of craniopharyngiomas [56,68], the author has been obtaining detailed preoperative neuropsychological testing. This includes the standard Wechsler Intelligent Scale for adult and children, the Wechsler memory scale and its modified form for children, verbal and nonverbal selection reminding tests, complex figure tests, and a variety of subtests to measure frontal lobe functions [68]. The entire battery takes an alert child about 4 to 5 hours to complete. The lower age limit for valid results is probably around six years, and there is no optimal test for younger children. These results are extremely important for monitoring the child's intellectual as well as psychosocial progress after initial treatment, and are currently a source of major controversy regarding whether radical excision or biopsy and radiation should be the treatment modality of choice for childhood craniopharyngiomas in children [56,68].

Finally, the magnitude of the therapeutic problem, the long-term prognosis, and the possible neurobehavioral sequelae following treatment should be discussed openly and extensively with the family before surgery. Parents must understand that their participation is vital

in the management of postoperative endocrinopathies, hyperphagia, obesity, memory deficits, and psychological maladjustment, to name a few. A conscientious social worker experienced in this childhood tumor and with psychotherapeutic leaning would be a valuable member of the treatment team.

Management of Hydrocephalus. Over 60% of children with craniopharyngiomas have obstructive hydrocephalus at the time of diagnosis. If the symptoms of raised intracranial pressure are not disabling, the author prefers to perform all the preoperative evaluations and preparations expeditiously without preresection shunting, and then put in bilateral external ventricular drains (EVDs), at the time of tumor resection to assist in brain relaxation. The drip chambers of the EVDs are set at physiologic levels after surgery for 3 to 4 days and then gradually raised to test the patient's CSF absorptive capability. Very often the hydrocephalus resolves after total or subtotal excision of the tumor, and the drains are removed. Permanent shunts are implanted only if hydrocephalus persists.

Not infrequently, children with large tumors and hydrocephalus present with acute neurological decompensation due to high intracranial pressure. The child may be lethargic, dehydrated from intractable vomiting and DI, and have subnormal adrenal and thyroid functions. In such cases, it is advisable to perform preresection ventricular shunting and defer the tumor resection so that the child's physiologic and hormonal homeostasis can be restored gradually over a week or so prior to major surgery. During this time, with resolution of headaches and vomiting and resumption of alertness, the child is also a better candidate for detailed neuro-ophthalmological evaluation and tedious neuropsychological assessment.

Surgical Approaches

THE SUBFRONTAL APPROACH. This is the author's preferred approach, since it can be used

as a single procedure for total excision of most craniopharyngiomas except for those eccentric large tumors that require staged procedures from several diverse angles. A bicoronal scalp flap is fashioned. A right osteoplastic frontal craniotomy is made so that the medial margin crosses the midline by 1.5 cm to gain control of the superior sagittal sinus. The frontal margin is flush with the orbital roof, and the lateral-posterior margin can be extended posteriorly to the sphenoid ridge if the pterional approach is to be adopted for certain parts of the tumor. Unilateral frontal lobe retraction is almost always adequate for exposure, and it minimizes the disastrous prospect of bifrontal damage with bilateral retraction. The right side is preferred for the right-handed surgeon.

The anteriormost portion of the superior sagittal sinus is doubly ligated and transected. The anterior falx is then completely detached from the crista galli to expose the interhemispheric fissure. For large tumors, it is always necessary to divide the right olfactory tract. Deep subfrontal retraction along the proximal olfactory tract will bring the right optic nerve and chiasm into view, at which time the prechiasmal cistern is quickly opened to allow egress of CSF. Time is well spent to patiently aspirate as much CSF as possible, for this allows the brain to sag backwards and reduces retraction pressure on the vital subfrontal deep nuclei. With gradual recession of the paraolfactory lobule, and with the falcial attachment removed, the surgeon eventually commands a completely unobstructed view of both optic nerves, both carotids, the entire chiasm, and the rostral optic tracts.

The lower pole of the tumor is now visible behind dense arachnoid adhesions between the optic nerves. Tumors with lateral extensions beyond the internal carotid can also be exposed by opening the proximal Sylvian fissure and retracting the temporal lobe backwards (the frontotemporal route). The tumor is first aspirated for fluid to reduce its volume, and the capsule is then opened in between the optic

nerves. Tumor is debulked through this inter-optic (prechiasmatic) space, and with collapse of the center, the capsule can be carefully peeled from the brain and optic structures in the plane between tumor capsule and arachnoid. Meticulously keeping the dissection within this plane will facilitate complete resection of tumor capsule and preservation of the brain and the surrounding large vessels [9]. A retrochiasmatic tumor often pushes the chiasm forward to make it appear prefixed, but this "prefixity" is lost as soon as further debulking allows the chiasm to sink down, thereby widening the interoptic space to enhance further tumor removal through this route.

The arterial feeders to the tumor from the anterior communicating and anterior cerebral arteries can be taken with impunity as long as the vascular supply to the chiasm and optic nerves is preserved. The lower pole of the tumor, even if it indents the diaphragma sellae, can usually be lifted up from it and removed. The upper pole of a small tumor can be grasped through the interoptic space and firmly pulled downward into the suprasellar cistern and then teased from its hypothalamic attachment. The lateral extent can be resected either between the optic nerve and carotid (the opticocarotid route), or lateral to the carotid within the proximal Sylvian cistern. Large calcium deposits must be crushed and removed piecemeal. The Cavitron ultrasonic aspirator may be helpful in the initial debulking, but cannot be safely used to remove the capsule. With alternation of these various routes, small tumors can usually be totally resected without traversing hypothalamic structures.

Many childhood craniopharyngiomas are very large and their upper poles often push the third ventricular floor upwards to reach the level of the foramen of Monro. The tuberal portion of the basal hypothalamus, from the mammillary bodies to the chiasm, is often stretched very thin and is actually coapted with the lamina terminalis to form a single membrane. Both the infundibular and supraoptic recesses are usually

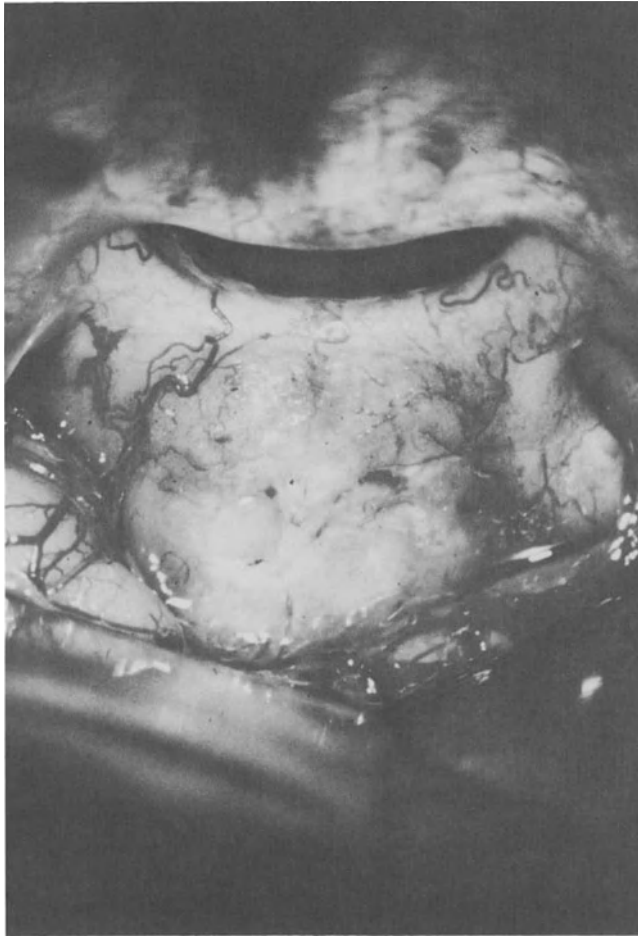


FIGURE 10-3. Intraoperative exposure of the lamina terminalis (same case as figure 10-1), greatly thinned out and pushed forward by the anterior dome of the tumor, which is showing through as a yellowish lobular mass. Note that the optic tracts are widely separated by the tumor and the vessels normally lying on the lamina terminalis are laterally displaced.

obliterated. It appears that the basal hypothalamic nuclei must be displaced laterally, because these children frequently do not have hypothalamic deficits, and traversing this coapted membrane usually produces no hypothalamic deficiency. The lamina terminalis is widely expanded behind the chiasm, and the yellowish gritty tumor can easily be seen through the diaphanous coapted membrane in between the laterally displaced optic tracts (figure 10-3). Puncturing

this membrane therefore provides access to the dome of the tumor in the retrochiasmatic cistern all the way back to the basilar artery without truly entering into the third ventricle. This translamina terminalis approach gives excellent exposure to the tumor dome, which can be dissected under direct vision from the hypothalamic floor and manipulated downwards to be removed either behind or in front of the chiasm [80]. The distorted pituitary stalk is recognized by its longitudinal striation due to the straight, parallel arrangement of the portal vessels [9, 33, 81], and it can occasionally be preserved by gently dissecting tumor off it. Most often the stalk is pushed anteriorly by the tumor and will be found and preserved early. The posteriorly displaced stalk is much more vulnerable to



FIGURE 10-4. The same view as in figure 10-3 after total resection of the tumor through the lamina terminalis, showing the tip of the basilar artery and the P₁ segments of the posterior cerebral arteries. Just in front of the basilar complex is the mamillary portion of the basal hypothalamus, having been pushed up and distorted by the tumor.

injury, since it is obstructed from view by the tumor bulk. The main tumor feeders from the posterior communicating arteries are divided at the lateral extent of this exposure, and the posterior pole of the tumor can often be dissected from the basilar and proximal posterior cerebral arteries with surprising ease, since these do not usually supply the tumor and are likely separated from the capsule by an intact membrane of Lillquist (figure 10-4).

If a large intrasellar component is present, it can be approached by drilling a window through the tuberculum sellae to enter the sphenoid sinus. The mucosa is preserved and pushed away to expose the anterior sellar wall, which is opened so that tumor can be directly extracted transphenoidally or pushed up into the retrochiasmatic space to be removed between the optic nerves. The sphenoid sinus is then packed with fat and fascia and the opening in the tuberculum closed by a dural flap.

STAGED PROCEDURES. Occasionally, lateral tumor extension into the choroid fissure cannot be adequately visualized by any of the above approaches to allow total excision by a single procedure. A second procedure using the sub-

temporal route is then necessary to remove the lateral portion after the main bulk has been resected. By itself, the subtemporal route is not recommended as a primary approach because of the high frequency of postoperative third-, fourth-, and sixth-nerve palsies. Also, the intrasellar portion of the tumor below the level of the diaphragma is not well visualized, and the approach does not permit either a transphenoidal or translamina terminalis option if they become necessary.

Because on coronal CT large craniopharyngiomas may appear to be completely within the third ventricle, they have been approached by the transcallosal route through the dilated lateral ventricle. In general, the CT appearance is misleading because the third ventricular floor, though grossly distorted, is still intact above the tumor, and a primary transventricular removal

from above has been associated with severe hypothalamic damage and poor results [18, 82]. With the very rare exception of the purely intraventricular craniopharyngiomas, this approach is only recommended as a second procedure if after the subfrontal operation a portion of the tumor is truly found to have penetrated far into the third ventricle and cannot be safely extracted from below. In this case, the transcallosal approach offers an excellent view of the residual tumor near the foramen of Monro, where adherence to large venous structures may make other less direct approaches hazardous.

Postoperative Complications and Management. Visual loss is the most common neurological deficit after radical or subradical excision. The preoperative visual status is the most important determining factor for subsequent visual outcome [33]. Children with total or near total blindness, particularly for longer than 3 to 4 days, do not usually regain any useful vision, but children with decreased acuity or constricted fields may improve after surgery. Another important prognostic factor is the duration of visual loss before surgery. Artero et al. [83] have shown that 87% of patients with visual impairment for less than a year showed some improvement after tumor resection, whereas only one third of patients improved if their visual symptoms had existed for longer than one year. In the series of Carmel et al. [33], 40% of children with total or subtotal resection had measurable improvement in visual function, versus 20% and 10% with visual deterioration following total and subtotal excision, respectively. In two of their patients, there was further worsening of vision following radiation therapy.

The degree of endocrine dysfunction is dependent on the aggressiveness of the surgery. With the recent push for total excision, treating hormone deficiencies has become an integral part of the total management of this tumor. DI is the most common postoperative endocrinopathy and also the one that requires immediate attention. In the series of Carmel et al. [33], all

children with total excision had DI, but only two thirds with partial excision had it. Hoffman et al. [24] have similar experience with their total and partial excision groups. DI sometimes occurs intraoperatively at the time when the pituitary stalk is transected. Excessive diuresis in the first few days after surgery is best treated with aqueous Pitressin®. If the long portal vessels on the pituitary stalk were damaged, there may be ischemic degeneration of the axon terminals in the neurohypophysis and release of stored antidiuretic hormone (ADH) 24 to 48 hours after surgery, with a rebound tendency towards water intoxication [9, 84]. This is of crucial importance in the postoperative patient with an edematous hypothalamus, and a short-acting ADH substitute is always preferable to Pitressin® tannate-in-oil. With the recent introduction of the intravenous form of desmopressin (DDAVP), postoperative DI is even easier to manage without the side effects of hypertension and renal shutdown associated with Pitressin®. Chronic DI can be satisfactorily managed with DDAVP nasal spray. It is interesting that although DI is almost universal after stalk sectioning, 10% to 15% of patients will regain partial production of ADH within two years, probably because of formations of new neurovascular units in the magnocellular portion of the supraoptic and paraventricular nuclei of the hypothalamus [85].

Corticosteroid deficiency due to loss of ACTH production is not a problem in the immediate postoperative period if preoperative steroids are given. The author prescribes high doses of synthetic glucocorticoids (such as dexamethasone) to control cerebral swelling. Because these have little mineralocorticoid effect, cortisone acetate in physiological doses is also used in addition. When it is appropriate to taper off the dexamethasone, cortisone acetate can be maintained indefinitely. Postoperative hypothyroidism requiring thyroid hormone replacement occurs in approximately 60%–80% of patients with total excision [5, 24, 86, 87]. FSH and LH deficiencies are also inevitable after total excision

[24, 86], and spontaneous puberty was not seen in Rougerie's series of 33 patients undergoing total resection [88]. Patients can be given synthetic estrogen and progesterone combinations at the expected age of puberty to impart secondary sexual characteristics and to mimic menstrual cycles, but sterility in females is permanent. Patients with a preserved pituitary stalk have been known to regain endocrine function much more fully and completely than those with stalk sectioning [5, 9, 89]. However, recovery of the exquisitely sensitive LHRH pacemaker function in the arcuate nucleus of the hypothalamus, vital to the induction of ovulation in females, has not been observed to date.

The growth rate remains low in most children following radical tumor resection because of growth hormone (GH) deficiency [90]. Growth can generally be maintained with GH replacement. In some children, however, the postoperative growth rate is normal or even faster than normal despite complete absence of measurable endogenous GH [79, 87, 90–94]. Growth associated with marked weight gain and hyperphagia can be attributed to hyperinsulinism [91, 92] and this certainly explains the continued growth in some of these children. However, Bucher et al. [95] found that 6 of 19 children with resected craniopharyngiomas and absent GH production had normal insulin level, but continued to grow normally because normal levels of insulinlike growth factors (IGF) (somatomedins) are sustained. IGFs are probably stimulated by increased prolactin secretion from the pituitary when the output of prolactin inhibitory factor from the injured hypothalamus is reduced. In contrast, six other children with pituitary infarction and low prolactin levels had correspondingly low IGF levels and retarded growth.

The most serious postoperative morbidity is due to severe hypothalamic damage, manifesting as hypersomnia, loss of thirst sensation, temperature dysregulation, profound amnesia, and disturbance of caloric balance [96]. With the advocacy of careful microsurgical tech-

niques, these florid syndromes are fortunately becoming less frequent [24, 33, 97, 98]. We are beginning to encounter milder versions of hypothalamic injury in children that are otherwise neurologically normal. One common neurobehavioral aberration is central hyperphagia. Seven of 16 of the large craniopharyngiomas resected by the author in toto by the translamina terminalis route had some degree of hyperphagia, but only in four was hyperphagia persistent and obesity a problem. The two most affected children, however, were seized with such an obsession with food and had such bizarre food-finding behaviors that they became pitiful social rejects. Sclafani and Berner [99] and Gold [100] recently postulated that central hyperphagia is due to injury to a serotonergic pathway originating from the anterior nucleus and preoptic area of the anterior hypothalamus. Limited trials with high tryptophan diet and serotonergic drugs, however, have not been successful in curbing appetite.

Another interesting neurobehavioral syndrome following total excision is abulia minor. The affected children have various degrees of slowness in motor action, ideation, and emotion. They lack spontaneity of action and thoughts, have slow and infrequent automatic body motions and gesticulations, lack enthusiasm to surroundings, show little exploratory behaviors, and have flat affects. They are unmotivated in play or school activities, and subsequently have poor progression in learning. It has been postulated that exploratory behaviors in animals and motivations in humans are related to the mesolimbic pathway projecting from the rostral midbrain to the medial septal nuclei, nucleus accumbens, and the anterior cingulate gyri [41, 42, 101]. This pathway could conceivably be injured by the deep subfrontal retractors during exposure of the lamina terminalis. Although Cavazzuti et al. [68] and Fischer et al. [56] reported a high incidence of frontal lobe dysfunction among children who had undergone radical tumor resection, others [9, 24, 55] have not noted this phenomenon. However, deficits

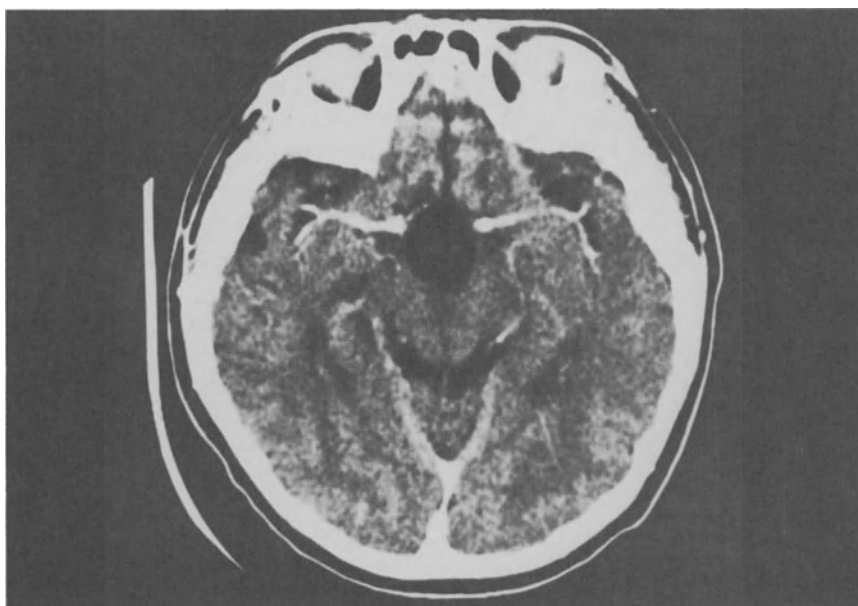


FIGURE 10-5. Postoperative CT (same case as figure 10-1), showing complete resection of tumor.

in short-term memory have been noted not infrequently. This is not surprising considering that the mammillary bodies are almost certainly manipulated during the dissection of the upper tumor capsule. Recently, Damasio et al. [102] have also demonstrated impaired memory retrieval function in patients with damage to the medial forebrain nuclei (an area just deep to the subfrontal retractor). They postulated that these nuclei serve a supplementary memory function by virtue of their intimate connections with the hippocampal system and wide areas of the association cortex [103, 104].

Postoperative Follow-up. A postoperative contrast CT should be obtained 2 to 3 weeks after surgery to detect whether any residual tumor is present (figure 10-5). Even experienced surgeons with meticulous microsurgical techniques are not exempt from leaving behind small pieces of tumor within operative blind spots, such as the underside of the chiasm and the anterior basal hypothalamus [9, 22, 80]. Residual specks of calcium or enhancing tumor fragments on the

immediate postoperative CT are indications for reexploration before exuberant scarring distorts normal anatomy and makes dissection more difficult. This should eliminate some of the cases of false cure that are reported in virtually every large series of craniopharyngiomas [22, 33, 80, 97].

If the immediate postoperative CT shows no residual tumor, or if the second attempt at excision accomplishes its goal, the next CT should be obtained in six months. MRI can be obtained as an alternate follow-up test, and it may be superior in delineating solid tumor from brain, but CT is more sensitive in picking up small calcium specks than MRI. Thereafter, a yearly CT or MRI should be adequate, since craniopharyngiomas are slow-growing lesions.

Complete endocrine evaluation including basal hormone levels and stimulation tests should be performed three months after surgery, to determine whether thyroid replacement should be continued. Cortisone replacement will almost certainly be necessary for at least one to two years, but the requirement for DDAVP may decrease after six months if the pituitary stalk was preserved at surgery [9]. At least a

year should elapse after surgery before it can be determined whether the child requires growth hormone injections, or whether normal growth continues due to sustained IGF levels. A low growth-hormone level has no bearing on the growth curve after craniopharyngioma resection [90, 93, 95].

Neuro-ophthalmological examinations should be done twice yearly. It is most useful for cases of known residual or recurrent tumor, when a subtle change in the visual field or acuity may signal a change in the growth status of the tumor before an actual increase in tumor size can be appreciated on CT.

It is convenient to utilize a check list of follow-up parameters at each six-month clinic visit. A complete neurological and ophthalmological examination should be recorded. The patient should be questioned about urinary output "breakthrough" in between doses of DDAVP so that dosage may be fine-tuned and recovery of endogenous ADH secretion capacity can be detected. All growth indices are measured. The body weight and the child's desire to eat are assessed. Weight gain may be due to excessive cortisone intake or to central hyperphagia, which responds partially to behavioral modification, psychotherapy, and serotonergic agents. An abridged neuropsychological evaluation should include a verbal recall test, complex figure duplication to assess nonlogic memory and spatial orientation and to detect perseveration, and object differentiation and proverb interpretation to measure frontal lobe function. The school record is a good indicator for the child's overall intellectual performance. It is also important to question the parents about the child's psychomotor activity level, willingness to participate in play and learning, enthusiasm to interact socially, and emotional tone. All things considered, uncontrolled eating and abulia minor remain the two most devastating handicaps to a child's psychosocial development following radical excision of craniopharyngiomas.

Stereotactic Gamma Irradiation. Recently, stereotactic radiosurgery using the gamma irradiation unit [105–108] has been showing some promise in controlling growth of small solid tumors and solid recurrences following aspiration of tumor cysts. The principle of radiosurgery is based on the fact that the biological effects produced by a single radiation dose are stronger than that produced by the same dose fractionated. Thus, if the radiation is delivered as a single dose to sharply circumscribed and precisely defined areas of tissue, tumor necrosis may be achieved with comparatively low doses [109]. The radiosurgery unit delivers 201 radially directed narrow beams of ^{60}Co gamma radiation towards a target region within a spherical sector. The system of apertures for each individual beam and the spatial arrangements of the ^{60}Co sources are designed to give oval-shaped dose distribution with very steep dose gradients in the border zones of the lesion, to minimize radiation damage to the surrounding optic pathways and hypothalamus. In order to adapt the irradiated volume to the shape of the tumor, a number of adjacent target points in a predetermined spatial pattern can be used [105]. For solid craniopharyngiomas, approximately 5000 rads are intended for the main parts of the tumor [110].

To date, only a small number of patients who had undergone this treatment modality are available for analysis. Backlund reported 9 patients with 15 years follow-up; four had solid residua following subtotal resection, and five others had solid tumor remnants after treatment of the cystic part by intracavitary ^{90}Y trium radiocolloid [111]. He reported no significant morbidity and "continued decrease in the bulk of the tumor" parallel with regression of clinical symptoms. A much more detailed look at a larger series of patients treated with stereotactic gamma radiation is needed to ascertain the long-term value of this therapeutic modality. At the moment, it is tantalizing as a nonsurgical alternative for small to moderate-sized solid cranio-

pharyngiomas, as well as for remnants found to be too hazardous to excise.

PRIMARY TUMOR, PREDOMINANTLY CYSTIC

Approximately 30% to 40% of craniopharyngiomas are predominantly cystic [54, 66, 108]. There are contradicting opinions in the literature regarding whether predominantly cystic tumors have better or worse prognosis than the solid ones [53, 54]. If the wall of the cyst is relatively thick and the maximum tumor diameter does not exceed 5 cm, total resection should probably be attempted. However, if the cyst wall is thin, the tumor may expand to enormous size and develop rambling pseudopods that insinuate into the substance of the frontal and temporal lobes. Total excision is difficult to achieve in these circumstances and may be associated with unacceptable surgical trauma to the brain.

Miles has advocated implantation of a catheter reservoir system into large cystic craniopharyngiomas so that periodic cyst aspiration can be performed whenever the tumor bulk produces symptomatic compression of the basal structures [112]. Others have supplemented cyst aspiration with external beam radiation [71]. While this is a viable alternative to more radical treatment for patients that are old and in poor general health, Shapiro et al. have shown that simple tumor biopsy and radiation carry a high recurrence rate and a short recurrence-free survival period [54]. Consequently, this treatment option is not recommended for children.

Intracystic Radionuclide Treatment

Swedish investigators at the Karolinska Institute have been using stereotactic instillation of beta-emitting radionuclide into the cavity of cystic craniopharyngiomas since the early 1950s [108]. The aim is to deliver a high dose to the inner cyst wall so that tumor cell necrosis can be induced and fluid accumulation arrested. The cyst volume can be estimated either by CT

volumetric analysis, or by a radionuclide dilution method in which a known quantity of a radioactive colloid such as Technetium ^{99m}S is stereotactically injected into the cyst and the cyst fluid–radiocolloid mixture later withdrawn for scintillation count. The radiation dose at the inner surface of the cyst wall is aimed at 20,000 to 40,000 rads, depending on the thickness of the wall, and the beta activity to be injected is determined by a beta-radiation dose formula derived by Loewinger et al. [113] utilizing the premeasured cyst volume and a volume–dosimetry factor from a function approximated for a spherical cyst [114]. Pure beta-emitting isotopes such as ^{90}Y and ^{32}P are preferred because beta rays have short tissue penetration, as opposed to ^{198}Au , which emits beta- and gamma energy and has been known to injure the surrounding hypothalamus [115]. ^{90}Y has a physical half-life of 2.67 days and a half-value tissue depth of 1.1 mm. As more than 95% of the radiation doses is delivered within the first five half-lives, decompression of the cysts can well be carried out about two weeks after the radionuclide injection, if required [73, 114]. ^{32}P has a longer half-life of 14.2 days but a shorter half-value tissue depth of 0.8 mm. It is a less desirable agent if evacuation of the cyst is necessary within a few days (as with impending visual failure), but is of value when the cyst wall is very thin [114].

The validity of the dosimetric determination is dependent on the assumption that the injected isotope has suspension stability within the cyst to remain homogeneous, that the cyst is spherical and unicompartmental, and that there is no change in the cyst volume during the exposure period. Most craniopharyngiomas are almost spherical, but some are multiloculated with 2 or 3 partially segregated compartments. In these cases, a separate dose calculation has to be made for each compartment [114]. Although leakage of the cyst content is theoretically possible through the puncture hole, Backlund [73, 114] and others [116–118] have shown that

leakage is in fact minimal in most cases. Leakage not only changes the planned dose to the cyst wall, but also carries the dreaded risk of radiation damage to surrounding vital structures. It can be detected by isotope assay in CSF and blood samples in the first few postoperative days, and if these determinations indicate a leakage, a profile diagram of the whole body or the liver can be performed [118].

Backlund reported experience with 14 cyst injections with ^{90}Y . The average follow-up was three years [73, 110]. In all cases, the dose aimed at the inner cyst wall was 20,000 rads. The CSF contamination was minimal and there was no blood contamination in any case. The procedures were well tolerated and most patients were ambulatory on the first postoperative day. All cases with symptoms and signs of increased intracranial pressure obtained almost immediate relief, and several patients had visual improvement. In four patients the preoperative cortisol requirement could be discontinued, and in three, the DI improved. All cysts have demonstrable shrinkage over time, and in three the suprasellar mass had dramatic regression.

The complication rate was low. Only one patient had partial unilateral blindness, one developed hypothyroidism, and two patients had mild psychiatric disturbances of "disregard and arrogance." A brief recent update of Backlund's series with up to 45 patients and a 15-year follow-up showed equally favorable results [98]. Another recent series reported by Kobayashi et al. [116] consisting of eight cases injected with ^{32}P and ^{198}Au also showed collapse and shrinkage of the cysts in all eight patients. Only one patient had an incomplete third nerve palsy, and one patient had a fatal recurrence 13 years later.

Intracavitary radionuclide may well prove to be the preferred treatment for large, rambling, thin-walled cystic craniopharyngiomas if a larger study continues to support its effectiveness in arresting tumor growth and if postoperative mortality and morbidity remain less than those associated with radical excision. A known

problem with intracystic radiation is the continued growth of a thick segment of the cyst wall that presumably has not received tumoricidal radiation dosage with this method. This can be either excised by an open procedure or treated by stereotactic gamma radiation [105].

RECURRENT TUMOR

When faced with a recurrent craniopharyngioma, the surgeon has three alternatives: radical surgery aiming at total excision; radical surgery followed by postoperative radiation (if prior radiation has not been given); and radiation alone if prior radiation has not been given. Sweet in 1980 described a series of 17 cases of recurrent tumors. Thirteen patients were referred after partial resections were attempted elsewhere, among whom Sweet was able to perform total excision in ten [23]. However, all four remaining patients who had recurrent tumors after Sweet's own prior attempt at total excision died after reoperation, three in the postoperative period of hypothalamic injury, and one of prompt tumor recurrence shortly after surgery. Sweet found that the original glial plane that separated the tumor capsule from the hypothalamus, the envelope that protected the hypothalamus and facilitated the first resection, was replaced by dense scarring that precluded safe dissection at reoperation. He concluded that a second attempt at total excision is fruitless and hazardous, and radiation alone should be given.

In 1981, Sung et al. [49] presented 22 children and 14 adults with recurrent tumors, and found that the five- and ten-year survival rates following radical surgery alone were 29.6% and 17.8%, respectively, whereas following radiation alone they were 77.8% and 75%. The five- and ten-year survival rates with surgery and postoperative radiation combined were the same, 70.9%, i.e., not much different from the results of radiation alone. They therefore recommended radiation as the sole therapy. However, when Carmel et al. [33] analyzed the results of only 22 children originally reported in Sung's series, they found that

the ten-year survival after either surgery or radiation alone was around 50%, whereas ten-year survival following a second attempt at total resection combined with postoperative radiation was 100%. Carmel also commented that total excision at reoperation was in some cases technically feasible, with only slightly higher risk than for the primary operation [9].

From these results, it seems reasonable for an experienced craniopharyngioma surgeon to undertake a second attempt at total excision of the recurrent tumor, with the knowledge that tumor fragments may be more adherent to vessel walls and hypothalamus than before, and that good common sense must be exercised to dictate how aggressive the dissection should be. Reoperation is especially recommended if the patient has already receive full-dose radiation during the first treatment, or if the solid component of a cystic tumor regrows following intracavitary radionuclide injection. If the surgeon is satisfied that a "total" excision of the recurrence has been accomplished, the patient should be followed by the same protocol as for primary solid tumors. If total excision was not possible, postoperative radiation should be given to control the residual tumor if radiation was never used before. If a patient returns a third time with recurrence after two attempts at total excision, or if an experienced surgeon is not available, a good case can be made for using radiation alone to prevent or slow further tumor growth.

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11. PITUITARY ADENOMAS IN CHILDHOOD

Dachling Pang

Incidence, Classification, and Pathology

Pituitary adenomas are exceptionally rare tumors in childhood. Whereas adenomas represent approximately 15% of all intracranial tumors in adults [1, 2], their incidence varies between 0.1% to 1.2% among pediatric brain tumors [3–5].

Pituitary adenomas can be classified according to their size and extent of involvement, endocrine function, and morphology. A microadenoma is less than 1 cm in diameter, usually contained within a radiographically normal-appearing sella. A macroadenoma is greater than 1 cm in diameter, often associated with an enlarged sella or with suprasellar extension. An adenoma is designated *invasive* if there is extensive destruction of bony structures around the sella or if the neurovascular contents of the cavernous sinus have been invaded. An adenoma can be called a carcinoma only if distant metastases are present.

Classification on the basis of endocrine function depends on whether the adenoma cells secrete specific hormones. Modern radioimmunoassay techniques can detect minute quantities of pituitary hormones in blood and tissues, and can determine whether the tumor secretes growth hormone (GH), prolactin (PRL), adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), or alpha subunits of the glycoprotein hormones.

Some pituitary adenomas are plurihormonal in that they produce more than one hormone. Others are null cell tumors because they appear to be nonsecreters. Recent immunocytologic staining shows that some of these endocrinologically silent tumors contain hormones but lack the ability to discharge them in sufficient amounts to affect endocrine equilibrium [6].

Progress in immunocytochemistry and electron microscopy has revolutionized the morphological classification of pituitary adenomas. Terms like acidophilic, basophilic, and chromophobic adenomas are no longer used because they give no indication of the biochemistry or cytogenetic origin of the tumors. Advanced immunoperoxidase techniques specifically and reliably demonstrate hormones in subcellular sites and permit close correlation between endocrine functions and cytogenesis of the tumor cells [2, 7]. Electron microscopy also reveals ultrastructural features that help in identifying hormonal function of the tumor cells by their characteristic secretory granules [2, 8].

Various series of childhood adenomas reported conflicting information concerning the secretory pattern and pathology of these tumors in children, but because of the small number of cases included in each series, the results must be carefully interpreted. For example, while over 70% of adenomas in adults are hormone secretors [2, 9], Raiti quoted 15 childhood non-secretory adenomas and suggested that childhood adenomas are mostly nonsecreters [10]. On the other

hand, over 70% of childhood adenomas reported by Richmond and Wilson are secretors [11]. Similarly, while Gaini et al. [11] described 15 cases of large invasive tumors among 17 children with adenomas and claimed that childhood adenomas tended to be more invasive, the series reported by Maira et al. [13] (six patients), DiRocco et al. [14] (13 patients), and Richmond and Wilson [11] (25 patients) documented 10% to 30% of invasive tumors, an incidence not dissimilar to that of adults. To date, there is no definitive evidence to suggest that the secretory and pathological behaviors of childhood adenomas are any different than those of adult tumors.

Clinical Features

Pituitary adenomas generally present in five clinical patterns: 1) headache; 2) neurological deficits due to tumor involvement of surrounding neural structures; 3) pituitary hypofunction due to suppression or destruction of functional anterior pituitary cells around the adenoma; 4) signs related to hypersecretion of hormone(s) produced by the adenoma; and 5) pituitary apoplexy.

HEADACHE

Headache is a common early symptom in adults with adenomas. It is not usually associated with increased intracranial pressure, but is most likely due to stretching of the pain-sensitive diaphragma sella or the dura lining the sella floor. The incidence of headache among children with adenomas varies between 8% to 100% [11, 14, 15]. This variability probably reflects the diverse ways in which children communicate their complaints to their elders.

NEUROLOGIC DEFICITS

The most common neurological deficit associated with pituitary adenomas is visual abnormality. This is usually due to suprasellar extension of the tumor and compression of the optic nerves, chiasm, or optic tracts, but can also be

related to disturbance of the blood supply to the optic apparatus [16]. Because the nasal and macular fibers course through the posterior half of the chiasm, a midline suprasellar tumor often causes bitemporal hemianopsia involving macular vision. However, virtually any combination of visual field abnormalities is possible [12]. Again, the incidence of visual failure among reported series of childhood adenomas is highly variable. In general, hypersecreting adenomas are less likely to cause visual problems because signs of hormonal hyperfunction usually present early when the tumor is still in the microadenoma stage, whereas endocrinologically silent tumors frequently reach large sizes prior to diagnosis.

Paralysis of the extraocular muscle is a relatively uncommon neurological manifestation of pituitary adenomas. When present, it usually signifies involvement of the cavernous sinus by an invasive tumor. The internal carotid artery offers some protection to the cranial nerves closest to it in the cavernous sinus, so that the oculomotor nerve is the most commonly involved, followed next by the abducens, and then the trochlear nerve [17]. Besides extraocular palsies, other neurological deficits such as hemiplegia [12] and personality changes due to compression of frontal, subfrontal, and temporal neuronal structures by tumors of massive size are exceedingly uncommon.

SIGNS OF HYPOPITUITARISM

Hypopituitarism in children with adenoma is most likely discovered because of growth failure. Thirteen of 15 children in the series of DiRocco et al. had more than two standard deviations less than expected height for age, and most of these also had blunted GH response to stimulation [14]. Another common feature is failure of sexual maturation among the adolescents. Fifty-two percent of Richmond and Wilson's patients have abnormally low Tanner staging and prepubertal response to luteinizing hormone releasing hormone (LHRH) challenge. Hypothyroidism and diabetes insipidus are

much less common, although preoperative assessment of these two hormonal axes must be thorough to avoid postoperative complications.

SIGNS OF HORMONE HYPERSECRETION

The prevalences of the individual types of pituitary adenomas in a representative large series, which includes patients of all ages, are as follows: prolactinomas, 29%, GH-secreting adenomas, 16%; corticotrophic cell adenomas, 14.4%; thyrotrophic cell adenomas, 0.5%, gonadotrophic cell adenomas, 3.3%, plurihormonal adenomas, 12%, and nonsecretory adenomas, 24.9% [18]. A much smaller series of childhood and adolescent adenomas shows comparable distributions of tumor types [11].

Hyperprolactinemia (serum PRL > 20 ng/ml) in patients with a pituitary tumor may occur as a result of autonomous overproduction by PRL-secreting adenoma cells, or through impingement on the hypothalamus and/or pituitary stalk so that the transport of PRL-inhibiting factor (PIF) from the median eminence to the adenohypophysis is interrupted, thus resulting in unrestrained overproduction by normal PRL cells. A PRL level > 150 ng/ml is almost certainly due to a PRL-secreting adenoma. In humans, PRL is essential for stimulation of breast tissue growth and for initiation and maintenance of lactation, provided that the glandular tissue has been appropriately primed by other hormones such as estrogen, progestins, corticosteroids, GH, and insulin. About 70% of women with high PRL have galactorrhea, whereas less than 5% of men with this tumor have this symptom, one reason why PRL tumors in men tend to be much larger than those in women at the time of diagnosis [19]. High serum PRL also disrupts the LHRH pacemaker mechanism in the arcuate nucleus of the hypothalamus and secondarily leads to cessation of the normally precise FSH/LH sequential output pattern necessary for the maintenance of normal menstrual cycles in women. Amenorrhea in postpubertal females with PRL tumors is almost universal, hence the classic syndrome of amenor-

rhea-galactorrhea in these women (Forbes-Albright syndrome). In men, inhibition of gonadotropin production due to high PRL levels leads to loss of libido. In addition, hyperprolactinemia has been shown to inhibit 5-alpha-reductase, which converts inactive testosterone to the biologically active dihydrotestosterone, a hormone necessary in high concentrations within the testicular tubules for normal spermatogenesis. This may explain some cases of male infertility associated with PRL tumors [20].

In the past, hyperprolactinemia was not considered a health hazard. However, Klubanski et al. recently described decreased bone density in 14 hyperprolactinemic women [21] and questioned the traditional view of hyperprolactinemia being a benign condition. In light of this new evidence, the prudent approach is probably to treat hyperprolactinemia whenever possible.

Patients who have elevated GH in childhood develop gigantism, with long arms and legs and nearly proportional increases in size of other body parts. In order for true gigantism to result, the onset of GH overproduction must occur in the preteen years. Once the epiphyses begin to close, excessive GH will produce acromegaly, with regional enlargement of bones and soft tissues rather than proportional lengthening of the limbs. In the series reported by Gaini et al. [12], only one six-year-old child had true gigantism and an 11-year-old and 15-year-old developed acromegaly.

In acromegaly, soft tissues in general enlarge. Excessive periosteal intramembranous ossification causes long bones to become thicker without gaining longitudinal growth, and membranous bones to become larger and more dense. Thus, the fingers, palms, and feet look massive compared to the rest of the body, and the facial features become characteristically coarse, with unsightly enlargement of the nose and lips. The crown of the skull becomes expanded circumferentially, and the jaw elongates and protrudes to result in severe malocclusion. The paranasal sinuses grow exuberantly, and the sebaceous

scalp takes on a thickened, corrugated look. Perhaps related to accelerated growth, the hypertrophic joints show early osteoarthritic changes and spinal stenosis may result. Thickening of ligaments and tendons cause multiple peripheral nerve entrapments, particularly carpal tunnel syndrome.

The most serious complications of acromegaly are related to the effect of GH on glucose metabolism and the cardiovascular system. Diabetes mellitus is a frequent finding. Proliferative changes in the myocardium and conducting system appear to cause a type of cardiomyopathy, and blood vessels in general undergo severe atherosclerotic changes. The combined effects of these changes lead to hypertension, cerebrovascular accidents, and early death. Recently, GH has also been known to affect the nervous system directly by interfering with certain peptide neurotransmitters; acromegalic patients appear to have a greater than normal incidence of epilepsy, dementia, and psychopathy [22, 23].

Of the three common pituitary hypersecretion syndromes, Cushing's disease, or hypercortisolemia due to a pituitary lesion, has the highest incidence of morbidity and persistence of symptoms after therapeutic intervention. Although ACTH-producing tumors are uncommon among pituitary adenomas, they constitute 30% of pituitary carcinomas reported in the literature [24, 25] and over 50% of invasive adenomas [26]. For these reasons, untreated Cushing's disease has a five-year survival rate of less than 50% [27, 28]. Death most often results from cardiovascular or infectious complications.

Females constitute over 75% of patients with Cushing's disease. The classic findings are moon facies, centripetal obesity, buffalo hump, thin skin, purple abdominal striae, ecchymoses, hyperpigmentation, and hypertension. Emotional disorders such as depression and psychosis are common. Adolescent females may present with menstrual irregularities, and symptoms of

glucose intolerance may give the first clue to the diagnosis of Cushing's disease. Occasionally, children may have such severe osteoporosis of their vertebrae that they present with catastrophic spinal pain due to pathological fractures or with rapidly progressive kyphosis.

Cushing's disease (hypercortisolemia due to a pituitary adenoma) must be distinguished from exogenous Cushing's syndrome (exogenous glucocorticoid ingestion), adrenal Cushing's syndrome (adrenal hyperplasia or adenoma), and ectopic Cushing's syndrome (hypercortisolemia due to an ACTH-secreting source outside the pituitary gland). Patients with the exogenous and adrenal syndromes have similar facies, acne, truncal obesity, and mental symptoms as those with Cushing's disease, but less than 20% will develop hypertension and none will have hyperpigmentation, since their ACTH is suppressed. Patients with the ectopic syndrome frequently have cutaneous hyperpigmentation due to the melanocyte-stimulating effect of their extremely high ACTH, but they also have a low incidence of hypertension. This puts in question the hypothesis that the hypertension in Cushing's disease has a hormonal basis. In many cases, hypertension, mental illness, and obesity persist despite adrenalectomy [29].

In the days when the popular treatment of Cushing's disease in children used to be bilateral adrenalectomy (in order to preserve other pituitary hormones), 8%–30% of patients returned months to years later with a characteristic triad of an enlarged sella tursica, elevated plasma ACTH, and bronze pigmentation of the skin (Nelson's syndrome) [30–32]. Although by definition these children do not have signs of hypercortisolemia, they present with headaches, visual abnormality, and cranial neuropathies due to a highly invasive pituitary tumor. It is generally agreed that the pituitary adenoma predated the initial manifestations of hypercortisolemia and that the sudden elimination of the suppressive effect of high peripheral cortisol following adrenalectomy leads to accelerated

growth of the ACTH adenoma. The lack of clinical signs of hypercorticoemia probably contributes to the late diagnosis of the pituitary lesion and allows exuberant growth of an already invasive tumor [33]. There does not appear to be any significant histopathological difference between the adenomas seen in Cushing's disease and Nelson's syndrome [2].

Thyrotropin- and gonadotropin-secreting adenomas constitute less than 4% of pituitary adenomas in adults [2, 18], and they are understandably rare in children. Only two cases of FSH/LH secreting tumors have been reported in children [14], both presenting with signs of precocious puberty, high estradiol and FSH/LH levels, and a postpubertal response to LHRH challenge. Other rare tumors are plurihormonal adenomas with more than one hormone secreted in excess. The most common combination is GH and PRL, produced either by mixed populations of somatotrophic and lactotrophic tumor cells, or by a single population of stem cells that presumably represent the common committed precursor of both GH and PRL cells. The patient will have prominent acromegalic features and signs of hyperprolactinemia, depending on the proportions of the two hormones [2]. Other even rarer combinations are GH and TSH; GH, PRL, and TSH; PRL and alpha subunit; or GH, PRL, and ACTH.

PITUITARY APOPLEXY

Rarely, a rapidly growing pituitary adenoma may outstrip its own blood supply and undergo ischemic necrosis, with resultant secondary hemorrhage [34]. The rapid expansion of the sella content causes sudden headache, nausea, and vomiting. Suprasellar and lateral extension into the cavernous sinus causes catastrophic visual compromise and ophthalmoplegia, respectively. If the hemorrhage has broken through the tumor capsule into the neighboring chiasmatic cerebrospinal fluid (CSF) cistern, the patient will present with signs of meningeal irritation such as stiff neck, fever, and photo-

phobia [35–38]. Rarely, these initial features may be followed by cardiovascular collapse due to acute failure of the ACTH–adrenal axis. Pituitary apoplexy constitutes a true neurosurgical emergency.

Diagnosis

RADIOGRAPHIC EXAMINATION

Computed tomography (CT) with intravenous contrast is a good starting diagnostic test if clinical examination suggests a pituitary adenoma. Thin axial sections of 1 mm thickness of the skull base and basal cisterns, and direct coronal sections of 1.5 mm collimation width from the planum sphenoidale to the clivus, will give a detailed survey of the sphenoid sinus, sella, suprasellar cistern, optic chiasm, hypothalamus, cavernous sinus, the internal carotid arteries, and the Circle of Willis. Asymmetry of the sella floor and subtle upward bulging of the diaphragma sella can be a clue to the laterality of a microadenoma not distinguishable by CT density from the normal gland and can be helpful information at the time of transsphenoidal surgery. The adenoma may enhance brightly, and its pattern of extrasellar extension, including carotid displacement, cavernous sinus encroachment, and sphenoid invasion can all be accurately assessed.

Magnetic resonance imaging (MRI) can display the anatomical relationship between any suprasellar tumor and the hypothalamus to better advantage than CT, and so should always be obtained when available. However, vascular and bony structures in the sellar and parasellar regions both show up as signal void on MRI, and therefore are better evaluated by CT. Intramural anatomy of the sphenoid sinus including its bony septae, important for the transsphenoidal approach, is also better visualized by CT.

Cerebral angiography, like plain tomography of the sella, is now seldom used as a diagnostic test for pituitary adenomas, except when a para-

sellar internal carotid aneurysm is suspected. This lesion is usually encountered in the older age group and is rare in childhood.

ENDOCRINOLOGICAL EVALUATION

For every suspected case of pituitary adenoma, pituitary function should be evaluated with two main objectives in mind: 1) to assess the competence of each hypothalamic–pituitary hormonal axis; and 2) to identify the hormone produced by a hypersecreting adenoma.

Assessment of Normal Pituitary Function. Each hormonal axis can be evaluated by measuring basal levels of the hormone and by assessing its reserve using provocative tests. GH is released in a pulsatile fashion by the adenohypophysis and serum levels are variable. In hypopituitary individuals, the mean basal level of GH can be marginal and nondiagnostic. GH reserve must therefore be tested, most commonly by insulin-induced (0.1–0.15 U/kg) hypoglycemia. In normal individuals, the plasma glucose usually falls below 40 mg/dl, and the GH level should be greater than 5 ng/ml. Because insulin hypoglycemia can also be used to assess ACTH reserve, it is the best single test for challenging both axes. However, it can be hazardous in patients with grossly impaired adrenal reserve, and it should also be avoided in the very young and very old, in those with cerebrovascular disease, and in patients with convulsive disorders. In these situations, GH reserve can be assessed by the arginine and L-dopa tests.

ACTH secretion follows a diurnal variation, being highest at 8:00 am and lowest at midnight. ACTH is difficult to measure, and plasma or urinary cortisol levels may have to be used to assess basal adrenal function. The mean plasma cortisol level of 4–6 samples collected over a 24-hour period should be 5–25 µg/dl, the urinary free cortisol should be < 100 µg/24 hours, and 17-hydroxysteroids should be 3–8 mg/24 hours. As mentioned, ACTH reserve can be demonstrated by the insulin hypoglycemic test, with the same restrictions as for the GH

axis. The peak stimulated plasma cortisol should be 2–3 times higher than the basal level. An alternative provocative test utilizes metyrapone, which inhibits 11-beta-hydroxylase in the adrenal cortex, thus blocking the conversion of 11-deoxycortisol to cortisol. The attendant drop in plasma cortisol releases ACTH, which in turn stimulates synthesis of 11-deoxycortisol and its metabolites, which can be measured in the urine as 17-hydroxycorticoids.

Basal thyroid function can be measured by the T₃, T₄, and free thyroxine levels. The free T₄ index is a good screening test because it takes into account both T₃ uptake and total T₄ in the serum. When these factors are low, TSH assay usually distinguishes between primary and secondary hypothyroidism. TSH reserve can be assessed following intravenous administration of thyrotropin-releasing hormone (TRH).

Basal PRL levels should be between 5–20 ng/ml. Lactotrope reserve can be tested by intravenous TRH, which should cause a 1–2-fold rise in PRL level within an hour. A blunted response with a low basal PRL level usually indicates inadequate PRL reserve, whereas an elevated PRL level with a subnormal response to TRH is consistent with a PRL-secreting adenoma.

The plasma levels of FSH, LH, estradiol, and testosterone can be meaningfully interpreted only if they are correlated with the age of the child. These hormone levels are understandably low or undetectable in prepubertal children, and they are variable in menstruating females, depending on the phase of their menstrual cycle. If low levels are found in the postpubertal patient, LHRH can be used to determine the adequacy of gonadotrope reserve.

The integrity of the neurohypophysis, i.e., the antidiuretic hormone (ADH) axis, can be evaluated by the standard water deprivation test.

Identifying Hypersecreting Adenomas. PRL levels greater than 20 ng/ml are abnormal. Besides PRL tumors, other common causes of

hyperprolactinemia include primary hypothyroidism (high reactive TRH output) and ingestion of phenothiazines. When the level is greater than 200 ng/ml, an adenoma is almost always found. The size of the tumor is roughly correlated with the level of serum PRL [39], although a microadenoma can secrete levels as high as 500 ng/ml. PRL levels > 800 ng/ml frequently imply an invasive tumor within the cavernous sinus where copious amounts of hormone are being discharged directly into venous blood [40].

In a pragmatic sense, no dynamic endocrine test is totally reliable for diagnosing a PRL tumor. TRH is an excellent stimulus for normal PRL cells but has virtually no effect on adenoma cells. While the normal response should be a 2–3-fold rise in PRL level, a flat TRH response is consistent with, but not exclusively diagnostic of, a pituitary tumor, since approximately 10% of patients with tumors demonstrate a measurable rise in PRL after TRH injection. Chlorpromazine also increases PRL levels in normal individuals, but not in patients with adenoma. It can be used as an alternate test agent, but the response tends to be even more variable. In general, provocative tests are not necessary if CT shows an adenoma or if the PRL level is over 150 ng/ml. Provocative tests are only indicated if the PRL level is only mildly elevated, or if the CT is equivocal.

In the acromegalic child, basal GH levels vary from 5 ng/ml to levels in the hundreds. When the level is > 40 ng/ml, a large tumor or even one with suprasellar extension and sphenoid sinus invasion may be present. A few acromegalic patients have levels in the low range between 4–10 ng/ml. Measurement of somatomedin C then becomes helpful in equivocal cases, since somatomedin C level is almost never normal in active acromegaly. The diagnosis is not in doubt if the hyperglycemia from an oral glucose tolerance test fails to suppress the hypersecretion of GH to levels below 5 ng/ml.

In Cushing's disease, the diurnal rhythm of the plasma cortisol is lost and the 24-hour urine

free cortisol and 17-hydroxycorticosteroids levels are elevated. In hypercortisolemia of adrenal origin, the ACTH is low, whereas in ectopic ACTH-secreting tumors, the ACTH is sometimes extremely high. With a pituitary ACTH tumor (Cushing's disease), the ACTH may be normal or only mildly elevated. ACTH level is therefore an unreliable indicator of the etiology of the hypercortisolemia. The definitive diagnosis of Cushing's disease is based on the failure of low-dose dexamethasone (0.5 mg orally, four times a day for two days) to suppress the level of cortisol by 50%, whereas a high dose (2.0 mg orally, four times a day for two days) is successful in suppressing it. Under these circumstances, a pituitary lesion is implicated with a confidence level of 90%. Patients with an ectopic ACTH-secreting tumor do not show suppression by either the high- or the low-dose dexamethasone.

In postpubertal children, gonadotropin-secreting adenomas should be suspected if the FSH/LH levels are high, provided there is no evidence of primary gonadal failure. However, a more common cause of high serum FSH/LH in children is precocious puberty due to causes other than an adenoma. TSH-secreting adenoma is suspected if the TSH level is high in the presence of clinical hyperthyroidism, and if TRH stimulation does not cause a rise in TSH.

MISCELLANEOUS EVALUATIONS

If CT shows suprasellar extension of the tumor, or if the patient has visual complaints, a detailed neuro-ophthalmological examination should be conducted to establish a baseline for monitoring the effect of treatment and for detecting early recurrences. Children with large suprasellar tumors compressing against the hypothalamus or frontotemporal structures should undergo a full neuropsychological evaluation. This is especially important if the subfrontal approach to the tumor is contemplated. Plain X-rays of the hands, feet, long bones, and skull can be obtained to determine bone age. Evidence of accelerated periosteal intramembranous ossifica-

tion in acromegalic patients may be seen on X-rays of the digits. Plain films of the axial skeleton will also demonstrate the osteoporosis and/or pathological fractures not infrequently seen in Cushing's disease.

Management of Specific Adenoma

PROLACTIN-SECRETING ADENOMAS

Three treatment options are available for PRL tumors: 1) medical therapy with bromocriptine; 2) operative extirpation through the transsphenoidal or transcranial route; and 3) radiation. PRL tumors are unique among pituitary adenomas in that they respond equally well to medical and surgical treatment, and so the choice between the two is not always clear-cut. Because radiation treatment generally incurs more problems among young children, this treatment option is usually relegated to the last in line when all else have failed.

Medical Therapy. Bromocriptine is a dopamine agonist that acts directly on lactotropes to inhibit their secretion of PRL. In 1978, Thorner and Besser [41] found that bromocriptine normalizes abnormally high PRL levels in over 95% of patients with hyperprolactinemia regardless of the etiology. Concomitant with this reduction, galactorrhea was abolished in 90% of women and normal ovulatory cycles returned in over 80%. These effects are generally evident within 1–3 weeks. In recent studies, bromocriptine has also been shown to cause reduction in tumor size in 60%–80% of large prolactinomas after as little as five days of treatment [42]. This tumor-reduction effect of bromocriptine is due not to a tumoricidal or antimitotic effect, but rather to its ability to shrink both the nuclear and cytoplasmic volumes of the tumor cells [43]. Patients so treated report few or no headaches, less visual disturbance, and, with time, improved libido and return of sexual function. The drug is well tolerated at the usual dosage range of 7.5 mg to 20 mg per day,

although a small number of patients experience nausea, vomiting, and light-headedness and have to discontinue treatment. The greatest drawback of bromocriptine therapy is that the beneficial effects only last as long as the drug is being administered. Upon withdrawal of treatment, the tumor promptly reexpands and the hyperprolactinemic state returns within a few days [44]. When used as primary treatment, bromocriptine must be continued indefinitely.

Surgical Therapy. Transsphenoidal microsurgery is ideally suited for microadenomas, macroadenomas confined to the sella, and adenomas with small suprasellar extensions. Depending on the consistency of the tumor, even large suprasellar extensions directly above the sella may be adequately managed by the transsphenoidal technique. Extension of tumor into the anterior and middle fossae is beyond the reach of the transsphenoidal exposure and is best managed by craniotomy.

The three main factors that influence the results of surgery for prolactinoma are tumor size, preoperative PRL levels, and the degree of invasiveness of the tumor. Numerous workers have shown that the best surgical results are obtained in patients with microadenomas [45–49]. Tumors with anterior and middle fossa extensions and/or invasion into the cavernous sinus are almost impossible to cure by surgery. PRL levels are closely related to tumor size; tumors associated with PRL levels < 200 ng/ml are usually microadenomas, and tumors associated with levels > 200 ng/ml are usually macroadenomas. If cure in prolactinomas is defined as normalization of PRL levels below 25 ng/ml, the cure rate with transsphenoidal surgery is 75%–80% if the preoperative PRL level is below 200 ng/ml; it drops to 30%–45% if the level is above 200 ng/ml [49, 50]. PRL levels higher than 1000 ng/ml are associated with intracavernous invasion and virtually never normalize after surgical treatment alone [40]. Among females with normalized PRL levels after surgery, over 70% will have

return of normal menstrual cycles, and almost all galactorrhea will cease [49]. When an experienced surgeon effects a gross, total removal of a microadenoma, the recurrence rate in five years is probably lower than 5% [48, 49, 51].

The operative mortality of transsphenoidal surgery in large centers is about 0.4%, and serious complications occur in another 2%–3% [20]. In general, it is a very safe procedure for children, except for those younger than four years when the size of the nasal passages preclude easy access to the sphenoid sinus. In terms of postoperative preservation of pituitary functions, McLanahan et al. [52] concluded that approximately 7% of patients will experience damage to one or more pituitary hormonal axes as a sequel to transsphenoidal surgery performed by an experienced surgeon.

Selection of Treatment. Despite the report of osteopenia in older women, prolactinoma is a relatively benign disease in children. The prevention of hypopituitarism and its far-reaching effects on growth and sexual development must be of prime consideration in the selection of treatment for hyperprolactinemic children. In children with PRL levels less than 150 ng/ml and a normal or equivocal CT or MRI, bromocriptine should be the primary treatment. In children with a radiographically demonstrable tumor confined within the sella or with minimum extrasellar extension, either bromocriptine or transsphenoidal surgery can be recommended, and the decision should be jointly made by the physician and well-informed parents. In young women with small adenomas who desire to become pregnant, transsphenoidal surgery is probably favored, since it achieves the best results without the potential ill effects of bromocriptine on pregnancy. Prolactinomas producing visual loss should be treated surgically without delay, as should the large tumors with extensive extrasellar spread. A high postoperative PRL level can be due to residual tumor or to damage of the pituitary stalk where PIF transport

is interrupted. It can be suppressed by bromocriptine indefinitely. Radiation therapy should only be considered if postoperative CT shows continued enlargement of residual invasive adenoma, if residual tumor is verified but the child cannot tolerate bromocriptine, or if bromocriptine is ineffective in suppressing high prolactin levels.

GH-SECRETING ADENOMAS

Treatment Modalities. All children with gigantism and acromegaly should be treated because of the associated high morbidity and mortality related to abnormalities in glucose metabolism and the cardiovascular system. Criteria for cure in acromegaly include clinical improvement, normalization of basal GH to below 5 ng/ml, and suppression of GH level to below 3 ng/ml during a glucose tolerance test. When the criteria are strictly observed, the results of transsphenoidal surgery are as follows [53]: patients with a preoperative GH less than 50 ng/ml and an adenoma less than 1 cm in size have a cure rate of 65%; those with GH level > 50 ng/ml or adenomas greater than 1 cm in diameter have a cure rate of 55%; and less than 50% of patients with invasive lesions enjoy a cure. If more liberal criteria are used for cure (GH < 10 ng/ml), satisfactory results are obtained in more than 90% of patients with microadenomas [54–56]. Thus transsphenoidal surgery is a safe and effective treatment for GH-secreting microadenomas, but its ability to achieve a cure diminishes with larger and more invasive tumors associated with high GH levels.

Conventional external beam radiation has been used as primary treatment for acromegaly in the past. The results from several large series showed that only 30%–40% of patients are cured by radiation, and the maximum GH-lowering effect does not occur until 1–2 years following treatment [57–59]. Although hypopituitarism is not a common sequelae in adults receiving the recommended dose range of 4000 to 5500 rads [60], radiation damage to

the other pituitary axes is not infrequently seen in children receiving concentrated radiation to their adenohypophysis [61]. Heavy-particle irradiation (e.g., alpha-particle and proton beam therapy) delivers large radiation doses to the adenoma and may achieve a cure rate (45%–60%) slightly higher than that of conventional radiation [62, 63], but it is associated with a 15%–25% incidence of hypopituitarism in adults [63] and maybe an even higher incidence in children. Because of the low rate of permanent cure, the long delay in achieving maximum therapeutic effect, and the danger of radiation injury to the immature nervous system, radiation therapy by whatever technique is not recommended as primary treatment for acromegaly.

Bromocriptine has been shown to cause significant lowering of GH in 60%–80% of patients with active acromegaly. However, less than 25% of these patients will actually have GH in the normal range or GH levels suppressible to below 3 ng/ml by a glucose load [60, 64, 65]. One advantage of bromocriptine treatment over surgery and radiation is that it leaves pituitary function intact. A number of GH adenomas will also show shrinkage with bromocriptine. However, discontinuation of treatment is followed by rapid elevation of GH to pretreatment levels and reexpansion of the tumor mass. Moreover, the daily dosage required to effect a response is often in excess of 30 mg, a dose level frequently associated with nausea, vomiting, and postural hypotension. Currently, bromocriptine is not advocated as primary treatment for acromegaly.

Selection of Treatment. Transsphenoidal surgery alone is probably the best treatment for acromegaly associated with microadenomas. Frequent postoperative monitoring of GH level is probably the most sensitive method to detect tumor recurrence. Return of high GH levels and abnormal responses to glucose loading with or without radiographic confirmation of recurrent tumor warrants treatment with external radia-

tion. All large tumors with extrasellar extension and local invasiveness are associated with a low cure rate by any single treatment modality and should therefore be treated by surgery and postoperative radiation. Bromocriptine is given to suppress GH secretion in the interim while waiting for the maximum effect of radiation to occur, which may take 2–3 years. A glucose tolerance test is ordered every six weeks to look for normalized GH physiology so that bromocriptine treatment may be discontinued. Bromocriptine is continued indefinitely if the GH levels remain high despite both surgery and radiation.

ACTH-SECRETING ADENOMAS

Cushing's Disease. Hypercortisolemia secondary to an ACTH-secreting pituitary adenoma is a very serious illness, not only because of the severe morbidity associated with high glucocorticoid levels, such as cerebrovascular accidents, hypertension, diabetes, gastrointestinal bleeding, and osteoporosis, but also because ACTH tumors are frequently invasive and occasionally carcinomatous, with a high propensity for recurrence. The goals of treatment are therefore, in order of priority, to reduce serum glucocorticoid levels rapidly, to eradicate tumor mass as thoroughly as possible, and, especially in children, to preserve pituitary functions. Ideally, a normal hypothalamic–pituitary–adrenal axis should be restored to avoid the necessity of replacement therapy.

Transsphenoidal surgery remains the primary treatment of choice for microadenomas. The cure rate is over 90% [33], and the reduction of cortisol is immediate. Even when larger tumors are included, several large series still report a cure rate of 75%–80% [27, 28, 66, 67]. The recurrence rate is less than 5%, the mortality and morbidity are low, and less than 7% of patients will have compromised pituitary function.

In cases of residual and recurrent tumors, or if no adenoma was found during sella exploration,

radical hypophysectomy has been recommended by some surgeons to consenting adults in order to minimize the possibility of sustained hypercortisolemia. In children, hypopituitarism should be avoided as much as possible. Jennings et al. found that external radiation was very effective in childhood Cushing's disease [15]. In their series of 15 children, 12 were cured of their disease within 18 months, and 10 of the 12 were cured within nine months. Moreover, all had preserved growth and sexual development, and all 12 cured children had normal adrenal axis with normal basal cortisol level and a physiologic response to metyrapone. No child had evidence of tumor recurrence up to 18 years after radiation treatment. Proton beam radiation gives an equivalent response rate, but the incidence of postoperative hypopituitarism is substantially higher.

While waiting for maximum response from radiation therapy, or if combined surgical and radiation therapy failed to suppress the hypercortisolemia, palliative medical management is used to reduce the deleterious effects of high circulating glucocorticoids. Cyproheptadine, a serotonin antagonist, and bromocriptine, a dopamine agonist, are thought to alter hypothalamic neurotransmitters that regulate corticotropin-releasing factor. Both have been shown to reduce ACTH release, and clinical remission occurred in a small number of patients with Cushing's disease [68, 69]. Recently, naloxone has also been shown to selectively suppress ACTH hypersecretion in Cushing's disease and Nelson's syndrome [70]. Other forms of drug therapy include aminoglutethimide, O,P'-dichlorodiphenyl-dichloroethane (O,P'-DDD), and trilostane. All three agents are toxic to the adrenal cortex by blocking certain stages of steroidogenesis, thereby preventing formation of the adrenal steroids, including cortisol. Because the block is complete, replacement of both mineralocorticoid and glucocorticoid is required when O,P'-DDD or aminoglutethimide is used.

Because the tumor in Nelson's syndrome is so often extensively invasive and responds so poorly

to treatment [27, 33, 71], bilateral adrenalectomy should be used to treat Cushing's disease only after all other therapy has failed.

Nelson's Syndrome. Contrary to previous belief, prophylactic radiation to the pituitary gland following bilateral adrenalectomy for Cushing's disease does not reduce the incidence of Nelson's syndrome [31]. Once established, the highly invasive tumor in Nelson's syndrome does not respond well to surgical resection. In most large series, less than 30% of patients undergoing surgery for Nelson's syndrome can hope to achieve remission of disease [28, 66, 67]. Even in children, pituitary function may have to be sacrificed in exchange for radical excision of the often extensive tumor. If obvious residual tumor is left, postoperative radiation should be given.

Technique of Transsphenoidal Surgery

This approach is ideal for microadenomas and small macroadenomas with limited suprasellar extension. Suprasellar extension as much as 15 mm above the diaphragma can usually be handled with this approach as long as it is directly above the sella. Tumors with anterior extension into the frontal lobe, lateral extension into the middle fossa, or posterior extension behind the dorsum sellae are better approached through a frontolateral craniotomy.

The patient is positioned supine with the head flexed 20° and tilted 30° laterally to the left. The nasal and septal mucosa is infiltrated with 0.5% marcaine and epinephrine (1:200,000) solution to minimize oozing of blood. A sublabial incision on the gingival mucosa is made from one canine fossa to the other, and the mucosa is subperiosteally elevated over both nasal floors and the right side of the nasal septum. The nasal spine is resected. The septal cartilage is detached from the midline palatine crest and from its posterior attachment to the vomer with a swivel knife. A double-bladed nasal speculum is introduced into the submucosal plane and the blades are widely opened,

pushing the superiorly hinged septal cartilage to the left. The sphenoid rostrum and the keellike edge of the vomer are then exposed.

In young children, the small nasal passages may require more forceful opening of the speculum blades with a special widener. This is especially true if acromegaly had caused hypertrophy of the turbinates. Sometimes, this maneuver causes diastasis of the maxillary syndesmosis; the maxillary bones usually reapproximate on removal of the speculum. Opening of the sphenoid sinus during the next stage is also more troublesome in children because the sinus is not well pneumatized before the age of 14 years. The bony septae and cancellous spicules often have to be removed by a microdrill before the sella floor can be exposed. The considerable oozing that follows can be tamponaded with Surgicel® (Johnson & Johnson, New Brunswick, NJ).

After opening the sella floor with a micro-punch, the dura is opened in a cruciate fashion. In children, there are often large venous lakes within the double-layered dural floor of the sella (the intercavernous sinus) so that profuse venous bleeding may occur on opening. Both leaves of the venous lakes must be grasped by the bipolar cautery and coagulated.

The different types of hypersecreting microadenomas are thought by Hardy to be located in fairly predictable areas of the gland [72,73]. The GH tumors are usually in the anterior portion of the lateral wings; the PRL tumors are in the posterior portion of the lateral wings; and ACTH tumors are in the central deep portion of the mucoid zone of the gland, just in front of the posterior lobe. Other authors are less devoted to this concept and have described a more randomized localization of microadenomas within the gland [20]. Nevertheless, the GH and PRL microadenomas are indeed more likely to be bulging out from the lateral contour of the gland; they can be easily curetted out since their consistency is normally soft or even gelatinous while the normal gland is tougher to feel. The ACTH tumors, in contrast, are often

hidden in the center of the gland and can only be found by making systematic horizontal and midline vertical incisions into the gland itself.

When dealing with macroadenomas with suprasellar extension, a lumbar subarachnoid catheter is inserted before the procedure. With aspiration and curettage of the central bulk of the macroadenoma, the superior capsule of the tumor often collapses towards the sella so that additional removal of the upper portion of the tumor can be achieved. The outline of the collapsed capsule can be visualized by fluoroscopy after 20–30 cc of air is injected into the basal cisterns via the lumbar catheter. Collapse of a stiff capsule may be aided by injecting saline into the basal cistern so as to accentuate the pulsations of the cerebrospinal fluid. However, 5%–10% of suprasellar adenomas are fibrous and can only be extracted piecemeal with a cautery loop.

After tumor removal, the cavity is lined with Surgicel®. If the cavity is large or if a CSF leak is present, it is patched with a fat and/or muscle graft. A nasal catheter is inserted into each nasal cavity and the extra space within the nasal passage is further packed with petroleum-jelly-impregnated gauze.

Complications of Transsphenoidal Surgery

The two most dreaded complications of transsphenoid surgery are intracranial hematoma and carotid perforation. Postoperative bleeding from the tumor bed is often due to residual tumor in inaccessible sites. A tortuous carotid artery may rarely be intrasellar and can be injured during curettage of the tumor. Bleeding from the carotid is often fatal, and even if it could be temporarily stopped, a carotid cavernous fistula may result several days later [74]. Damage to the hypothalamus can occur from vascular insufficiency or surgical trauma. Permanent visual loss occurs in less than 0.8% of cases [74]. Most cases are due to surgical trauma, but postoperative swelling of the intrasellar muscle or fat graft may cause delayed compression of the chiasm.

CSF rhinorrhea is rare with microadenomas but may occur with large tumors that had caused incompetence of the diaphragma sella or if the basal arachnoid is transgressed during dissection of the tumor dome. It is a potential cause of postoperative meningitis. Occasionally, CSF rhinorrhea does not occur until postoperative radiation has created an "empty sella."

Minor complications include nasal septal perforation, saddle nose deformity, nasal obstruction, and recurrent sphenoid sinusitis or mucocoele [75]. Most of these are avoidable with meticulous surgical technique.

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12. CEREBRAL HEMISPHERE GLIOMA

Melvin Deutsch

The cerebral hemisphere gliomas are found most often in adults, and thus childhood cerebral gliomas have not been extensively reviewed and reported, as have the other common pediatric intracranial tumors such as medulloblastoma, brainstem glioma, optic glioma, and cerebellar astrocytoma. In some reported series, the pediatric cerebral gliomas of a particular histology are included together with the same histological types of other sites such as the infratentorial region. Sometimes, series have been reported in which many different histological types have been included in the category of cerebral or hemispheric tumor without separately reporting data on the various histological types. Often, childhood cerebral gliomas have been included in reported series compiled of mainly adult patients. Thus, compared to the other common pediatric brain tumors, there is relatively little published material concerning the biology, treatment, and therapeutic results for the childhood cerebral hemisphere gliomas of all histological grades that compose a large proportion of childhood brain tumors.

Cerebral hemispheric tumors compose about one quarter of the childhood brain tumors [1, 2, 3]. About one half of the hemispheric tumors are gliomas of the astrocytic series. Often supratentorial gliomas are reported in a broad sense, including not only hemispheric tumors, but also the deep midline tumors involving the midline structures such as optic chiasm–hypothalamus and upper brainstem–midbrain. These latter types are the subjects of other chapters. This chapter will be concerned

with the gliomas (non-PNET, nonependymoma) involving the cerebral hemispheres.

The cerebral hemispheric gliomas can be divided into two broad categories: 1) biologically less aggressive or low-grade gliomas, often referred to as “benign”, and 2) biologically aggressive or malignant glioma. This division is appropriate, since the two groups differ in respect to clinical presentation, recommended therapies, and prognosis. Nevertheless, it is not a strict division. So-called histologically benign gliomas may behave aggressively, leading to early progression and death. Occasionally, the histologically benign tumor will transform into a histologically malignant and clinically more aggressive lesion over time.

Incidence

In a review of 275 cases of childhood brain tumors seen from 1968–1985, Jacobi and Kornhuber reported 70 cases (25%) involving the cerebral hemispheres–lateral ventricle region [2]. Of these latter patients, 21 had astrocytoma, 10 glioblastoma multiforme, 2 oligodendroglioma, and 3 gangliocytoma. Similarly, Laurent and Cheek reported that 54 of 203 childhood brain tumors occurred in the cerebral hemispheres, and of these, 15 were benign astrocytoma and nine “malignant” astrocytoma [3]. Three were ganglioglioma. Other hemispheric tumors in both series included primitive neuroectodermal tumor (PNET), ependymoma, sarcoma, meningioma, hamartoma, and metastasis. Yates et al. also reported that cerebral

hemisphere tumors composed 25% of childhood intracranial tumors [1]. In a review of 461 cases of children under age 16 years referred for radiotherapy with a diagnosis of intracranial tumor, Bloom stated that 88 had cerebral hemisphere gliomas (excluding verified ependymoma) [4]. However, this included tumors involving the third ventricle and hypothalamus. In 43 children with astrocytoma, histological grading was available. Seventeen had grade I or II tumors and 26 had grade III and IV tumors.

Dohrman et al. reported 43 cases of glioblastoma multiforme among 488 children with central nervous system primary tumors in the Connecticut Tumor Registry (1935–1973) [5]. Twenty-two (4.5%) occurred in the cerebral hemispheres. In their review of nine large series of glioblastoma multiforme patients reported between 1947 and 1967, children accounted for 0.6%–7.9% of the reported cases. Similarly, in their literature review of large series of intracranial neoplasms in children, glioblastoma multiforme of all sites accounted for 1.9%–10.7% of cases.

Oligodendrogliomas occur mainly in adults. However, in a series of 54 cerebral oligodendrogliomas reported by Chin et al., 16% had the onset of symptoms before age 20 years, although the diagnosis was often confirmed many years later [6].

In their review of the Connecticut Tumor Registry cases of primary central nervous system tumors from 1935–1975, Dohrman et al. identified only 12 children with oligodendrogliomas [7]. Eleven occurred in the cerebral hemispheres, representing less than 2% of the primary CNS neoplasms in this series of children. In Dohrman et al.'s review of the literature on oligodendroglioma, children made up between 5.9% and 15.9% of cases in series comprising more than 22 total patients [7], and in their review of childhood brain tumor reports between 1939 and 1977, oligodendrogliomas accounted for 0%–3.3% of cases. Mork et al., in a review of the Cancer Registry of Norway covering the years 1953 through

1977, verified 208 patients with oligodendroglioma, 17 of whom were ≤ 20 years of age at diagnosis [8]. Ludwig et al. confirmed a diagnosis of oligodendrogliomas in 323 patients in the files of the Armed Forces Institute of Pathology (AFIP) [9]. Six patients were ≤ 20 years of age.

Symptoms and Signs

The presenting signs and symptoms of a cerebral tumor are dependent on the site and size of the lesion rather than on histology. In general, a long history of symptoms and signs is more suggestive of a low-grade rather than a high-grade tumor. However, even a malignant glioma may have a long history of symptoms, which suggests the possibility that such tumors may have been mainly low-grade gliomas for a long interval. Today, it is unlikely that many patients with cerebral tumors are symptomatic for more than several weeks or months prior to being evaluated with computer tomography (CT) or magnetic resonance imaging (MRI). Prior to the availability of these noninvasive accurate imaging modalities, it was not uncommon for the diagnosis of low-grade glioma to be made after a many-year history of symptoms, usually seizures. Understandably, invasive procedures such as angiography and pneumoencephalography were not often done as screening procedures in the absence of definitive neurological deficits.

In a 1962 report on 20 children with cerebral astrocytoma (benign), Gol noted that 15 had headache and eight had seizures at diagnosis [10]. Eleven also presented with vomiting. Symptoms were present for 1–126 months prior to diagnosis. However, papilledema was noted in 80%.

Dohrman et al. reported the mean duration of symptoms for patients with cerebral glioblastoma to be 12.7 weeks [5]. All these children were diagnosed prior to the availability of CT scanning. Headache occurred in 85% and nausea and vomiting in 65%. Thirty-five per-

cent (35%) of patients presented with seizures. Less common presenting symptoms were paresis (25%), diplopia (25%), and lethargy (20%).

Mercuri et al., in a review of 41 children with cerebral hemispheric supratentorial astrocytoma, reported that vomiting was the most frequent presenting symptom, being present in 85% of cases [11]. Headache was presented at diagnosis in 62% of cases, and 55% of patients also had epilepsy. As in Gol's series, 85% had papilledema on physical examination. Less frequently noted neurological signs were pyramidal track signs in 40%, visual disturbance in 30%, cranial nerve disorder and sensory disorders in 20% each, and aphasia in 15%.

Ludwig et al., in their series of 323 patients of all ages with oligodendroglioma, reported that headache was the most common symptom and was present in 78.3% of patients; seizures were present in 70.3% [9]. Papilledema was present at diagnosis in 47.3%, visual loss in 49.4%, dementia in 45.5%, ataxia in 39.3%, and nausea in 38.5%. However, in the series of 208 patients reported by Mork et al., seizures were the most common presenting symptom and were present in 57% of patients, whereas headache was present in only 22% of patients [8]. Similarly, Chin et al. reported seizure activity in 86.5% of their patients (adults and children). Only 23% presented with headaches [6].

In the oligodendroglioma series of Mork et al., the median duration of symptoms prior to diagnosis was 20.5 months [8]. Twenty-five percent (25%) of patients had symptoms more than six years prior to diagnosis. Ludwig et al. noted that 45% of their patients had had symptoms for less than one year prior to diagnosis and 63% had had symptoms for less than three years [9]. In both of these series, the majority of patients were diagnosed prior to the availability of CT scanning. The most common site for oligodendroglioma is the frontal lobe, which is involved in about one half of all cases.

In a report on 11 children with oligodendroglioma, Dohrman et al. reported an average interval of 50 weeks (median 12 weeks) from

onset of symptoms to diagnosis [7]. However, three patients had symptoms for over ten years prior to diagnosis. The most common presenting sign was motor seizures, which occurred in 64% of patients. Nausea and vomiting occurred in 55% and headache in 45%. Also, symptoms referable to cranial nerve dysfunction occurred in 45% of patients. Papilledema was observed in 45% and paresis in 27%. Thirty-six percent (36%) of patients had no neurological deficit at diagnosis and were evaluated for seizure activity.

Diagnosis

The presence of a cerebral hemispheric tumor is readily confirmed by CT or MRI.

Prior to the availability of the CT scanner, the radiographic diagnosis of an intracranial tumor was made on the basis of plain skull radiographs, arteriography, or ventriculography. Today, routine plain skull radiographs are seldom performed prior to evaluation with CT or MRI. In 1962, Gol reported abnormalities on plain skull films in 15 of 20 children with cerebral "benign" astrocytoma [10]. Evidence of increased intracranial pressure was noted in 13 and calcification in two. Angiography and pneumoencephalography are very rarely performed once CT or MRI has demonstrated an intracranial mass lesion.

In a CT evaluation of a large brain tumor population consisting of adults and children, Kazner et al. reported that 150 of 153 astrocytomas (low-grade) were hypodense on precontrast CT. Enhancement after administration of contrast was seen in only two patients, both of whom had gemistocytic astrocytomas. About one half of 157 anaplastic astrocytomas were hypodense or isodense on precontrast CT. The remainder were hyperdense or of mixed density. About 80% showed enhancement with contrast. Seven hundred and eleven (711) glioblastoma multiforme tumors were evaluated with CT. About 80% were hyperdense or of mixed density on the precontrast CT. Ninety-

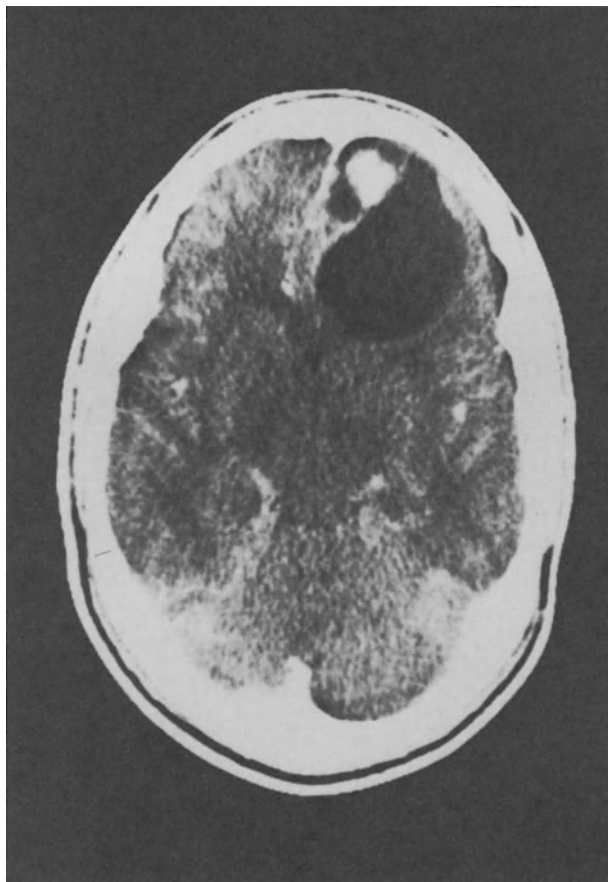


FIGURE 12-1. Sixteen-year-old male with headache for several weeks. CT and gross appearance at surgery suggested low-grade astrocytoma. Both the nodule and the cyst wall were glioblastoma multiforme.

seven percent (97%) showed contrast enhancement. Peritumor edema was rarely associated with low-grade astrocytoma, being noted in only 3 of 140 cases. Over one half of the anaplastic astrocytomas and at least 90% of the glioblastoma multiforme tumors had peritumor edema on CT [12].

Joyce et al. also reported that most low-grade supratentorial astrocytomas did not enhance with contrast, whereas 19 of 21 grade III–IV astrocytomas showed inhomogeneous enhancement. Only 3 of 11 grade I–II lesions showed enhancement. Practically all astrocytomas, regardless of grade, were hypodense on CT precontrast [13].

However, for hemispheric cerebral gliomas in children, the CT findings are not reliable in predicting histological grade. Pedersen et

al. recorded the CT findings of 15 childhood benign suprasellar astrocytomas, 11 grade I and four grade II, involving the cerebral hemispheres (nine cases) and deep midline structures (six cases) [14]. Eleven tumors were hypodense or isodense precontrast, but 14 of 15 showed enhancement with contrast. Peritumor edema was detectable on CT in only three cases. Calcification was not present in any case. A cystic lesion with a mural nodule suggests a low-grade glioma, but even glioblastoma multiforme may present with this picture (figure 12-1).

Seventy percent (70%) of 174 oligodendrogliomas were hyperdense or of mixed density

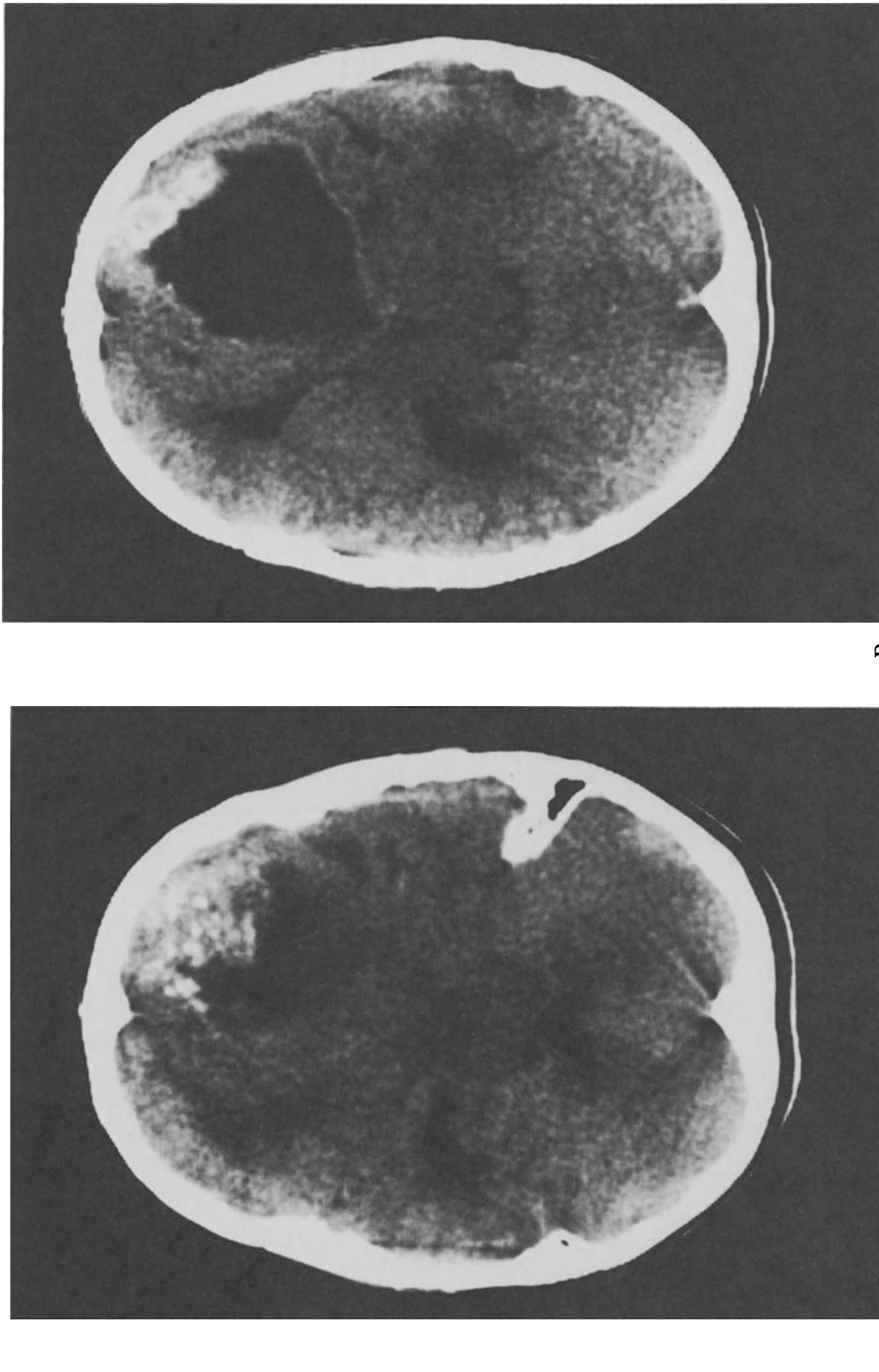


FIGURE 12-2. Unenhanced CT. Five-year-old male with oligodendroglioma. A. Extensive calcification. B. Large low-density region.

on precontrast CT [12]. Slightly less than half showed contrast uptake, and this was seen only in the anaplastic oligodendrogliomas. Calcification was noted in 70% of cases (figure 12-2). It was less frequently seen in the anaplastic oligodendrogliomas. In a review of 22 patients of all ages with oligodendrogliomas, Vonofakas et al. also noted calcium present in 20 cases (91%). All tumors showed areas of decreased density. Possible or definite cystic changes were noted in seven cases. Enhancement with contrast was observed in 14 of 22 cases, and all had histologic features of malignancy.

MRI may indicate more extensive low-density extension (tumor versus edema) than is apparent on CT.

With the availability of CT and MRI, it is unusual to see a child with a cerebral hemisphere glioma present with symptoms of greater than several months duration, regardless of histologic type.

Treatment

The indications for surgery in patients with supratentorial hemispheric gliomas are to establish the histological diagnosis by removing adequate samples of the tumor and to decrease tumor mass.

With stereotactic techniques, it is possible to obtain multiple samples of a tumor along a single trajectory path. This technique to establish a diagnosis is indicated for patients with tumors situated deeply in the hemispheres or with tumors in functionally important sites where surgical exposure poses the risk of neurologic damage. This technique is also indicated for establishing a diagnosis in patients unable to tolerate conventional craniotomy because of concomitant medical problems.

Resection of tumor, even if partial, not only provides tissue for diagnosis, but also may relieve mass effect and pressure on normal structures, thus improving the patient's neurological status. Theoretically, resection may reduce the number of tumor cells to a level more likely to

be beneficially affected by radiation or chemotherapy. Also, removal of the central necrotic core of a malignant glioma may decrease the number of viable but hypoxic radioresistant tumor cells. For adults with malignant glioma, there is substantial neurosurgical opinion that gross total resection should be attempted whenever feasible [16].

Shapiro has pointed out that resection of a malignant glioma is more likely to alleviate symptoms than to produce additional symptoms and that resection should be considered in terms of its role for producing immediate neurological improvement [16].

Low-grade Astrocytoma

For the low-grade glioma, total resection alone may suffice to provide long-term cure. Leibel et al. reviewed 147 patients of all ages with low-grade glioma [17]. Fourteen patients undergoing complete resection without postoperative radiotherapy were all alive at five years. However, 11 had cerebellar astrocytomas, but three were adults with totally resected cerebral astrocytomas. Fazekas also suggested total resection alone when possible as the treatment of choice for grade I–II astrocytoma [18]. The addition of postoperative radiotherapy after complete resection did not provide benefit in his series, which included all ages and sites.

Laws et al. evaluated multiple possible prognostic factors in 461 cases of low-grade astrocytoma of the cerebral hemispheres [19]. All patients had survived at least 30 days from operation. Age under 20 years at diagnosis was the most important prognostic feature. Eighty-three percent (83%) of this group survived five years, compared to a 35% five-year survival for patients age 20–49 years of age and only a 12% five-year survival for patients 50 years of age or older. A long prediagnosis symptomatic period (> six months) and the presence of seizures were associated with improved survival rates. Symptoms and signs at diagnosis associated with a poor outcome

were the presence of headaches, papilledema, altered consciousness, personality changes, and language deficits. Preoperative and postoperative neurologic and performance status also correlated well with outcome. Total resection conferred a better five-year survival (61%) than radical subtotal resection (44%) or biopsy/subtotal resection (32%).

For the patient with a subtotal resection of a low-grade glioma, postoperative radiotherapy appears beneficial. Of 108 patients with incomplete resection (all sites and ages) reported by Leibel et al., 37 had no postoperative radiotherapy and five- and ten-year survivals were 19% and 11%, respectively [17]. None of 19 patients available for 20-year follow-up were alive. For patients receiving postoperative radiotherapy after incomplete resection, the corresponding five-, ten-, and 20-year survival rates were 46%, 35%, and 23%, respectively. Total radiotherapy doses ranged from 3500–5500 rads. For cerebral astrocytomas, the five- and ten-year survival rates after surgery alone were 23% and 15%, respectively. After surgery and radiotherapy, the corresponding five- and ten-year survival rates were 35% and 24%.

Shaw et al. reported 49 patients ($5 \leq 18$ years old) treated with biopsy or subtotal resection and postoperative radiotherapy for a supratentorial low-grade glioma [20]. Two thirds of the patients received a total dose ≤ 5040 rads and one third received ≥ 5200 rads. For the total group, five- and ten-year survival rates (Kaplan-Meier) were 62% and 14%, respectively. Median survival was 6.5 years. The estimated five-year survival rates varied with the actual histopathology. For the five patients with pilocytic astrocytoma, the five-year survival was 100%. For 20 patients with oligodendroglioma or mixed astrocytoma–oligodendroglioma, five-year survival was 83%, but for the 24 patients with astrocytoma, it was only 40%. Radiation factors such as total dose and volume (whole-brain versus partial-brain irradiation) did not have an effect on survival. For 20 patients with treatment failure, preoperative and

postoperative CT scans, simulation films, and portal films were available. All developed recurrence within the radiation portal (ten whole-brain, ten partial). In ten patients with tumor progression, reoperation or autopsy revealed that four had transformation of their tumor to a higher grade. This report emphasizes that low-grade supratentorial gliomas, other than the pilocytic variety, are not truly benign. Although five-year survival is much better than that for high-grade glioma, very few patients are alive at ten years.

Mercuri et al., in reporting long-term follow up of 29 children with supratentorial hemispheric astrocytoma, noted that 17 cases had cystic tumors and that total removal was possible in 11 (65%) [11]. However, total removal was possible in only 2 of 12 cases with solid tumors. Of 11 cases with cystic tumors treated by total removal, there was only one death. The other ten patients were alive for at least five years at the time of the report. Two patients with solid tumors underwent total removal, and one was alive at greater than five years. Eleven patients received postoperative radiotherapy, but details of the radiotherapy are not presented. Six were long-term survivors. Of 15 patients with pilocytic astrocytoma, 13 were long-term survivors. Of 14 patients with non-pilocytic astrocytoma, nine were long-term survivors. In 13 cases, total removal was accomplished and there were 11 long-term survivors. Among the 16 cases undergoing partial removal, there were 11 long-term survivors. Of 17 cystic tumors, there were 15 long-term survivors. Of 12 solid tumors, there were seven long-term survivors. Thus, patients with the best prognosis were those with pilocytic tumors that could be totally removed. The authors recommend total removal as the treatment of choice, and for cystic tumors undergoing total removal, they do not believe that radiotherapy is indicated. For solid tumors, the pilocytic astrocytoma had a better prognosis. Only 1 of 3 patients with an oligoastrocytoma was a long-term survivor. The small number of

TABLE 12-1. Childhood low-grade supratentorial astrocytoma survival

Series	Tumor (#)	Treatment	Survival	
			5 years	10 years
Bloom [4]	Grade I, II (17)	RT	62%	48%
Laws et al. [19]	Age ≤ 19 years (52)	Surgery +/- RT	83%	
Farwell et al. [23]	Age < 20 years (27)		58%	
Gol [10]	Age ≤ 15 years (20)	Surgery +/- RT	5 operative deaths 15 alive, 9 ≥ 5 years	
Mercuri et al. [11]	All age ≤ 16 years (29)		75.8%	
	All age ≤ 16 years (13)	Total resection	85%	
	All age ≤ 16 years (16)	Partial resection	69%	
	Pilocytic (15)		87%	
	Nonpilocytic (14)		64%	
	Cystic (17)		88%	
	Noncystic (12)		58%	
Shaw et al. [20]	Adults and children (49)	Partial resection and RT	62%	14%

(#): Number of patients; RT: radiation therapy.

patients treated with radiotherapy in this series precludes comment as to its efficacy. Other reports have also documented a favorable outlook of adult patients with pilocytic astrocytoma of the cerebrum (table 12-1).

Palma and Guidetti reported a series of 51 cases of cystic pilocytic astrocytomas of the cerebral hemispheres [21]. Two thirds were in patients under age 20 years. Two patients died postoperatively. Of 35 patients available for long-term follow up, one died six years after surgery from uncontrolled seizures, but tumor was not detected by angiography. All other patients were alive at greater than five years from surgery. Only 12 had received radiotherapy. Therapeutic outcome did not depend upon excision of the cyst wall. Three patients were alive (one with recurrence) after two or more surgical procedures. Eighty-two percent (82%) of the long-term survivors were considered to be in "good" condition. The favorable prognosis for adults with pilocytic astrocytoma was also reported by Garcia and Fulling [22].

For a group of 88 children with cerebral hemispheric glioma excluding verified ependy-

omas, Bloom reported overall five- and ten-year survival rates of 45% and 38%, respectively [4]. In 43 patients, histological grading was available. Patients with grade I and grade II tumors had a 62% five-year survival. Patients with grade III and grade IV tumors had a 28% five-year survival. This was much better than the observed 6% five-year survival for adults with high-grade glioma during this time period. Seventy-nine (79) children actually completed radical radiotherapy for cerebral hemispheric glioma. For all histological types including unbiopsied presumed gliomas, children with tumors involving the cerebral hemispheres or lateral ventricles had a 43% five-year survival. Gliomas involving the third ventricle had a 71% five-year survival and those involving the thalamus had only a 28% five-year survival.

In Gol's series of 20 children with cerebral astrocytoma, there were five operative deaths [10]. Five of the 15 remaining patients received radiotherapy, since all had gross residual tumor. All 15 patients were alive 1–216 months with only one patient "possibly" having recurrence.

Farwell et al., in a review of childhood central nervous system tumors from the Connecticut

Tumor Registry, noted that cerebral hemisphere astrocytomas, grades I and II, had a 58% five-year survival [23].

Muller et al. evaluated 137 patients of all ages with supratentorial astrocytomas (low-grade) that recurred [24]. Using a histological classification consisting of three stages (I–III), 72 were initially stage I (least malignant) and 65 were stage II (intermediate). Only 14% of the initial stage I astrocytomas were unchanged at recurrence, but 55.5% had progressed to stage II histology and 30.5% had progressed to glioblastoma multiforme. Of the 65 initially stage II astrocytomas, 55.4% were still stage II histologically at recurrence, but 44.6% had progressed to glioblastoma multiforme. For the entire group (stages I and II) only 37.2% were histologically unchanged at first recurrence. No tumor became more benign. The median intervals between first surgery and reoperation or death were 31.5 months and 15 months for patients with astrocytoma initially stages I and II, respectively. For stage I tumors that progressed to glioblastoma multiforme, the median interval was 37 months. For stage II tumors that progressed to glioblastoma multiforme, the median interval was 12 months. Initial postoperative radiotherapy was not a factor in causing malignant progression.

Currently, there are several prospective cooperative group trials evaluating radiotherapy for low-grade supratentorial glioma in adults. The Mayo–North Central Cancer Treatment Group Study is evaluating 5040 rads in 28 fractions versus 6480 rads in 36 fractions as postoperative therapy. In all cases, radiotherapy is administered just to the localized tumor volume. Patients eligible for this study are those with “ordinary astrocytoma” (low-grade), oligoastrocytoma, or oligodendroglioma who have undergone any type of surgical resection. Patients with pilocytic astrocytoma are accepted if they have had only a biopsy. The European Organization for Research and Treatment of Cancer (EORTC) is carrying on two studies involving patients who have had less than total

resection for astrocytoma, oligoastrocytoma, or oligodendroglioma. In one study, patients are randomized between 4500 rads in 25 fractions to a localized volume versus 5940 rads in 33 fractions to a localized volume. The second study randomizes patients between observation versus 5400 rads in 30 fractions to a localized volume.

The Brain Tumor Cooperative Group (BTCG) is currently carrying out an evaluation of radiotherapy for low-grade supratentorial glioma in adults. This study compares radiotherapy administered immediately after pathological diagnosis with radiotherapy administered only at time of progression as determined by clinical and/or radiographic evidence. This study will also compare the quality of survival in patients receiving immediate radiotherapy with those receiving delayed radiotherapy. Patients will be eligible for this study if they have a pathologic diagnosis of astrocytoma, oligodendroglioma, mixed astrocytoma–oligodendroglioma, or well-differentiated glioma, not otherwise specified. Patients with juvenile pilocytic astrocytomas of the cerebrum will not be included in this study. Patients with disabling neurological signs or symptoms are excluded from randomization and treated immediately with radiotherapy. Radiotherapy is administered to the tumor volume as defined on CT scan as all contiguous regions of low density plus a 2 cm margin or defined by MRI scan as a 1 cm margin around all regions of high T2 signal. Fifty-four hundred (5400) rads is administered in 30 fractions. Patients randomized to immediate postoperative radiotherapy are treated within three weeks of diagnosis. Patients in the delayed radiotherapy arm are treated only at the time of tumor progression as determined by neurological examination, performance status, and radiographic findings. This study seeks to answer the question of whether or not radiotherapy for low-grade supratentorial glioma should be administered right after diagnosis or only at the time of disease progression. The end-points in this study will be length of sur-

vival and quality of survival as determined by neurological examinations and evaluation of mental status.

Oligodendroglioma

Oligodendrogliomas may benefit from postoperative radiotherapy, especially if incompletely excised. Chin et al. reported a five-year survival of 82% (9 of 11) in patients treated just by surgery versus a 100% (24 of 24) survival for patients treated with postoperative radiotherapy [6]. In the group receiving just surgery, there were six cases with proven or suspected recurrence within five years. In the postoperative radiotherapy group, five patients had suspected recurrence prior to five years. Sheline also demonstrated improved results for patients with oligodendroglioma treated with postoperative radiotherapy versus surgery alone [25]. For 13 patients treated by surgery alone, the five-year survival was 31%. Only 2 of 8 patients at risk for ten-year survival were alive. Eighty-five percent (11 of 13) of patients receiving postoperative radiotherapy were alive at five years and 55% (6 of 11) at ten years (table 12-2).

On the other hand, Reedy et al. found no difference in the five-year survival rate between patients with oligodendroglioma receiving postoperative radiotherapy versus those treated with surgery alone [26]. Ten-year sur-

vival data were not presented. There were only two patients in this series under age 20 years.

In the series of childhood oligodendrogliomas reported by Dohrman et al., ten patients had surgery and seven also received radiotherapy (doses and volumes not specified) [7]. At the time of publication, six patients were alive 5–13 years after treatment. There was no statistically significant difference in survival between patients treated with surgery alone versus surgery and radiotherapy. However, for the two groups of patients, extent of surgery was not noted and patients were not randomized.

In the series of Mork et al., there were 175 patients with oligodendroglioma who survived at least one month from surgery. Of this group, the five-year survival rate was 34.2% [8]. The median survival time was 35 months. By ten years, the survival of this group was about 10%. There was a trend towards improved survival in those patients undergoing total tumor excision as opposed to less extensive surgery. There was also a trend towards improved survival for patients under age 20 years as opposed to older patients. Median survival was 61 months in the younger group versus 37.5 months in the older patients. The median survival was 11 months longer for those patients who received postoperative radiotherapy as opposed to those treated by surgery alone.

TABLE 12-2. Oligodendroglioma survival: Patients of all ages

Series	Treatment (#)	Survival	
		5 Years	10 Years
Chin et al. [6]	Surgery (11)	82%	
	Surgery + RT (24)	100%	
Reedy et al. [26]	Surgery (21)	67%	
	Surgery + RT (27)	63%	
Mork et al. [8]	Surgery +/- RT (175)	34.2%	10%
Sheline et al. [25]	Surgery (13)	31%	25%
	Surgery + RT (13)	85%	55%
Dohrmann et al. [7] (all children)	Surgery +/- RT (10)	6 alive 5–13 years	

(#): Number of patients; RT: radiation therapy.

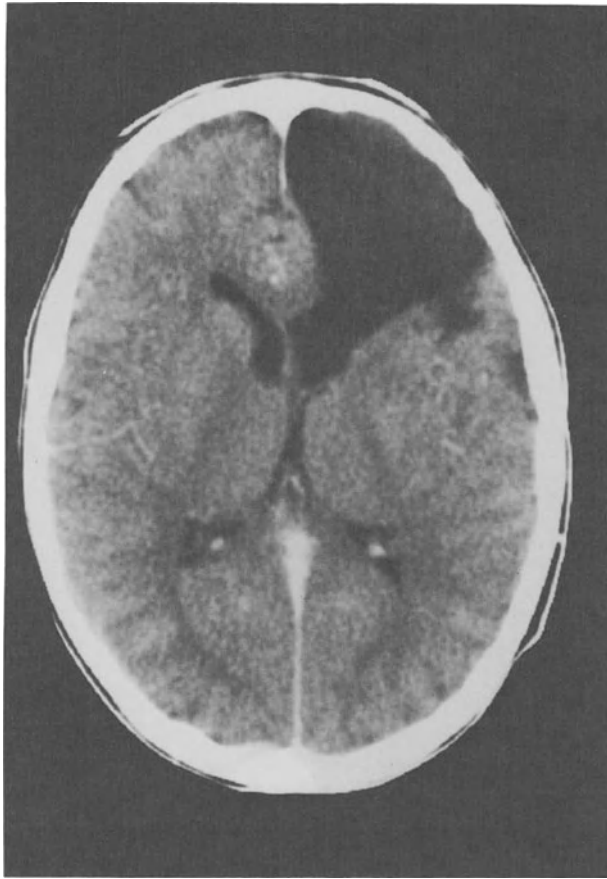


FIGURE 12-3. Same patient as in figure 12-2. CT with enhancement after gross total resection of oligodendroglioma.

Ludwig et al. classified their series of oligodendrogliomas in four different grades (A–D) based on the amounts of endothelial proliferation, necrosis, nucleus/cytoplasmic ratio, cell density, and pleomorphism [9]. Tumors with the least amount of these features were judged to be grade A, whereas tumors with all of these features were grade D. The duration of symptoms prior to diagnosis did not correlate with tumor grade. The median survival for the entire group was 53 months. The median survival after diagnosis for grade A patients was 94 months, grade B patients 51 months, grade C patients 45 months, and grade D patients 17 months. For grade A patients, the five-year

survival was 71%, for grade B 45%, for grade C 43%, and for grade D 0%. There are no large series of childhood in oligodendrogliomas in which this histological grading system has been used.

Muller et al. reviewed 52 cases on oligodendroglioma of all ages that subsequently recurred [27]. Using a histological staging system that graded tumors from I to III, 23 tumors were initially stage I (least malignant) and 29 were initially stage II (intermediate). At recurrence, six of the stage I oligodendrogliomas remained histologically unchanged, but 15 were histologically stage II and two were glioblastoma multiforme. Of the 29 initially stage II oligodendrogliomas, six were glioblastoma multiforme at recurrence, 20 remained as stage II, and three were oligoastrocytoma stage

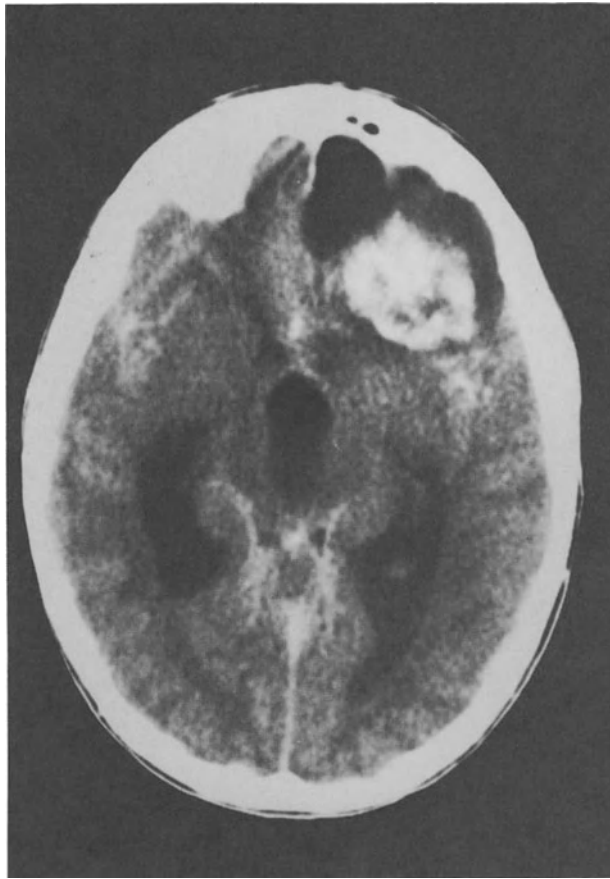


FIGURE 12-4. Same patient as in figures 12-2 and 12-3. Recurrent tumor after total resection alone. Tumor at recurrence had histologic features of malignancy.

II. The median time from diagnosis to recurrence in the stage I oligodendrogliomas was 42 months versus 22 months for the stage II oligodendrogliomas. Only 17 patients had received radiotherapy initially. The authors believed that radiotherapy did not promote malignant change.

For children under age three years with low-grade or benign glioma, the author prefers to delay radiotherapy, especially if the surgeon believes a gross total excision has been accomplished and postoperative radiological imaging suggests complete removal (figure 12-3). Even after partial removal in the young child, radiotherapy will be delayed if possible until the child is at least three years of age. Such cases are watched closely for evidence of recurrence or progression (figure 12-4). Physical examin-

ation and imaging studies are repeated at 4–6-month intervals. For all other patients, postoperative radiotherapy is administered unless gross total removal is considered likely as determined by the neurosurgeon's assessment and postoperative imaging studies. Radiotherapy is administered only to the area of initial involvement. Total doses of 5000–5500 rads are administered at 160–180 rads per day.

Although there is a suggestion that chemotherapy may be beneficial in children with low-grade optic chiasm glioma [28], chemotherapy has not been evaluated to any great extent in children with low-grade hemispheric gliomas.

TABLE 12-3. Childhood supratentorial malignant glioma survival

Series	Tumor	Treatment (#)	Survival	
			5 Years	10 Years
Bloom [4]	Grade III, IV	Surgery + RT (26)	28%	23%
Dohrmann et al. [5]	Glioblastoma multiforme	Surgery + RT (22)	4%	
Phuphanich et al. [39]	Malignant glioma	RT + C (27)	Median survival 180 weeks 45%	

(#): Number of patients; RT: radiation therapy; C: Chemotherapy.

However, Bloom reported 15 patients with low-grade malignancy (seven oligodendrogliomas and eight grade I–II astrocytomas) recurrent after initial surgery and radiation who were treated with a nitrosurea, and 11 (73%) showed a definite objective response to treatment [29]. The response rate was much lower for patients with recurrent high-grade astrocytoma.

High-grade Glioma (Table 12-3)

For high-grade cerebral gliomas, it is unlikely that resection alone, regardless of how extensive, would provide long-term survival. However, the high-grade astrocytoma study performed by the CCG reportedly demonstrated that the extent of surgical resection was a significant prognostic factor [30]. The prognosis was significantly worse for those children who underwent biopsy rather than partial or complete resection. But it is not clear whether the poor prognosis is related to the actual extent of resection or some other factors that may have prevented resection. It is possible that children undergoing just biopsy had more extensive tumors or were in poorer clinical condition.

Salazar et al. reviewed 148 cases of intracranial astrocytoma of all sites, ages, and grades [31]. All were treated with radiotherapy following surgery. For the grade III–IV astrocytomas, a total resection was associated with improved length of survival. There is a suggestion from the BTSG studies that more extensive resection is associated with longer survival.

Although high-grade gliomas may disseminate via the CSF pathways, the incidence is low at diagnosis and routine craniospinal axis irradiation is not indicated in the absence of proven dissemination. Until 1983, patients in the Brain Tumor Study Group (BTSG) protocols received whole-brain irradiation to 6000 rads in 6–7 weeks. Then, Brain Tumor Cooperative Group (BTCCG) protocols for newly diagnosed malignant glioma in adults required whole-brain irradiation, 4300 rads/25 fractions with an additional 1700 rads/10 fraction boost to the tumor volume as defined by the area of enhancement on CT scan plus 2 cm margin. In 1989, BTCCG protocols for adult malignant glioma were amended so that patients would be irradiated with large portals to adequately cover the tumor as determined by enhancement on CT scan plus a 3 cm margin. As much as possible of the normal brain is to be excluded from the high-dose volume. Many other clinicians recommend large-field irradiation for malignant glioma as opposed to whole-brain irradiation, and current Radiation Therapy Oncology Group (RTOG) protocols for malignant glioma use large fields defined as providing a 2 cm margin around the enhancing lesion and the peritumor edema to administer most of the radiation. Additional radiation is given to just the tumor as demonstrated by enhancement on the CT scan plus a 2.5 cm margin. In the current Children's Cancer Group (CCG) high-grade supratentorial malignant glioma protocol, radiotherapy is ad-

ministered to the tumor as demonstrated on CT scan with a 3–4 cm margin. For adults with malignant glioma, conventional radiotherapy entails 6000 rads in 6–7 weeks. In children with malignant cerebral glioma, the recommended dose is 5400 rads in six weeks at 180 rads per day. For children under age three years, a 10% reduction in dose is suggested.

Marsa et al. treated six children with cerebral hemispheric gliomas with radiotherapy, 5000–6100 rads [32]. Two children with glioblastoma multiforme died at four and 26 months, respectively. Of two children with astrocytoma, one died at 81 months and the other was alive at 55 months following a second resection for recurrent tumor. Of two children with mixed astrocytoma–oligodendroglioma, one died at 13 months and the other was alive and free of disease at 72 months.

Dohrman et al. reported a mean survival of 14.5 months from diagnosis for 43 children with glioblastoma multiforme at all sites [5]. Survival at one year was 45% but at two years was only 9%. Only one patient in this entire group lived ten years. Patients receiving surgery and radiotherapy did better than those receiving just radiotherapy. Patients who had received just surgery fared the worst.

In adults with malignant glioma, various fractionation schemes have been evaluated for the treatment of malignant glioma. The BTSG evaluated 110 rads administered twice daily to a total dose of 6600 rads [33]. There was no significant benefit as compared to conventional fractionation schemes. The Radiotherapy Oncology Group (RTOG) has been evaluating twice-daily fractions of 120 rads with doses up to 8160 total [34]. So far, although there does not seem to be any increased morbidity from these hyperfractionation schedules, there is no definite improvement in survival. Currently, hyperfractionation, 100 rads twice daily to a total dose of 7200 rads, is being evaluated in children with brainstem glioma, and preliminary observations indicate some possible improvement compared to historical controls [35].

For the most part, experimental radiotherapy modalities that have been tried in adults with malignant glioma have not been extensively evaluated in children with cerebral gliomas.

Chemotherapy has produced a small but statistically significant improvement in survival for adults with malignant glioma when added to radiotherapy. BTSG protocols demonstrated a slight improvement in median survival and survival at 18 months for patients receiving radiotherapy and a nitrosurea versus those receiving radiotherapy alone [36]. So far, no combination of chemotherapeutic agents has produced a significant advantage over BCNU alone when used after radiotherapy.

In children with malignant hemispheric glioma, there has been only one prospective randomized trial (CCG-943) evaluating adjuvant chemotherapy. This trial accrued patients for over five years from 1976 to 1981. In 1986, Allen et al. reported that there were 63 randomized patients in this study [37]. Forty-six percent (46%) were grade III and 42% were grade IV. Patients were to receive 5200 rads in 5½ to 6 weeks. Children under four were to receive 4500 rads in 5 to 6 weeks. Radiotherapy was administered to the involved tumor volume with a 3–4 cm margin on all sides. Both arms received the same radiotherapy. One arm also received chemotherapy. During radiotherapy, vincristine, 1.5 mg/M² was administered weekly for six treatments. Four weeks after radiotherapy was completed, patients in the chemotherapy arm received eight cycles of chemotherapy as follows: CCNU, 100 mg/M² on day 1, vincristine, 1.5 mg/M² on days 1, 8, and 15, and prednisone, 40 mg/M² per day, days 1 through 14. Four weeks later, the cycle was repeated. Allen et al. reported that disease-free survival in the chemotherapy arm at 30 months was 43.8%, while in the radiotherapy alone arm, it was 21.3%. The median disease-free survival for the chemotherapy arm was 25 months versus nine months in the radiotherapy arm. A later update by Finley and Goins in 1987 stated that there were 58 eligible patients

entered into this study and the five-year NED survival was 45% for the chemotherapy arm versus 13% for the radiotherapy arm [30]. As noted above, children who had only a biopsy as opposed to any surgical resection did worse. Also, the presence of mitosis or necrosis in the pathological specimen was associated with a significantly poorer outcome.

Currently, the CCG is carrying out a prospective randomized protocol for children with supratentorial malignant glioma. Both arms receive radiotherapy, 5400 rads/30 fractions over six weeks to the tumor volume and a generous margin. One arm receives the same chemotherapy regimen as in the previous study consisting of vincristine, CCNU, and prednisone. The second arm uses the 8-in-1 regimen of Bleyer et al. [38]. In this arm, the patient receives two cycles of this regimen prior to radiotherapy and then for eight cycles thereafter administered at six week intervals.

Other nonrandomized series have also indicated a possible advantage of chemotherapy for malignant supratentorial glioma in children. Phuphanich et al. reported on 27 childhood malignant gliomas seen between 1975 and 1982 [39]. Twenty involved the cerebral hemispheres and seven involved the thalamus. All had subtotal resection for biopsy. Fifteen patients received radiotherapy alone, and there was tumor progression in 14 with a median time to progression of 65 weeks. Twelve patients received radiotherapy and chemotherapy, usually a nitrosurea alone or with other agents, and there were seven patients with progression. The median time to progression was 130 weeks in this group. These differences are not statistically significant. Patients under age ten had a better prognosis than older patients. For all patients, the one-year survival was 80% and the five-year survival was 45%.

For children under age three years, considerations should be given to delaying radiotherapy. Currently, the Children's Cancer Group is evaluating the use of chemotherapy alone (8-drugs-in-1-day regimen) for infants with

radiation delayed until evidence of progression or when the child is over age three years. It is still too early to state whether or not delaying radiotherapy will prejudice the patient's survival.

Undoubtedly, children with cerebral hemispheric malignant gliomas do much better than adults, although the long-term survival rate is still less than 50%.

Salford et al., in a review of the Swedish Cancer Registry, identified six patients surviving more than ten years among 1147 patients with a histopathologically verified supratentorial astrocytoma, grade III or IV [40]. Of these six long-term survivors, three were children, age 7–11 years, at time of diagnosis. All had received radiotherapy, but none had received chemotherapy. Interestingly, two of these children had seizures for 4 and 5 years, respectively, prior to diagnosis. A third child had headache and vomiting for two weeks prior to diagnosis. It is not stated as to how many patients in the total group were children. However, the fact that 3 of the 6 long-term survivors are children indicates that the prognosis for children with supratentorial grade III or IV astrocytoma certainly is better than for adults.

Ganglioglioma

The term *ganglioglioma* was first suggested by Courville in 1930 [41]. The tumor is composed of ganglionic cells and glial elements. The ganglioglioma is a rare tumor more commonly found in children than in adults. Johannsson et al. reviewed 15 cases of ganglioglioma; 11 occurred in patients ≤ 21 years of age, representing 7.6% of central nervous system tumors seen in their pediatric population [42]. Sutton et al. reported 14 cases of childhood cerebral ganglioglioma, which represented about 4% of histologically proven brain tumors in their pediatric population [43]. Garrido et al. reported 14 children with ganglioglioma, which represented an incidence of 1.7% of their total

number of childhood central nervous system tumors [44]. In seven of these patients, tumor occurred in the cerebral hemispheres.

In the series reported by Sutton et al., presenting symptoms averaged 1.5 years in duration and ranged from 1–74 months [43]. Garrido et al. also reported a duration of symptoms from one month to ten years for their cases of cerebral hemisphere ganglioglioma [44].

The most commonly presenting symptom in the series of Sutton et al. was seizures, the type depending upon the site of the tumor [43]. Only 3 of 14 patients presented with headache. On CT examination, a low-density cystic area was noted in ten patients. Calcification was seen in only three patients.

Total resection is the treatment of choice. In the 14 patients reported by Sutton et al., ten underwent a total resection and with a follow-up of 1–66 months, none had developed recurrence [43]. Four patients had partial resection for biopsy and all received postoperative radiotherapy. Two required reoperation for recurrent disease. In the series of 14 patients, only one patient died. This patient's tumor involved the thalamus and had been treated with biopsy and postoperative radiotherapy.

Of the seven patients with cerebral hemisphere ganglioglioma reported by Garrido et al., all underwent partial resection [44]. Only two received postoperative radiotherapy, yet all were alive 1–11 years following surgery. These authors suggest radiotherapy only if there is histological evidence of malignancy.

In the series reported by Johannsson et al., 6 of 11 patients under age 21 years had cerebral hemispheric tumors and all received postoperative radiotherapy except for one patient who had just surgery [42]. All patients were alive 2–7 years following diagnosis. Administered tumor doses were not stated.

Total resection, if possible, is the treatment of choice, and in such patients postoperative radiotherapy is not indicated. Following incomplete resection, postoperative radiotherapy should be considered. In such cases, radiation

should be confined to just the tumor site and doses of 5000–5500 rads over six weeks should be administered. This would be similar to the treatment for low-grade astrocytoma or oligodendroglioma. For the young child, one might consider careful follow-up after incomplete resection, with radiotherapy delayed until evidence of progression.

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13. SUPRATENTORIAL PRIMITIVE NEUROECTODERMAL TUMORS

Paul M. Zeltzer

Sarah J. Gaskill

Arthur E. Marlin

Background

THE REIGNING CONTROVERSY IN NEUROPATHOLOGY

The primitive neuroectodermal tumor (PNET) of the brain has engendered significant controversy in neuropathology since it was named by Hart and Earle in 1973 [1]. They described 23 supratentorial tumors that did not fit distinctly into the then current histological classification of brain tumors. However, this humble beginning evolved into an academic debate that is still unresolved [2–7].

The purpose of this chapter is to give the reader a comprehensive understanding of 1) the context in which this tumor has been described, 2) its clinical features, 3) its pathology, 4) treatment methods for supratentorial PNETs, and 5) the basis for the diagnostic approach and follow-up.

ARGUMENTS FOR THE PNET

In the original report, the diagnoses of the tumors originally submitted to the Armed Forces Institute of Pathology (AFIP) for consultation were the following: cerebral neuroblastoma, cerebral medulloblastoma, undifferentiated tumor, malignant cellular ependymoma, and astroblastoma [1]. It was from this group of embryonal or poorly differentiated tumors that Hart and Earle selected their cases. As they point out in their article, the stage of differen-

tiation at which a tumor was called a PNET as opposed to when it had sufficient (glial or neuronal) “differentiated” characteristics to be called a glioma or neuroblastoma was arbitrary. They used 90%–95% undifferentiated component as their cutoff point.

Rorke and others have now generalized the concept of PNET and propose to simplify the classification of all childhood brain tumors, and the embryonal group in particular [3, 4]. The hypothesis underlying this approach is that neoplastic transformation of primitive neuroectodermal cells in subependymal zones at all levels of the central nervous system (CNS) may develop into tumors composed of similar cells. More specifically, it has been observed that tumors identical in appearance to the medulloblastoma of the posterior fossa can arise in the cerebrum, spinal cord, pineal region, and other sites. Thus derivatives of the external granular layer are not limited to cerebellar tumors.

It is conceded that the amount of (un)differentiation is arbitrary, and it is proposed that all tumors that appear small, round, and blue on routine histochemical stains of the brain in childhood be classified by the descriptive approach of Rorke [3, 4]. For example, if the tumor is mostly undifferentiated but with some neuronal features, it is a PNET with neuronal differentiation; for an undifferentiated tumor with some glial and ependymal features, it is a PNET with

glial and ependymal differentiation, etc. It is emphasized that this description is independent of location within the central nervous system.

Amid this controversy, it must be remembered that the original purpose of classification is to give prognostic information about the clinical behavior (natural history, response to therapy) of the tumor group being classified. When the therapies were ineffective, the classification was more of an academic exercise. Now over half of the children with medulloblastomas (i.e., infratentorial PNET) and one third of the supratentorial PNETs are surviving with modern treatment methods. A classification with predictive value for tumor response is thus desirable.

A potential practical application of classification is to predict which tumors may spread within and outside the neuraxis. Currently, we lack histopathologic correlates to predict neuraxis or extra-CNS axis spread.

ARGUMENTS AGAINST THE PNET

Against the adoption of a revised classification of embryonal childhood brain tumors that would include the PNET as a basis for classification are the following arguments [6, 7, 8]:

1. The definitions do not rest on a cytogenetic data base. By this it is meant that the classification does not acknowledge and in fact blurs the distinct differences in histology that have been described.
2. All the tumors are being placed in a "waste basket" category. The PNET was described as a group of tumors that did not fit into the current schema, and now the whole group is being categorized similarly.
3. The relative frequency of the tumors in different sites may be related to the window of time that the cells are mitotically active. The frequency of posterior fossa medulloblastomas (PNET) may be related to the larger number of cells dividing at a point in the migratory pathway during differentiation compared with the similar-appearing tumors in the pineal region or spinal cord. Placement of all the tumors in the same category does not lead to insights of causation or prevention.
4. Lastly, the purported diagnoses of PNET are being made on sometimes suboptimal specimens that may be unrepresentative of the entire tumor. While 50–100 g of tumor may be aspirated, sometimes only 1–4

TABLE 13-1. Age, sex, and survival of patients with supratentorial PNETs

Author, year	No. of patients	Mean age (yrs.)	Age range (yrs.)	Male	Female	Means survival (months)
Hart and Earle, 1972	23	8	0–24	15	8	18
Kosnik, 1978	18	3	0–10	8	10	6
Markesberry, 1979	3	16	7–24	0	3	—
Duffner, 1981	3	7	6–16	1	2	24
Baum, 1983	7	4	1–8	5	2	14
Bruno et al., 1983	6	7	0–14	3	3	13
Ganti, 1983	13	—	0–16	8	5	25
Jenkin, 1983	5	8	3–12	3	2	37
Knapp, 1983	2	2	2	1	1	—
Priest, 1983	12	5	1–13	3	9	50
Wald, 1983	9	5	1–8	3	6	19
Wara, 1983	10	10	2–26	5	5	36+
Ashwal, 1984	5	3	0–7	2	3	30
Crouse, 1985	1	7	7	1	0	—
Gaffney, 1985	18	17	0–35	11	7	36

TABLE 13-2. Locations of tumors and seeding of supratentorial PNETs at diagnosis

Author, Year	No. of patients	Frontal	Parietal	Temporal	Occipital	Ventricle	Hemisphere	Spine/Other	Seeding at diagnosis
Hart and Earle, 1972	23	9	4	4	2	1	1	0	
Markesberry, 1979	3	1	1	1					
Duffner, 1981	3	2					1		
Baum, 1983	7	3		1			1	2	
Bruno et al., 1983	6	1	0	1	0	2	1	1	
Ganti, 1983	13								3/13 2/5
Jenkin, 1983	5	1	2	2					
Knapp, 1983	2		2						
Priest, 1983	12	2	7				1	1	
Wald, 1983	9	2	5	2					
Wara, 1983	10	2	4		3			1	
Ashwal, 1984	5	1	1		1	1			1/2 3/18
Gaffney, 1985	18								

TABLE 13-3. Presenting symptoms of patients with supratentorial PNETs

Author, year	No. of patients	Mean duration of symptoms (months)	Headache	Emesis	Seizure	Eye signs	Hemiparesis
Hart and Earle, 1972	23		9	6	5	4	4
Kosnik, 1978	18	0.75 +					
Duffner, 1981	3	3.5	3	3	1	3	2
Bruno et al., 1983	6	0.25–3					
Ganti, 1983	13		+		+	+	+
Priest, 1983	12	2–10					
Wald, 1983	9	1					
Ashwal, 1984	5	1.5					

specimens may be taken for histopathology, and these may be suboptimally prepared and fixed for histomorphologic examination.

Presenting Features

AGE

The mean ages of 2–16 years differed among series, presumably on the basis of referral patterns. However, from most reports, this embryonic tumor appears at a mean age of six years [1, 9–22], with most occurring between 2 and 10 years of age (table 13-1). Most large series demonstrate a male predominance, which is also true for other brain tumors.

LOCATION

All areas of the brain are represented. In the combined series of 116 patients representing 13 reports, the frontal and parietal areas were identified most frequently as primary sites of tumor [1, 9–21]. Combined sites were mentioned in some series but not in others. The smaller series had somewhat different data, probably reflecting small sample size (table 13-2).

INCIDENCE

Because of series selection biases, the true incidence of the supratentorial PNET is difficult to document. The PNET as a percentage of all

childhood CNS tumors was approximated to be 2.5% [16] and 2.8% [18]. With the new proposed reclassification of embryonal brain tumors, the “incidence” of this diagnosis will surely rise [3, 4].

SYMPTOMS, TYPE, DURATION, SURVIVAL

The presenting symptoms were mentioned in a minority of the series, which were mostly pathology-, treatment-, or survival-based. As with other types of brain tumors, the duration and type of symptoms usually reflect the physical location of the tumor and/or its pressure effects (table 13-3).

The clinical picture is relatively nonspecific considering the large mass that is typically found at diagnosis. When mentioned, the symptom/sign complexes most commonly represented increased intracranial pressure, such as headache, emesis, papilledema, and seizures, and eye signs of proptosis, strabismus, and weakness/hemiparesis (focality). These represent mainly frontoparietal presentations. Poorly reactive pupils, personality changes, lethargy, ataxis, and nuchal rigidity were less frequent [9, 10] (table 13-3).

It was surprising that a few patients had prodromes of up to three years, considering that this is an aggressively growing tumor. The average was about one to three months.

The survival from start of symptoms was about 18 months, but among the series mean times were from 8 to 50 months. It was not

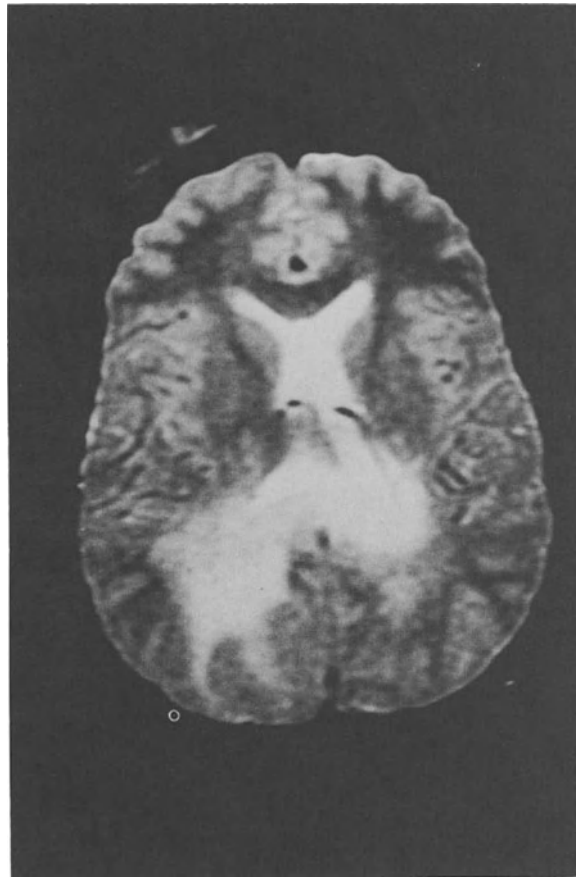


FIGURE 13-1. Fourteen-year-old male with supratentorial PNET crossing the midline to involve both cerebral hemispheres.

possible to determine the relationship between different treatments and survival (table 13-1).

Diagnosis

PRE-COMPUTED-TOMOGRAPHY-(CT) SCAN ERA

It must be emphasized that the majority of reported patients with PNETs were from the pre-CT-scan era. Many in the series had a mix of diagnostic studies consisting of arteriograms, pneumoencephalograms, brain scans, and CT scans. Myelograms were performed or reported only rarely. Thus we do not know the true

extent of disease at diagnosis or at relapse within or outside the intracranial cavity, since these studies were retrospective in nature.

Plain radiographs will show the nonspecific findings of increased intracranial pressure. Radioisotope brain scans demonstrate the lesion but do not usually add to CT scan findings. Angiography may assist in presurgical planning by identification of involvement and displacement of major vessels. Most of these procedures have been replaced by magnetic resonance imaging (MRI) and the computed tomographic (CT) scan (figure 13-1).

FEATURES ON CT SCAN

The first report that specifically described the CT features of PNETs consisted of 13 cases, 12 of which were supratentorial [23].

The reported tumor locations were in general agreement with previous reports. In addition, bony erosion was noted in one case. Neuraxis seeding was implied in 9 of 13 from the positive enhancement in the subarachnoid or ventricular areas. Irregular or coarse calcification was noted in 6 of 13. The scan characteristics of the tumors were described as both hyperdense and hypodense; both types had solid, necrotic, and cystic appearances. Most had very sharp tumor margins and minimal contiguous edema, differentiating them from gliomas, which tend to be invasive and hypodense. All 13 enhanced with contrast: 8 of 13 had solid and 5 of 13 had ring enhancement, the latter implying central necrosis.

TUMOR MARKERS

One patient with a pineal tumor and bony metastases was reported to have a minimal (two-fold) raised vanillylmandelic acid (VMA) and homovanillic acid (HVA) excretion. Another had raised levels of serum neuron-specific enolase [24]. One patient had minimal uptake of meta-iodobenzylguanidine (MIBG) (J. Dekraker, personal communication, 1986). In one series alpha-fetoprotein (AFP) was reported as positive, but this was probably a malignant teratoma or endodermal sinus tumor and not a PNET [19]. No other tumor markers have been described.

Pathology

BIASES IN CASE SELECTION

The retrospective assembly of cases reported to be PNETs are in fact heterogeneous. Hart and Earle's report included cases previously diagnosed as cerebral neuroblastoma and cerebral medulloblastoma, and undifferentiated small-cell neoplasm. And in one report, choroid plexus tumors, germinomas, and lymphomas were included [17] and only ependymomas and pineoblastomas were included for discussion of PNET. In yet another report, the cases were reported as central neuroblastomas [10], while in others, pineoblastoma and medulloblastoma

were not included [14]. In support of Rubinstein's critique of many cases having insufficient documentation, two reports [10, 16] did not include details of histopathological criteria or examples.

HISTOLOGIC FEATURES

Grossly, the PNET presents as a discrete and sharply demarcated tumor with an overall cystic quality. Large areas of necrosis are typically noted, as are areas of hemorrhage. The edge of the neoplasm may show some hypertrophic neuroglial reaction [23]. The tumor occurs in descending frequency in the frontal, parietal, temporal, and occipital lobes; only rarely is it bihemispheric [1].

Few reports included detailed descriptions of the histopathological features or how representative the tissue samples were of the entire tumor, e.g., how many samples of each tumor were inspected. It is not clear which studies used the 90%–95% undifferentiated criteria of Hart and Earle (table 13-4).

The cells are histologically malignant with little cytoplasm, moderate sized nuclei, and frequent mitoses. They are tightly packed in sheets or clusters with four basic patterns: collagenous, trabecular, alveolar, and focal perivascular rosettes. A mesenchymal component was also described [1].

Most studies report the presence of neuronal differentiation, but rosettes or large cells were the apparent criteria. Likewise, glial differentiation was described using Glial Fibrillary Acidic Protein (GFAP), Phosphotungstic Acid Hematoxylin (PTAH), or routine staining [25]. No consistent criteria were used. This difficulty is highlighted by the fact that 3 of 13 cases that were GFAP-positive (glial) had no cytomorphological evidence for glial differentiation [18] (table 13-4).

The data can be summarized collectively by saying that the tumors are characterized by variable-sized round blue cells that resemble the germinal matrix cells of the embryonic neural tube. Usually present are necrosis, endothelial

TABLE 13-4. Histopathologic features of supratentorial PNETs

Author, Year	No. of patients	Path unknown	Neuronal	Glial	Ependymal	Oligo	Necrosis	Mixed	Endothelial	Other
Hart and Earle, 1972	23		7/23	3/23				6/23		7/23
Markesberry, 1979	3		0/3	0/3	0/3	0/3	1/3		2/3	
Duffner, 1981	3		1/3	+	-	0/3	3/3	-	+	
Knapp, 1983	2		2/2	0/2	1/2	0/2	1/2	1/2		
Priest, 1983	12		0/11	1/11	5/11	2/11		4/11		1/11
Ashwal, 1984	5									+ AFP
Gaffney, 1985	18		9/18	11/18	1/18	7/18	13/18		14/18	

proliferation, and cells with variable expression of neuronal, glial, or ependymal (Flexner–Wintersteiner rosettes) features. Whether these are entrapped normal cells or examples of the neoplastic phenotype is unknown.

Electron microscopy reveals two prominent patterns [20]. The most frequent shows small nucleoli with the pars fibrosa greater than the pars granulosa pattern. There is scanty cytoplasm containing a small number of mitochondria and golgi, but numerous ribosomes and polysomes are present. Intracellular junctions are lacking. The second pattern has more cytoplasm with abundant mitochondria, golgi apparatus, and microvillous processes in addition to ependymal features.

The concept has been evolved by Kosnik [26] and others that the PNET cell (precursor) is multipotential. The putative cell then could give rise to all brain tumors defined by the mature cell types, including even a teratoma. Whether the central PNET is related to a histologically similar tumor arising in peripheral nerves [27] or to the so-called Askin or chest wall tumor with similar histological features [28] is an exciting hypothesis but as yet unproven.

Prognostic Features

HISTOLOGY AND TREATMENT

Several features of either the tumor or the treatment may have an influence on ultimate survival. At the time of initial surgery, there is unusually sharp demarcation of the tumor from normal brain. Interestingly, the completeness of resection at initial surgery was associated with prolonged survival in the collective series [29].

The perioperative mortality rate was quite high, even acknowledging that the reviewed series spanned over 20 years in some instances [16, 30]; 3 of 5 patients died within the first month [16]. The factors responsible for this were ascribed to the large size of the masses and the infant population. It was not stated whether the vascularity of the tumor was associated with

this complication.

The influence of histopathologic features on survival was examined by one author. All eight patients with histologically undifferentiated tumors were dead at 30 months, while 3 of 5 children with differentiated features were alive at 7, 9, and 11 years, respectively [18]. All long-term survivors also received craniospinal radiation and chemotherapy [18]. This contrasts with the data on medulloblastoma, in which any differentiation was associated with poorer survival [31].

METASTATIC SPREAD

The precise incidence of neuraxis spread of PNET at diagnosis or during therapy or relapse is unknown, since these data have not been systematically collected. For practical reasons, the natural history of the PNET is important to define in relation to other tumors of the neuraxis, since treatment strategies are dependent on this knowledge. The series in table 13-2 indicates that from 0%–33% had neuraxis dissemination either at diagnosis or during therapy. The mentioned sites include subarachnoid, skeleton, and cerebrum in addition to the cerebrospinal fluid. The marrow was not examined in this series. Thus the PNET group shares a natural history more in common with medulloblastomas than with anaplastic gliomas.

Treatment

SURGERY

The goals of surgery can be summarized as follows:

1. Intercede to preserve life with relief of increased intracranial pressure and mass effects
2. Remove as much tumor as possible and provide adequate tissue for the most accurate histological diagnosis
3. Repair structures to provide normal cerebrospinal circulation

After defining an intracranial mass lesion suggestive of a PNET, surgery remains the definitive diagnostic procedure and mainstay of treatment. Preoperative management consists of pharmacologic reduction of increased intracranial pressure with corticosteroids, diuretics, and if clinically indicated, the use of ventricular drainage.

The mass of tumor is usually discernable from the surrounding brain. The tumor tends to be soft and friable and is easily debulked using a Cavitron ultrasonic aspirator (CUSA). Laser techniques may aid in removal of tumor around vital structures, but in general are not necessary.

Extrapolating from the results with medulloblastoma, gross total removal is highly desirable and may even effect improved survival (A. Evans, personal communication, 1986). If gross total removal is not possible, debulking for future adjuvant therapy is advised. The extent of postoperative tumor removal should be assessed by CT scan with and without enhancement within the first six days to avoid postoperative artifacts. Myelography and cytologic analysis of lumbar spinal fluid is usually performed 7–14 days after surgery in order to evaluate the extent of disease and to plan for radiation therapy.

Postoperatively, if hydrocephalus persists, a shunting or diversionary procedure may be necessary. The use of Millipore filters to prevent micrometastases is still controversial [32].

The type of surgeries that were performed and how they may have influenced survival are difficult to document. Gaffney et al. report 2 of 15 biopsies only and 13 of 15 partial/subtotal resections [18]. Usually the type of resection will be dictated by the anatomic location of the tumor and the condition of the patient. Gaffney et al. reported that 5 of 5 infants less than one year of age at diagnosis who received subtotal resection and no additional (radiation) therapy died within eight months of diagnosis [18]. No other studies were available for comparison. We can conclude that more aggressive resection and adjuvant therapy will both be necessary for prolonged survival with this neoplasm.

RADIATION THERAPY

The gold standard for treatment of central nervous system neoplasms, even in young children [33], has been and continues to be radiation therapy. But its consequent neuropsychological toxicity on the maturing brain [21, 34–36] has prompted the search for a less toxic approach. Only recently has chemotherapy for brain tumors been demonstrated to be effective in adding survival benefit to that of radiation [37].

Review of the reported radiation treatments for PNET demonstrates considerable heterogeneity and lack of a standard approach. Local, whole-brain, and neuraxis irradiation all have been administered with a range of doses [9–11, 13, 14, 16–18]. Retrospectively, no one approach was clearly superior to the others. Over 4500 cGy tumor dose was administered to most children. However, both infants and older children received less for undefined reasons [33].

The reported series are remarkable for the early deaths (which are probably underreported) [11, 16] that are not due to radiation toxicities. No clear trend was apparent, in that both older children and infants were in the early death group.

Recommendations based on the available data are difficult to make. The CCSG is now treating all children with PNET over the age of 18 months with craniospinal irradiation. The Pediatric Oncology Group is reserving craniospinal therapy for children over 36 months of age. Generally this would consist of 5500 cGy to the tumor, and 3500–4100 cGy to the spine with 3500 cGy to the whole brain. In a retrospective analysis of radiation therapy using greater and less than 4500 cGy administered dose, no patient receiving less than 4500 cGy were long-term survivors [29]. In another study, the cutoff for survival in children less than five years of age was 4000 cGy [33].

CHEMOTHERAPY

Chemotherapy treatment for brain tumors is relative new. Compared to radiation therapy,

which has been used to treat cancer for over 65 years, chemotherapy has only a 20-year history [38]. It has demonstrated tumoricidal effects on histopathologically similar tumors (medulloblastoma) when used both as a single agent and in combination, as well as in the de novo and relapsed setting. Most of these early studies were prior to the CT-scan era, and the responses were based on subjective evaluation rather than objective criteria [39].

All the studies on PNET were retrospective and compared a variety of chemotherapy combinations plus radiation with radiation therapy alone. Bruno et al. used vincristine, a nitrosourea (CCNU), and prednisone with radiation in one patient who was a 3½-year survivor [16], while two other cases receiving radiation alone died. Two others died without therapy. Of six patients receiving chemotherapy (vincristine CCNU; or vincristine, prednisone, procarbazine and chlorambucil) plus radiation, one died at eight months and five were alive at more than 1, 1, 1, 2, and 4 years, respectively [10]. Duffner et al. treated three patients who survived 16, 18, and 39 months with methotrexate, vincristine, BCNU, and dexamethasone [21]. Gaffney et al. reported 3 of 6 patients who were long-term survivors, two of whom also received neuraxis irradiation [18]. Too few patients were treated in other series [15, 19] to draw any conclusions.

Ashwal et al. reviewed several series and compared patients treated with chemotherapy at recurrence (mean time to recurrence = 20 months) with those treated adjuvantly after radiation (mean time to recurrence = 10 months) [19]. The chemotherapies were different, as was patient selection. The only conclusion possible to derive is that chemotherapy may be effective in prolonging survival, but the optimal individual agent or combination has not been defined.

The Childrens Cancer Study Group has included all intracranial PNETs in its current (medulloblastoma) trial comparing three- and eight-drug chemotherapy plus radiation. This will be the first prospective trial designed

to answer questions of 1) extent of spread at diagnosis, 2) comparative response to three- and eight-drug chemotherapy plus radiation therapy, and 3) effect of chemotherapy alone on infants less than 18 months old (P.M. Zeltzer, personal communication, 1986).

Recommendations

DIAGNOSTIC WORKUP

The pretherapy and diagnostic algorithm for suspected PNET is identical for the diagnostic evaluation of other brain tumors:

1. Complete history and physical examination
2. Baseline neurological examination
3. Unenhanced CT scan to assess normal anatomy, presence of calcification or recent bleeding, relative tumor density, CSF flow
4. Enhanced CT scan to assess tumor vascularity and blood-brain barrier disruption
5. MRI may be superior, but its exact role remains undefined
6. Chest X-ray to rule out other primary tumors
7. Bone marrow aspiration and biopsy to assess tumor spread
8. A battery of baseline neuropsychological studies prior to radiotherapy.

AFTERTHERAPY FOLLOW-UP

Surgical recommendations include a complete resection. If this is not possible, than maximal debulking is advised. Two types of postsurgical assessment are necessary:

1. A postoperative enhanced CT scan should be administered within the first six days. This is necessary to evaluate residual disease and response to later therapy. The timing prior to seven days postoperation will avoid the postoperative-scan artifact [40].
2. Myelography and spinal fluid cytology are necessary to stage the patient and plan for

local radiotherapy should there exist an impending complete spinal blockage. PNETs spread through the neuraxis in about 33% of cases.

3. CT scans should be obtained about every three months for the first two years, during which most relapses occur.
4. If myelography or marrow are positive, they should be repeated within a month of the start of active therapy to assess tumor response.
5. A yearly neuropsychological assessment should be conducted.

SPECIAL PROBLEMS IN INFANTS

Infants pose special problems for the physician who is planning treatment. There was a high perioperative mortality in the infants (with larger masses) [16]. The drastic sequelae of radiation to the developing brain have been well documented [21, 35].

Unfortunately there is no age cutoff in childhood after which radiation can be considered safe for the developing nervous system. Several studies have been recently reported that demonstrate that chemotherapy can produce short-term responses in PNETs and similar tumors without any radiation [41, 42]. How long these responses will last is unknown. The CCSG and Pediatric Oncology Group are currently testing the feasibility of using chemotherapy-only protocols for infants and young children (L. Kun and P. Zeltzer, personal communication, 1987).

It may be advisable to send infants with PNETs to one of these centers for experimental therapy rather than treating them with radiation, which may have severe or devastating effects on their consequent neuropsychological functioning.

SIDE EFFECTS OF TREATMENTS

The side effects of treatment for supratentorial PNETs are difficult to quantitate and are not specifically mentioned in the literature. They can be related to the following factors:

1. The site of primary tumor: Surgical removal of occipital tumors may be associated with homonymous hemianopsia, while motor-strip lesions could be associated with hemiplegia.
2. Preoperative condition: Brainstem or uncus herniation may leave the patient respirator-bound or with movement problems.
3. Postoperative complications: Meningitis or increased pressure could necessitate a shunt [32].
4. Radiation therapy: Few patients receiving neuraxis irradiation may get granulocytopenia or thrombocytopenia. The longer-term effects on endocrine [43] and neuropsychological development [34] are more important.
5. Chemotherapy: Short-term myelosuppression and infections. Longer-term effects are on pituitary–gonadal dysfunction, hypothyroidism, and second tumors [43].

In summary, the supratentorial PNETs still represent a diagnostic challenge because of the current controversies in their nomenclature and our past therapeutic failures. They represent a challenge, since the optimal therapies are still being developed. With newer techniques of molecular biology and monoclonal antibodies, the diagnostic dilemma may be resolved and combined modality therapy for this tumor group may provide improved length and quality of survival.

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14. MENINGIOMA

Melvin Deutsch

Meningiomas occur mainly in adults, with children composing only 1%–8% of cases [1–7] (table 14-1). Less than 3% of childhood brain tumors are meningiomas [8–12]. In some reports, sarcomas arising from the meninges have been included as meningiomas without a clear statement that these were indeed malignant meningiomas. Thus, differences in the reported incidences of childhood meningioma may be explained in part by 1) the inclusion or exclusion of various subtypes such as angioblastic meningioma and meningeal sarcoma, 2) different patient populations, and 3) referral patterns.

Meningiomas are extremely rare in children under age two years. Wakai et al. [13], in a review of 200 congenital tumors from the world literature, found seven cases of meningiomas. At least six other children, two months to two years of age, have been reported [8, 14–17].

Etiology

As with most other intracranial tumors, the etiology of meningioma is uncertain. In Cushing's series, a history of trauma was recorded in 101 cases (93 intracranial, 8 spinal) [1]. In 24 cases, meningioma appeared subsequent to an injury which caused a swelling, scar, or depressed fracture corresponding to "the tumor's obvious point of origin." One of his patients, a 13-year-old male, had sustained a skull fracture with tearing of the falx at birth. At operation, a meningioma of the falx, at the site of the injury, was discovered. There have been several other reported instances of meningioma following

penetrating gunshot wounds [21, 22] or skull trauma [23], and even one case in which a meningioma developed around a metal wire that had been propelled intracranially from an explosion 20 years previously [19]. On the other hand, there have been strong opinions expressed against the likelihood that head trauma predisposes to intracranial tumor [24].

In patients with von Recklinghausen's neurofibromatosis, there is an increased incidence of meningioma, often multiple. In the series of 48 patients collected by Merten et al. [9], 5 of 6 patients with multiple discrete meningiomas had neurofibromatosis. Herz et al. [18] reported that 19% of meningioma patients aged 13–18 years had neurofibromatosis. In the series of 51 children with meningioma reported by Deen et al., 12 (23.5%) had neurofibromatosis. Five of these 12 had spinal meningiomas and three had orbital or optic nerve-sheath tumors. There have been reports of familial meningioma apparently associated with neurofibromatosis. [25]. However, there are also several reported occurrences of meningiomas in families without definite neurofibromatosis [26–28] including an example of twin boys with multiple meningioma [29]. The author is aware of a family without a history of neurofibromatosis in which three siblings, all adults, have intracranial meningioma. The possibility of associated neurofibromatosis should be considered in any child with multiple meningiomas or where there is a family history of meningioma, acoustic neuroma, or neurofibromatosis. Similarly, the possibility of meningioma should be con-

TABLE 14-1. Incidence of children in various series of meningioma

Series	Time period	Total number of patients	Number of children	Comment
Cushing and Eisenhardt	1908–1932	313	6 (1.9%)	2 under age 10 years 1 intracranial 1 spinal
Mirimanoff et al.	1962–1980	225	3	1 under age 10 years
Yamashita et al.	1941–1979	336	26 (7.7%)	4 under age 10 years
Adegbite et al.	1956–1979	114	6 (5.3%)	1 under age 10 years
Chan and Thompson	1960–1981	350	4 (1.7%)	3 under age 10 years
Deen et al.	1907–1980	2456	41 (1.7%) ^a	11 under age 12 years

^a Cranial tumors.

sidered in any child with neurofibromatosis who presents with evidence of one or more intracranial tumors.

In most adult series of meningiomas, there is a clear preponderance of females. Among children with meningioma, the male:female ratio is about equal, with perhaps a slight excess of females [7, 9, 18–20].

The increased incidence of meningiomas in adult women has led to speculation concerning the possible effect of female sex hormones on the etiology and stimulation of meningiomas. Cases of meningioma have been described involving the sella area that were associated with visual deterioration during pregnancy, only to have reversal of the visual deterioration postpartum [30, 31]. An increased incidence of meningioma associated with breast cancer has been described, again suggesting a possible role of female sex hormones in the etiology of meningioma [32, 33]. In children, it is unlikely that hormonal influences are related to the etiology of meningioma, since the sex incidence is about equal.

Ionizing radiation has been implicated as a cause of meningioma. From the first decade of the twentieth century up until about 1959, superficial radiation was frequently used to cause temporary alopecia in the treatment of tinea capitis. The most frequently used technique divided the entire scalp into five regions that were each treated using superficial 60–100 KV X-rays with the aim of delivering a dose

sufficient to cause complete but temporary epilation. In Israel, during the years 1949–1960, approximately 20,000 children under age 15 were treated with scalp irradiation for tinea capitis [34].

Two large studies from Israel have reviewed 42 and 43 patients, respectively, who developed meningiomas following scalp irradiation [35, 36]. In both series, compared to unirradiated meningioma patients, postirradiation meningiomas were more likely to occur in younger patients and to be located at the convexity, falx, and parasagittal areas. Also, postirradiation meningiomas tended to have a more aggressive histological appearance and a higher recurrence rate. The cerebral hemispheres received doses up to 140 rads by the technique used to treat tinea capitis [34]. However, many irradiated patients in both series had permanent alopecia and scalp skin scarring, suggesting that perhaps much higher doses were delivered. The location of the meningiomas at the higher-dosed areas of the brain (parasagittal, falx, and convexity) as opposed to the base-of-skull sites suggests a correlation between dose to the meninges and subsequent formation of irradiation-induced meningioma.

One large follow-up study of 1548 patients irradiated for tinea in the United States when compared to a control population of nonirradiated patients with tinea did demonstrate an increased incidence of cancer and leukemia in

the irradiated group, but there were no meningiomas reported [37]. It is interesting that the markedly increased incidence of postirradiation meningiomas as reported from Israel has not been seen in other countries. This may be related to differences in delivered dose and possibly to some as yet unexplained genetic or environmental factors. In the patients irradiated for tinea capitis, all meningiomas developed after the age of 20 years.

There have been case reports of patients developing meningioma 7–27 years after relatively high doses of radiation administered for intracranial tumors [38–41] (figure 14-1).

Whereas radiotherapy administered to the scalp during childhood may be the etiology of

an occasional meningioma developing in an adult, it is probably an extremely rare cause for meningioma developing during childhood, since in such cases the latent period following radiation is usually measured in decades.

Pathology

Cushing proposed a classification of meningioma which included nine major types (table 14-2). Counting subtypes, there were thus 22 different terms used to cover all variations of meningioma. Cushing himself felt that the subdivisions of a given type were “fundamentally unimportant.” Except for the Cushing type VI, of which there were six examples in his



FIGURE 14-1. Meningioma in a 15-year-old male who was treated with craniospinal axis irradiation at age three years for medulloblastoma.

TABLE 14-2. Histopathologic classification of meningiomas of Cushing and Eisenhardt

Type I	Meningothelial, not reticulin- or collagen-forming
Type II	Meningothelial, whorl pattern with tendency to form reticulin or collagen
Type III	Fibroblastic benign type, reticulin- or collagen-forming
Type IV	Angioblastic
Type V	Epithelioid, not reticulin- or collagen-forming
Type VI	Fibroblastic malignant type, sarcomatous
Type VII	Osteoblastic
Type VIII	Chondroblastic
Type IX	Lipoblastic

Note: With variants, the classification contains 22 different entities.

series and which had an unfavorable prognosis (longest survivor 2.5 years), there was little prognostic value in his classification.

Russell, in 1950 [42], adopted Courville's classification [43], and this is probably one of the more commonly used classifications. Other classifications are presented in table 14-3 [9, 19, 43-45].

There is some debate as to whether or not angioblastic meningioma should be considered as a meningioma or separately as a vascular neoplasm (hemangioblastoma or hemangiopericytoma). In the large series of 243 patients reported by Earle and Richany [45], the angio-

blastic variety was not seen in patients under age 20 years. Pitkethly et al. [46] reviewed "angioblastic meningiomas" from the AFIP and separated them into hemangioblastic (type IV variant 3 of Cushing) or hemangiopericytoma (type IV variant 1 of Cushing). Only two hemangiopericytoma types occurred in patients under age 20, but as a group, the hemangiopericytomas appeared at an earlier age and tended to recur locally and metastasize extracranially. Kernohan and Uihlein [47] included them as sarcomas and felt that hemangiopericytomas should not be considered as meningiomas, since they were found in other organs of the body. Two of their 25 patients with hemangiopericytoma were under age 20 years (both under age nine).

Merten et al. [9] reviewed pathological material on 75 patients under age 20 years with a diagnosis of meningioma collected from 35 institutions. They classified only 48 cases as being meningioma, 11 as sarcoma, and five as angioblastic meningeal tumors. Eleven patients had miscellaneous diagnoses such as glioma, granuloma, fibromyxoma, chordoma, and choroid plexus tissue. Merten et al. separated meningiomas into only three types (table 14-3). They felt that angioblastic meningiomas were actually vascular tumors (hemangioblastoma or hemangiopericytoma); they also excluded sarcomatous meningiomas with the opinion that such tumors were not meningioma. They stated that only a few tumors in their series showed malignant change.

TABLE 14-3. Classification of meningiomas

Bland and Russell [44] 1938	Courville [43] 1945	Zulch [19] 1965	Earle and Richany [45] 1969	Merten et al. [9] 1974
Endotheliomatous	Syncytical	Endotheliomatous	Meningothelial	Meningiotheliomatous
Fibroblastic	Transitional	Fibromatous	Fibroblastic	Psammomatous
Angioblastic	Fibrous	Angiomatous	Mixed type	Fibroblastic
Xanthomatous	Angioblastic	Malignant	Angioblastic	
Myxomatous	Sarcomatous	(sarcomatous)	Sarcomatous	

There were five meningiosarcomas among 13 children with meningioma in the series reported by Crouse and Berg [11]. Of 13 children with meningioma reported by Leibel et al. [48], three were sarcomas.

In 1975, Ludwin et al. [49] reported on a series of 17 meningiomas characterized by a papillary pattern that was associated with other histological criteria of malignancy. Eight patients were age 13 or under. Pasquier et al. [50] recently reported seven cases of papillary meningioma and collected an additional 39 from the literature. Nine were patients under age 18 years. Twenty-six patients (56.5%) developed recurrence 0.3–22 years after operation. Five additional cases under age 20 with papillary meningioma are reported by Deen et al.; four of these patients had recurrence [7]. The papillary variant of meningioma is usually associated with one of the common meningioma components.

Compared with adult meningiomas, most reports on childhood meningiomas suggest a higher incidence of cases with histologic characteristics of malignancy, such as frequent mitosis or invasion of the brain.

There has been some confusion concerning the separation of primary sarcomas of the meninges and brain from malignant meningioma. Zulch believed that meningiomas with sarcomatous degeneration formed a “transition to the fibrosarcomas” [19]. Russell and Rubenstein [51] noted that malignant meningiomas may evolve into a final histological appearance typical of spindle cell sarcoma. Kernohan and Uihlein [47] separated sarcomas of the brain and meninges from meningioma. Of their 241 sarcomas, 96 were fibrosarcomas and 25 heman-giopericytomas. Many of the cases in these latter two histological classifications would be included as meningiomas in various other series. The tendency of some meningiomas to show more malignant change with recurrence and finally to evolve into a histological picture of sarcoma has been noted [51].

Sites of Involvement

Most childhood intracranial meningiomas are supratentorial (table 14-4). However, there may be a higher incidence of posterior fossa meningioma in the childhood cases than in the adults [7, 9, 18, 48]. Among the supratentorial meningiomas of childhood, a large proportion (15%–30%) involved the lateral ventricles [9, 18].

Karp et al. [52] reported 25 primary orbital meningiomas. Ten patients (40%) were less than age 20 years. Eight were female. Six patients under age ten years were all female.

Symptoms of childhood meningioma will necessarily depend upon the location of the tumor. Headache is reported in about one half of children, and seizures in about one third. In the series reported by Merten et al. [9], seizures, with one exception, occurred in patients with parasagittal or convexity tumors. Papilledema is present in approximately 50% of patients. Visual problems are seen in up to 50% of patients.

Herz et al. [18] reported the average duration of symptoms to be 1.5 years in children 2–12 years old and 2.2 years in children 13–18 years old. Of the 48 patients collected by Merten et al. [9], 25 had symptoms for 12 months or less and an additional eight had symptoms for up to 24 months prior to diagnosis. Two of their patients had symptoms for greater than five years, and two additional patients had no symptoms at the time of discovery of their tumors.

Merten et al. [9] reported tumor calcification detected on skull roentgenograms in 15 of 48 patients. Five of eight intraventricular meningiomas were calcified (figure 14-2). Hyperostosis was noted in 11 patients, destruction of adjacent skull in ten and calvarium thinning in nine. Plain skull X-ray evidence of increased intracranial pressure was noted in 12 patients. Skull radiographs were available on 36 patients in the series of Deen et al. and showed signs of increased intracranial pressure in ten [7].

TABLE 14-4. Sites of cranial meningiomas

Site	Adults ^a					Children		
	Cushing and Eisenhardt (295)	Wara et al. (213)	Mirimanoff et al. (207)	Yamashita et al. (331)	Deen et al. (41)	Merten et al. (47) ^c	Herz et al. (58) Ages 2-12	Herz et al. (54) Ages 13+
Parasagittal-falx	24.4%	24.4%	18.4%	29.3%	7.3%	14.9%	20.0%	9.0%
Convexity	18.3%	19.7%	22.7%	15.4%	29.3%	14.9%	23.0%	4.0%
Sphenoid ridge	18.0%	27.7%	17.4%	12.1%	12.2%	14.9%	7.0%	4.0%
Posterior fossa	7.8%	11.7%	15.0%	6.9%	17.1%	19.1%	10.0%	15.0%
Olfactory groove	9.8%	5.2%	10.6%	10.0%			2.0%	
Para sellar	9.5%	8.9%	13.5%	13.0%		6.4%	7.0%	
Ventricular	1.4%	1.9%		4.2%	4.9%	17.0%	26.0%	37.0%
Orbit	0.3%		2.4%	1.2%	7.3%	12.8%	2.0%	
Other ^b	10.5%	0.5%		7.9%	22.0% ^d		5.0%	25.0%

Notes: () Total number of cranial cases.

^a Adult series includes a few children.^b Other includes multiple.^c 6 patients with multiple tumors: 3 posterior fossa, 2 supratentorial, 1 posterior fossa and ventricle^d 4 middle fossa, 4 optic nerve sheath, 1 basofrontal.

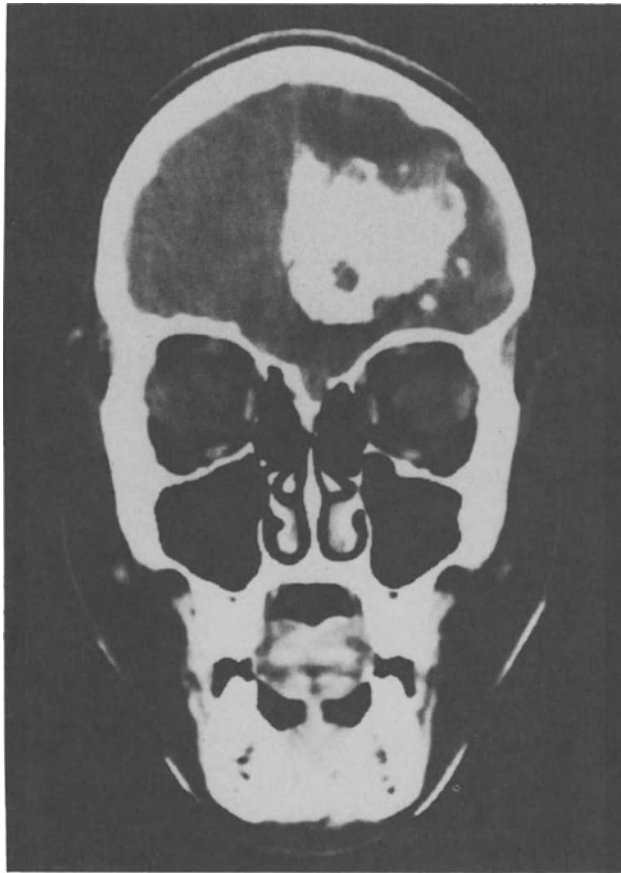


FIGURE 14-2. Fourteen-year-old male with large calcified meningioma. Unenhanced CT scan.

Prior to the advent of computerized tomography (CT), angiography and pneumoencephalography were the most accurate radiographic methods used to identify and locate intracranial tumors. In the series of Merten et al. [9], angiographic studies in 30 patients revealed vessel displacement by a mass in 24 of 30 patients and tumor staining in 13. New et al. [53] reported angiography to be accurate in identifying an intracranial mass in 94%–96% of meningioma patients. In the patients with a positive angiogram, the diagnosis of meningioma was considered probable or certain in 83%. The CT characteristics of meningioma do not vary according to histological subtype or even location [54]. Usually there is intense enhancement with

clearly defined margins. New et al. [53] found the enhanced CT examination to be slightly more accurate than angiography for the detection of intracranial meningioma. With the accuracy of CT plus or minus angiography, there is little need for pneumoencephalography.

Tumors in the basal skull region and the posterior fossa tend to show little or no edema on CT. Also, heavily calcified tumors usually are associated with minor or no edema. However, meningiomas in the lateral convexity, superior parasagittal, and anterior frontal regions are associated with moderate to marked edema in 42%–62% of cases [53].

Treatment and Outcome

As in adults with intracranial meningioma, optimum therapy in children is complete resection.

Often, the terms *total resection* or *complete resection* are used without further amplification. The importance of precisely describing the nature of the surgical procedure for meningiomas was well demonstrated by Simpson in 1957 [55]. He classified operations for meningioma into five distinct grades.

Grade I. Macroscopically complete removal of the tumor with excision of its dural attachment and abnormal bone. This also entails resection of a venous sinus if the tumor arises from the wall.

Grade II. Macroscopically complete removal of the tumor with coagulation of the dural attachment.

Grade III. Macroscopically complete removal of the intradural tumor without resection or coagulation of the dural attachment or of extradural extension such as in a venous sinus or hyperostatic bone.

Grade IV. Partial removal.

Grade V. Simple decompression.

Even with Simpson's grade I type operation, which was performed on 90 patients, there were eight (9%) symptomatic recurrences. Of 114 patients undergoing a grade II operation, there were 18 recurrences (15%). Follow-up ranged from 3–29 years. The recurrence rate was higher for the grades III–V operations, but it is important to note that there were patients with long-term symptom-free survival in these groups.

With the use of CT and magnetic resonance imaging (MRI) for detecting asymptomatic recurrent tumor, it is probable that the recurrence rate for all groups will be higher. In children, the importance of doing a complete resection is well demonstrated by the fact that there are very few reported cases of long-term disease-free survival in any child not undergoing complete resection of meningioma.

The majority of children undergoing complete resection are cured. Merten et al. had 28 patients in whom total resection was accomplished, and all were surviving 0.9–25 years at

the time of report [9]. Of 20 children in whom there was only partial resection or biopsy, only five were alive at the time of publication, but all had recurrent tumor. The details of therapy in the partially resected tumor cases were not given. Of the nine children with meningioma reported by Herz et al. [18], six had a total resection initially and all were alive free of disease. Two had incomplete resections with subsequent total resections for recurrence, and both of these were alive—four years and seven years, respectively—at the time of report. One patient died one month following initial surgery.

In the series of 13 patients reported by Leibel et al. [48], only two had a complete resection as the initial therapy. One was alive and well four years following surgery and the second died of intercurrent disease at three years. All patients undergoing a subtotal resection as the initial treatment, including three with postoperative radiotherapy, had subsequent recurrence. One child who had a subtotal resection for recurrence followed by radiotherapy was alive and well six years later, and a second child who had radiotherapy at time of recurrence followed by complete removal was alive and well 17 years later.

Cooper and Dohn [56] reported that 3 of 7 patients with childhood meningioma had total resection as the initial therapy and all three were alive and well 4–30 years later. Two additional patients subsequently died, but details of their surgery were not given. One additional patient had a subtotal removal of tumor and was described as “doing well” one year later. The last patient had radiotherapy after a gross total removal for a second recurrence and was described as doing well $3\frac{1}{2}$ years later.

Details of therapy were not given in the report of Deen et al., but 20 patients (39%) had definite evidence of tumor recurrence [7]. Meningiomas at the skull base had a 76.9% recurrence rate compared to 32.2% for convexity tumors in children. Posterior fossa tumors had a poor prognosis (21% 20-year survival). However, “several patients” with recurrence were alive at greater than 20 years. Histology

may have prognostic significance. The papillary variant had a poor progress in this series, with 4 of 5 having recurrence. The aggressive nature of papillary meningioma was also noted by Ludwin et al. [49].

Radiotherapy has been used in adults for the treatment of subtotally resected meningioma, recurrent meningioma, or malignant meningioma. Retrospective data from the series of Wara et al. [3] indicate that following subtotal resection, radiotherapy delays or prevents recurrence. Forty-three of 58 patients (74%) treated with subtotal resection without postoperative radiation experienced a recurrence. Of 34 patients treated with subtotal resection and postoperative radiation, only 10 (29%) developed recurrence. The same authors also demonstrated a benefit of radiation as treatment for recurrent tumor following initial subtotal resection. Of 16 patients treated with radiation for recurrence, seven were alive and well 1–9 years later. Of 27 patients treated with further surgery, only five were alive and well 1–23 years later. Seventeen of this latter group had died of tumor. The authors recommended a postoperative tumor dose of at least 5000 rads.

Taylor et al. also reported improved control rates with radiotherapy after subtotal excision versus subtotal excision alone (82% versus 18% at ten years) [57]. Similarly, for recurrent meningioma, radiotherapy alone or after resection was more effective than just repeat resection. All patients were treated with 5000–6300 rads at 180–200 rads/day.

Carella et al. [58] reported 43 patients with meningioma treated with postoperative radiotherapy. Forty-two had residual disease and one had a malignant meningioma considered to be totally removed. They state that the usual tumor dose was 5500–6000 rads in 6 to 6½ weeks. Radiation was limited to the tumor bed with “a margin.” Of these 43 patients, 41 were alive and well 2–10+ years. Fourteen patients were treated with radiotherapy for recurrent tumor after initial surgery. Five patients showed improvement. A further 11 patients were

treated with radiotherapy as the primary treatment, all without pathological confirmation. All 11 were alive 3–6 years later. Nine showed improvement in neurological function. The authors also demonstrated changes on CT, such as lucency developing in the tumors, in two of these latter patients, suggesting a response to radiotherapy.

It is difficult to make conclusions about the value of radiotherapy in childhood meningioma. Reported cases receiving radiotherapy are few, and often the follow-up intervals are relatively short. Considering the extremely unfavorable outlook for children treated with only subtotal resection, it seems advisable to administer postoperative radiotherapy in all cases where there is residual tumor. It would seem necessary to irradiate only the site of residual tumor. Multiple field arrangements should be used to ensure a homogeneous dose distribution within the volume considered at risk of harboring residual tumor. CT and MRI are extremely valuable in treatment planning. Doses of at least 5000 rads should be administered over six weeks. For older children, especially those with gross residual tumor, doses of 5500 rads should be administered over 6–7 weeks. In all cases of malignant meningioma of childhood, postoperative radiotherapy should be considered unless there is reasonable certainty of a complete resection (Simpson grade I or II procedure).

For children under three or four years of age, radiotherapy after subtotal resection probably could be delayed, especially if the tumor has benign characteristics. Such children should be followed rather frequently, every 4–6 months, with CT scanning and/or MRI in the hope that progression of disease will be delayed until such time as radiotherapy, alone or after a further attempt at resection, could be administered safely.

Chemotherapy has not been used with regularity in the treatment of meningioma. Certainly, it seems appropriate to consider chemotherapy regimens, such as used for medulloblastoma or malignant glioma in children, for those patients

with malignant meningioma who have progression of disease after surgery and radiotherapy.

The preponderance of adult females with meningioma, apparent growth acceleration during pregnancy, and the association of meningioma with breast cancer has prompted investigations to determine whether or not female hormones play a role in causing or stimulating meningioma. Studies have indicated that meningiomas may bind estrogen and progesterone [59–61]. Jay et al. [62] demonstrated that meningiomas from four different patients in tissue culture were stimulated by estrogen and also progesterone. Tamoxifen, an antiestrogen, stimulated growth of 3 of the 4 tumors. Estradiol produced the most marked stimulation of growth of all four meningiomas tested. Progesterone inhibited the growth stimulation produced by estradiol. Tamoxifen also inhibited estradiol growth stimulation in 3 of the 4 cultures.

Jaaskelainen et al. [63] used medroxyprogesterone acetate, 100 mg IM once weekly, to treat five postmenopausal women with intracranial meningioma. There were no responses. Markwalder et al. [64] used Tamoxifen, an antiestrogen, to treat six patients with meningioma. Only one patient had an “unspecific” tumor response. At present, the data concerning hormonal influences on meningioma are too preliminary to be translated into effective therapy.

Failure of therapy is most often manifested by local recurrence, although rarely, extracranial metastases and dissemination via the CSF have been described [1, 7, 48, 65]. As in adults, children with meningioma may survive for many years even with the recurrent tumor. In the series of Leibel et al. [48], four patients died with disease between 9–18 years from diagnosis and a fifth patient was described as being alive with disease at nine years. Even children with recurrence may have prolonged survival or possibly cure, after surgery with or without radiotherapy. This is well illustrated by case 1 of Chan and Thompson [6], a patient who had her initial resection of a meningioma at age 2½ years.

She had subsequent resections for recurrence at age 14, 20, 25, 27, and 30 years. Eleven years after the last resection, she was reported to be alive and well. Thus, “curative” therapy is warranted not only for primary but also for recurrent meningiomas.

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15. EPENDYMOMAS

Craig L. Silverman
Patrick R.M. Thomas
William Cox

Ependymoma and ependymoma variants (choroid plexus papilloma and subependymoma) constitute a relatively small portion of primary childhood intracranial tumors but have generated intense controversy among clinicians. First described by Storch almost 100 years ago, but more formally recognized as a truly separate entity over 50 years ago in a monograph by Bailey and Cushing [1] ependymoma still poses unanswered basic questions regarding classification, pathology, biologic behavior, prognostic staging parameters, and optimal treatment. This chapter will review these controversies in an attempt to arrive at a rational basis for appropriate classification, staging, and management.

Incidence and Location

Ependymoma accounts for 2%–10% of primary intracranial tumors in children and approximately 10% of gliomas in children [2]. It is primarily a disease of the young, though adult patients constituted 50% of patients in the older series, especially those including intramedullary spinal cord ependymomas, a disease that occurs primarily in adults and only rarely in children.

The distribution of ependymomas by location has been reported as 25%–40% occurring above the tentorium and 60%–75% occurring below the tentorium (table 15-1). Of the infratentorial lesions, one half arise from the lateral recesses of the fourth ventricle with the re-

maining half arising from the floor, posterior medullary velum, or the obex. The supratentorial lesions are approximately equally divided between those tumors that are intraventricular and those in the parenchyma, lying near, but not necessarily attached to, the lateral ventricles. Approximately 25% of the supratentorial intraventricular lesions arise in the third ventricle, with the remaining 75% arising from the lateral ventricles.

Age and Sex

Considering only pediatric patients, approximately 85% are ten years old or younger and 13%–15% are under two years of age. In the series of Dohrmann et al., the median age was 5.4 years, with a peak at approximately one year [3]. Liu et al. found a bimodal distribution with one peak at approximately two years of age and a second peak in the 7–9-year age range [4]. Coulon and Till reported similar data, with a peak at 1–2 years of age and a second peak in the 5–6-year age range [5]. There seems to be no sex predominance in most series, especially for supratentorial lesions, though Shuman et al. noted a 2:1 male predominance for infratentorial and a 5:1 male predominance in children with spinal cord lesions [6].

Signs and Symptoms (Table 15-2)

As is the case with other intracranial lesions, the signs and symptoms of ependymoma at

TABLE 15-1. Distribution of ependymomas in children by site

Series	Supratentorial	(%)	Infratentorial	(%)	Spinal	(%)
Coulon [5]*	13/43	(30)	30/43	(70)	0/43	(0)
Kircheff [10]	14/59	(24)	45/59	(76)	0/59	(0)
Pierre-Kahn [29]*	15/47	(32)	32/47	(68)	0/47	(0)
Liu [4]*	13/31	(42)	18/31	(58)	0/31	(0)
Shaw [7]*	11/33	(33)	22/33	(67)	0/33	(0)
Mork [26]	10/36	(28)	24/36	(67)	2/36	(5)
Read [19]*	7/25	(28)	14/25	(56)	4/25	(16)
Dohrmann [3]*	18/44	(40)	26/44	(60)	0/44	(0)
Shuman [6]*	18/74	(24)	50/74	(68)	6/74	(8)
Marks [17]*	16/36	(44)	16/36	(44)	4/36	(12)
Svien [28]		(40)		(60)		(0)
Fokes [32]		(25)		(70)		(5)
Total	135/428	(30)	277/428	(66)	16/428	(4)

*Pediatric series.

TABLE 15-2. Signs and symptoms of ependymomas in children

Common symptoms	Percentage	Common physical signs	Percentage
Headache	80%	Papilledema	90%
Nausea/Vomiting	75%	Ataxia	85%–90%
Difficulty walking	60%	Nystagmus	40%–50%
Seizures	33%	Cranial nerve abnormalities	10%
Diplopia	15%		
Vertigo	10%		
Lethargy	10%		
Decreased visual acuity	5%		

presentation will vary according to the site(s) involved. Since ependymoma is primarily an infratentorial lesion, most patients present with cerebellar signs and symptoms. The most common are headache (80%), nausea and vomiting (75%), ataxia (60%), and, less commonly, vertigo, lethargy, increasing head diameter, diplopia, decreased visual acuity, and occasionally, cranial nerve abnormalities or personality changes. Seizures occur at initial presentation in one third of patients with supratentorial lesions.

The most common physical finding in these children is papilledema, found in up to 90% of patients. Nystagmus can also be found in 40%–50% of cases, and cerebellar signs usually are present with infratentorial lesions. Ataxia

is also present in up to 85%–90% of patients.

The duration of symptoms in children is usually six months or less. Coulon and Till reported that 34 of 43 patients had symptoms present for less than six months prior to diagnosis [5]. Shaw et al. reported the median duration of symptoms to be $2\frac{1}{2}$ months for their pediatric patients [7].

Diagnostic Workup

In the past, diagnostic workup for these patients began with routine skull films. In Barone and Elvidge's series, radiographic evidence of increased intracranial pressure was noted in 12 of 45 patients [8]. Coulon and Till found abnormal plain skull films in 32 of 43 patients [5].

Suture separation was present in 27 patients and general vault thinning in seven. Calcification was noted in eight cases. Approximately 25% of supratentorial lesions contained calcification detected on X-ray. Cobb and Youmans noted that approximately 13% of lesions are calcified, though most of these appear to be choroid plexus papillomata [2].

Nuclear medicine brain scans have been done in the past with an approximately 50% incidence of positive findings. Ventriculography was an excellent diagnostic test; in Barone and Elvidge's series, 41 of 43 ventriculograms were positive, not surprising with tumors that usually have an intraventricular component [8].

Those modalities have now been supplanted by computed tomography (CT). In a recent series, Armington et al. evaluated supratentorial ependymomas and ependymblastomas with CT: 38% were noted to be calcified, and 94% were greater than 4 cm in size, of which three quarters were well marginated [9]. Ninety-five percent had positive contrast enhancement, and 56% of the lesions had a cystic component. They noted that 75% of the supratentorial tumors had a periventricular or intraparenchymal component in comparison to the infratentorial lesions, of which 80%–100% had an intraventricular component. The differential diagnosis includes astrocytoma, primitive neuroectodermal tumor, choroid plexus papilloma, and the occasional subependymal astrocytoma.

Routine investigation of the spinal cord using myelography and CT for possible subarachnoid implants is usually not recommended for the asymptomatic patient, though it is highly accurate for symptomatic lesions. High-risk groups such as those with infratentorial high-grade lesions should undergo evaluation.

Staging and Prognostic Signs

There is no currently accepted staging system for ependymoma. Kricheff et al. [10] first proposed a system for infratentorial ependymoma in 1964:

- T1: A lesion confined to the fourth ventricle.
- T2: A lesion involving the fourth ventricle and extending to the cisterna magna.
- T3: Beyond the cisterna magna to either the cerebellar pontine cistern or to the cervical subarachnoid space.
- T4: Gross invasion of the cerebellum or brainstem.
- M1: Distant disease: within the CNS or beyond it.

Histology was specifically excluded from this staging system.

In 1975, Salazar et al. disputed the value of the above staging system and also reported no prognostic effect for sex or tumor site, though they did note that patients had a better prognosis if the tumor was confined to the fourth ventricle [11]. They did demonstrate that tumor grade was very important, as have numerous other authors [7, 12–15]. Garrett and Simpson demonstrated that a good post-operative neurological status was prognostically favorable, as was increased age (over 18 years) [16]. Site has been identified in many series as important, though other factors such as histologic grade may override the independent importance of site [17–20]. Metastatic disease within the central nervous system (CNS) is a poor prognostic factor, although data are scarce. Shaw et al. reported the presence of hydrocephalus to be a positive prognostic factor for survival [7].

West et al. have proposed a staging sheet for data accumulation to determine prognostic factors [21]. Any system should incorporate age, location of the tumor, size, relationship to the ventricles, presence or absence of tumor in the subarachnoid space, pathologic grade, and myelography results.

Pathology

Ependymomas are glial neoplasms derived from ependymal cells. Dohrmann et al. [3] believe that the tumor arises from the cells lining the

ventricles and central canal, and Cobb and Youmans [2] believe that it is derived embryologically from the ependymal lining of the neural tube. Histologically, the tumors consist of uniform cells usually surrounding blood vessels forming pseudorosettes.

In the older literature, Spiller [22] first noted gliomatosis, and Bailey and Cushing called this entity a medulloepithelioma. In 1932, Kernohan and Sayre subdivided ependymomas into cellular, mixed, papillary, and epithelial types [23], though Liu et al. believe that glandular is a more descriptive term for epithelial tumors [4]. The World Health Organization, however, has classified ependymal tumors as myxoid, papillary, subependymal, and anaplastic.

One debated issue is whether to designate choroid plexus papilloma and subependymoma as variants of ependymoma or as separate entities. Cobb and Youmans believe that the choroid plexus papilloma is derived embryologically from the same ependymal lining of the neural tube as true ependymoma and is not a separate entity [2]. Liu et al. demonstrated that the ultrastructure of choroid plexus papillomas has areas of transition that closely resemble the other true ependymoma histologies [4]. Arguments against choroid plexus papilloma as an ependymoma variant are the younger age group, male predominance, and the much improved prognosis, though occasionally patients succumb to persistent disease [4, 23].

Subependymoma seems to have a much different, more benign clinical history. It is mostly found incidentally at autopsy, and histologically mimics the normal architecture of the embryonic subependymal glial plate. Cobb and Youmans believe that it behaves much more like a hamartoma than a malignant lesion, though it has been noted at the periphery of true ependymoma subtypes [2, 24, 25].

Another major controversy centers around the existence or nonexistence of ependymoblastoma. This term was first used in the 1930s by Kernohan to describe a more malignant-appearing ependymoma characterized by increased disorderliness of architecture, increased cellular den-

sity, marked pleomorphism, giant cells, and an increased mitotic rate [23]. Ependymoblastoma soon became confused with the anaplastic ependymoma or malignant ependymoma (Svien's grade IV) in the literature. However, Mork and Rubenstein recently described a tumor that morphologically appears to be a dedifferentiation to a more embryonic pattern, more similar to a highly cellular primitive neuroepithelial tumor than a true anaplastic ependymoma [26]. This group of tumors appears in a younger age group (median age two years) and seems to have an increased propensity for leptomeningial spread. The clinical course of this entity also tends to be more malignant than even highly anaplastic ependymomas.

It is interesting to note that in tissue cultures from what morphologically appears to be pure ependymoma, both ependymal cells and astrocytes have been cultured [27]. Liu et al. described ependymoma tumors to be morphologically very heterogenous, with very few cells having the typical cilia and blepharoblasts that are usually described. Most cells resemble astrocytes or undifferentiated cells [4].

At present, the most common pathological classification system involves grading the individual cells and pattern. Svien et al. [28] proposed a four-grade system:

Grade I: The cells appear much like the normal ependymal cells, with the architecture well formed and no evidence of anaplasia.

Grade II: The architectural pattern is less organized, with some early anaplasia but without mitotic figures.

Grade III: There is a fragmentary pattern, the cells approximately equally divided between normal-appearing ependymal cells and pleomorphic cells.

Grade IV: There is no discernible pattern, marked pleomorphism, and 4–5 mitotic figures per high-power field.

Histologic Grade

In the series of Svien et al., approximately one half of the patients presented with grade I, and

one third presented with grade III or IV lesions [28]. When analyzing only their pediatric population, approximately one half had grade I, but 40%–45% had grade III or grade IV lesions. When Svien et al. reanalyzed the data to evaluate location versus histologic grade, supratentorial lesions were approximately 40% low-grade and 60% high-grade, but for infratentorial lesions in the pediatric age group of percentages were approximately reversed, 64% low-grade and 36% high-grade. This distribution has been confirmed in other clinical studies. Shaw et al. reported that approximately 50% of the supratentorial lesions were high-grade, but only 10% of the infratentorial lesions were high-grade [7]. In the series of Pierre-Kahn et al., 86% of the supratentorial lesions were “malignant,” as opposed to only 50% of the infratentorial lesions [29] (table 15-3).

The impact of grade on survival has been documented in many series. However, other possible prognostic factors, such as location and size as well as treatment volume and dose, are often not reported or unavailable, and thus the true impact of grade alone is unclear. For example, in Kim and Fayos’ series [15], five-year survival was reported as 67% for patients with well-differentiated tumor but only 21% for patients with poorly differentiated tumors. However, they also noted that patients with supratentorial lesions did better than infratentorial lesions. Patients who had received greater than 45 Gy survived as long as those who had received less than 45 Gy, but Kim and Fayos did not indicate the distribution of well-differentiated and poorly differentiated histologies within groups [15]. Thus, it is unclear what was the actual effect of grade alone on

survival, independent of other factors, especially treatment. In a surgical series, Svien et al. noted that the three-year survival rate of patients with grade I tumors was 79.3% compared to 28.6% for patients with grade II tumors, and 11.1% and 9.1% for patients with grade III and IV tumors, respectively [28].

In the analysis of another series for the impact of grade on survival, Liu’s well-differentiated tumors, the so-called *cellular A* tumors, and choroid plexus papillomas had excellent three-year survival rates, while less-differentiated *cellular B* and *cellular C* lesions had 67%–100% mortality within three years and all ependymoblastoma patients died [3]. Pierre-Kahn et al. noted that 66% of all tumors classified as malignant recurred and/or metastasized as opposed to only 35% of the “benign” histologies [29]. Garrett and Simpson reported a 78% five-year survival for all patients (both adults and children) with well-differentiated histologies versus 42% survival for those with moderately differentiated histologies and only 23% for patients with poorly differentiated lesions [16]. However, intracranial tumors tended to be moderately or poorly differentiated, whereas spinal tumors were mostly well differentiated. No subsetting according to site or age versus grade was presented. In the series of Dohrmann et al., children with ependymoma did better than ependymoblastoma patients regardless of site [3] (table 15-4). Grading has definite prognostic values, and helps predict biologic behavior in terms of both local control and subarachnoid metastatic potential.

Site (Table 15-4)

The prognostic value of site of the ependymoma has been retrospectively examined in the literature. Again, as with histology, it is often difficult to single out the impact of site alone from other possible prognostic factors such as grade and size, since supratentorial lesions tend to be both larger and less differentiated than infratentorial lesions. Also, treatment factors have prognostic effect. Kricheff et al. noted that

TABLE 15-3. Site versus grade in childhood ependymomas*

Grade	Supratentorial	Infratentorial
Low-grade	40%–50%	60%–90%
High-grade	50%–60%	10%–40%

*Data from Salazar [11], Dohrmann [3], Svien [28], and Pierre-Kahn [29].

TABLE 15-4. Survival—Intracranial ependymoma

Series	Patient population	Five-year survival
Kim [15]	All patients	36.5%
	ST ^a	46.3%
	PF ^b	33%
	Well-differentiated	67.7%
	Poorly differentiated	21.5%
Dohrmann [3]	All ependymoma	23%
	Ependymoma ST ^a	32%
	Ependymoma PF ^b	14%
	All ependymoblastoma	15%
	Ependymoblastoma ST ^a	22%
Salazar [11, 13]	Ependymoblastoma PF ^b	0%
	Grade I, II	39%
	Grade III, IV	26%
Bloom [12]	All patients	47%
Garrett [16]	All patients	43%
Mork [26]	"Typical" ependymoma	25.2%
	Anaplastic	16.6%
Marks [17]	ST ^a	35%
	PF ^b	59%
Chin [20]	All patients	37%

^aST = supratentorial.^bPF = posterior fossa.

the average survival of patients with supratentorial lesions was only 2.8 years, compared to six years for infratentorial lesions after local irradiation with 40–50 Gy [10]. Garrett et al. reported increased survival for patients with spinal cord and cauda equina lesions, though 95% of these patients had well-differentiated lesions, and most were adult [16]. In their series, Garrett et al. did not classify the intracranial lesions by tentorial location, grade, or age. In the series of Liu et al., supratentorial lesions tended to do worse, although when the grade of the lesion was taken into account, there was little difference in results [4]. Marks and Adler found an increased recurrence rate for supratentorial lesions and believed that it was due to the larger initial size and a greater amount of residual tumor postoperatively [17]. The CT data of Armington et al. confirm these findings [9]. In a review of the literature published by Chin et al. [20], there was a better five-year survival for infratentorial lesions

than for supratentorial lesions in series that reported both adult and pediatric patients, but in Dohrmann's pediatric series, patients with supratentorial lesions did better than patients with infratentorial lesions [3].

Time to recurrence also seems to be related to site. Marks and Adler reported that recurrences from supratentorial lesions manifest themselves earlier than recurrences from infratentorial lesions [17]. Site, per se, has some prognostic value, but grade and size may be more important.

Treatment

SURGICAL RESECTION

After the diagnostic workup is complete, surgical resection, if possible, is recommended. Mork and Loken reported the clinical course of 14 untreated children—all died within three years [30]. For infratentorial lesions, a midline

suboccipital craniotomy is the procedure of choice, usually with a C1 or C2 laminectomy to allow better examination of the foramen magnum. If inspection of the infratentorial lesion demonstrates invasion of the foramen of Luschka, a more thorough examination of the cerebellar–pontine area is indicated. These tumors can extensively invade the subarachnoid space and encase the medulla and grow out through the foramen of Luschka [2, 29, 31–33]. Although complete resection is the goal, the location, especially in the floor of the fourth ventricle, often precludes complete excision without significant morbidity [23, 34]. The reported operative mortality for all ependymomas ranges from 11% to 40% with as high as 50% operative mortality reported for infratentorial lesions, especially during attempted total removal [33, 34, 35] (table 15-5). Even the removal of the more benign choroid plexus papilloma is associated with an operative mortality of 18–30% and long-term morbidity of 25% [2]. Both mortality and morbidity have decreased in the more modern era due to better intraoperative techniques, postoperative care,

and possibly a more conservative approach to patients. Therefore, because of the potential life-threatening problems associated within an attempted total resection, few tumors are totally resected (table 15-5). In the series of Garrett and Simpson [16], only 14% were totally resected, which is in good agreement with earlier series [8, 32, 34, 35]. In the earlier surgical literature, long-term cures with surgery alone occurred in 7%–20% of patients, though few were children [8, 32–34]. A significant proportion failed locally regardless of site [2, 8, 32, 35]. Results are improved if postoperative deaths are eliminated from the five-year analysis [32, 34, 35]. Therefore, for the majority of lesions, surgery alone was long ago abandoned as appropriate treatment in favor of radiation after resection. The value of complete excision has never been proven, though Shaw et al. did demonstrate improved local control rates after complete excision [7].

SPINAL SEEDING

The controversy concerning the potential for spinal disease based on grade and location is

TABLE 15-5. Operative procedures and mortality rates

Series	Complete resection	Partial resection of biopsy only	Operative mortality
Garrett [16], 1983	14% (7/50)	86% (43/50)	7%
Coulon and Till [5], 1977	11% (5/43)	89% (38/43)	20%
Pierre-Kahn [29], 1983			
(Infratentorial)	25% (8/32)	75% (24/32)	24%
(Supratentorial)	67% (10/15)	33% (5/15)	
Shaw [7], 1987	12% (4/33)	88% (29/33)	N/A
Barone [8], 1970	15% (7/47)	85% (40/47)	32%
Salazar [13], 1983	11% (3/28)	89% (25/28)	N/A
Phillips [18], 1964			26% prior 1940
Ringertz [34], 1949			19% after 1940
(Infratentorial)			50%
(Supratentorial)			30%
Mork [30], 1977			
(Infratentorial)			25%
(Supratentorial)			17%
Shuman [6], 1975			28%

Note: N/A = not applicable.

of prime concern when considering appropriate volumes to be treated, especially in younger pediatric patients. Cranial–spinal axis irradiation is not without significant morbidity, and an appropriate estimation of the potential for dissemination is important in assessing the risk/benefit ratio of irradiating the entire neuroaxis.

One important point involves the difference between clinically apparent and pathologically positive subarachnoid disease. There have been numerous reports concerning the incidence of clinically apparent subarachnoid disease in patients with ependymoma, ranging from 0% to 50% [36–41]. In the largest pediatric series, Dohrmann et al. reported no example of clinically apparent subarachnoid metastasis in 44 patients [3]. Liu et al. had no case with metastasis among 29 patients [4]. However, Coulon and Till reported that 5 of 43 patients (11.5%) had tumor cells in cerebrospinal fluid (CSF) obtained preoperatively [5]. In two patients, the tumor was supratentorial, and in three it was infratentorial. Two of the five cases were considered benign ependymoma. None had symptoms of seeding. It is not clear as to how many of the total 43 patients actually had cytology studies performed on CSF. This incidence is in good correlation with the 12% incidence found by Shuman et al. at autopsy [6]. In Salazar's series, only 3% of patients (mostly children) had clinical evidence of subarachnoid implants, but 30% had dissemination at autopsy [11, 13]. Conversely, Kircheff et al. reported one patient with clinical seeding, but none of 12 with dissemination at autopsy [10]. Phillips et al. noted 2 of 42 patients with clinical evidence of seeding [18] (table 15–6).

The relationship between site of the ependymoma and histology on gross subarachnoid implants or positive CSF cytology has also been investigated by numerous authors. In the series compiled by Pierre-Kahn et al., the incidence of dissemination for supratentorial lesions was extremely small [29]. Only 1 of 27 patients with high-grade lesions (3.7%) had documented subarachnoid implants, and none of 22 patients

TABLE 15-6. Incidence of spinal cord involvement: Intracranial ependymoma

Series	Patient population	Spinal cord involvement
Bloom [12]	All patients	7/35 (20%)
	PF ^a	5/24 (21%)
	PF ^a High-grade	4/14 (29%)
	All high-grade	5/19 (26%)
Kim [15]	All patients	11/32 (34%)
	PF ^a	10/21 (48%)
	ST ^b	1/1 (9%)
Salazar [11]	ST ^b	3/21 (14%)
	PF ^a	5/31 (16%)
Renaudin [37]	All patients	3/19 (16%)
Phillips [18]	All patients	2/42 (5%)
Marks [17]	All patients	5/46 (11%)

^aPF = posterior fossa.
^bST = supratentorial.

with low-grade supratentorial lesions had spinal cord implants by myelography. For infratentorial lesions, however, there was a significant incidence of either clinical or autopsy evidence of spinal cord involvement. For the high-grade lesions, 15 of 29 (51.7%) had dissemination, and even 15% of low-grade infratentorial lesions had spinal cord involvement [29]. This is in agreement with Svien et al. who, at autopsy, found that all cases with spinal cord involvement had primary infratentorial lesions, usually high-grade [40]. Kim and Fayos documented eight symptomatic and three asymptomatic metastasis in 32 patients (33%) and noted that the incidence by site and histology was highest for infratentorial lesions—48% (10 of 21) [15]. Bloom reported a 21% incidence of seeding for all posterior fossa lesions, 26% for all high-grade lesions, and 29% for high-grade posterior fossa lesions [12].

Variations in the reported incidences of spinal cord involvement by ependymoma reflect the diligence with which evaluations are carried out. Autopsy series will detect asymptomatic lesions that may be otherwise overlooked. Similarly, if myelography and CSF cytology studies are not done at diagnosis and again at the time

of intracranial relapse, the true incidence of spinal cord involvement will not be appreciated. Some series include ependymoblastoma and anaplastic lesions and thus there will probably be an increase in incidence of cord involvement in such reports. Also, series differ in patient population, age, primary tumor site, and treatment. In patients treated with craniospinal axis irradiation, the incidence of subsequent cord involvement will be lower than observed in patients treated with localized irradiation.

RADIOTHERAPY

The major questions concerning radiotherapy for ependymoma are the appropriate volume and dosages as related to tumor location, histology, and age of the patient. In reviewing most clinical series, it is difficult to separate the impact upon outcome of dose and volume from other prognostic factors, such as histological grade, tumor size, site, and age.

Local recurrence is the main cause of failure and may be as high as 70%, though in some series this figure is derived by assuming that all deaths are secondary to local recurrence, even in the absence of biopsy or good radiographic proof of recurrence. Marks and Alder, relying on biopsy or strict radiographic criteria to make the diagnosis of local recurrence, noted that 16 of 20 supratentorial lesions recurred, as did 50% of infratentorial lesions [17]. Shaw et al. noted that the recurrence was always in the original field even with partial brain irradiation, but the recurrence rate was lower after complete resection [7].

As noted in the previous section, subarachnoid dissemination determined by autopsy, myelography, CSF cytology, or on clinical examination may account for a significant incidence of failures. The magnitude is dependent on both the primary site and the histologic grade.

Most series have used survival as their end-point, arguing that recurrences are not salvageable and death soon follows recurrence [5, 7, 11, 15]. For the most part, this assumption is true, although occasionally supratentorial

recurrences have been reoperated upon with success [2, 4, 7, 29].

There is a strong suggestion that higher doses provide improved survival rates. Even radiotherapy considered inadequate by modern standards—3600 rads over four months—provided increased survival compared to no radiotherapy [38]. Marks and Adler documented increased local control for infratentorial lesion (7 of 10 versus 5 of 15), with doses exceeding the equivalent of 1400 ret (50 Gy/28 fractions) [17]. Salazar noted similar results with 10 of 18 patients surviving five years following doses equivalent to 1350 ret or more versus 1 of 10 surviving with less than 1350 ret [11, 13]. Phillips et al., irradiating only the involved regions, reported 13 of 15 patients surviving five years following doses greater than 45 Gy but only 1 of 10 surviving with doses less than 35 Gy [18]. Garrett and Simpson reported improved five-year survival with doses exceeding 45 Gy, especially with an increased treatment volume, i.e., craniospinal irradiation (CSI) [16]. Shuman et al. [6] also reported increased survival with doses greater than 45 Gy, as did Kim and Fayos [15].

The effect of increasing treatment volumes on survival is also documented. Shaw et al. reported a 46% failure rate after partial brain irradiation, but only 28% following whole-brain irradiation, but without a survival benefit [7]. Read documented a three fold increase, from 10% to 35% in five-year survival, for patients treated with progressively larger fields, from small fields to craniospinal axis [19]. Marks and Adler reported increased local control rates for infratentorial lesions treated with craniospinal irradiation versus posterior fossa irradiation with or without whole-brain irradiation (62% versus 33%) [17]. Salazar noted that only 3 of 14 patients survived five years when the treated portal area was less than 160 cm² (minimum whole-brain dimensions) versus 8 of 14 survivors with volumes exceeding that minimum requirement [11, 13]. Garrett and Simpson documented a trend towards increasing

survival with craniospinal irradiation versus local radiotherapy [16].

When grade is taken into effect, technique does have a definite impact. Salazar noted no survivors with high-grade lesions when “inadequate” irradiation was given, but 5 of 6 survivors when “adequate” irradiation was delivered. Only 4 of 15 patients with low-grade lesions survived with “inadequate” radiotherapy versus 2 of 2 with “adequate” radiotherapy (defined as fields greater than 160 cm² and doses greater than 1350 ret equivalent) [13]. Also, he noted that only 1 of 10 patients treated with CSI had recurrence.

In all of the above-mentioned series, patients were not randomized between different radiotherapy doses and treatment volumes. It is possible and even likely that more aggressive treatment in terms of dose and volume was administered to more recently diagnosed patients who may also have benefited from earlier diagnosis with CT, better supportive care, and more extensive resections. Patients treated more aggressively may have been in better clinical condition with less neurological deficits than those treated with just local irradiation. Thus, while it is likely that increasing the dose and volumes provides higher control rates for ependymoma, it is not yet clear as to which patients require craniospinal axis irradiation prophylactically.

The Pediatric Oncology Group protocols now recommend 54.4 Gy/28–33 fractions (1400–1500 ret) to the primary tumor, but only 45–48 Gy for the very young patients (table 15-7). The recommended prophylactic

dose to the whole brain for high-grade and supratentorial low-grade tumors is 40 Gy. High-grade tumors also receive 35.20 Gy to the spinal cord.

Treatment volume is a more complex issue, and one has to consider the potential for dissemination to both the spinal cord and the supratentorium, as well as the possible morbidity of large-field irradiation, such as pituitary dysfunction, intellectual and behavioral problems, short stature, and carcinogenesis.

Infratentorial lesions have a high potential for local recurrence but also a significant potential for spinal cord seeding (15%—low-grade tumors, 50%—high-grade tumors), and need local plus or minus spinal irradiation for low-grade lesions and craniospinal irradiation for high-grade lesions. The Pediatric Oncology Group is now evaluating these issues concerning dose and volume (table 15-7). Craniospinal irradiation is recommended for ependymoblastoma due to its malignant course and potential for leptomeningeal spread.

CHEMOTHERAPY

A variety of chemotherapeutic agents have been tried in patients with recurrent metastatic disease, but with very limited success [21, 31, 42]. Phase II agents such as dibromodulcitol have shown limited efficacy, as has cis-platinum [43, 44]. Similarly, the response rates to multi-agent regimens such as PCV (procarbazine, CCNU, vincristine) and CVM (CCNU, vincristine, methotrexate) has been low [45, 46].

Adjuvant trials using CCNU and vincristine have shown initial delay in tumor progression

TABLE 15-7. Radiotherapeutic guidelines for treatment*

	Intratentorial low-grade	Intratentorial high-grade	Supratentorial low-grade	Supratentorial high-grade
Whole-brain	—	40.00 Gy	40.00 Gy	40.00 Gy
Primary tumor	54.00 Gy	54.40 Gy	54.40 Gy	54.40 Gy
Spinal cord	—	35.20 Gy	—	35.20 Gy

*Adapted from Pediatric Oncology Group Protocol #8532.

but no improvement in survival at five years [12, 36, 45–48]. Some larger retrospective series include patients treated with adjuvant chemotherapy, but do not separately report on them, indirectly suggesting lack of effect. At present, the indications and value of adjuvant chemotherapy for ependymoma are not clear. The Childrens Cancer Group (CCG) currently includes patients with ependymblastoma and malignant ependymoma in adjuvant chemotherapy protocols evaluating CCNU, vincristine, and prednisone versus the 8-drugs-in-1-day regimen of Bleyer et al. [49].

Choroid Plexus Papilloma and Carcinoma

These ependymomal-variant but separate pathological entities are derived from ependymomal lining of the neural tube [1]. While the papilloma consists of normal-appearing choroid plexus cells, the malignant variety consists of sheets of undifferentiated, anaplastic cells with frequent mitotic figures, hyperchromatic and pleomorphic nuclei, and often necrosis [50, 51]. The differential diagnosis includes ependymoma, ependymblastoma, and metastatic adenocarcinoma. Choroid plexus papilloma and carcinoma compose 0.5%–3% of intracranial neoplasms in children. Their distribution is as follows: lateral ventricle 43%; fourth ventricle, 39%; third ventricle, 10%; choroid plexus angle, 9% [52]. Most occur in children under 12 years of age, with a mean age of $2\frac{1}{2}$ years. The vast majority of choroid plexus tumors are biologically benign, and can be effectively treated with surgery [2, 8, 33, 53]. However, the carcinomatous variety is very aggressive, with a high incidence of both craniospinal and extraneural metastases [50, 54–57]. MacComb and Berger [50] and others have reported only a nine-month average survival with disappointing response rates to aggressive irradiation and chemotherapy [54, 55, 57].

Spinal Cord Ependymoma

These primary spinal cord tumors are quite rare in children and tend to make up only 4.5% of pediatric ependymoma series (table 15-1). They tend to occur almost exclusively in the cauda equina, but can occur in the thoracic and lumbar regions [6]. They have a relatively slow natural history marked by slow progressive low extremity weakness and paresthesias [17, 47, 58].

Reports of results for pediatric patients alone are scarce. In Read's series, only four patients presented with spinal cord lesions. Two patients were irradiated with small fields, and two with larger fields, using doses of 40–45 Gy, with all patients doing well [19]. In the series of Shuman et al., no child did well without radiotherapy after surgery, but all three patients who received at least 30 Gy were alive and symptom-free at five years [6]. For adult patients, five-year survival rates of 70%–85% are reported, with most patients enjoying little or no deficits, even after surgery and 45 Gy [8, 16, 17, 58–60].

Conclusions

Despite numerous retrospective reports, there remain unanswered questions concerning appropriate radiotherapy with regard to histology and site. There is now an ongoing Pediatric Oncology Group protocol designed to answer some of these questions, wherein infratentorial lesions with well-differentiated histologies will receive local irradiation alone, while less-differentiated lesions will be treated with craniospinal irradiation. Supratentorial lesions are treated with whole-brain irradiation plus boost (plus spinal irradiation for high-grade lesions). In all patients, the primary tumor will receive 54.40 Gy/33 fractions with a 10% reduction in dose for infants and children less than three years of age (table 15-7). All patients undergo pre-treatment myelography, CSF analysis, and CT scanning in addition to neuropsychological

testing. This study should provide valuable data concerning the incidence of dissemination at diagnosis and relapse, as well as demonstrating the true impact of grade on local control and survival with standardized radiotherapy. For a relatively rare tumor with so many possible subsets, large cooperative studies offer the best mechanism to study these patients in a short time interval.

Aggressive radiotherapy to the primary tumor is of primary importance based on substantial data demonstrating that local recurrence is the main cause of failure. Infratentorial lesions, especially high-grade lesions, must be considered at high risk to disseminate, and spinal irradiation may be appropriate even for low-grade lesions. Supratentorial lesions, even high-grade, tend to recur locally and only occasionally metastasize. The role of surgical debulking needs to be evaluated more thoroughly, based on data suggesting increased local failure rates with larger tumor burdens and suggestive data correlating local control with extent of surgical resection. Chemotherapy has not yet been thoroughly explored for this relatively rare tumor type, and cooperative group studies will be necessary to accrue large enough numbers of patients to further evaluate adjuvant chemotherapy. The Pediatric Oncology Group study should provide data to identify patient characteristics predicting a poorer prognosis; adjuvant chemotherapy should be considered for such patients. With proper radiotherapy, long-term survival is possible in about 50% of patients. However, further evaluation for subtle late effects must continue as we become more aggressive in our approach to these young children.

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16. INTRACRANIAL GERM-CELL TUMORS

Melvin Deutsch

Histologically, the types of germ-cell tumors arising intracranially are identical to the gonadal varieties. Unfortunately, a diverse and often confusing terminology has been applied to the intracranial germ-cell tumors (table 16-1). The germinoma, histologically identical to testicular seminoma or ovarian dysgerminoma, is the most common intracranial germ-cell tumor. When arising in the suprasellar area, it has sometimes been referred to as *atypical teratoma* or *ectopic pinealoma*—an unfortunate choice of terms. In the Japanese literature, intracranial germinoma, regardless of location, is often referred to as pinealoma. Teratoma is another term often used in a confusing manner without a qualifying adjective such as benign, immature, or malignant. The benign teratoma has mature elements of the three germ-cell layers without any evidence of malignant transformation. Some authors use the term *malignant teratoma* to refer to a nongerminoma malignant germ-cell tumor that could be either embryonal carcinoma, endodermal sinus tumor, or choriocarcinoma. Endodermal sinus tumor is also called yolk sac tumor by some clinicians. In addition, there are mixed tumors with various combinations of the different histological germ-cell tumors.

Intracranial germ-cell tumors arise most often in the pineal region. The relative inaccessibility of this region to surgery prior to the 1970s has confounded an accurate estimate of the incidence of the various histological types of these tumors. Intracranial germ-cell tumors appear to be more

common in Japan than in Europe and North America. Sano and Matsutani reported that germinomas represented 4.8% of all intracranial neoplasms in their series of children [1]. Arita et al. reported 49 patients with primary intracranial germ-cell tumors treated in Osaka, Japan, and this represented approximately 15% of childhood brain tumors seen during the same period [2]. Yates et al. in a series of childhood brain tumors treated in Toronto reported that intracranial germ-cell tumors comprised 2.3% of the total patient population [3].

A wide variety of histological tumor types may arise in the pineal region (table 16-2). Between different surgical series of pineal tumors, there is wide variation in the incidence of the various histological types. In the large series from Japan reported by Sano and Matsutani, germ-cell tumors comprised 73% of pineal region tumors. In a large surgical series from France [4], germ-cell tumors represented only 23% of pineal region tumors, and this incidence is similar to the 33% incidence reported by Bruce and Allen from the United States [5]. Often, pineal tumors and suprasellar germinoma have been combined together in reports, even though most of the pineal tumors did not have histological confirmation of tumor type. Wara et al. presented data from a survey of Childrens Cancer Study Group (CCG) Institutions of 118 patients with pineal and suprasellar tumors treated between 1960 and 1975 [6]. Of this group, 57 patients underwent biopsy. Ten patients did not have germ-cell tumors. In

TABLE 16-1. Intracranial germ-cell tumors: Terminology

Germinoma–Pinealoma–Atypical teratoma
Teratoma Benign
Malignant
Embryonal cell carcinoma
Endodermal sinus tumor–Yolk sac tumor
Choriocarcinoma

TABLE 16.2. Histologically verified pineal region tumors

	Sano and Matsutani	Lapras et al.	Bruce and Allen
Germ-cell tumors	77	20	10
Germinoma	58	10	2
Nongerminoma	19	10	8
Pineal-cell tumors	6	25	11
Pinocytoma		9	4
Pineoblastoma	6	16	7
Ependymoma	8	4	
Glioma	12	21	8
Other	3	16	1
Total	106	86	30

other small series with some histologically verified pineal region tumors, the reported incidence of germ-cell tumors varies from 10%–70% [7–11]. The difference in the incidence of the different histological types observed in various series probably reflects differences in referral patterns and opinion concerning the indications for surgical exploration of pineal region tumors. In reports of series containing biopsied and unbiopsied pineal region tumors, it is not clear as to what factors accounted for the decision whether or not to operate on individual patients.

Jennings et al. in 1985 reported a literature review of 389 cases of pathologically verified germ-cell tumor [12]. Benign and malignant teratomas were grouped together, since many reports did not separate or differentiate the benign, immature, and malignant types. Mixed tumors were classified according to the most malignant tissue present according to an ascend-

ing order of malignancy as follows: germinoma, teratoma, embryonal carcinoma, endodermal sinus tumor, and choriocarcinoma. Using this classification, 65% of the germ-cell tumors were germinoma, 18% teratoma, 5% embryonal carcinoma, 7% endodermal sinus tumor, and 5% choriocarcinoma. Forty-nine percent (49%) of the germinomas arose in the suprasellar area and 38% in the pineal region, whereas 65% of the nongerminoma germ-cell tumors arose in the pineal region versus 18% in the suprasellar area. Eight percent of the germinomas and 3% of the non-germinoma germ-cell tumors were present in both sites at diagnosis. Other sites of origin included the basal ganglia–thalamus region, fourth ventricle, and lateral ventricles. While these data do indicate that suprasellar germ-cell tumors are more likely to be of the germinoma variety, the percentage of germinomas occurring in the pineal region may be underestimated, since patients with a high likelihood of germinoma involving the pineal region on the basis of age, sex, marker studies, etc. may have been less likely to undergo surgical exploration.

Ueki and Tanaka reported a series of 74 intracranial germinomas of which 45 (61%) arose in the pineal region and 14 (19%) arose in the suprasellar region [13]. Seven involved both sites and eight involved other sites.

Sex and Age

For all intracranial germ-cell tumors, there is a marked male predominance. In some series, the male:female ratio for pineal germinomas is about 10:1 [1, 13]. For pathologically confirmed germinomas of all sites, the male:female ratio was 1.88:1 [12]. Conversely, females are more likely than males to be afflicted with germinoma of the suprasellar region. For the nongerminoma germ-cell tumors, the male:female proportion is at least 3:1.

The majority of patients with intracranial germinoma are in their second decade of life. The nongerminoma germ-cell tumors tend to occur at an earlier age than the germinomas.

Diagnosis

DIAGNOSTIC RADIOLOGY

On computed tomography (CT) examination, germinomas are isodense or more frequently hyperdense, and there is marked uniform enhancement with contrast. Peritumor edema usually is not present. A calcified pineal body is present in the majority of cases of pineal germinoma. Usually, the pineal calcification will be surrounded by or displaced by tumor. Rarely, calcification is within the tumor substance. In a series of nine germinomas studied by CT, Inque et al. noted the largest tumor dimension to be 3.5 cm [14]. The smallest tumor measured 1.8×1.2 cm.

Nongerminoma germ-cell tumors usually are of mixed density on CT. Jooma and Kendall described six malignant teratomas of which five were of mixed density on CT [10]. Three contained fat and four were partially calcified. Three were well demarcated. Surrounding edema was seen in only one case. Two benign teratomas

presented on CT as large, irregular, well-defined, mixed-density lesions containing fat and without surrounding edema. Occasionally, teeth within a benign teratoma can be identified on radiographic examination [15].

Zimmerman et al. suggest that CT findings and the patient's age and sex can suggest the histology of a pineal region tumor [15]. Bruce and Allen believe that the CT and magnetic resonance imaging (MRI) are helpful in diagnosing the presence of a pineal region lesion, but are not accurate in determining pathology [5] (figure 16-1).

NEUROLOGICAL SIGNS AND SYMPTOMS

Neurologic symptoms and signs associated with intracranial germ-cell tumors depend mainly on location. Signs of increased intracranial pressure are noted in the majority of patients with pineal tumors [1, 16, 17, 18]. Papilledema has been reported in at least 70% of cases with pineal tumors. Headache is the most frequent presenting complaint among patients with pineal

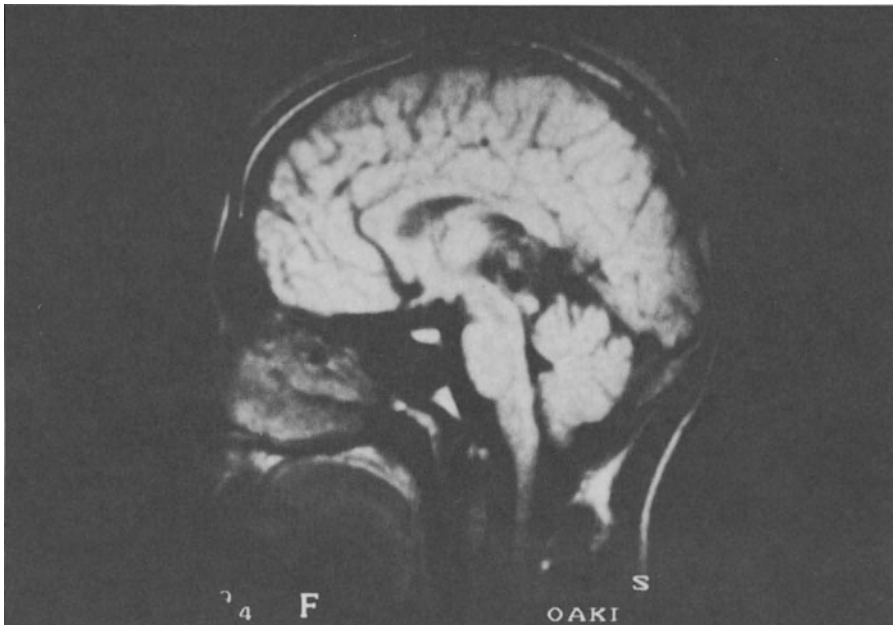


FIGURE 16-1. Preoperative sagittal MRI. Fifteen-year-old white male with immature teratoma with elevated AFP in serum and CSF.

region tumors regardless of histology, and occurs in at least 70% of patients at diagnosis. Vomiting is present in about 55% to 60% of patients.

Kageyama et al. noted the presence of Parinaud's sign (paralysis of upward gaze) in 28 of 37 patients (76%) and Argyll–Robertson pupil in 17 of 37 patients (48%) with pineal germinoma [16]. Diplopia was present in about one third of patients with pineal tumors. Other reports note Parinaud's sign in less than 50% of cases [10, 11]. Sung et al. noted visual symptoms in 64% of patients with pineal tumors [7]. Less frequent presenting neurological signs are mental changes, lethargy, sixth-nerve weakness, and signs of cerebellar dysfunction.

Among the suprasellar tumors, visual disturbances (decreased visual acuity, field deficits) are present in about two thirds of patients [7, 16, 19]. Headache and vomiting are present in at least half of patients at diagnosis.

Hemiparesis is a frequent finding in patients with germ-cell tumor of the basal ganglia–thalamus area (7 of 7 patients) [16]. Mental changes were seen in 3 of the 7 patients.

In a review of the literature, Jennings et al. reported that the symptomatic interval prior to diagnosis was much longer for germinomas than for the nongerminoma germ-cell tumors [12]. It was longer for germ-cell tumors of suprasellar origin as opposed to pineal region tumors. Females were also noted to have a longer prediagnosis symptomatic interval. Inque et al. reported a patient with diabetes insipidus and a normal CT scan in whom six months later a suprasellar germinoma was demonstrated by CT [14]. Allen et al. also reported normal CT scans in three patients with diabetes insipidus at 29, 29, and 40 months, respectively, prior to diagnosis of suprasellar germinoma [20]. Similarly, Pomarede et al. reported six patients with diabetes insipidus who had normal CT or pneumoencephalogram studies, 15 months to three years prior to diagnosis of germinoma [21].

Because of their location, intracranial germ-

cell tumors are often associated with endocrine disturbances. The majority of patients with suprasellar germinoma have diabetes insipidus at diagnosis [7, 16, 19, 21–23]. Diabetes insipidus is less common in patients with pineal tumors. Hypopituitarism is also very commonly seen with suprasellar germ-cell tumors and was noted in 15 of 15 patients with suprasellar germinoma reported by Kageyama et al., as opposed to only 9 of 37 patients with pineal germinomas [16]. Precocious puberty was seen in only 1 of 37 patients with a pineal germinoma. It was noted in 2 of 7 patients with germinoma of the basal ganglia and/or thalamus. Sung et al. reported precocious puberty in 3 of 61 patients with pineal region tumors and 2 of 16 with suprasellar tumors [7]. Jennings et al. reported diabetes insipidus in 18% and hypothalamic–pituitary failure in 19% of nongerminoma germ-cell tumors arising in the pineal region [12]. Growth hormone deficiency was documented in 11 of 13 patients with intracranial germinoma evaluated by Pomarede et al. [21]. Sklar et al. also noted that 7 of 7 evaluated germinoma patients had growth hormone deficiency [22]. Differences in the reported incidences of pituitary dysfunction associated with intracranial germ-cell tumor probably reflect varying degrees of thoroughness of evaluation.

Only 5% of patients with germinoma, histologically verified, had precocious puberty [12]. It appeared to be more common in germinomas of the basal ganglia–thalamus region. Fifty-five percent of choriocarcinomas were associated with precocious sexual development. Similarly, Ueki and Tanaka reported precocious puberty in 5.4% of patients with intracranial germinoma in contrast to 7 of 27 (26%) patients with nongerminoma germ-cell tumor [13].

Precocious puberty may be seen with a variety of intracranial lesions. Hibi and Fujiwara collected data on 281 cases of precocious puberty [24]. One hundred thirty-two (132) patients had an intracranial lesion as the cause of their precocious puberty. Forty-six patients, 44 male,

had intracranial germ-cell tumors. Thirty-nine patients, 19 male and 20 female, had a hamartoma as the cause of precocious puberty. Sixteen other tumors responsible for precocious puberty included glioma verified in 11 and suspected in two others, colloid cyst in one, and an unknown type of tumor in two patients. Of 101 patients with intracranial tumors causing precocious puberty, 74 were male. Among 31 patients with a nontumor intracranial lesion, 28 were female and only three were male. Of the 46 patients with intracranial germ-cell tumor, 21 were located in the pineal region, eight in the suprasellar region, and 14 in the thalamus or basal ganglia. Three patients had tumor involving all three sites. Histology was available in 25 of these 46 patients. Only six had pure germinoma, and at least eight had choriocarcinoma as a component. At least 37 tumors produced human chorionic gonadotropin (HCG).

TUMOR MARKERS

The intracranial germ-cell tumors, like their gonadal counterparts, may produce alpha-fetoprotein (AFP) and HCG. The detection of these products in tumor tissue, serum, or CSF is helpful in establishing the diagnosis of germ-cell tumor and its component histological types.

In a series of 386 patients with testicular germ-cell tumors, Javadpour reported that 84% of nonseminoma testicular germ-cell tumors were associated with elevated serum levels of AFP and/or HCG [25]. An elevated serum AFP was never seen with pure seminoma, but an elevated serum level of HCG occurred in 7.7% of seminoma cases.

Washiyama et al. studied 32 intracranial germ-cell tumors with immunoperoxidase staining to assess the presence of AFP, HCG, and also placental alkaline phosphatase (PLAP) [26]. PLAP was demonstrated in 26 of 32 germ-cell tumors of all histologies. However, it was not present in 89 non-germ-cell intracranial tumors. Thus, the demonstration of PLAP in tumor tissue strongly suggests a germ-cell tumor diag-

nosis. HCG was present in 3 of 15 germinomas and 2 of 2 choriocarcinomas. Mixed tumors with embryonal carcinoma often contained HCG. AFP was not found in mature teratoma, germinoma, or choriocarcinoma but was frequently seen in tumors containing embryonal carcinoma and yolk sac tumor (endodermal sinus tumor).

Kageyama et al. measured serum AFP, HCG, and carcinoma embryonic antigen (CEA) in 14 patients with presumed or proven germinoma [16]. Only two cases, both involving the basal ganglia-thalamus, had elevated serum levels of HCG. Eight patients with malignant teratoma all had elevated serum AFP. HCG was also elevated in three.

Kida et al. evaluated 17 cases of AFP-secreting intracranial germ-cell tumors [27]. Ten arose in the pineal region. AFP serum levels ranged from 100–20,000 ng/ml. Three also had elevated serum HCG. Histology was verified in 16 of the 17 patients. Nine patients had endodermal sinus tumor, six had immature teratoma with endodermal sinus tumor, embryonal carcinoma, or germinoma, and one had embryonal carcinoma. The serum AFP levels did not correlate with tumor size pretreatment but did correlate with tumor size during therapy. Allen et al. also reported a correlation between CSF marker levels and response to therapy [28].

Therapy and Outcome

NON-GERM-CELL TUMORS OF THE PINEAL REGION

For gliomas of the pineal region and third ventricle, the same guidelines for therapy apply as for gliomas of similar grade in other sites. Biopsy or partial resection should be considered, and even a gross total resection may be possible in about half of the patients [4]. Similarly, other histologically benign tumor types may be amenable to gross total resection and cure. Such cases include pineocytoma, epidermoid tumors, benign cysts, and meningiomas. The pineoblastoma should be treated according to the guide-

lines for therapy of PNET. A current Childrens Cancer Group (CCG) protocol is evaluating two different chemotherapy regimens plus cranio-spinal axis irradiation for such patients.

GERM-CELL TUMORS

The design of proper therapeutic regimens for a particular tumor type depends upon knowledge of the interaction between various prognostic factors and outcome in terms of patterns of failure (table 16-3). For the intracranial germ-cell tumors, histology is probably the most important prognostic variable. Germinomas and benign teratomas have a much better prognosis than the nongerminoma germ-cell tumors. Unfortunately, very little is known as to how other possible prognostic factors affect disease-free survival and patterns of relapse. Intuitively, extent of disease in terms of the primary tumor and the presence of dissemination should have an impact on outcome.

TABLE 16-3. Intracranial germ-cell tumors: Factors possible affecting outcome

I. <i>Histology</i>
A. Germinoma vs. nongerminoma
B. Teratoma: Benign vs. malignant
C. Nongerminoma: Choriocarcinoma vs. other types
II. <i>Age</i>
A. Children vs. adults
III. <i>Marker studies</i>
A. Presence of AFP, HCG in serum, CSF
IV. <i>Origin of tumor</i>
A. Suprasellar vs. pineal vs. other sites
V. <i>Extent of tumor</i>
A. Intraventricular extension
B. CSF cytology:
1. Site: Lumbar vs. ventricular CSF
2. Time: Preoperative vs. postoperative
C. Myelography
VI. <i>Treatment</i>
A. Surgery: Shunt, biopsy, resection
B. Radiotherapy:
1. Dose
2. Volume: Local vs. whole-brain vs. cerebrospinal axis
C. Chemotherapy

Intracranial germinomas, like their gonadal counterparts, are radiosensitive, and control rates with radiotherapy are high. In their review of literature on pathologically confirmed cases, Jennings et al. reported a statistically significant difference in survival for germinoma versus the nongerminoma germ-cell tumor types [12]. The five-year survival for intracranial germinoma of all sites was about 60%. For all nongerminoma germ-cell tumors, five-year survival was about 25%. Ueki and Tanaka reported outcome in 61 patients with intracranial germ-cell tumor from all sites presenting since 1956 at their institution [13]. Of these 61 patients, ten never received radiotherapy and died. Fifty-one were treated with radiotherapy, and 31 (61%) were alive at the time of the report. Some of the deaths were due to non-tumor or unknown causes.

In smaller series, reported five-year survival rates for germinoma are over 75% with select subgroups experiencing 100% survival [29–31]. Obviously, these latter patients all had survived surgical procedures and completed radiotherapy.

Several reports concerning therapy for intracranial germinoma have noted deaths from causes other than tumor in a substantial proportion of patients who expired. Fatal hemorrhage after shunt insertion has been reported [17]. Deaths due to hormonal or metabolic problems have also been documented. Fields et al. had 2 of 9 patients die free of disease [32]. One died of uncontrolled endocrine dysfunction due to patient noncompliance, and the other died of hyperosmolar coma. Sano and Matsutani, reporting on a series in which 16 patients died, noted that one patient died of hormonal insufficiency and eight died from unknown causes [1]. Thus, it is extremely important that patients have careful monitoring of their endocrine status posttherapy.

Results of therapy for the nongerminoma malignant germ-cell tumors are significantly worse than for germinoma or mature teratoma. In their review of the literature on pathologi-

cally confirmed germ-cell tumors, Jennings et al. reported the worst prognosis for choriocarcinoma [12]. Teratomas, embryonal carcinoma, and endodermal sinus tumors were not significantly different in terms of survival, and about one half of patients were dead within one year. Matsutani et al. reported a five-year survival of 33.6% for 29 nongerminoma malignant germ-cell tumors treated with surgery and radiotherapy [33]. The details of radiotherapy in terms of dose and field size were not presented. The author stated that "remote tumor metastasis or dissemination" was observed in 46% of patients. Kida et al. reported dissemination to the spinal cord in 5 of 16 patients with intracranial AFP-producing tumors [27]. Two additional patients developed metastasis to extra-CNS sites.

EXTENT OF DISEASE

There are no large series of prospectively staged intracranial germ-cell tumors, and thus the true incidence of dissemination at diagnosis for the various histological types is unknown. In their literature review of pathologically verified cases, Jennings et al. reported that 8% of germinomas and 3% of the non-germinoma germ-cell tumors involved both the pineal region and the suprasellar area [12]. CT evidence of intraventricular dissemination is occasionally present at diagnosis. Jooma and Kendall noted intraventricular dissemination in 2 of 17 pineal germinomas at diagnosis [10].

The actual incidence of malignant cells in the CSF for the various types of germ-cell tumors is difficult to ascertain.

Sano reported that a positive diagnosis of pinealoma (germinoma) could be made on the basis of CSF cytology in about 60% of cases [34]. His method involved removing 2–20 cc of CSF by either the lumbar or ventricular route and then filtering it through a millipore filter. The cell components in the fluid were collected on the filter and then cultured and incubated for 3–14 days. During this culture period, neoplastic cells migrate from the filter, adhering to

the wall of the bottle. The diagnosis can be made on the proliferation patterns of neoplastic cells. Information is not presented as to the incidence of a positive cytology by this method for fluid from the ventricular site versus the lumbar puncture site. Information is not presented as to whether or not there was a difference in cytology findings preoperatively versus postoperatively.

Inque et al. reported nine cases of intracranial germinoma in which the CSF demonstrated tumor cells in all cases [14]. Shibamoto et al. reported CSF cytology findings in 16 patients with histologically confirmed or suspected intracranial germinoma [35]. Four of eight patients with pineal tumors had a positive cytology whereas 8 of 11 patients with a suprasellar or intrasellar tumors had a positive cytology. Two of three patients with tumors in both locations had positive cytologies, as did 2 of 4 patients with tumors involving the basal ganglia or thalamus. Allen et al. reported malignant cells in the CSF in 4 of 11 patients with germinoma [20]. Four patients with nongerminoma germ-cell tumors had negative cytological studies. Pomarede et al. found malignant cells in 5 of 12 patients with germinoma [21]. Interestingly, one patient had malignant cells present in CSF one year before there was radiologic evidence of tumor.

Ueki and Tanaka reported CSF cytology results on 25 patients with germinoma, three of which were confirmed by biopsy [13]. Twenty-one patients had malignant cells demonstrated in ventricular and/or lumbar CSF. Malignant cells were present in ventricular CSF from 17 of 20 patients and lumbar CSF from 11 of 20 patients. Six patients with a positive cytology from ventricular CSF had negative lumbar CSF cytology. Conversely, only one patient with a positive lumbar CSF had a negative ventricular CSF.

Allen et al. noted evidence of dissemination in 7 of 11 newly diagnosed patients with intracranial germinoma [20]. Multiple intraventricular metastases were noted in three patients,

and CSF contained malignant cells in four. Myelography in eight germinoma patients revealed filling defects consistent with subarachnoid spread in two. This probably represents the largest group of germinoma patients prospectively staged with myelography.

There are very few data concerning the prognostic significance of a positive CSF cytology for intracranial germinoma. In most reported series, data are not presented concerning the site from which CSF was withdrawn nor the temporal sequence in relationship to a surgical procedure or biopsy. It is not known whether or not the presence of malignant cells in CSF from the lateral ventricle has the same significance as malignant cells in CSF from a lumbar puncture. There are no data from the many surgical series as to whether or not a postoperative CSF sample (from any site) is more likely to contain malignant cells, perhaps as a result of surgical manipulation of the tumor. Similarly, the significance of a postoperative positive CSF sample versus a preoperative sample is not known. Of 21 patients with a positive CSF cytology reported by Ueki and Tanaka, nine had died and 12 were alive at one month to nine years [13].

It is not clear whether or not the presence of malignant cells in CSF is indeed an indication of dissemination and the need for craniospinal axis irradiation. In spite of a high incidence of positive CSF findings, Sano and Matsutani report subsequent dissemination via the CSF pathways in only 3 of 60 patients [1]. They indicate that the majority of their patients were treated with irradiation of just the primary area, although they do state that some patients also had craniospinal axis irradiation.

Ueki and Tanaka reported metastasis to the spinal cord in only 3 of 74 patients with intracranial germinoma in spite of a high incidence of positive CSF findings and the use of radiotherapy only to the primary tumor volume [13]. However, only 51 of 74 patients were treated with radiotherapy. The other 23 had died prior to institution of radiotherapy or diagnosed prior to the availability of radio-

therapy. Of the 51 irradiated patients, only 31 were alive. It is quite possible that at least some of the patients dying either before radiotherapy could be administered or from intracranial recurrent tumor had asymptomatic spinal cord involvement.

For all newly diagnosed cases of germ-cell tumor, regardless of histology, the author suggests myelography and CSF cytology from a lumbar puncture site. Also, specimens from the lateral ventricle, if available, should be examined for malignant cells. Measurements of AFP and HCG in serum and CSF should be obtained on all patients with suspected or proven germ-cell tumors. For the nonbiopsied, presumed germ-cell tumor, the presence of AFP indicates endodermal sinus or embryonal carcinoma elements and thus not a pure germinoma. For the germinoma, it is not clear if the presence of HCG in the serum or CSF has prognostic importance. Germinomas seem to have a good prognosis even if the HCG is elevated [2]. For the nongerminoma malignant germ-cell tumor, the presence of HCG and/or AFP in serum and CSF pretreatment probably does not impact on the already poor prognosis of these tumors.

AGE AND PROGNOSIS

Age is of prognostic importance in patients with pineal germinoma. For patients treated with resection and postoperative radiotherapy to the involved region, Sano and Matsutani reported that patients under 15 years of age had a five- and ten-year survival rate of 81.4% and 81.4%, respectively [1]. For patients over 15 years of age, five- and ten-year survival rates were 54.8% and 48%, respectively. For intracranial germinomas at all sites, patients under 15 years of age experienced five- and ten-year survival rates of 86.9% and 86.9%, respectively, whereas for patients over 15 years of age, it was 65% and 60.2%, respectively. For a group of patients with unbiopsied pineal region tumors, Jenkin et al. reported a five-year survival rate of 81% for patients under age 25

years, whereas for patients over 25 years of age, the five-year survival rate was only 37% [8]. Similarly, Wara et al., in a report of pineal and suprasellar region tumors, most of which were unbiopsied, also noted that patients under 30 years of age had a much better survival than older patients [6]. It is likely that in these two latter series, older patients, especially with unbiopsied tumors, were more likely to have gliomas.

For patients with nongerminoma germ-cell tumors, the majority of patients are children. There are no data as to an effect of age on prognosis for the nongerminoma germ-cell tumor. For patients with any type of intracranial germ-cell tumors, there are no data as to whether or not the incidence of dissemination at diagnosis is related to age.

Treatment

SURGERY

Shunts. Since a majority of patients with intracranial germinoma, especially those involving the pineal region, present with increased intracranial pressure, a ventriculosystemic shunt is frequently inserted prior to therapy, especially if resection is not planned. Several reports have described tumor dissemination via shunts into the abdomen in patients with intracranial germ-cell tumors of both the germinoma and nongerminoma types [36–40]. Kun et al. also demonstrated tumor emboli in the proximal end of a removed shunt in a patient who later was found to have intra-abdominal metastasis from a primary intracranial germinoma [38]. It is not apparent whether or not dissemination via the shunt is more likely with a particular histological variety. Bamberg et al., in a literature review, reported metastasis to the abdomen in 4 of 21 patients with endodermal sinus tumor of the pineal region [39]. All four had shunts in place.

Jennings et al. reported the incidence of abdominal and pelvic metastasis in shunted patients (all types of intracranial germ-cell

tumor) to be 10% [12]. Thus, it is imperative that protective shunt filters be utilized in situations where ventriculosystemic shunts are necessary.

Extra-CNS metastasis from intracranial germ-cell tumor may occur even in the absence of a ventriculosystemic shunt [41–43]. The possible role of surgical manipulation of the tumor in facilitating extra-CNS dispersion of intracranial germ-cell tumor is unknown. However, Borden et al. reported a case of pineal germinoma with bone and lung metastasis [44]. This patient did not have biopsy or resection but did have a ventriculocisternostomy.

Resection. Prior to the 1970s, most reported series of pineal tumors consisted of mainly nonpathologically verified tumors many presumed to be germ-cell tumor on the basis of clinical presentation, location, age, and sex. Prior to the 1970s, operative mortality was high and resections were usually incomplete. CT and MRI now provide precise details about the size and shape of a pineal tumor, its extension, even its consistency, and also the surrounding anatomy. Improvements in neurosurgical technique, such as the operating room microscope, ultrasonic aspirator, laser beam, etc., have improved the surgeon's capability not only to approach pineal region tumors for biopsy, but also to accomplish gross resections. Lapras et al. have used the occipital supratentorial, and transtentorial approach for pineal region tumors since 1970 [4]. Of 86 patients, there have been five postoperative deaths (5.8%). In 56 patients undergoing total removal for a variety of lesions, 46 (82%) were alive (survival intervals not presented). Among ten germinomas, six had total resection and nine were alive.

Hoffman et al. also suggested surgery for all pineal region tumors and reported an operative mortality of 4.3% (1/23) for pineal tumors treated between 1975 to 1982 [17].

Sano and Matsutani reported 60 germinomas treated by resection and postoperative radio-

therapy [1]. There was no operative mortality. Thirty-two arose in the pineal region, 20 in the suprasellar area, and eight in other areas. These authors used the occipital transtentorial approach or an infratentorial supracerebellar approach for pineal tumors and a subfrontal approach for suprasellar tumors. Postoperative radiotherapy, 5000–6000 rads at 100–200 rads daily, was administered via small portals to a localized volume. More recently, an unknown number of patients were treated with craniospinal axis irradiation. For all patients, the three-, five-, and ten-year survival rates were 81.4%, 74.8%, and 69.3%, respectively. Suprasellar germinomas had a better prognosis than pineal tumors. For 20 patients with suprasellar tumors, survival at five and ten years was 100% and 92.3%, respectively, whereas for the patients with pineal tumors, five- and ten-year survival was 64.7% and 60.1%, respectively. The authors suggest that the better results obtained with suprasellar germinoma may be due to easier and more extensive resections than possible for pineal tumors. Of this group of 60 patients, 16 died. Causes of death were unknown in eight, and two others died of other disease. Two patients with pineal tumors had local recurrence, and 3 of 60 had dissemination via the CSF pathways. The low incidence of dissemination suggests that surgery did not promote tumor dissemination. However, data were not presented as to how many of these patients had craniospinal axis irradiation.

For mature (benign) teratoma, complete resection is frequently possible and often curative. Matsutani et al. reported a ten-year survival rate of 78.3% with 16 mature teratomas treated by resection [33]. Lapras et al. also reported five patients with benign teratoma alive without recurrence following total resection [4]. Of five malignant teratomas, only two underwent total removal and three were alive. (Survival intervals were not reported.)

It has been suggested that biopsy may promote dissemination via the CSF pathways. Wara et al., in review of the CCG experience, re-

ported spinal metastasis developing in 5 of 36 patients with biopsy-proven germinoma (14%) [6]. One of seven patients with malignant teratoma developed spinal metastasis, and 2 of 7 patients with pineal parenchymal tumors developed spinal metastasis. Conversely, only 1 of 59 unbiopsied patients developed spinal metastasis (1.7%). None of the patients who developed spinal metastasis had received prophylactic spinal cord irradiation. Similarly, Jenkin et al. noted a higher incidence of cord involvement in patients with biopsy-proven germinoma as opposed to those with an unbiopsied presumed germinoma [8]. Sung et al. also noted spinal cord metastasis developing in 3 of 10 patients with biopsy-proven suprasellar germinoma [7]. Among four patients with biopsy-proven pineal germinoma, spinal cord involvement subsequently developed in three cases.

The incidence of relapse in the spinal cord may be underestimated in all reported series. It is doubtful that many patients with recurrent intracranial germ-cell tumor were evaluated with myelography at the time of relapse. Thus, it is possible that many patients dying with recurrent intracranial tumor may have had spinal cord involvement. Deutsch has demonstrated that a high percentage of patients with recurrent medulloblastoma intracranially have evidence of asymptomatic cord involvement when evaluated with myelography [45].

One approach to the treatment of a presumed germ-cell tumor is to consider radiotherapy alone with a shunting procedure if necessary. If serum and CSF are negative for AFP, the tumor is unlikely to be the more aggressive nongerminoma endodermal sinus tumor or embryonal carcinoma. However, the presence of HCG may be seen with germinoma or with the very highly aggressive choriocarcinoma. If both markers are negative, and CSF cytology is likewise negative or suggestive of germinoma by cytology, a trial of low-dose radiotherapy has been suggested. After the administration of 2000 rads, the patient is reevaluated by CT, and if there is

good regression, germinoma is considered likely and radiotherapy is continued. If there is very little or no response by CT evaluation at 2000 rads, the presumed diagnosis is a nongerminoma tumor and using localized portals, radiotherapy can be continued to a full dose as for a glioma.

Using this approach, one may irradiate a benign but nonresponsive lesion that might best be managed by resection. Also, in the patient with HCG elevation, choriocarcinoma cannot be excluded, and such patients might be candidates for chemotherapy. A PNET might be responsive yet require more extensive treatment, such as high-dose craniospinal axis irradiation and chemotherapy. Also, an occasional nongerminoma germ-cell tumor that does not produce AFP will be treated as a germinoma.

Some investigators have suggested surgery if there is no response to the 2000 rad trial dose [16]. However, surgery after radiotherapy may be more difficult, and a total resection may be less likely [4].

RADIOTHERAPY

In the treatment of intracranial germ-cell tumors with radiotherapy, there are basically two controversies: 1) Should radiotherapy be administered just to the region of the tumor plus or minus the entire ventricle system or to the entire brain plus or minus the spinal cord? and 2) What is the optimum radiation dose for treatment of germinoma?

Investigators advocating irradiation of just the involved region of the brain report high survival rates with local irradiation and correspondingly a low incidence of dissemination to the spinal cord. Conversely, other reports indicate an appreciable incidence of dissemination via the CSF pathways after irradiation of just the local tumor region.

Ware et al. treated 19 patients with either unbiopsied pineal region tumors or suprasellar germinoma with portals that usually included the entire ventricle system but not the spinal axis [29]. Fifteen patients were alive, free of disease, 2–21 years following therapy. In this

series, there was no instance of relapse in the spinal cord. Linstadt et al., from the same institution, reported a study of 33 patients, 13 with biopsy-proven germinomas [30]. Only two patients were treated with prophylactic spinal cord irradiation. None of the 13 biopsy-proven germinoma patients developed recurrence. In the unbiopsied group, five-year actuarial disease-free survival was 72%. Only three patients had local recurrence, and at autopsy, two were found to have non-germ-cell tumor. Among 19 unbiopsied patients treated without spinal cord radiotherapy, one developed subsequent cord involvement. At laminectomy, germinoma was found. These authors suggest that spinal cord irradiation be reserved for those patients presenting with malignant cells in the CSF, documented subarachnoid metastasis, or gross tumor spill into the CSF from a surgical procedure. Similarly, Salazar et al. recommended whole-brain irradiation or at least fields sufficiently large to encompass the entire ventricular system for the treatment of pineal region tumors [46]. Irradiation of the spinal cord electively was not recommended.

Bradfield and Perez treated 17 patients with either confirmed germ-cell tumor or unbiopsied tumors of the pineal or suprasellar region using large cranial portals (non-whole-brain) [47]. Four patients developed recurrent tumor in the spinal cord. In two, the pathologic diagnosis was germinoma, and in two others, histopathology was unknown.

Sung et al., in a report on 61 pineal region tumors and 16 suprasellar tumors presumed to be germinoma, noted an increased incidence of subsequent spinal cord tumor in patients undergoing a biopsy procedure as opposed to those with unverified tumors [7]. Three of four verified germinomas involving the pineal region subsequently developed spinal cord involvement. Four of ten histologically verified suprasellar germinomas subsequently developed relapse in the spinal cord. In total, 8 of 14 histologically verified germinomas metastasized to the cerebral or spinal subarachnoid space.

Jenkin et al. noted relapse in the spinal cord in 3 of 13 patients treated with cranial irradiation for pineal germinoma [8]. Hoffman et al. reported metastasis to the spinal cord in 3 of 15 patients with germinoma [17]. None had been treated with spinal cord irradiation at diagnosis.

In a review of Childrens Cancer Study Group (CCSG) institutions, Wara et al. reported spinal cord involvement in 5 of 36 patients with histologically confirmed germinoma who did not receive prophylactic irradiation of the cord [6]. Interestingly, only 1 of 59 patients with an unbiopsied pineal or suprasellar region tumor subsequently developed spinal cord involvement.

In a large series of 60 patients with histologically verified intracranial germinoma treated by resection and postoperative radiotherapy, usually just to the involved region, Sano and Matsutani reported only three instances of subsequent CSF dissemination [1]. However, eight patients died of unknown causes. Interestingly, Sano previously reported that about 60% of patients with germinoma had malignant cells in the CSF [34]. In spite of this high incidence of a positive CSF cytology, the incidence of dissemination was rather low.

Shibamoto et al. treated 70 patients for presumed or histologically verified intracranial germinoma [35]. The diagnosis was based on histology in 30 cases, CSF cytology in 12 cases, and on clinical and radiographic findings in 28. The primary tumor site alone was irradiated in 34 cases. The entire craniospinal axis was irradiated in 22 cases, the whole brain in four cases, and the ventricles plus spine in six cases. For all patients who completed radiotherapy, the five- and ten-year survival rates were 86% and 79%, respectively. Survival and relapse-free survival did not differ significantly for the four different treatment groups. Of the 40 patients who did not receive whole-brain irradiation, five developed intracranial recurrence, four adjacent to the primary site but one distant. Among the 26 patients who received whole-brain irradiation, there was no intracranial recurrence. One patient receiving craniospinal

axis irradiation developed spinal cord metastasis thought to be due to inadequate coverage of the entire spinal column. The authors suggest radiation just to the involved region with a wide margin for patients with a negative CSF cytology and no evidence of metastasis.

Amendola et al. reported 12 patients with pineal region tumors, histology unverified, treated with just local irradiation, and there was no evidence of recurrent tumor in any patient with 12–30 years of follow-up [31]. None had received craniospinal axis irradiation. Among 15 patients with confirmed pineal germinoma, two patients subsequently developed cord involvement. One had been treated with craniospinal axis irradiation.

Fields et al. did not observe recurrence in nine patients treated with craniospinal axis irradiation for suprasellar germinoma [32]. Two patients died without evidence of tumor at about one year following therapy.

The optimum dose for irradiation of germinoma has not yet been established. The histologically identical testicular seminoma and ovarian dysgerminoma are curable with modest doses of radiotherapy in the range of 2500–3000 rads administered over three weeks. In many reports on germinoma, radiotherapy doses of at least 4500 rads have been administered to the primary tumor. In many of the series reported from Japan, the primary germinoma has been treated with 5000–6000 rads [1, 13, 14, 35, 48]. Nevertheless, there have been reports of patients with presumed or biopsied germinoma who have been treated successfully with much lower doses. Amendola et al. reported long-term control of disease in 12 patients with presumed pineal region germinomas [31]. Seven were treated with doses to the primary tumor of 3000–4200 rads. Abay et al. reported improved local control using radiation doses greater than 4000 rads for unbiopsied pineal region tumors [11]. However, in this series, patients were treated without a histological diagnosis. Autopsies on nine patients did not reveal any germinomas. Thus, it is

possible that at least some of the failures at low dose were not radiosensitive germinoma.

Inque et al. followed nine patients with intracranial germinoma with CT evaluations during therapy [14]. All tumors disappeared by the time 3300 rads had been administered. In two patients, there was complete disappearance of the tumor at 1600 and 1800 rads, respectively. Three other tumors disappeared by the time 2000 rads had been administered. In spite of the rapid disappearance of tumor with low doses, the authors still recommended the administration of 4500–5500 rads. Ueki and Tanaka also report that most intracranial germinomas disappear by CT evaluation after the administration of 800–2000 rads [13]. Takeuchi et al. also reported complete responses at 1000–1200 rads [23].

Sung et al. reported intracranial relapses in 15 of 32 patients with mainly unbiopsied pineal and suprasellar tumors treated with 3800–4500 rads [7]. For the patients treated with 5000–5500 rads, the incidence of intracranial relapse was only 10% (4 of 40).

Shibamoto mentioned four patients with intracranial germinoma treated with 1950–4100 rads, and all were free of recurrence at 5–16 years [35].

Fields et al. recommend 4500 rads to the primary tumor [32]. In this series, the spinal cord was irradiated prophylactically with 2000–3000 rads and there was no evidence of recurrence.

In the series reported by Shibamoto et al., the spinal cord was irradiated prophylactically with 2400–2700 rads and there was only one recurrence, thought to be due to inadequate coverage of the lower thecal sac [35].

From the available reported data on germinoma, it appears that 4500–5000 rads is adequate for irradiation of the primary tumor. It is possible, and even likely, that lower doses may be sufficient for local control in the majority of patients with germinoma. For the prophylactic irradiation of the craniospinal axis, 2500–3000 rads is probably adequate. Fortunately, the majority of patients with intra-

cranial germinoma are in the second or third decades of life, and thus there should be less late serious sequelae such as interference with growth and intellectual impairments than would be anticipated with a younger age group, such as the medulloblastoma patient population.

Ueki and Tanaka noted a better prognosis with small versus larger germinomas, but they did not give a definition of small or large in terms of measurements [13]. Perhaps larger tumors should be treated with higher doses of radiation.

The nongerminoma malignant germ-cell tumors require higher doses of radiotherapy for local control. The overall cure rate is much lower than for germinoma. Such patients should be treated with craniospinal axis irradiation. The site of the primary tumor should receive 5400 rads in 30 fractions. The craniospinal axis should be treated with 3600 rads in 20 fractions. Perhaps, for younger children without any evidence of dissemination, a lower dose to the craniospinal axis may be adequate. In patients with dissemination, higher doses should be considered to areas with gross metastasis.

CHEMOTHERAPY

One might expect that extra-CNS metastatic lesions from an intracranial primary germ-cell tumor would respond similarly to chemotherapy as would metastasis from a testicular primary. Indeed, several reports have described favorable responses with combination chemotherapy in the treatment of extra-CNS metastasis from primary intracranial germ-cell tumors.

Wilson et al. used cis-platinum, vinblastine, cyclophosphamide, and bleomycin to treat a patient with intra-abdominal metastasis and ascites from a primary suprasellar yolk sac tumor [36]. The patient also received maintenance vinblastine, chlorambucil, and actinomycin-D. The patient experienced a complete response but subsequently developed recurrent intracranial disease. Neuwelt et al. reported a complete response of intra-abdominal metastatic germinoma from a primary intracranial ger-

minoma using cis-platinum, vinblastine, and bleomycin for six courses [37]. The patient was well one year later. Kun et al. treated intra-abdominal metastasis from a primary basal ganglia germinoma with vincristine, nitrogen mustard, and whole-abdominal radiotherapy [38]. The patient was alive and free of disease 38 months from detection of metastasis. Gay et al. treated metastasis involving bone from a primary suprasellar germinoma using cis-platinum, vinblastine, and bleomycin administered for a 16-month period [41]. The patient was alive and free of disease 14 months later. A complete response of lung lesions was reported by Borden et al. using chlorambucil, actinomycin-D, and methotrexate [44].

Several examples of recurrent germinoma within the central nervous system have responded well to cis-platinum, velban, and bleomycin regimens [37, 49] and even to adriamycin, vincristine, and bleomycin [50].

Kida et al. reported the use of adjuvant chemotherapy in patients with nongerminoma germ cell tumors [27]. Nine patients were treated with cis-platinum alone or in combination with other agents, usually bleomycin and vinblastine. Four patients were alive at 7, 9, 23, and 59 months, respectively, following treatment. In contrast, six patients were treated with either no chemotherapy or regimens not containing cis-platinum. All were dead by four years, one month. Matsutani et al. also reported eight patients treated with cis-platinum, vinblastine, and bleomycin for intracranial malignant germ-cell tumor, and four survived for more than two years without recurrence [33]. Allen et al. used high-dose methotrexate and then BCNU and radiotherapy to treat a child with choriocarcinoma presenting with multiple intracranial lesions [28]. Two courses of methotrexate caused an elevated CSF HCG level to revert to normal. The child was alive and well 2½ years after diagnosis.

Allen et al. treated four patients with intracranial malignant teratoma using a four-drug regimen containing cyclophosphamide, vin-

blastine, bleomycin, and cis-platinum [20]. Two patients were disease-free at 12 and 21 months from diagnosis, respectively. The same group treated 11 patients with intracranial germinoma using either high-dose cytoxan, 60–100 mg/kg administered in two doses over two days, or the above four-drug regimen with actinomycin rather than cyclophosphamide. Ten of the 11 intracranial germinoma patients had complete disappearance of all evaluable disease after two courses of chemotherapy. One had a partial response. In patients with a complete response, the administered radiotherapy consisted of 3000–4500 rads administered to the local region. Six patients received cranio-spinal axis irradiation with doses of 2000–3600 rads. Ten patients were in continuous disease-free remission 20–89 months from diagnosis. For intracranial germinoma showing a complete response to chemotherapy, the authors suggest 3000 rads to the primary tumor and 2000 rads to the craniospinal axis.

Summary

Intracranial germinomas are among the most curable of all brain tumors. Still, there are many unresolved issues concerning the proper management of these good-prognosis patients. Germinomas are very sensitive to radiotherapy, but the optimum dose is as yet not established. While many clinicians administer 5000 rads or more to the primary tumor, the rapid response as noted on CT and reported cures at lower doses suggest that many patients could be cured with lower doses, perhaps 3000–4000 rads. Despite a high incidence of positive CSF cytology findings in patients with germinoma, cure rates are high with local radiotherapy. There are no accepted guidelines as to which patients should have prophylactic craniospinal axis irradiation. Obviously, patients with a positive myelogram or CT demonstration of multiple lesions require extensive field irradiation. The significance of a positive CSF cytology has not been established in terms of prognosis and therapy.

More data are needed concerning pretherapy extent of disease for all types of intracranial germ-cell tumors. CSF cytology from lumbar and ventricular sites, myelography, and CSF and serum markers should be done in all newly diagnosed patients, and restaging should be repeated at time of relapse in order to determine patterns of failure. It is possible that a substantial proportion of patients with intracranial recurrence have subclinical spinal cord involvement.

The role of surgery in the management of intracranial germ-cell tumors is debatable. With improved imaging and marker studies, it may be possible to select a subgroup of patients, highly likely to have germinoma, for treatment without even biopsy. There is also concern that resection or even biopsy may promote dissemination of tumor within the CSF pathways and even to extra-CNS sites. Similarly, there is concern that ventriculostomy shunting may promote access of tumor cells to regions beyond the central nervous system.

Finally, sporadic reports indicate that intracranial germ-cell tumors may be as responsive to chemotherapy as their gonadal counterparts. Further improvements in outcome, especially for the poor-prognosis nongerminoma germ-cell tumors, will be realized with the use of improved adjuvant chemotherapy regimens.

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17. MIDLINE INTRA-AXIAL TUMORS (NUCLEAR AND BRAINSTEM)

A. Leland Albright

Midline intra-axial tumors occur in the diencephalon and in the brain stem. Tumors in those two sites should be considered separately because they differ greatly in clinical features, therapy and outcome: approximately 70% of children with diencephalic tumors live five years after diagnosis, whereas only 30% of children with brain stem gliomas survive that long (figure 17-1) [1, 2].

Nuclear Tumors

Tumors in the diencephalon have been called diencephalic, thalamic, hypothalamic, third ventricular, basal ganglial, and nuclear. The latter term will be used in this chapter because it connotes both the central location and the involvement of deep nuclei. Approximately 7%–10% of pediatric brain tumors are nuclear, with 5%–7% in the basal ganglia and 2%–3% in the hypothalamus. Nuclear tumors affect the sexes and hemispheres equally and occur most often in children 3–10 years old, with a median age of seven years. Less than 5% of these children have neurofibromatosis.

SIGNS AND SYMPTOMS

One third of children with nuclear tumors are symptomatic for less than a month before diagnosis, one third for 1–4 months, and the remainder for five months to three years. Symptoms include extremity weakness (50%), seizures (17%), and the nonspecific symptoms of hydrocephalus (headaches 70%, vomiting

50%, lethargy 50%, blurred vision 25%) [3]. If the hypothalamus is involved, symptoms such as precocious puberty, the diencephalic syndrome, or diabetes insipidus have localizing value. The diencephalic syndrome of Russell occurs infrequently, even in children with hypothalamic tumors, although most such children have abnormalities of body weight.

The most common clinical signs are hemiparesis (75%) and papilledema (50%); no other signs occur in more than half of all patients. No symptom or sign accurately predicts duration of survival, although children without focal neurologic signs tend to survive longer [4].

DIAGNOSTIC TECHNIQUES

Nuclear tumors are best localized by either computed tomography (CT) or magnetic resonance imaging (MRI) scans (figure 17-2). Such scans usually show unilateral tumors, which are generally less than 5 cm, and which occur more often in the thalamus than in the caudate or striatum. On CT, approximately 30% contain foci of calcification, 20% are partially cystic, and 85% have associated hydrocephalus. Tumors containing calcium or cysts may have a more benign course. Typical tumors are isodense, but enhance considerably after injection of a contrast agent. However, such enhancement has not correlated with histologic tumor grade [3]. MRI scans usually display the tumor best on the T1-weighted images and on the first echo of T2-weighted images. The apparent tumor boundaries on MRI are often larger and more clearly

defined than on CT, and the distinction between hypodense tumor and peritumoral edema is made more accurately.

Although skull X-rays occasionally show nuclear calcification, they are unnecessary in centers with high-quality CT or MRI scans. Lumbar punctures are generally contraindicated because of the risk of herniation from mass effect and hydrocephalus. Current quality scans usually obviate the need for angiograms.

OPERATIONS

Nuclear tumors traditionally have not been operated on for either biopsy or decompression because the operative mortality prior to the 1970s ranged from 25%–40%. However, morbidity and mortality have declined substantially, and such operations are increasingly performed. Reasons for obtaining a tissue diagnosis in nuclear tumors include the following: 1) to determine the tumor grade, which will determine the subsequent need for chemotherapy; 2) to exclude nonneuroectodermal tumors such as hamartomas, lymphomas, and germinomas, especially in the hypothalamus; 3) occasionally, to decompress cysts and tumor mass, avoiding the multiple shunt catheters that are needed if the tumors isolate portions of the ventricular system; and 4) perhaps to lengthen survival.

Stereotactic biopsies are indicated for ill-defined, nonenhancing tumors with little mass effect, especially bilateral hypothalamic tumors, and for well-defined masses in children without neurologic deficits. Ideally, such biopsies are performed in the CT scanner with a spiral biopsy needle, sampling sequentially deeper levels of the tumor, beginning with peritumoral edema, then the tumor periphery, and finally the tumor core. In children, such biopsies require a general anesthetic, but the biopsy is adequate to diagnose more than 95% of tumors, and the risk of intratumoral hemorrhage requiring evacuation is less than 2% [5]. Stereotactic biopsies are difficult in children less than two years old because their heads are

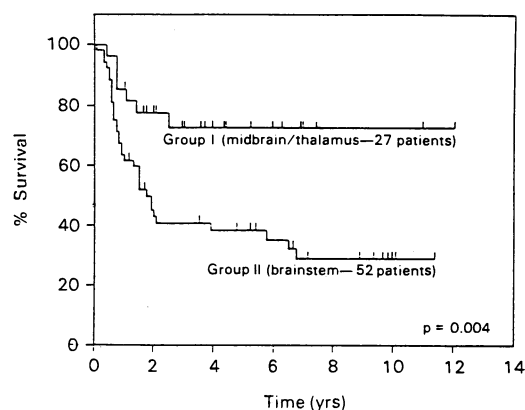


FIGURE 17-1. Survival percentages of children with thalamic/midbrain and brainstem tumors. The survival curves are significantly different ($p = 0.004$). (Reprinted from [1] with permission.)

smaller than most stereotactic frames. Open needle biopsies appear to entail higher risks of hemiparesis (8%) and of being nondiagnostic (8%) [3].

Open biopsies and decompressions are appropriate for some nuclear tumors, usually those that are relatively discrete, with substantial size or mass effect, or with cysts, especially if pre-operative neurologic deficits are present. The operative approach to the tumor depends on its location. Nuclear tumors in the caudate and thalamus are usually approached through the anterior corpus callosum, but posterior–lateral thalamic tumors, especially those with lateral cysts, are often approached through the cyst by an incision in the parietal cortex. Inferior hypothalamic tumors lying within the suprasellar cistern can be approached by elevation of the inferior frontal and temporal lobes. The use of intraoperative evoked potential monitoring probably decreases the risk of such operations. Somatosensory evoked potential monitoring is useful during most nuclear tumor operations, although for those in the hypothalamus and inferior–posterior thalamus, visual evoked potentials are more appropriate.

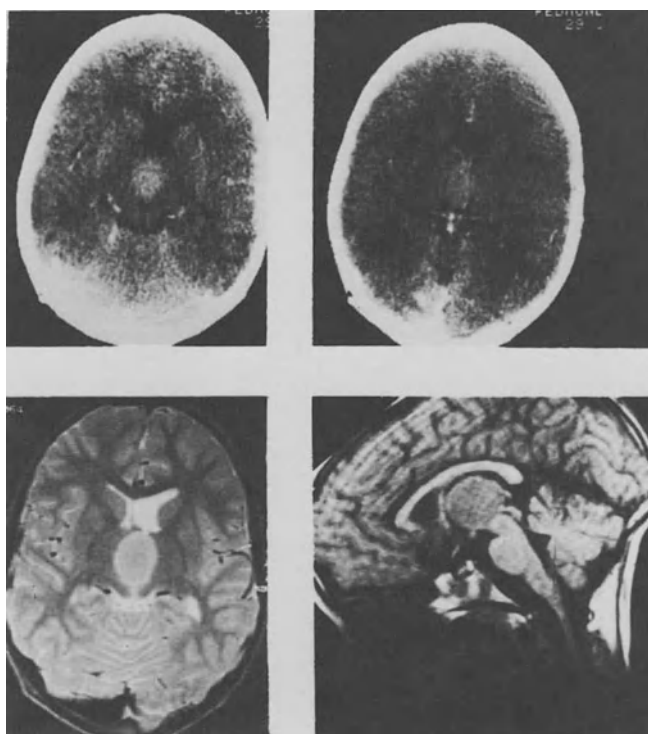


FIGURE 17-2. Contrast-enhanced CT (Top) and T2-weighted MRI (bottom) scans of a pilocytic nuclear astrocytoma.

Nuclear tumors in children can often be extensively removed by microsurgical techniques and adjuncts such as the ultrasonic surgical aspirator or lasers, working from within the tumor toward its periphery (figure 17-3). The mortality from subtotal or total removals of nuclear tumors is now approximately 2%, and the risk of morbidity such as hemiparesis or visual field deficit is 15%–25%, depending on the extent of resection and on the distinction between tumor and adjacent normal parenchyma. Such removals may delay the need for radiotherapy in low-grade tumors, allowing time for further brain maturation, and for high-grade tumors may prolong survival. Data from the Children's Cancer Study Group protocol 943 indicate that children with supratentorial anaplastic astrocytomas survive significantly longer after subtotal or total resections than

after biopsy alone, but few tumors in that study were in the deep nuclei [6]. Unless the mass effect of nuclear tumors is decreased surgically, approximately 60% of children will need a CSF shunt to treat hydrocephalus at or soon after the time of diagnosis.

PATHOLOGY

Approximately two thirds of nuclear tumors in children are low-grade neoplasms, primarily astrocytomas and, less frequently, mixed gliomas or subependymal giant-cell astrocytomas [3,4]. Hypothalamic tumors are even less likely to be anaplastic gliomas, but the frequency of germinomas or teratomas in those sites is greater. Tumor histology in nuclear tumors is usually uniform: moderately cellular astrocytomas with moderate pleomorphism and hyperchromatism but without mitoses, hemorrhage, or necrosis. One third of nuclear tumors

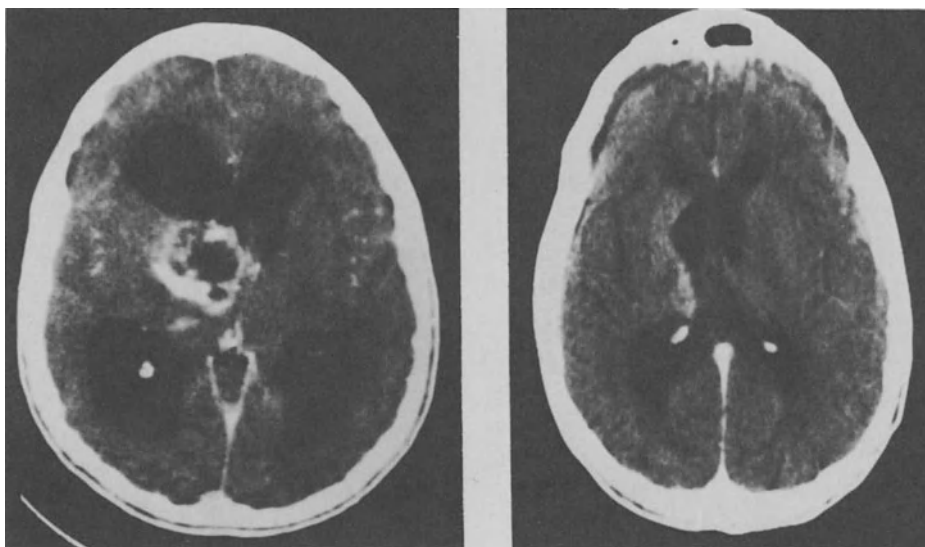


FIGURE 17-3. Contrast-enhanced preoperative (left) and postoperative (right) CT scans of a child with an anaplastic astrocytoma.

are high-grade, primarily anaplastic astrocytomas. Glioblastomas, primitive neuroectodermal tumors, and malignant mixed gliomas occur less frequently. The pathologic diagnosis correlates strongly with outcome. The mean postoperative survival time of children with low-grade nuclear tumors is approximately five years. For those with high-grade tumors, the mean postoperative survival time has been approximately one year, and nearly all have died within three years [3, 4].

RADIOTHERAPY AND CHEMOTHERAPY

The value of radiotherapy for low-grade nuclear tumors is debatable. Published data indicate that 40%–70% of children who undergo radiotherapy survive, but the tumor grade was known for few of those patients. No randomized clinical trial has been completed to compare the survival of irradiated and nonirradiated children with low-grade nuclear gliomas. For children with high-grade gliomas, radiation is given routinely to the involved tumor volume (ideally estimated by MRI rather than by CT) plus a 1 cm margin, rather than to the whole brain or to the craniospinal axis. Radiotherapists recommend 5000–5500 cGy over six weeks. Tumor recurrences are almost always at the

primary tumor site rather than at distant sites. Interstitial radiation has been used in a few children with nuclear tumors, either alone or as an adjunct to external radiotherapy, but its current role is primarily for recurrent tumors.

The role of chemotherapy for patients with anaplastic nuclear tumors is uncertain; no published data prove or disprove the benefit of chemotherapy. Benefit can be inferred from the CCG 943 data, which show that chemotherapy prolonged survival by approximately 20% for children with anaplastic gliomas in the cerebral hemispheres [6].

FOLLOW-UP CARE

After the initial hospitalization, children with low-grade tumors need repeat CT or MRI scans every six months for 2 to 3 years and annually for two additional years. Those with high-grade tumors need more frequent evaluation—scans every four months for two years, every six months during the third and fourth years, and a final scan at five years.

The quality of life for children with nuclear tumors is proportional to their condition at the

time of diagnosis. Tumor recurrences usually occur within three years after diagnosis. Cystic recurrent tumors can be treated effectively by the stereotactic injection of ^{32}P or ^{90}Y into the tumor cyst. In children, nuclear tumors appear to undergo malignant degeneration less frequently than brainstem gliomas do, and the histology of solid recurrences is often the same as that of the initial biopsy. Operations are occasionally advisable to debulk recurrent solid tumor before adjuvant therapy, to exclude radiation necrosis, and, in infants less than two years old, to “buy time” for additional brain maturation before radiotherapy.

Brainstem Tumors

Midline intra-axial tumors below the tentorium occur in the brainstem (the midbrain, pons, and medulla). They comprise approximately 10% of pediatric brain tumors, are the third most frequent infratentorial tumor (following medulloblastomas and cerebellar astrocytomas), and are heterogeneous in their CT/MRI appearance, histology, and outcome [7, 9]. Those localized in the midbrain enhance more frequently after contrast injection and appear to have a biology more similar to nuclear tumors than to tumors

in the pons and medulla. Brainstem gliomas have no sex or ethnic predilection, and the tumors are not associated with any inheritable syndrome; fewer than 5% of children with brainstem gliomas have neurofibromatosis. The prognosis for the few children with neurofibromatosis appears to be better than for those without it. Age at onset ranges from infancy to 18 years, with a median of 5–6 years; onset after age ten is less common. Prognosis is not related to age at diagnosis.

SIGNS AND SYMPTOMS

Brainstem gliomas most frequently begin in the pons. They infiltrate extensively between normal neural structures, separating rather than destroying them, and may not cause symptoms until the pons is quite enlarged. Initial symptoms include cranial nerve palsies (often multiple, bilateral, and progressive), diplopia, unsteadiness, and extremity weakness. Changes in personality and behavior, such as irritability and weight loss, are common, presumably because of tumor involvement in frontopontine pathways. Although headache and vomiting are common, hydrocephalus at the time of diagnosis is unusual. Symptoms are usually present for two months or less before diagnosis, and the children are usually alert and active when diagnosed. Children who present with cranial nerve palsies have a significantly worse prognosis than those without such palsies (figure 17-4) [7]. Other clinical symptoms and signs have not correlated with outcome.

DIAGNOSTIC TECHNIQUES

Brainstem gliomas are diagnosed by CT or MRI scans. Electroencephalograms, lumbar punctures, and angiograms are rarely used now. Prior to fourth-generation CT scanners, the differential diagnosis included brainstem encephalitis, demyelinating disease, vasculitis, and other posterior fossa tumors. Using current CT and MRI scanners, physicians can correctly diagnose brainstem gliomas (although they cannot identify the grade of glioma) in appro-

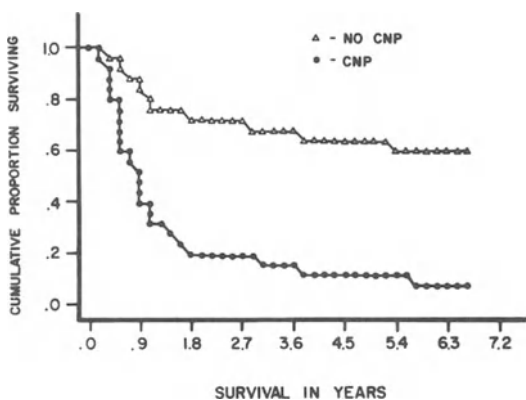


FIGURE 17-4. Actuarial life table for children without and with cranial nerve palsies (CNPs) as a presenting symptom of their brainstem glioma. The curves are significantly different ($p = 0.0001$).

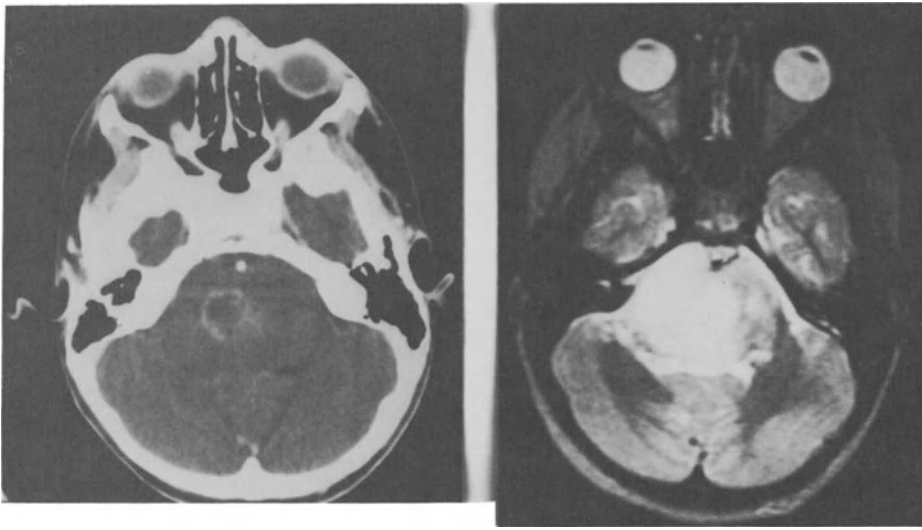


FIGURE 17-5. Contrast-enhanced CT (left) and T2-weighted MRI (right) scans of a low-grade brainstem astrocytoma.

ximately 90% of cases (figure 17-5). CT images typically show a hypodense pons without distinct tumor margins, and without calcifications or cyst formation, with posterior displacement of the fourth ventricle. Hypodense tumors usually extend into the midbrain and medulla. The prognosis is apparently worse for hypodense tumors than for isodense or hyperdense tumors [7,8]. Approximately 60% of brainstem gliomas enhance after administration of contrast material; there has been no correlation between tumor enhancement and either tumor pathology or prognosis. The extent of tumor on CT scan has correlated with outcome: children whose tumors involve the entire brainstem have a significantly worse prognosis than those with localized tumors. Only 15%–20% of tumors are well-defined masses on CT. The isodense, contrast-enhancing tumors that are dorsally exophytic into the fourth ventricle are often resectable low-grade gliomas with a better prognosis. Less than 10% of brainstem gliomas are cystic, and the effect of cyst formation on prognosis is uncertain.

As with nuclear tumors, the extent of brainstem gliomas shown on MRI scans exceeds that shown on CT scans in over 50% of cases [10]. On MRI, brainstem gliomas exhibit greater tumor heterogeneity than is evident on CT, and

can be distinguished from unaffected adjacent tissue with greater accuracy than by CT.

OPERATIONS

The rationale for obtaining a tissue diagnosis in brainstem gliomas is controversial. Biopsies are opposed by some because brainstem gliomas can be accurately localized by MRI, biopsies historically have caused substantial morbidity, biopsies are said to be unrepresentative of the entire tumor histology, and biopsy results usually do not alter the treatment. Advocates of biopsy reply that the biopsies are needed to exclude the infrequent lesions (such as encephalitis, occult vascular malformations, or demyelinating disease) that should not be treated by radiotherapy (figure 17-6), that the current mortality is less than 1% and the morbidity less than 5%, that biopsies are representative of tumor histology, and that low-grade gliomas should be treated differently than anaplastic gliomas.

Biopsies are probably indicated in the following instances: 1) the 15% of brainstem gliomas that are well-localized, enhancing masses—especially those at the cervicomedullary junc-



FIGURE 17-6. MRI (left) and CT (right) scans of an angiographically occult brainstem arteriovenous malformation (AVM), diagnosed initially as a brainstem glioma.

tion or mesencephalon, or exophytic tumors, that may be resectable low-grade gliomas and would need only conventional radiotherapy, or that might be gangliogliomas (or AVMs) and require no radiotherapy; 2) to decompress cysts; and 3) to provide research or prognostic information as part of brainstem glioma protocols—for example, to determine if hyperfractionated radiotherapy is more effective for low-grade than for high-grade gliomas.

Brainstem gliomas can be biopsied stereotactically using CT guidance and a transcerebellar or a transcoronal approach (figure 17-7) [11, 12]. Such biopsies provide adequate tissue for diagnosis, with low morbidity and without mortality, in more than 95% of patients. Open biopsies, for most tumors, are done through a retromastoid approach to the lateral pons, but those with an exophytic component into the fourth ventricle are preferably approached by a suboccipital craniotomy. As with nuclear tumors, intraoperative monitoring of somatosensory evoked potentials and brainstem evoked potentials appears to increase the safety of open biopsies or tumor decompressions.

PATHOLOGY

Approximately 60% of biopsied brainstem gliomas have been low-grade astrocytomas or mixed gliomas, and the remainder are anaplastic astrocytomas or glioblastomas [7, 8]. Tumor diagnosis correlates well with survival times: the likelihood of surviving two years is only 14% for children with high-grade gliomas, versus 65% for those with low-grade gliomas (figure 17-8) [7]. Several histologic features correlate with survival: survival is significantly shorter in children whose biopsies contain mitoses and significantly longer in the few children with Rosenthal fibers or calcification.

RADIOTHERAPY AND CHEMOTHERAPY

Radiotherapy to the tumor and a margin is standard, but ineffective, treatment. With a dosage of 5000–5500 cGy, 85% of children stabilize or improve temporarily [1]. Although spinal cord metastases occasionally occur, they are nearly always associated with tumor recurrence at the primary site, are rarely symptomatic, and do not occur frequently enough to warrant craniospinal irradiation. Hyperfractionated radiotherapy may improve survival: in preliminary results, survival times of children receiving 7200 cGy (100 cGy bid) were sub-

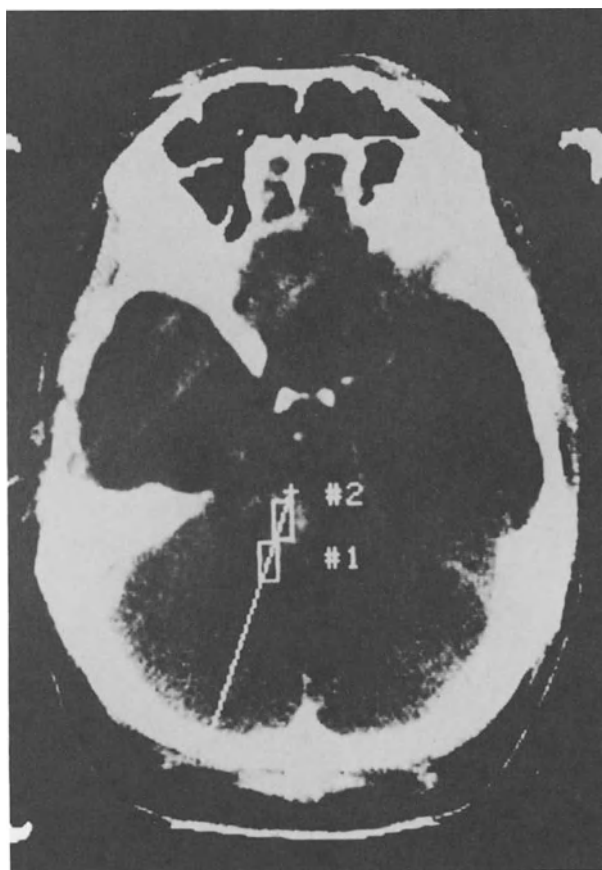


FIGURE 17-7. CT scan showing the trajectory and biopsy loci for a transcerebellar CT-directed stereotactic biopsy of a brainstem glioma.

stantially better than those receiving 6400 cGy (120 cGy bid) or conventional radiotherapy, with no apparent increase in toxicity at 18 months [13]. Chemotherapy has been ineffective with common drugs (CCNU, vincristine, procarbazine, 5-fluorouracil, cyclophosphamide) and is currently reserved for children whose tumors recur after radiotherapy.

FOLLOW-UP CARE

Children are usually followed with CT or MRI scans every 4–6 months after diagnosis. Serial brainstem evoked potentials deteriorate before, or at the time of, recurrence, which is usually signaled by a decrease in activity, trouble swallowing, and greater weakness. Approximately 70% of brainstem gliomas recur, and 80% of those recurrences occur within two years after

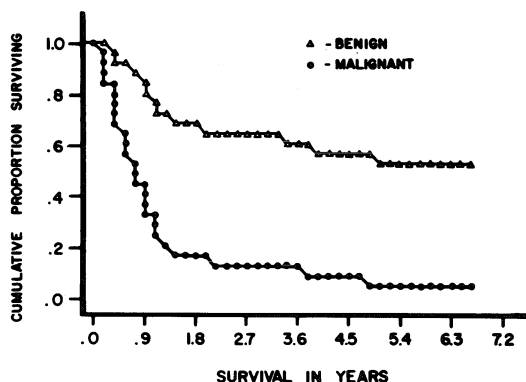


FIGURE 17-8. Actuarial life table for children whose biopsies revealed low-grade (benign) and high-grade (malignant) brainstem gliomas. The curves are significantly different ($p = 0.0001$).

diagnosis. Ninety-five percent of recurrences are within the radiation field. CT images of recurrent tumors often show ringlike enhancement.

Reoperations are rarely indicated for recurrent brainstem gliomas. Biopsies of recurrent tumors reveal more anaplastic histology than that seen in the initial biopsy, and children usually die within three months after recurrence is diagnosed. The only rationale for reoperation is to exclude radiation necrosis and perhaps to provide an additional 3 to 6 months of life if the child is in good condition, has a focal recurrence, and is to receive additional chemotherapy.

At autopsy, the majority of tumors are glioblastomas rather than low-grade or anaplastic astrocytomas. The difference in histology between biopsy and autopsy results probably represents both tumor dedifferentiation and sampling error. Dedifferentiation is supported by the lack of glioblastoma foci in large removals of low-grade gliomas, and by recurrent tumors being more anaplastic than the original, rather than a recurrence of the initial low-grade glioma. Sampling error is supported by the fact that only limited biopsies can be obtained from diffuse, ill-defined brainstem gliomas.

Twenty to twenty-five percent of children survive longer than five years and are apparently cured of their tumor [1, 2, 7, 8]. Their survival is due to radiotherapy, rather than to operations or chemotherapy.

Hopes for improved survival currently rest on hyperfractionated radiotherapy combined with innovative chemotherapy using sequential non-cross-resistant agents or bone-marrow rescue techniques.

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18. MEDULLOBLASTOMA

Melvin Deutsch

The term *medulloblastoma* was first used by Bailey and Cushing in 1925 to describe an infiltrating tumor found most often in the roof of the fourth ventricle in children and composed of small round cells [1]. This tumor previously had various designations such as sarcoma, gliosarcoma, neuroblastoma, neurocytoma, spongioblastoma, and glioma. The authors recommended surgery for decompression followed by radiation therapy, which was first used for their patients in 1919. Patients surviving the operative procedure who had radiation therapy experienced an average survival greater than 19 months compared to only seven months in those patients surviving surgery but not receiving postoperative radiotherapy. In 1930, Cushing reviewed his experience with 61 cerebellar medulloblastomas [2]. Only one patient survived five years before ultimately succumbing to recurrence and spinal metastasis. This patient had received four postoperative radiation treatments and had remained in remission for four years after his initial surgery. Realizing the propensity of medulloblastoma to disseminate to the spinal meninges, some of Cushing's patients did receive postoperative radiotherapy to the posterior fossa and spinal cord.

In spite of the apparent responsiveness of medulloblastoma to radiation, long-term survival was extremely infrequent prior to 1950. In 1949, Lampe and MacIntyre, in a review of the literature, found approximately 27 medulloblastoma patients who survived more than three years [3]. Of these, 12 were alive up to nine years "presumably without clinical evidence of disease."

In 1938, Lampe and MacIntyre began treat-

ing medulloblastoma by irradiation of the entire craniospinal axis in a segmental fashion starting first with the primary site and then irradiating the anterior portion of the skull and spine [3]. In 1949 they reported that 7 of 25 patients treated in this fashion were alive free of disease 33–92 months following therapy. In 1954, the same authors presented further follow-up of the seven survivors who were still alive 6 to 11 years after completion of radiotherapy [4]. Three patients showed signs of brain damage, and a fourth had a strokelike episode from which he recovered. Three other patients were alive and well without evidence of brain damage.

In 1952 Patterson and Farr reported the results of craniospinal irradiation in 27 patients treated since 1941 [5]. The three-year survival was 65% (11 of 17). Of 13 children, seven were alive at three years.

Of all the brain tumors in children, medulloblastoma has been the one in which the most dramatic improvements in survival have been achieved over the past 50 years. In contrast to the dismal therapeutic results obtained during the first four decades of this century, five-year disease-free survival rates over 50% are now being reported, with certain subsets of patients having at least a 70% long-term disease-free survival [6–10]. Although neurosurgeons and radiation oncologists have proposed that this improvement is due to advances in their respective specialties, there are probably multiple factors involved, such as:

1. Decreased operative mortality and morbidity due to improvements in surgical technique, advances in anesthesia, and use of

- corticosteroids, as well as more extensive resection of the primary tumor
2. Improvements in radiation therapy equipment, namely supervoltage radiotherapy, which allows for the administration of homogeneous high doses to the craniospinal axis without severe skin reactions
 3. Improved diagnostic imaging modalities such as computerized tomography (CT) and magnetic resonance imaging (MRI), which allow for earlier diagnosis and better assessment of tumor extent
 4. Increased use of myelography and cerebrospinal fluid (CSF) cytology studies for staging and identification of high-risk subsets
 5. Chemotherapy, which may be improving the disease-free survival for certain subsets

Age and Sex Distribution

In every reported series of medulloblastoma patients, there is a preponderance of male patients. This male preponderance in some series is as high as 2.7:1 [11]. In an unselected series of 143 children age 19 years or younger recorded in the Connecticut Tumor Registry since 1935, there were 82 males and 61 females for a male:female ratio of 1.3:1 [12]. In a population-based series of 368 children from Great Britain who underwent surgery for medulloblastoma, the male:female ratio was 1.85:1 [13]. In McFarland's large review of the literature from 1925 to 1967, the male:female ratio was 1.8:1 [14]. In several other reported series consisting of over 100 patients, the male:female ratio was at least 1.5:1 [15–18].

Medulloblastoma is mainly a disease of childhood. The median age of 143 patients age 19 years or younger in the Connecticut Tumor Registry was five years [12]. In the series of 122 patients of all ages reported by Berry et al., the median age was seven years [6]. Obviously, in those series that include adult patients, the median age is slightly higher. In the author's own series of 116 newly diagnosed patients between 1955 and 1986, the median age is six

years, with only nine (7.8%) age 18 years or older.

Medulloblastoma is uncommon in infants. Park et al. had only three patients under one year of age in their series of 144 children [18]. Farwell et al. reported 11 children under age one year in the Connecticut Tumor Registry series of 143 patients under age 19 years [12]. Bloom et al. had two patients of 82 under one year of age [19]. The author's series of 116 patients includes six infants under age one year.

Clinical Features

As was noted by Cushing in 1930, headache, vomiting, and ataxia constitute the triad of symptoms most commonly seen with medulloblastoma [2]. These are the symptoms of a posterior fossa mass causing obstructive hydrocephalus. Most series report vomiting in at least 80% of newly diagnosed patients and headaches in at least 70%. Bongartz et al. reported headache, vomiting, and vertigo in 89% (25 of 28) of newly diagnosed patients [20]. In the large series reported by Park et al., headache occurred in only 65% of patients and recurrent vomiting in 47% [18]. However, 76% of patients had papilledema. The incidence of papilledema in newly diagnosed patients can be as high as 88% [21]. Ataxia is reported in over 50% of newly diagnosed patients and in the series of Smith et al., was seen in 81% of newly diagnosed patients [21]. Less common at presentation are diplopia, cranial nerve palsies, head tilt, and seizures.

It is unusual for patients with medulloblastoma to present with symptoms longer than six months duration. In the series of Nuchel and Anderson, 82% of patients diagnosed from 1963 through 1975 had symptoms for less than six months and 59% had symptoms for less than three months prior to diagnosis [22]. Park et al. reported that 76% of patients had symptoms for less than 12 weeks and 51% for less than six weeks prior to diagnosis [18]. Mazza et

al. also reported that 72% of their patients had symptoms for less than three months [23]. Bongartz et al. reported that 89% of their patients had symptoms for less than three months [20].

In a large series of over 300 patients diagnosed between 1955 and 1978, the duration of symptoms did not vary with regard to age, site (lateral versus midline), or tumor histology (classical versus desmoplastic) [17].

With the availability of noninvasive diagnostic imaging modalities such as CT and MRI, it is likely that the average time interval prior to diagnosis of a medulloblastoma is shorter today than in the past. In the author's own experience of newly diagnosed medulloblastoma patients, the overwhelming majority of patients diagnosed within the past several years have had symptoms for less than two months.

Medulloblastoma usually arises in the vermis or midline of the cerebellum. A lateral or hemispheric origin is seen in about 20% of cases and is more common in older patients. In the series reported by Muller et al., 43.3% of patients over 15 years of age had lateral or hemispheric tumors compared to 13% of patients under age 15 years [17]. Arseni and Ciurea reported a hemispheric or lateral location in 12% of 197 children under age 16 years [15]. Of 79 adults patients, 43 (54%) had a lateral location.

Pathology

Until recently, many authors used the pathologic classification of medulloblastoma proposed in 1964 by Rubinstein and Northfield, which divided medulloblastoma into two broad categories: classical and desmoplastic [24]. The desmoplastic medulloblastoma contains an extensive network of fibrous tissue that divides the tumor into islands of cells. The classical medulloblastoma is a diffuse cellular tumor consisting of small round cells with scant cytoplasm. The majority of patients have the classic medulloblastoma. Only about 14% have the

desmoplastic variety. The incidence of desmoplastic medulloblastoma is higher in adults than in children. Muller et al. reviewed the initial surgical pathology on over 300 medulloblastoma patients [17]. The desmoplastic variety was seen in 15.2% of all patients. In patients over age 15 years, the desmoplastic variety occurred in 27.3% of cases versus an 11.8% incidence in patients under age 15 years. In the younger age group, this variety occurred with equal frequency regardless of location (medial versus lateral). In the patients over age 15 years, there was a slightly higher incidence of desmoplastic medulloblastoma in the lateral location. Similarly, Park et al., in their review of 144 newly diagnosed children, reported the desmoplastic variety in only 15% of patients [18]. In the series of 201 patients reviewed by Chatty and Earle, 21% were of the desmoplastic variety [11]. The remainder were considered to be classical medulloblastoma.

Rorke has proposed a classification for all primitive neuroectodermal tumors (PNETs) in which medulloblastoma is considered a posterior fossa PNET [25]. Using this classification, Packer et al. have divided medulloblastoma into two broad subdivisions: PNET-undifferentiated and PNET-differentiated [26]. This latter group may include PNET with glial differentiation, ependymal differentiation, neuronal differentiation, or multipotential differentiation. The PNET-undifferentiated corresponds to the classical medulloblastoma, which according to Packer et al. has a better prognosis than the PNET with differentiation.

Kopelson et al. subclassified medulloblastomas according to the presence or absence of and the amount of cytoplasmic processes, necrosis, mitosis, and desmoplasia [8].

Staging and Tumor Extent at Diagnosis

Medulloblastoma is one of the few intracranial tumors for which a staging system is practical in terms of describing extent of disease and providing prognostic information. The primary

tumor may spread locally to adjacent structures such as the brainstem, upper spinal cord, mid-brain, and cerebellar surface. In addition, there can be dissemination within the central nervous system manifested by supratentorial implants, spinal cord lesions, and malignant cells within the CSF. Medulloblastoma will occasionally disseminate beyond the central nervous system.

In 1969, Chang et al. suggested a staging system with a T (tumor) and M (metastasis) category [27]. In that era, prior to the advent of CT, the primary tumor was staged according to surgical findings. The M staging was by clinical, surgical, and radiographic findings, but the authors did not propose a systematic workup for determining stage (table 18-1).

Retrospective staging according to the T staging of Chang is difficult, but in those series where it has been done, the majority of primary medulloblastomas fall into the T2 or T3 stage (table 18-2). In the recently completed Children's Cancer Group (CCG) and International Society of Pediatric Oncology (SIOP) studies, the majority of tumors were T3, T4 as opposed to T1, T2 [28]. Bloom et al. reported brainstem involvement (stage T3B) in at least 33% of their patients [19].

With the advent of CT, the size and extent of the primary posterior fossa medulloblastoma can be fairly accurately assessed. The majority of tumors measure 3–5 cm in maximum dimension on the CT scan. Hydrocephalus is present in the majority of patients and thus, by the classification of Chang et al., CT scan findings would indicate that the majority of newly diagnosed medulloblastomas are at least T3.

The allocation of patients according to M stage varies rather widely in the reported series. In the series of Harisiadis and Chang, six patients were considered to have gross nodular seeding in the spinal subarachnoid space, but only one patient had a myelogram as part of the initial evaluation [29]. Presumably the other five patients had clinical evidence of cord involvement (table 18-3). In the CCG medullo-

blastoma study, 83% of patients were considered to be MO [28]. However, the majority of patients did not have myelography or even CSF cytology studies performed.

The TM staging system of Chang et al. has several problems. The M1 stage does not take into account the site from which the CSF was removed or the time in relationship to surgery. It is possible that tumor cells found in the CSF soon after resection of the primary tumor may have been liberated into the CSF pathways by

TABLE 18-1. Operative staging system for cerebellar medulloblastoma

Stage	Description
T1	Tumor less than 3 cm in diameter and limited to the classic midline position in the vermis, the roof of the fourth ventricle, and less frequently to the cerebellar hemispheres
T2	Tumor 3 cm or greater in diameter, further invading one adjacent structure or partially filling the fourth ventricle
T3A	Tumor further invading two adjacent structures or completely filling the fourth ventricle with extension into the aqueduct of Sylvius, foramen of Magendie, or foramen of Luschka, thus producing marked internal hydrocephalus
T3B	Tumor arising from the floor of the fourth ventricle or brainstem and filling the fourth ventricle
T4	Tumor further spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain, or tumor extending to the upper cervical cord
M0	No evidence of gross subarachnoid or hematogenous metastasis
M1	Microscopic tumor cells found in cerebrospinal fluid
M2	Gross nodular seedings demonstrated in the cerebellar or cerebral subarachnoid space, or in the third or lateral ventricles
M3	Gross nodular seedings in spinal subarachnoid space
M4	Metastasis outside the cerebrospinal axis

TABLE 18-2. T-stage distribution

Series	T stage					Total
	T1	T2	T3	T4	TX	
Harisiadis [29]	5	20	29	4		58
Kopelson [8]	3	14	17	4	5	43
Silverman [10]	11	21	9	5	3	49
Berry [6]	5	45	51	12	9	112
CCG	T1, T2	34%	T3, T4	66%		
SIOP	T1, T2	41%	T3, T4	59%		

TABLE 18-3. M-stage distribution

Series	M stage					Total
	M0	M1	M2	M3	MX	
Harisiadis [29]	20	6	9	6	17	58
Kopelson [8]	21	2	1	3	16	43
Berry [6]	100 (82%)	3	12	1	6	122
Deutsch [7]	28 (54%)	7	3	14		52
CCG	M0 83%	M1–M3	17%			

surgical manipulation of the tumor. It is unknown whether or not this has the same prognostic implication as tumor cells found to be present before manipulation of the primary tumor or after a several-week interval from surgery. It is likely that more frequent sampling of the CSF over time would reveal a higher incidence of positive cytologies. The site from which the fluid is removed may have some bearing upon the likelihood of finding tumor cells. Deutsch reported very few patients with a positive CSF cytology when the fluid was removed from the lateral ventricle via a shunt prior to operative intervention on the posterior fossa tumor [7]. However, those patients who did have a positive CSF from the shunt preoperatively also had other evidence of dissemination, such as a positive lumbar puncture CSF cytology and/or demonstrated lesions on myelography.

Balhuizen et al. reported CSF cytology findings on 17 patients with medulloblastoma [30]. All 17 had at least one preoperative CSF cytology study. Four preoperative samples from two patients of the 17 (11.7%) contained malignant

cells. Of 11 patients with postoperative cytology studies, 10 patients (91%) had malignant cells in a total of 21 samples. Intervals from the time of surgery were not reported. From the 17 patients, 20 ventricular CSF samples were obtained and six were positive. Of 69 lumbar CSF samples, 20 were positive. However, information is not available as to how many samples from each site were preoperative or postoperative. Nor is it stated how many patients had positive preoperative and postoperative samples.

Deutsch reported results of CSF cytology studies on 50 newly diagnosed patients [7]. Twenty-two patients had cytology studies preoperatively on fluid from the lateral ventricle, and three contained malignant cells (13.6%). Two of these three patients had spinal cord involvement. The third also had malignant cells in CSF from a lumbar puncture site postoperatively. A fourth patient with "atypical cells" in ventricular CSF had cord involvement. Four patients had cytology studies performed on CSF from a lumbar puncture site preoperatively. Three had malignant cells, and one of

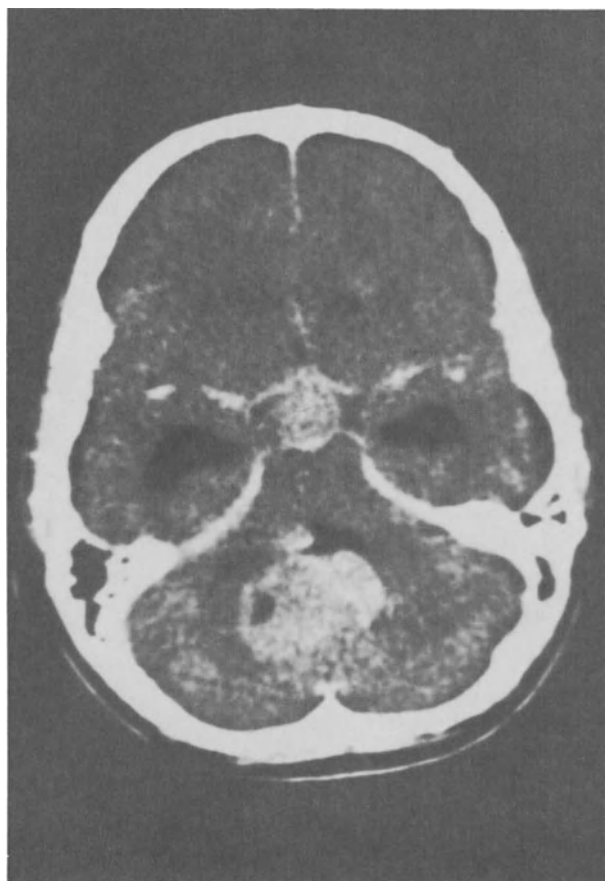


FIGURE 18-1. Metastatic medulloblastoma in suprasellar cistern at diagnosis.

these patients also had cord and supratentorial involvement.

Forty-one patients had cytology studies on CSF from a lumbar puncture site postoperatively, and 11 (26.8%) contained malignant cells. Seven also had cord involvement. One additional patient had a CSF sample from the lateral ventricle postoperatively that contained malignant cells. He also had cord involvement.

All together, 16 of 50 patient had a positive CSF cytology at diagnosis either preoperatively or postoperatively. Of 26 patients with a preoperative cytology study, six (23%) had malignant cells. Of 42 patients with a postoperative CSF cytology study, 12 (28.6%) contained malignant cells. More frequent samplings of CSF preoperatively and postoperatively, as was apparently done by Balhuizen et al., would

probably yield a higher incidence of positive findings [30]. Interestingly, eight patients had spinal cord or supratentorial involvement with a negative CSF cytology.

The author recommends that all CSF samples, whether taken from the lateral ventricle or a spinal puncture site, be submitted for cytology studies. The presence of malignant cells in the CSF, regardless of the time in relationship to the primary surgical procedure, should be considered as M1 disease. However, the significance of malignant cells in the CSF taken from the fourth ventricle or cisterna magna at the time of the surgical procedure is uncertain and is not considered to be M1 disease.

Prior to the routine use of CT scanning, the

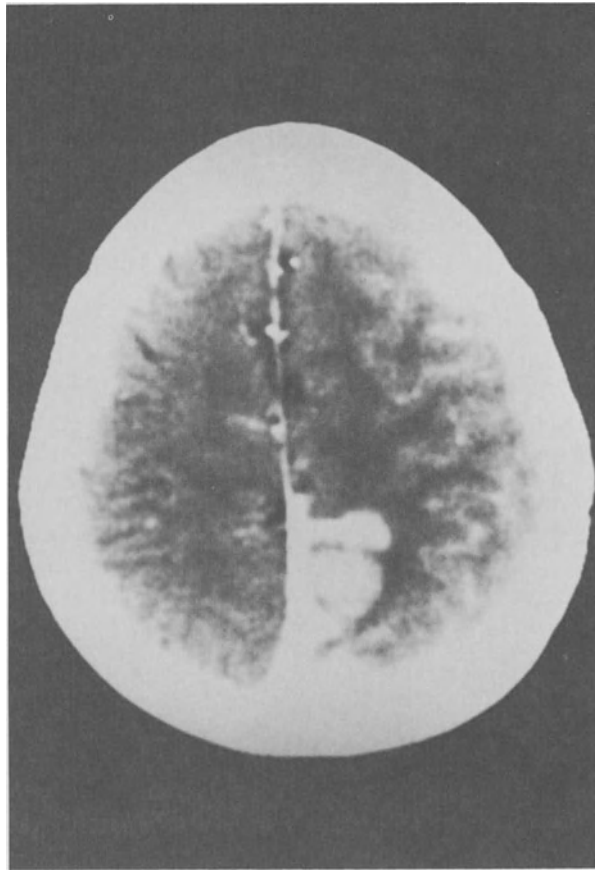


FIGURE 18-2. Extensive metastatic medulloblastoma in the left parietal lobe at diagnosis.

true incidence of supratentorial metastasis at diagnosis was unknown. Pneumoencephalography occasionally demonstrated supratentorial lesions involving the ventricular system. However, most patients considered to have M2 disease from the era prior to CT scanning probably had gross nodular seedings demonstrated in the cerebellar subarachnoid space at the time of surgery. In the author's experience of 52 carefully staged newly diagnosed patients, only five had evidence of supratentorial metastasis at diagnosis [7]. In three of these patients, tumor was noted in the suprasellar cistern, and one also had spinal cord involvement (figure 18-1). Two others had extensive supratentorial involvement, and one also had spinal cord involvement (figure 18-2). Thus, 2 of the 5 patients

with supratentorial metastasis at diagnosis also had spinal cord involvement. These latter two patients also had malignant cells in the CSF. The other three patients with just supratentorial metastasis did not have malignant cells in their CSF.

The propensity of medulloblastoma to disseminate via the CSF pathways has been appreciated since the 1920s. It is therefore surprising that it was not until 1975 that myelography and CSF cytology studies were suggested for all newly diagnosed medulloblastoma patients [31]. The rationale behind this evaluation was to identify patients with subclinical but gross tumor deposits beyond the posterior fossa that would then be irradiated to doses higher than the usual conventional prophylactic doses. By 1980, Deutsch and Reigel reported 16 conse-

cutive newly diagnosed medulloblastoma patients who were evaluated by myelography, and seven had abnormal myelograms [32]. None of these seven patients had clinical evidence of cord involvement. In addition, patients with recurrent intracranial medulloblastoma were also subjected to myelography with the frequent finding of unsuspected cord involvement. Dorwart et al. in 1981 reported 1 of 9 newly diagnosed patients and 3 of 9 with intracranial recurrence who had spinal cord involvement on myelography [33]. At the University of Pittsburgh, 52 newly diagnosed medulloblastoma patients have been subjected to myelography. Fourteen have had evidence of cord involvement [7].

Documented dissemination beyond the central nervous system at diagnosis is very rare. Allen and Epstein reported bone marrow involvement in 1 of 25 newly diagnosed patients with medulloblastoma [34]. An additional patient with a pinealblastoma also had bone marrow involvement at diagnosis. Neither patient had a preoperative shunt, and bone scans were negative. Both children had spinal cord involvement. Currently, bone marrow examination is being done prospectively on children in the CCG medulloblastoma protocols.

Chin et al. proposed a staging system based upon CT findings that takes into account the extent of surgical resection, the presence of irreversable hydrocephalus, the necessity for a shunting procedure, CSF findings, myelography, and bone marrow biopsy (table 18-4) [35].

Laurent et al. propose a classification system for medulloblastoma based on the presence or absence of metastasis, pathological appearance, amount of tumor remaining after resection, and the age of the patient (MAPS) [36]. The M classification is expanded to include six different designations, M0–M5 (table 18-5).

The TM staging scheme of Chang et al. is probably the most widely used. The prognostic value of the T staging has not yet been verified, but the M stage definitely identifies a subset with a worse prognosis [7].

TABLE 18-4. Computer-assisted tomography staging system [35]

Stage	Description
Stage I	Localized medulloblastoma 1. Completely resectable tumor confined to posterior fossa 2. No gross residual tumor on postoperative CT 3. No evidence of irreversible hydrocephalus 4. Negative myelography, CSF cytology, bone marrow biopsy
Stage II	Invasive medulloblastoma 1. Incompletely resectable—extension into brainstem, cervical cord, or outside posterior fossa 2. Gross residual tumor on postoperative CT 3. No evidence of irreversible hydrocephalus 4. No evidence of dissemination
Stage III	Regional medulloblastoma—microscopic subarachnoid metastases 1. Tumor infiltrating into leptomeninges or ventricular system 2. Subarachnoid tumor deposits on microscopic examination 3. CSF contains malignant cells 4. Persistent irreversible hydrocephalus on postoperative CT—systemic shunt necessary 5. Myelogram and bone marrow biopsy negative
Stage IV	Metastatic medulloblastoma A. Spinal cord involvement at surgery or on myelogram B. Extra-CNS metastases

Surgery for Medulloblastoma

In Cushing’s series, operative mortality was about 30% [2]. He did note that patients surviving radical attempts at excision seemed to have a longer survival. The high operative mortality prompted many to limit surgery to just biopsy and decompression. Improvements in perioperative supportive care, including the use of corticosteroids to reduce edema, preoperative shunting to relieve hydrocephalus, and noninvasive imaging techniques, have all

TABLE 18-5. MAPS classification for medulloblastoma

Metastases (M)	
M0	No evidence of metastases
M1	Cells in the CSF or leptomeninges
M2	Nodular seeding, supratentorial compartment
M3	Nodular seeding, spinal cord
M4	Nodular seeding in two compartments (supratentorial and/or infratentorial and/or spinal)
M5	Systemic metastases
Age (A)	
A1	> 3 years
A2	< 3 years
Pathology (P)	
P1	Microscopic appearance: classic nondifferentiated
P2	Microscopic appearance: anaplastic, multiple differentiated cell lines
Surgery (S)	
S0	No residual tumor
S1	Residual tumor < 1.5 cm (largest diameter)
S2	Residual tumor > 1.5 cm (largest diameter)
S3	Residual tumor of any size invading brainstem structures
S4	Residual tumor extending into supratentorial and/or spinal compartment

contributed to decreasing the operative mortality and morbidity previously associated with surgery for medulloblastoma. These advances have contributed to making extensive resection of the posterior fossa medulloblastoma more feasible. The widespread use of the operating microscope has also been a factor. Over the past decade there has been an increasing tendency for neurosurgeons to attempt gross total resection of primary medulloblastoma (table 18-6).

The term *total removal* indicates that all visible tumor was removed (figure 18-3). The term *biopsy* is self-explanatory. This means that just a small fragment of tumor was removed for histological examination. In some reports, the terms *subtotal resection* and *partial resection* are used interchangeably. Some authors make a distinction between the two terms, *subtotal* indicating that the great majority of the tumor was removed but that there was still visible residual, and *partial* indicating that just a small portion (< 50%) of the tumor was removed. The percentage of patients undergoing total resection of medulloblastoma varies from series to series and may reflect the neurosurgeon's philosophy and experience. More recently diagnosed patients tend to be subjected to attempted total resection on the basis of recent

TABLE 18-6. Extent of resection

Series	Dates	No. patients	Total	Subtotal	Partial	Biopsy
Silverman [10]	1954–1978	47	21	24		2
Harisiadis [29]	1963–1975	58	5	34	8	11
Kopelson [8]	1962–1979	41	9		29	3
Raimondi [38]	1968–1979	47	13	20	10	4
Bongartz [20]	1969–1977	28	15	7	5	1
Bloom [19]	1950–1964	79	23		50	6
Gerosa [69]	1975–1980	30	15		13	2
Norris [37]	1969–1974	11	3	7		1
	1975–1979	11	11			
Hershetter [16]	1940–1983	118	49 (42%)	60		9
Berry [6]	1958–1978	122	44 (36%)	66		12
Stiller [13]	1971–1977	368	89 (24%)	216 (59%)		58 (16%)
Total		960	297 (31%)	434	115	109 (11%)
CCG	1975–1981		38.5%			
SIOP	1975–1979		45.5%			

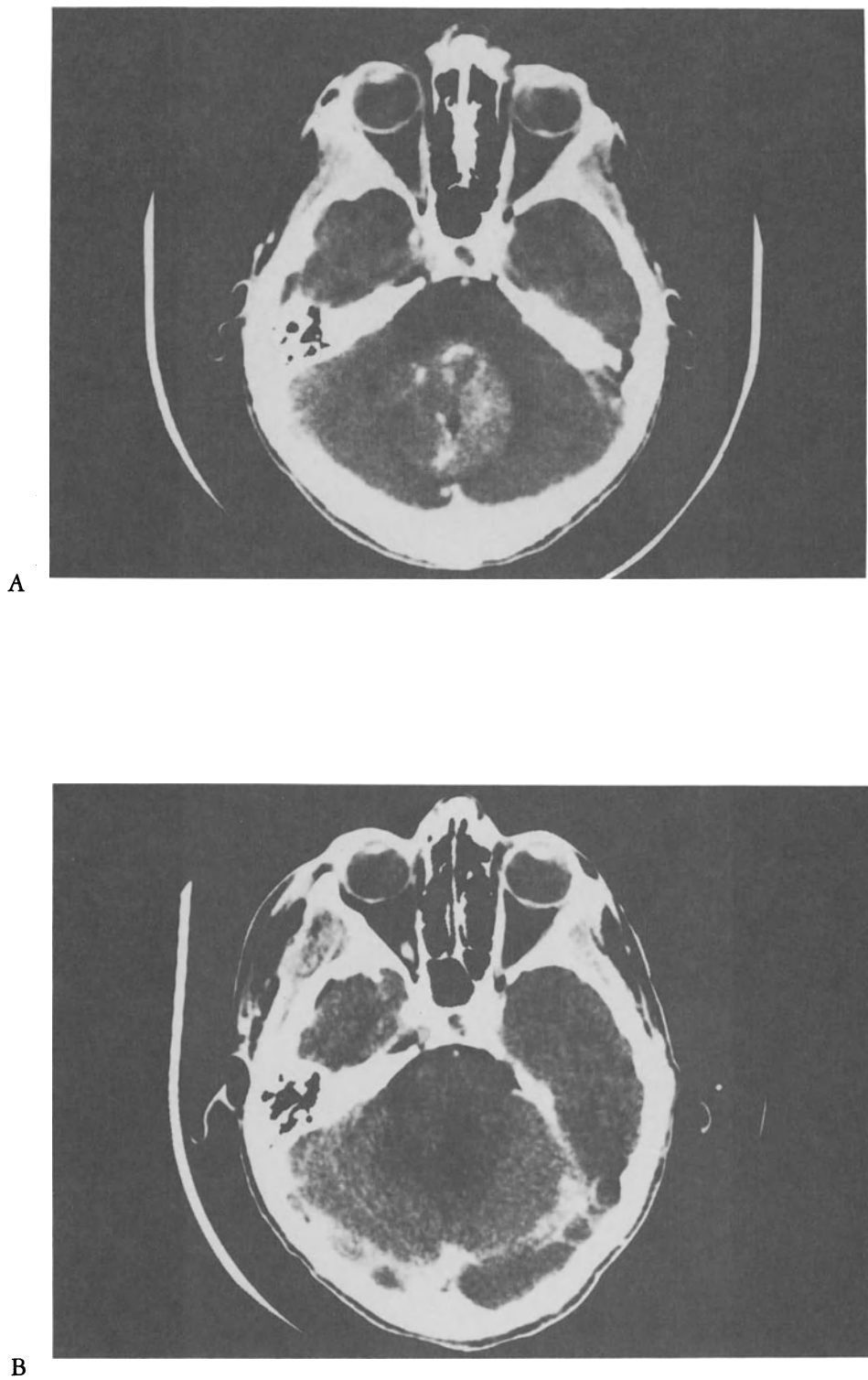


FIGURE 18-3. A Medulloblastoma preoperative. B. Postoperative gross total removal. CT with contrast.

reports indicating improvements in survival associated with gross total removal [6, 9, 37, 38]. Albright suggests that approximately 75% of T1, T2 tumors and almost 50% of T3, T4 tumors can be totally removed [39].

In the recently completed CCG and SIOP studies, gross total resections were accomplished in 38.5% and 45.5% of cases, respectively [28]. Norris et al. in 1981 reported on 11 consecutive patients with medulloblastoma in whom a gross total resection was accomplished [37].

As patients are being diagnosed earlier and without the need for invasive procedures, it is possible that more patients will present with smaller tumors and also in better clinical condition. Thus, the percentage of patients whose tumors are amenable to gross total resection may increase. There seems to be an intuitive feeling among clinicians that gross total resection should be associated with improved local control and survival rates.

Very few patients are currently being subjected to just biopsy without resection of medulloblastoma. In the CCG and SIOP trials, only about 3% of patients had just a biopsy. Data are not available from these trials as to why patients having just a biopsy did not have more extensive resections attempted. It is not clear whether or not such patients had very extensive tumor or were just in extremely poor clinical condition and were believed to be unable to tolerate a more extensive surgical procedure. In most large retrospective reviews, less than 10% of the patients have just a biopsy. Again, it is not clear from most reports why more extensive surgery was not done in the biopsied patients.

Shunts

Shunts are effective in relieving hydrocephalus and often provide rapid improvement in the patient's clinical condition. Since many patients will have reestablishment of the CSF pathway following resection of the primary tumor, permanent shunts may not be necessary. Temporary

external shunts are often used prior to posterior fossa craniotomy if it is likely that obstruction to CSF flow can be relieved. Recently there has been concern that the use of internal shunts may promote the dissemination of malignant cells to extra-CNS sites. In a large series reported by Berry et al., systemic relapse occurred in 18 patients [6]. Fifteen of these patients had a ventriculostomy shunt. In three patients, a filter was used in the shunt system. The rate of systemic relapse for patients with a shunt procedure was 20% (15 of 74) and for patients without a shunt it was 6% (3 of 48). However, in their series there was no difference in five-year survival between shunted and nonshunted patients.

Park et al. reported that only 1 of 24 patients with a filtered shunt preoperatively developed systemic metastasis [18], whereas 5 of 25 with an unfiltered shunt developed systemic metastasis.

Albright and Reigel in 1977 reported on the management of increased intracranial pressure in 86 patients with posterior fossa tumors (medulloblastoma, astrocytoma, ependymoma) [40]. Forty-seven patients did not have a shunt procedure prior to posterior fossa surgery, 12 patients had external ventricular drainage (EVD), and 27 had an internal shunt preoperatively. Postoperative morbidity and mortality were decreased in the group of patients shunted preoperatively. Within one year of surgery, internal shunting was required in 7 of the 47 patients who did not have preoperative shunting or EVD and in 6 of the 12 patients who had a preoperative EVD.

Papo et al. treated 30 medulloblastoma patients with preoperative EVD [41]. Two of these patients required internal shunting before craniotomy, and one additional patient had an internal shunt inserted less than ten days postoperatively. Six additional patients required internal shunting 3–5 weeks postoperatively. Thus, 9 of the 30 patients treated initially with a preoperative EVD subsequently required internal shunting.

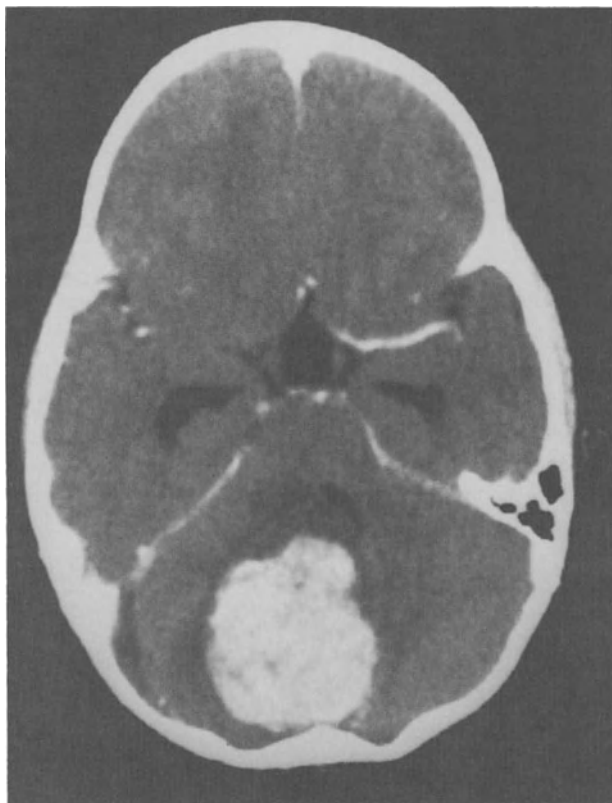


FIGURE 18-4. Recurrent medulloblastoma. At age 18 months, the child underwent gross total resection. She was treated with 8-drugs-in-1-day chemotherapy for about one year. Radiotherapy was withheld because of her young age. Three months prior to this CT scan, MRI did not show any evidence of tumor.

Chin et al. have described a correlation between postoperative nonreversible hydrocephalus requiring internal shunting and a poor prognosis [35, 42]. They postulate that nonreversible hydrocephalus is due to tumor infiltration of the subarachnoid space.

Radiotherapy

As late as the 1970s, there were still some patients with medulloblastoma being treated with irradiation of just a portion of the craniospinal axis (table 18-7) [14, 20, 43–46]. Considering the known propensity for medulloblastoma to disseminate via the CSF pathways and the fact that dramatic improvements in survival associated with craniospinal axis irradiation were demonstrated by the early 1950s, it is not clear as to why there were still many patients

being treated with less than craniospinal axis irradiation.

Prior to the availability of CT scanning, the true incidence of relapse in the supratentorial brain was not appreciated. As late as 1968, MacFarland et al. suggested that radiation be limited to the posterior fossa and spinal cord [14]. It is more difficult to understand why there were patients with medulloblastoma being treated with radiation just to the posterior fossa or whole brain. The high incidence of relapse in the spinal cord had long been recognized [2].

Patients treated with less than craniospinal

TABLE 18-7. Outcome in patients treated with partial CNS irradiation

Series	Dates	Regions treated (no. patients)	Survival
Landberg [43]	1946–1974	Posterior fossa (21)	1 alive, 10 years
	1951–1968	Posterior fossa + cord (16)	4 alive, 10 years
McFarland [14]	1940–1966	Posterior fossa + cord (11)	5 alive $\geq$ 7 years; 2 subsequently dead
Bongartz [20]	1969–1977	Posterior fossa (7) Posterior fossa + cord (5)	All dead by 3 years
Onoyama [44]	pre-1965	Whole brain (16)	3 alive, 7–14 years
Jekin [45]	1940–1952	Posterior fossa $\pm$ cord (16)	All dead by 4 years
Kim [46]		Less than cerebrospinal Axis (10)	3 alive

irradiation for medulloblastoma occasionally have been cured (Table 18-7). However, it is now well recognized that the entire craniospinal axis is at risk for recurrence. At present, it is impossible to identify a subset of medulloblastoma patients who would do equally well with irradiation of less than the entire craniospinal axis. Therefore, there is general consensus that all newly diagnosed medulloblastoma patients be treated with craniospinal irradiation. The only exception might be for very young children, in whom the risk of serious sequelae from craniospinal irradiation is considerable. Currently, the CCG is accepting patients under age 18 months into a protocol using chemotherapy after surgery. Radiotherapy is delayed until age three years or until there is evidence of tumor progression. Such children should have frequent CT and MRI examinations in addition to CSF cytology studies so that recurrence can be detected in time for radiotherapy to offer a reasonable chance of cure (figure 18-4). CSF analysis for putrescine levels may offer another means to detect recurrent medulloblastoma early (see below).

With the widespread introduction of super-voltage radiotherapy in the 1950s, skin reactions no longer limited the amount of radiation that could be administered for brain tumors. The greater depth dose penetration of cobalt-60 and megavoltage X-rays as compared to orthovoltage (250 KV) made it possible to deliver homogeneous high doses of radiation to

the craniospinal axis. Reports by Bouchard [47] and Bloom et al. [19] concerning long-term survivors indicated that the majority were leading normal lives. The ability to deliver higher doses and the apparent lack of serious sequelae prompted many radiation oncologists to intensify therapy to levels considered maximally permissible. By the late 1960s and 1970s, many radiation oncologists were administering 5000–5500 rads in 5–6 weeks to the posterior fossa and 3500 rads or more at 180–200 rads per day to the remainder of the craniospinal axis [6, 10, 48–50]. In the current Children's Cancer Group Medulloblastoma Protocols, standard therapy consists of 3600 rads/20 fractions directed to the craniospinal axis with a total dose of 5400 rads/30 fractions to the posterior fossa. Treatments are administered with daily doses of 180 rads per fraction. Patients with demonstrable disease beyond the posterior fossa are given additional boost doses to localized volumes.

Chemotherapy

It is only in the past decade that chemotherapy has been used for the treatment of newly diagnosed pediatric brain tumors. The concept of a blood–brain barrier interfering with the access of systemically administered chemotherapy to the central nervous system limited the choice of drugs considered likely to be beneficial. Nitrosoureas (CCNU, BCNU, PCNU, and

Methyl-CCNU) are lipid-soluble and therefore cross the blood–brain barrier. It is possible that the blood–brain barrier may be disrupted by the presence of tumor, thereby allowing access of drug into tumor-containing areas of the CNS. However, systemically administered chemotherapy may not reach tumorocidal levels in the CSF, and this has prompted the consideration of intrathecal chemotherapy for medulloblastoma.

Surgery and radiotherapy offer long-term survival rates of at least 50% for certain good-prognosis subsets of medulloblastoma. However, for patients presenting with evidence of dissemination beyond the posterior fossa, long-term survival is less than 50%. Thus, there is an impetus to develop adjuvant chemotherapy regimens for use in newly diagnosed medulloblastoma patients. It is possible that an effective adjuvant chemotherapy regimen might permit a safe decrease in the dose administered to the craniospinal axis.

Hematopoietic depression secondary to irradiation of the entire skull and spine almost always occurs but is reversible. Pharyngitis, esophagitis, and nausea may result from irradiation of the spine. Many chemotherapeutic agents do cause hematopoietic depression, nausea, and vomiting, and thus the possibility of increased toxicity must always be considered when chemotherapy is used concomitantly with radiation. Methotrexate, either intravenously or intrathecally, can potentiate late radiation damage to the central nervous system (see chapter 22 in this volume).

Adjuvant chemotherapy for malignant gliomas in adults has produced some improvement in survival, but this improvement is measured by a several-week increase in median survival [51]. Contrary to the situation with most other malignancies, multiple drug regimens evaluated for adult malignant gliomas have not been proven superior to BCNU alone.

Responses to chemotherapy have been noted in patients with recurrent medulloblastoma, occasionally leading to long-term control. The

drugs most often used for treatment of recurrent medulloblastoma have been the nitrosureas, vincristine, and methotrexate alone or in combination. To a lesser extent, cis-platinum, cytoxan, procarbazine, and triethylene melamine have been used. Occasional long-term responses have been noted, but overall the number of patients evaluated has been small. The reader is referred to Zeltzer [52] for an extensive tabulation of chemotherapy results for recurrent medulloblastoma.

Results of adjuvant chemotherapy for newly diagnosed medulloblastoma have been reported from several institutions and from two large cooperative group trials [28]. In almost all cases, combinations of drugs have been used, and most regimens included vincristine.

Results of Therapy

There is a wide variation in the reported survival rates of children with medulloblastoma over the past 40 years. In some series, only patients completing prescribed therapy are included in survival statistics, and thus these reports will show a better survival than series that include all diagnosed patients including those dying before completing therapy. With better supportive care and much lower operative mortality rates, the majority of patients diagnosed within the past decade do complete the intended course of radiotherapy.

Operative mortality rates of 20%–30%, which were common before 1960, have decreased markedly [14]. Park et al. have reported no operative deaths among 60 medulloblastoma cases treated since 1973 [18]. Albright reported one operative death among 65 cases of medulloblastoma [39]. That patient was comatose at the time of admission because of herniation.

In almost every large reported series spanning several decades, more recently diagnosed patients have a better survival than patients diagnosed over 15 or 20 years ago. In their review of 143 cases of childhood medulloblastoma in the Connecticut Tumor Registry since

1935, Farwell et al. showed that patients diagnosed in the ten-year period from 1967 to 1978 had a statistically significantly improved survival ($p < 0.05$) than children diagnosed prior to 1967 [12]. Untreated patients were more likely to be diagnosed in earlier years. In the large series of all surgically diagnosed patients from Great Britain, the five-year survival for patients diagnosed in the period 1971–1974 was 27% [13]. For those patients diagnosed in 1975–1977, five-year survival was 38%. Hershatter et al., in their review of medulloblastoma patients dating back to 1940, also reported that patients diagnosed in the 1940s had a much poorer survival than patients diagnosed in later years [16]. One of the most dramatic changes in survival over a short period of time is seen in the report by McIntosh, who reported on 87 consecutive medulloblastoma patients diagnosed in a ten-year period from 1965 through 1974 [53]. Of 46 patients presenting from 1965 through 1969, only one patient survived five years (2%). Of 41 patients presenting in the 1970–1974 period, there were 11 five-year survivors. Improved radiotherapy (megavoltage equipment and higher doses) was considered to be the main cause of this improvement in survival.

In almost all series, the more recently diagnosed patients usually were treated with higher doses, were more likely to have extensive resection of the primary tumor, and also underwent more extensive evaluation (CT scanning, myelography, CSF cytology) and had better supportive care.

Age versus Prognosis

Several authors have suggested that younger children with medulloblastoma have a worse survival than older children. Berry et al. reported that patients under five years of age did worse than older children, and the difference in survival approached statistical significance when compared against patients age 11–30 years ($p = 0.06$) [6]. Bloom et al. reported a

five-year survival of 31% for children age 0–4 years as compared to 33% for children age 5–9 years and 33% for children age 10–14 years [19]. However, relapse and death seemed to occur sooner in the younger children. The one-year survival for children age 0–4 years was 47% compared to 77% and 82% for the children age 5–9 years and 10–14 years, respectively. In the series reported by Park et al., patients six years of age or older had a 59% five-year survival [18]. Younger children had a 41% five-year survival. Survival curves in this younger age group reached a plateau at five years following surgery. In the older age group, the plateau in survival was seen at seven years from surgery. For children completing a course of radiotherapy, Stiller and Lenox reported that children age 0–4 years had a worse three-year survival than older children, but survival was the same at six years for the two groups [13].

In two large series of patients treated inadequately by current standards, improved survival was seen in older patients [11, 17]. It has been suggested that age at diagnosis plus nine months is the follow-up interval from diagnosis during which the patient is at risk to have recurrence [54]. Thus, by this theory, older patients may have a longer disease-free interval than younger patients. Hughes, in a report concerning 15 patients with medulloblastoma age 16 years or older, noted that only one patient had developed relapse prior to three years from diagnosis [55]. All other patients with relapse had at least a three-year disease-free interval. Indeed, in most series, failure seems to occur within this period of risk as determined by age at diagnosis (Collin's law) [56].

Two possible explanations for a poorer survival in younger patients are:

1. Younger children have a higher incidence of advanced disease
2. Younger patients are treated with less intensive radiotherapy

Chin and Maruyama noted that “pre-school age” children were more likely to have extensive

primary tumor than older patients [42]. They noted that two-thirds of “advanced cases” were seen in this younger age group, and 88% of all advanced primary tumors were noted in patients younger than ten years of age.

Younger patients are more likely to have dissemination at diagnosis than older patients. In the Pittsburgh series of 52 staged patients, 11 of 18 (61%) patients under age five years had evidence of dissemination at diagnosis [7]. Eight of these patients had myelographic evidence of spinal cord involvement. Of 34 patients over age five years, only 38% (13 of 34) had evidence of dissemination at diagnosis. Allen and Epstein also reported an increased incidence of dissemination at diagnosis in children under five years of age [34]. Thus, it is possible that the poor prognosis reported to be associated with young age is related to an increased incidence of dissemination at the time of diagnosis. Unfortunately, the majority of patients reported in the literature did not have staging myelography or CSF cytology studies performed, and thus the true incidence of the various M stages according to age is unknown. In the series of staged treated patients from Pittsburgh, all five patients under age five years with M0 disease were alive and well with a minimum follow-up of 54 months from diagnosis. In a series of unstaged patients treated at the University of Pittsburgh in the ten-year period prior to 1974, there was no difference in survival between patients younger or older than five years [57].

Sex of Patient versus Prognosis

Several reviews have indicated an improved survival for female patients versus male patients [19, 42]. On the other hand, several large series have failed to reveal a significant advantage to either sex [10, 13, 14]. In fact, Park et al. noted a slightly better five-year survival among male patients (53% versus 47%) [18].

Among 52 staged patients from the University of Pittsburgh, the incidence of dissemination

was 36% in female patients versus 52% in males [7]. However, the series of 25 patients reported by Allen and Epstein had eight with evidence of dissemination at diagnosis, and seven were female [34].

For 71 male patients diagnosed since 1956 at the University of Pittsburgh and evaluated in the Department of Radiation Oncology, the five-, ten-, and 15-year overall survivals are 44.5%, 37.4%, and 37.4%, respectively. For 45 female patients seen in the same period, the corresponding five-, ten-, and 15-year survivals are 42.5%, 33.2%, and 27.7% (unpublished data).

Pathology and Prognosis

There have been conflicting reports concerning the prognostic value of the classical-desmoplastic classification of medulloblastoma. Chatty and Earle reported better survival in patients with desmoplastic medulloblastoma [11]. Five of their seven long-term ten-year survivors had the desmoplastic variety. All of these five latter patients were over age 15. Specifics concerning the therapy administered to patients in this series were not given. Muller et al., on the other hand, reported no difference in mean survival time between patients having the classical versus the desmoplastic variety of medulloblastoma [17]. Park et al. reported a slightly better survival for patients with classical medulloblastoma versus the desmoplastic variety [18]. The five- and ten-year overall survival rates for the classical type were 50% and 44%, respectively, versus 37% and 30%, respectively, for the desmoplastic variety.

Using the PNET classification of Rorke, Packer et al. analyzed 38 consecutive newly diagnosed medulloblastoma patients seen between 1975 and 1981 [26]. Twenty patients were considered to have the PNET-undifferentiated variety, eight patients had PNET with one line of cellular differentiation and ten patients had PNET with tumors differentiating along more than one cellular line (glial, epen-

dymal, or neuronal). The four-year disease-free survival was 70% for patients with PNET-undifferentiated as compared to 32% for those with PNET-differentiated. For the PNET-differentiated group, the four-year disease-free survival was 63% for those tumors with one line of cellular differentiation versus 10% for those with multidifferentiation. However, by six years the disease-free survival rate was only 21% for the PNET-uni-differentiation group.

Packer et al. also found a correlation between pathologic classification and clinical presentation. The PNET-undifferentiated tumors occurred more commonly in children older than seven years. All T1–T2/M0 patients had PNET-undifferentiated tumors. The PNET-undifferentiated tumors were more frequently totally resectable. In patients with T3–T4/M0 tumors, there was a significant correlation between disease-free survival and histological subgroup. Nine of 14 patients with PNET-undifferentiated tumors survived as compared to only 4 of 18 patients with PNET-differentiated tumors ($p = 0.004$). In patients undergoing a total resection, the importance of histological subgrouping was not clear. However, in patients undergoing a partial resection, those with the PNET-undifferentiated tumors had a better survival (8 of 11) compared to no survivors among 11 patients with the PNET-differentiated tumors. Further evaluation of this histological classification in a larger number of patients is awaited.

Kopelson et al. subclassified medulloblastomas histologically according to the amount of cytoplasmic processes, necrosis, mitosis, and desmoplasia [8]. Increasing amounts of cytoplasmic processes, necrosis, and mitosis were scored progressively from 0 to 3. Desmoplasia was scaled from 0 to 3 with decreasing amount. Using all four factors together, the authors divided patients into high or low tumor scores. There was a statistically significant difference in survival, favoring those with a low tumor score (more desmoplasia, less cytoplasmic processes, less necrosis, and less mitosis).

Sites of Recurrence

In almost every reported series of medulloblastoma patients, the most common site of relapse is the posterior fossa. In part, this reflects the ease of recognizing signs and symptoms of tumor in the posterior fossa. In the era prior to CT scanning, recurrence in the posterior fossa was often determined on a clinical basis. Without doing invasive procedures such as angiography and pneumoencephalography (PEG), metastases in the supratentorial area were not likely to be discovered antemortem. In 1968, from their review of the literature on medulloblastoma, McFarland et al. postulated that persistent or recurrent tumor in the posterior fossa was the most common cause of death [14]. This same review of the literature revealed that of patients with tumor recurrence beyond the posterior fossa, 94% had spinal involvement and only 6% had supratentorial involvement. McFarland et al. believed that the low incidence of cerebral lesions was related to flow patterns of CSF. However, they also suggested that cerebral lesions might not have been recognized clinically.

In most reviews, the posterior fossa is the first site of relapse in slightly less than 50% of patients with relapse (table 18-8). However, in most series, recurrent tumor in the posterior fossa is a component of initial failure in over 50% of patients with relapse. In the recently completed CCG study, recurrence in the posterior fossa occurred in 55.1% of patients with relapse [28]. The experience at the University of Pittsburgh with patients who were prospectively staged since 1974 and in whom extensive reevaluation was carried out at time of relapse differs somewhat from most reported series [7]. Of 45 patients who were diagnosed over one year ago, there have been 18 relapses. Only 3 of 18 patients had an initial relapse just in the posterior fossa. The posterior fossa was a component site of relapse in only 8 of 18 patients (44%). This was identical to the incidence of relapse in the supratentorial compartment.

TABLE 18-8. Sites of first relapse

Site of relapse	Series (number of relapsed patients)					
	Berry (52) [6] 1958–1978	Harisiadis (32) [29] 1963–1975	Deutsch (18) [7] 1974–1986	Silverman (31) [10] 1954–1978	Hershetter (54) [16] 1940–1983	Brand (17) [9] 1974–1983
<i>Single</i>						
Posterior fossa	19	8	3	14	26	4
Spinal cord	1	5	1	1	11	
Supratentorial	6	2	2	3	4	1
Systemic	15	2	2	5	3	1
<i>Multiple</i>					10	
All posterior fossa	29 (56%)	19 (59%)	8 (44%)	22 (71%)		12
All spinal cord	6 (11.5%)	11 (34%)	7 (39%)	8 (26%)		9
All supratentorial	11 (21%)	9 (28%)	8 (44%)	5 (10%)		2
All systemic	18 (35%)	3 (9%)	5 (28%)	5 (10%)		2

Two of 18 patients had an isolated systemic relapse, and both were in bone. However, systemic relapse was a component of first relapse in 5 of 18 patients (28%), which is only slightly less than the 34.6% incidence of systemic recurrence as a site of failure in the Toronto series reported by Berry et al. [6]. In the Toronto series, systemic relapse was the sole site of first failure in 28.8% of patients. In the Pittsburgh series, 4 of the 5 systemic relapses occurred in patients who were initially M3 stage. Only one of 33 non-M3-staged patients developed systemic metastasis.

Four of 12 patients with initial M3 disease relapsed in the spinal cord. Only 3 of 33 patients without spinal cord involvement at diagnosis had subsequent relapse in the spinal cord. The reported incidence of spinal cord relapse in the Pittsburgh series may be underestimated. Six patients did not have myelography at the

time of intracranial relapse, since their overall clinical status was extremely poor and further therapy was not being contemplated.

Supratentorial lesions may remain asymptomatic until reaching substantial size. With the use of CT for follow-up, supratentorial lesions are being discovered much more frequently than previously. In a series of patients treated since 1974, Deutsch reported recurrent tumor supratentorially in 44% of relapsed patients (8 of 18) [7]. This is a higher incidence than reported in most series. Several patients developed recurrent tumor in the anterior cranial fossa just above the cribriform plate (figure 18-5). This has been noted by others and may be related to blocks used to shield the orbits [58-60].

Posttherapy CT and/or MRI are the simplest and most accurate imaging techniques for determining the presence of intracranial tumor, and



FIGURE 18-5. Asymptomatic recurrent medulloblastoma in left side of the anterior cranial fossa.

they should be performed every three months for the first two or three years. Occasionally, an asymptomatic intracranial recurrence will be demonstrated.

Follow-up CSF cytology studies have been performed routinely on all children with medulloblastoma at Children's Hospital in Pittsburgh. A positive CSF cytology is helpful to confirm suspected recurrent tumor. Among 18 staged patients with recurrent tumor, six had malignant cells in the CSF at relapse [7]. All had clinical or radiographic evidence of recurrent tumor at the time of the positive cytology.

Myelography has not been performed as part of routine follow-up unless there is evidence of spinal cord involvement. If possible, myelography should be done on all patients with intracranial recurrent tumor. Asymptomatic cord lesions have been discovered at the time of intracranial recurrence [33]. However, many patients are in poor clinical condition at the time of intracranial relapse, and unless further aggressive therapy is being considered, myelography is not suggested. In the future, MRI may prove to be an effective modality for evaluating recurrent tumor in the spinal cord.

Marton et al. have used CSF polyamine levels to monitor medulloblastoma patients post-therapy [61]. Among 32 patients, 15 had elevation in CSF putrescine levels prior to detection of other evidence of recurrence. In eight additional patients, CSF putrescine levels were elevated at the time of recurrence. There were

three false-negative determinations—no increase in CSF putrescine levels at time of recurrence. However, there were no false-positive results. It is not clear how long before documentation of recurrence the CSF polyamine levels were elevated.

Phillips et al. had three patients with medulloblastoma who demonstrated transient elevations of CSF putrescine levels without developing evidence of recurrent tumor 26–40 months later [62]. None of these three patients had infection or hydrocephalus that could account for the elevations in CSF polyamine levels.

Stage and Outcome

Harisiadis et al. reported a correlation between T stage of the primary tumor (Chang classification) and survival at five and ten years (table 18-9) [29]. In a retrospective review, Kopelson also reported a decreased incidence of posterior fossa relapse for T1, T2 patients compared to T3, T4 patients, and a significantly improved five-year survival of 82% for the T1, T2 patients versus 46% for the T3, T4 patients [8]. On the other hand, Berry et al. reported that T1, T2 patients had an identical survival to those with T3, T4 tumors (57% at five years) [6]. Unexpectedly, Hershatter et al. reported a statistically significant correlation between survival and high T stage [16]. In their retrospective review, T4 patients did better than T3 patients, who did better than T2 patients. The

TABLE 18-9. T stage and outcome

Series	T stage	(no. patients)	Survival*	
Harisiadis [29]	T1	(5)	75% 5-year	75% 10-year
	T2	(20)	50.5%	43.7%
	T3	(29)	32.3%	13.2%
	T4	(4)	0	0
Kopelson [8]	T1T2	(19)	82%	
	T3T4	(21)	46%	
Berry [6]	T1T2	(50)	57%	
	T3T4	(63)	57%	

* Actuarial survival.

authors were unable to explain this unexpected finding except to point out the possible fallacies associated with retrospective staging. The CCG study showed no significant difference in disease-free survival between T1, T2 tumors versus T3, T4 tumors [28]. In the SIOP Study, T stage correlated with disease-free survival at five years [28].

Bloom et al. assessed the prognostic importance of brainstem involvement at diagnosis [19]. Five-year survival was practically the same regardless of whether or not the brainstem was involved (32% versus 36%, respectively). However, by seven years, survival in the group with brainstem involvement had dropped to 14% while remaining at 30% for the group without initial brainstem involvement.

Harisiadis and Chang reported that patients with M2, M3 disease did worse than patients with M0, M1 disease [29]. Berry et al. reported a 58% survival for patients with M0 disease versus a 47% survival at five years for patients with M1–M3 disease ($p = 0.19$) [6]. In the CCG study, the disease-free survival for M0 patients at 54 months was 58.2% versus 31.8% for patients with M1–M3 disease ($p < 0.001$) [28]. These studies, as with most other reviews of medulloblastoma in the literature, concern patients who were not thoroughly staged at diagnosis. In the series reported by Berry et al., elective myelograms and cytology studies were not performed [6]. Eighty-two percent (82%) of patients were considered to have M0 disease. This is similar to the M stage distribution in

the CCG study, in which 83% of patients were considered to have M0 disease [28]. It is very likely that staging with myelography was carried out only in those patients presenting with symptoms suggestive of cord involvement. The number of patients considered to be free of metastatic disease is probably overestimated in these retrospective reviews. Likewise, the number of patients considered to have dissemination beyond the posterior fossa is probably grossly underestimated.

Of the 45 prospectively staged patients treated at the University of Pittsburgh since 1974 with at least one year of follow-up, the five-year disease-free survival is 73.3% for M0 patients and 49.1% for M1–M3 patients [7]. Absolute survival is 86.5% for the M0 patients and 53.7% for the M1–M3 patients (table 18-10).

The series of medulloblastoma patients reported by Allen and Epstein showed a much poorer survival for patients with M1–M3 disease at diagnosis [34]. Only 3 of 8 patients were alive 8–11 months following diagnosis. Interestingly, patients with evidence of dissemination beyond the posterior fossa were less than five years of age.

Brand et al. divided patients into high- and low-risk groups on the basis of age, T stage, and extent of resection [9]. Favorable factors are age greater than five years, T stage T1, T2, and gross total resection. Patients having at least 2 of 3 features are considered good risk. For the good risk group, five-year relapse-free survival

TABLE 18-10. Extent of dissemination (M stage) and outcome

Series	M stage	(no. patients)	Survival*
Berry [6]	M0	(100)	58% 5-year overall
	M1–M3	(16)	47%
CCG [28]	M0	(193)	58.2% NED, 4½ years
	M1–M3	(39)	31.8% NED
Deutsch [27]	M0	(24)	73.3% NED 5-year
	M1–M3	(21)	49.1% 86.5 overall 53.7

* Actuarial survival.

was 80% versus 39% for the high-risk group. For each group, survival was independent of whether the craniospinal axis received 2500 rads or 3000–4000 rads.

Surgery

There are at least two anecdotal cases mentioned in the literature of children who have had prolonged survival after surgery alone for medulloblastoma. McIntosh mentioned a patient alive and well six years following complete removal of a medulloblastoma [53]. Farwell et al. reported one case from the Connecticut Tumor Registry who survived over ten years after just surgery [12]. No other details are available concerning either of these long-term survivors. Regardless of the apparent completeness of the surgical resection of a medulloblastoma, one must always assume that there is still residual tumor in the posterior fossa.

Cushing noted that patients surviving more extensive resection had a better survival [2]. In most series, the percentage of patients undergoing just biopsy is 10% or less. In several retrospective reviews, patients undergoing biopsy have a poorer survival than those undergoing total or subtotal resection [6, 16, 28, 29, 38]. However, this poor survival may be a reflection of more advanced disease and/or poorer clinical condition, rather than a definite indication that more extensive surgery is better than lesser surgery. Bouchard reported a small number of patients treated by needle biopsy and radiotherapy in which the five-year survival was 40% (4 of 10) [47]. For patients undergoing a surgical removal and radiotherapy, the five-year survival was 22% (6 of 27). Bouchard also noted that none of the ten children having radiotherapy after just a biopsy developed evidence of seeding along the subarachnoid CSF pathways.

Norris et al. compared two groups of patients in which the radiotherapy was similar but the surgical procedure on the posterior fossa was different (table 18-6) [37]. The group of pa-

tients diagnosed from 1975–1979 all had a gross total resection of the tumor, whereas only 3 of 11 patients diagnosed in the preceding five years had a gross total resection. The relapse-free survival at four years was 38% for the earlier group and 84% for the latter group. The one failure in the latter group had a systemic recurrence. In the earlier group, five patients had a relapse in the posterior fossa. Altogether, only 2 out of 14 patients undergoing total resection had relapse compared to 6 of 7 patients undergoing subtotal resection or biopsy. The relapse-free survival for the earlier group of patients seems to be lower than expected. Information was not provided concerning T and M staging of patients in the two groups. Staging with myelography and CSF cytology apparently was not performed. Thus it is possible that in this small series, there may have been other factors contributing to the worse outcome in the earlier group of patients.

In the CCG Medulloblastoma Study, there were no significant differences in disease-free survival or recurrence in the posterior fossa after total, subtotal, and partial resections, but the few patients who had just biopsy did significantly worse [39]. Also, in the recent SIOP study, there was no difference in disease-free survival between children having total and subtotal resections, but disease-free survival was worse after biopsy or partial removal [39].

In a survey of 304 children who received a complete course of radiotherapy, Stiller and Lenox reported that survival was significantly higher for children under age five years whose tumors were totally resected than for those who had residual disease present after operation [13]. However, there was no difference in survival for children age 5–14 years between those undergoing total resection and those undergoing partial removal. In this age group, the children who had just biopsy did worse. The poorer prognosis associated with biopsy may have been related to advanced stage, since 13 of 43 such patients were considered to have “inoperable” tumor.

In some reported series, there is a survival advantage for total resection versus lesser procedures (table 18-11). However, none of these series randomized patients between different surgical procedures. Thus it is possible and very likely that patients undergoing total resection had smaller tumors and were less likely to have evidence of dissemination than patients treated with lesser surgical procedures. In addition, patients undergoing total resection are more likely to have been diagnosed in recent years and may have benefited from other factors, such as earlier diagnosis with CT scanning, shunting, better supportive care, and supervoltage radiotherapy.

In the series reported by Kopelson et al., although the numbers are small, patients with T1, T2 primary tumors did equally well whether they had gross total excision or partial excision [8]. Silverman et al. reported that local control and survival was not influenced by the extent of resection but rather by the dose to the posterior fossa [10]. Mealey and Hall also stated that survival was not related to extent of resection [63].

Considering the relatively low mortality associated with an attempted total resection of a medulloblastoma, it is hard to argue against such an attempt as long as the procedure is not likely to harm the individual patient. Still, it is difficult to be sure that the extent of surgical resection really does influence prognosis in comparably staged patients. Given the strong surgical recommendations for doing gross total removals whenever possible, it is highly unlikely that a prospective randomized study comparing two different surgical procedures will ever be carried out. For the patient in whom gross disease beyond the posterior fossa is demonstrated, it hardly seems worthwhile to attempt a total resection of the posterior fossa tumor. In such cases, subtotal resection with reestablishment of the CSF flow is appropriate.

Radiation Dose and Survival

Several reviews have indicated a correlation between the dose administered to the posterior fossa and subsequent survival. In the series reported by Berry et al., patients receiving

TABLE 18-11. Extent of resection and outcome

Series	Resection	(No. patients)	Survival 5 years*
Berry [6]	Total	44	64%
	Subtotal	66	56%
	Biopsy	12	33%
Silverman [10]	Total	21	51%
	Subtotal	24	57%
	Biopsy	2	
Bloom [19]	Total	23	40%
	Partial	50	33%
Hershatter [16]	Total	49	42%
	Subtotal	60	30%
	Biopsy	9	0%
Raimondi [38]	Total	13	42%
	Subtotal, partial	30	30%
	Biopsy	4	25%
Harisiadis [29]	Total	5	20%
	Subtotal	33	49%
	Partial, biopsy	16	25%

* Actuarial survival.

greater than 5200 rads to the posterior fossa had an improved survival compared to those receiving lower doses [6]. Harisiadas and Chang also showed some correlation between administered dose to the posterior fossa and subsequent five-year survival [29]. The study by Silverman et al. demonstrated a marked reduction in posterior fossa relapse and markedly improved five- and ten-year survivals associated with 5000 rads or more administered to the posterior fossa [10]. Kopelson et al. also demonstrated a lower incidence of posterior fossa relapse associated with doses of 5000 rads or more [8]. Stiller and Lenox also reported improved survival with posterior fossa doses ≥ 4500 rads in children age 5–14 years. In the younger children there was no correlation between the posterior fossa dose and survival. Landberg et al. reported a group of 13 patients treated with craniospinal irradiation in whom the posterior fossa dose was 4200 rads [43]. The actuarial ten-year survival for this small group was 53%, which compares favorably with those series in which higher doses were administered. In the series reported by Hershatte et al., the dose to the posterior fossa did not correlate well with incidence of failure in the posterior fossa [16]. In fact, a good percentage of their long-term survivors received less than 4000 rads to the posterior fossa.

Between 1956 and 1986, 93 patients were treated with craniospinal axis irradiation at the University of Pittsburgh. Seventeen patients received a posterior fossa dose of 5000–5250 rads, and the five-year survival for this group was 76.5%. For 28 patients receiving > 5380 rads to the posterior fossa, five-year survival was 63.1%. Of these 45 patients receiving > 5000 rads to the posterior fossa, 40 were treated since June, 1974. Forty-eight patients received posterior fossa doses < 5000 rads. Only eight were treated since 1974, and seven of these were very young children. Of this group of 48 patients, 18 (37.5%) survived five years and 13 (27.1%) are still alive at more than eight years (unpublished data).

In a series of 45 staged patients from the University of Pittsburgh who were analyzed for sites of treatment failure versus administered dose, there was no definite correlation between administered dose and relapse at a particular site [7]. The eight relapses in the posterior fossa occurred in patients who had received 4950–5450 rads, and five of these patients had received ≥ 5250 rads. Relapses in the supratentorial brain occurred after doses of 3226–4950 rads. Three of the four patients with M3 disease who subsequently relapsed in the spinal cord had received 3450 rads to the entire cord plus an additional 900–1000 rads boost to areas of involvement. The fourth patient, a five-month-old infant, received 2040 rads to the entire cord with a 1500 rads boost to involved areas.

In most series, it appears that the more recently diagnosed patients received higher doses to the posterior fossa. A more recently diagnosed patient may also be benefiting from earlier diagnosis through the use of CT and MRI in addition to more extensive surgery and better supportive care. Thus, it is not entirely clear that higher doses are definitely needed. In the series by Kopelson et al., the patients with T1, T2 tumors did well with posterior fossa doses of 4000–5000 rads [8]. It is not clear whether or not lower doses could be safely administered to patients undergoing total resection. In the series by Hershatte, one subgroup treated with relatively low doses to the craniospinal axis and posterior fossa did better after total resection than after subtotal resection [16]. For the patients receiving “proper” irradiation, the extent of surgical resection did not seem to impact upon survival. Current Children’s Cancer Group Protocols for medulloblastoma suggest 5400 rads/30 fractions to the posterior fossa for children over three years of age. It is believed that this dose is the maximum that can be safely administered and that it should provide the greatest degree of local control.

The dose necessary for craniospinal irradiation (beyond the posterior fossa) is more controversial. For gross metastatic deposits de-

monstrated in the supratentorial region or subarachnoid spinal cord, it seems advisable to treat such lesions with at least 4500 rads in 5–6 weeks. The question of an adequate prophylactic dose to the craniospinal axis for those patients without demonstrable dissemination or with just malignant cells in the CSF (M1) is more problematic. Over the past several decades, there has been wide variation in the recommended administered doses to the craniospinal axis. More recently, 3500–4000 rads is the suggested dose for craniospinal axis prophylaxis, but it is not clear that such doses are indeed associated with improved survival [9, 64, 65].

Although there are very few reported series composed of M-staged patients, several reviews have indicated that craniospinal axis doses of less than 3000 rads may be sufficient. Brand et al. have demonstrated that for a subset of patients considered to be good risk on the basis of age, T stage, and surgical resection, craniospinal axis doses of 2500 rads are as effective as higher doses [9]. For poor-risk patients, there was no difference in survival between patients receiving 2500 rads and those receiving 3000–4000 rads to the craniospinal axis. All patients received 5500 rads to the posterior fossa.

A report by Deutsch on unstaged patients treated prior to 1974 at the University of Pittsburgh revealed that survival was identical for patients receiving spinal cord doses less than 2700 rads and for those receiving greater than 3000 rads [64]. Two long-term survivors had received 700 rads/5 fractions and 1400 rads/13 fractions, respectively. Brown et al. also reported four long-term survivors who received spinal cord doses of 1963–2250 rads [65]. However, Stiller and Lenox reported a trend towards improved survival in patients age 5–14 years who received higher doses to the spinal cord (> 3000 rads) [13]. In this age group, the incidence of spinal cord metastasis at five years was 41% for those who received < 3000 rads and 14% for those who received higher doses. For children under five years of age, the dose to

the spinal cord did not influence the incidence of spinal cord metastasis.

Because of the sequelae of craniospinal irradiation (see chapters 22 & 23 in this volume), there is impetus in trying to lower the dose of craniospinal irradiation in a subset of medulloblastoma patients. A current CCG and Pediatric Oncology Group (POG) study involves two different doses of craniospinal axis irradiation (2340 rads/13 versus 3600 rads/20) with the posterior fossa dose being 5400 rads/30 in both arms. Patients eligible for this randomization are those with T1, T2, T3A, tumors in whom there is less than 1.5 cc residual tumor after resection and in whom there is no evidence of dissemination beyond the posterior fossa (M0).

Adjuvant Chemotherapy and Prognosis

Prior to 1975, the reported experience of adjuvant chemotherapy for newly diagnosed medulloblastoma patients was limited to a few small nonrandomized series. Jundt reported 19 newly diagnosed medulloblastoma patients treated with vincristine and methotrexate given in six-week courses separated by one-month intervals over a period of 18 months [66]. Chemotherapy was started after completion of radiotherapy. In comparison to historical controls from the same institution, there did not seem to be definite benefit to this regimen. Chemotherapy was well tolerated.

Venes et al. treated eight newly diagnosed medulloblastoma patients with vincristine alternating weekly with cyclophosphamide administered for two years [67]. Chemotherapy was started after completion of radiotherapy. All eight patients were alive from one year four months up to over seven years from diagnosis. Morbidity was considered mild.

Thomas et al. treated five newly diagnosed medulloblastoma patients rather aggressively with chemotherapy during and after radiotherapy [68]. In two patients, BCNU was administered along with intraventricular and intrathecal methotrexate. Two patients just

received the intraventricular methotrexate during radiotherapy and one received only BCNU during radiotherapy. All patients also received vincristine and were maintained on high-dose intravenous methotrexate and intrathecal methotrexate after completion of radiotherapy. Four patients experienced serious complications and four died, three from complications and one with recurrent tumor. A fifth patient was reported as being alive but demented and experiencing convulsions. A second group of four patients was treated without intraventricular methotrexate, and BCNU was not administered during radiotherapy. These four patients were reported as being alive 6–35 months from therapy and without evidence of severe toxicity.

Van Eys et al. in 1981 reported results of a Southwest Oncology Group (SWOG) study that evaluated adjuvant chemotherapy in patients with medulloblastoma and ependymoma [69]. After completion of radiotherapy, patients were randomized to receive either vincristine, methotrexate intrathecally and hydrocortisone, or no chemotherapy. Sixty-three patients were entered into the study, but only 34 patients with medulloblastoma were evaluable. Survival was slightly improved (not statistically significant) for patients not receiving chemotherapy. Two patients receiving adjuvant chemotherapy died with myelosuppression.

In the series of 304 patients completing radiotherapy reported by Stiller and Lennox, 90 also received adjuvant chemotherapy [13]. Almost all patients received vincristine. The majority also received a nitrosourea. There was no evidence of a beneficial effect on survival from chemotherapy.

Adjuvant chemotherapy for medulloblastoma has been evaluated in two large prospective randomized studies containing a no-chemotherapy control arm [[28]. These studies are the SIOP and CCG trials that were started in 1975 and 1976, respectively, and completed in 1980 and 1981, respectively. Each trial included over 200 newly diagnosed patients. Both trials compared radiation alone with radiation and ad-

juvant chemotherapy consisting of CCNU and vincristine. In both studies, each arm received similar radiotherapy. The craniospinal axis was treated with 3500–4000 rads administered in 4½ to 6 weeks, and the posterior fossa received 5000–5500 rads administered over 6–7 weeks. The chemotherapy arm of each study included vincristine, 1 mg/M² administered weekly during radiotherapy for eight doses. Four weeks following completion of radiotherapy, patients were started on eight six-week cycles. Each cycle consisted of vincristine, 1.5 mg/M² on days 1, 8, and 15. CCNU, 100 mg/M² was administered orally on day 1. In the CCG trial, prednisone, 40 mg/M² was given daily in three divided doses for the first 14 days of each post-radiation chemotherapy cycle. Both studies showed a slightly improved disease-free survival for the chemotherapy arm. The disease-free survival rate at 54 months was 59% for the chemotherapy arm versus 49% for the control arm in the CCG study, while in the SIOP study, the chemotherapy arm had a 55% disease-free survival rate versus 43% for the control arm [28]. In both studies, it was the group with T3, T4 lesions that showed benefit from chemotherapy. Patients with T1, T2 lesions did not show any benefit from chemotherapy.

The CCG trial also evaluated chemotherapy for relapsed patients. Procarbazine, CCNU, and vincristine were used for patients relapsing on the control arm, and procarbazine was used alone for relapsed patients who had received adjuvant chemotherapy. Results of this salvage therapy have not yet been published.

Berry et al. found no difference in survival for their CCG patients treated with adjuvant chemotherapy (vincristine, CCNU, and prednisone) and those treated just with radiotherapy [6]. All patients were diagnosed in the same period of time since 1975. The three-year survival was 66% for the 22 patients treated with adjuvant chemotherapy and was exactly the same for the 26 patients not receiving adjuvant chemotherapy.

Review of 21 patients with stage M1–M3

newly diagnosed medulloblastoma by Deutsch did not reveal any benefit to adjuvant chemotherapy [7]. Ten patients received adjuvant chemotherapy and six relapsed. There were six relapses among the 11 patients who did not receive adjuvant chemotherapy. Five M0 patients received adjuvant chemotherapy, and there was one relapse.

Kopelson et al. found no difference in survival between five patients who had received adjuvant chemotherapy and 21 who did not for advanced medulloblastoma (T3, T4 and/or M2, M3 and/or tumor score ≥ 6) [8].

Currently, the CCG is carrying out two different medulloblastoma studies. For patients considered to have a relatively good prognosis, chemotherapy will not be administered. This study will evaluate and compare two different radiation dose levels administered to the craniospinal axis. For the poor-risk medulloblastoma patient, chemotherapy will be administered to both arms. One arm will receive the standard chemotherapy as was administered in the CCG 942 protocol. The second arm will be treated with *8-drugs-in-1-day* chemotherapy as described by Bleyer et al. [70]. Two courses of the 8-drugs-in-1-day regimen will be administered prior to radiation and then afterwards for eight more cycles.

Summary

Remarkable progress has been made in the therapy of medulloblastoma. The five-year disease-free survival for newly diagnosed patients staged and treated at the University of Pittsburgh since 1974 is 62.6% [7]. The overall survival at five years is 76.7%. For subsets of patients from other centers, the five-year disease-free survival is over 70% (tables 18-9, 18-10). Undoubtedly, improvements in radiation have played a major role in the improved results of medulloblastoma therapy. It is not entirely clear whether or not more extensive resections of the primary tumor and perhaps even of the metastatic foci provide increased control rates if high doses of radiotherapy are administered.

It is possible that more extensive resections of the primary tumor together with lower doses of radiotherapy might provide the same control rates as higher doses of radiation. Likewise, the smaller primary tumors may do as well with lesser resections or even lower doses of radiation to the posterior fossa than the currently recommended 5400 rads in 30 fractions.

Patients presenting with dissemination beyond the posterior fossa at diagnosis (M1–M3) are at greater risk for therapeutic failure than M0 patients. It is this group that requires more than standard craniospinal irradiation if improvements in survival are to be obtained. It is expected that the current cooperative group studies evaluating chemotherapy in the poor-risk medulloblastoma patient will define the role of chemotherapy for patients with large primary tumors, dissemination at diagnosis, and/or residual tumor in the posterior fossa greater than 1.5 cm³.

The dose of radiation necessary for the prophylactic irradiation of the supratentorial brain and spinal cord in the patient with M0 disease is more controversial. Twenty-five hundred rads to the supratentorial brain and spinal cord may be adequate for certain subsets of patients. Currently there is a CCG–POG study evaluating two different dose levels of radiation to the supratentorial brain and spinal cord (3600 rads/20 versus 2340 rads/13). Both arms receive 5400 rads/30 to the posterior fossa.

Current and future studies will hopefully clarify the prognostic and therapeutic importance of pathological subclassification, age, sex, and stage for newly diagnosed patients. Thus, for the individual patient, it may be possible some day to recommend extent of the surgical procedure, amount of administered radiotherapy, and the need, if any, for adjuvant chemotherapy.

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19. CEREBELLAR ASTROCYTOMAS

Harold J. Hoffman

Mitchell S. Berger

Laurence E. Becker

Historical Perspective

Cerebellar astrocytomas occupy a fascinating niche in the history of neurosurgical oncology. One has only to read the case histories of Bailey and Cushing in their classic monograph on gliomas to realize that this particular brain tumor was associated with the largest postoperative survival periods of any glial neoplasm [1]. Cushing also remarked that a "cure" was possible if the mural tumor nodule was removed from its cystic cavity [2].

The incidence of brain tumors in the pediatric age group approximates 2.5 cases per 100,000 population per year [3, 4]. As a group, central nervous system (CNS) neoplasms continue to rank as the most frequent solid tumor and second most common cancer of childhood [5, 6]. The most frequently occurring intracranial tumor is the glioma, and the vast majority of these tumors in childhood originate in the cerebellum [3, 6–12]. Astrocytomas slightly outnumber medulloblastomas in most clinical series, thereby making the cerebellar astrocytoma the most common pediatric brain tumor [13–19]. Fortunately, it has a favorable prognosis when compared with other intracranial tumors in children, and long-term survival is the rule and not the exception [12, 15, 20].

In a group of patients reviewed at the Hospital for Sick Children, Toronto, the incidence of cerebellar astrocytomas was greatest between the ages of 4 and 10 years (median: 6 years).

Another peak period was identified during the first half of the second decade of life. This is in agreement with other reports in the literature that claim similar statistics [6, 15, 21, 22], although some authors show a somewhat greater average age at the time of diagnosis due to inclusion of adult patients [13, 23–25]. In our group of patients, an almost equal number of females and males was documented, which is also in accordance with previous studies [14, 26, 27]. In two series, however, a distinct female predominance was noted [20]. Gol, however, reported a predominantly male distribution in patients with cerebellar astrocytomas and observed a rather sharp decline in the number of females harboring the tumor after the age of ten years [28].

Symptoms and Signs

Typically, the duration of symptoms prior to obtaining a diagnosis may vary from a few weeks to several years [13, 21, 29]. In our experience, the average history was 8.5 months, and over 80% of the patients were symptomatic for a year or less prior to their hospitalization. This was similar to Obrador's series of patients [17], while Ringertz and Nordenstam noted that the majority of their patients (80%) complained of symptoms for a longer period of time, i.e., two years or less [30]. One of our patients presented to the hospital with an abrupt onset

of headaches and rapid progression to coma. At surgery, an intratumoral hemorrhage was verified. This occurrence is extremely unusual and has previously been documented in only one case [31]. Patients who harbor midline cerebellar tumors may have a shorter duration of symptoms [32]. Infants and younger children also tend to have a brief history in comparison to older children and adolescents [21, 22].

In Cushing's original paper describing his experience with 76 cases of cerebellar astrocytomas, he commented upon a peculiar feature of the clinical history, namely quiescent intervals of weeks or months when the patient remained asymptomatic [23]. Following this, the symptoms returned, and were usually more pronounced. Others have also noted this varying and worrisome course and have ascribed this feature to the compliance of the younger skull in its adaptation to increased intracranial pressure [5, 9, 21]. This compensatory aspect of the pediatric cranium is nearly always lost by the fifteenth year of life [33].

Table 19-1 lists the symptoms and neurological findings in those 42 patients with cerebellar astrocytomas retrospectively analyzed at our institution during the past ten years. As

would be expected, symptoms referable to increased intracranial pressure (i.e., in order of decreasing frequency, headache, vomiting, unsteady gait) were most often observed. This has been a consistent finding in virtually every reported series to date of children diagnosed as having cerebellar astrocytoma. Newer diagnostic modalities, including computed tomography (CT) and magnetic resonance imaging (MRI), have not changed the incidence of these symptoms, although the duration of the clinical history prior to discovering the lesion has certainly been lessened. Although commonly documented in the past, blindness is fortunately an extremely rare occurrence, and can now be prevented in nearly every instance [34]. Nearly 30% of Cushing's and Grant's patients developed this tragic complication of long-standing hydrocephalus, thereby emphasizing the lack of diagnostic tools available to the clinician during the early years of neurosurgery [22, 35]. It is still not unusual to examine an irritable infant with a large head and full fontanelle whose vomiting and gait dysfunction has been insidiously labeled as gastrointestinal disorder and clumsiness, respectively [12]. Because infants and young children may often adjust

TABLE 19-1. Symptoms and signs of 42 cerebellar astrocytomas. Hospital for Sick Children, Toronto, 1975-1986

Symptoms	%	Signs	%
Headache	84	Papilledema	84
Vomiting	74	Truncal ataxia/Poor tandem gait	74
Unsteady gait	69	Appendicular dysmetria	39
Increased head size	14	Head tilt	22
Marked lethargy	12	Horizontal nystagmus	14
Diplopia	10	Sixth-nerve paresis:	
Decreased visual acuity	10	Unilateral	22
Falling toward the side	10	Bilateral	5
Neck pain	7.5	Unilateral facial weakness	5
Neck stiffness	5	Unilateral facial hyposthesia	2.5
Vertigo	5	Hemiplegia	2.5
Slurred speech	5	Optic atrophy	2.5
Retro-orbital pain	2.5		
Coma	2.5		
Blindness	2.5		

to their neurological deficits and hide their true feelings, one must have a high index of suspicion when the typical symptoms of raised intracranial pressure secondary to a posterior fossa tumor are present.

This high incidence of papilledema in our group of patients is generally recognized in the literature and again exemplifies the ill effects of intracranial hypertension [5, 35, 36]. Optic atrophy indicative of chronic papilledema is rarely seen owing to earlier detection. The presence of papilledema during infancy and early childhood underscores the misconception that this finding requires closed sutures. As Matson emphasized, funduscopy, although frustrating, must be attempted in children of all ages to complement the evaluation of slowly increasing intracranial pressure [15]. The next most common finding was truncal ataxia. This results in a wide-based gait and prevents any attempt to walk in tandem. It is generally accepted that midline cerebellar masses result in a pronounced truncal ataxia with little effect on the limbs [12, 28]. A stronger correlation exists between hemispheric lesions and extremity dysmetria, making this finding of greater localizing value [36, 37].

Cranial nerve dysfunction is usually in the form of a sixth-nerve palsy [22]. Due to its known correlation with increased intracranial pressure, caution must be used when considering this as a localizing sign. Nystagmus may also be falsely localized to the cerebellum, without consideration of a vestibular origin resulting from secondary compression from a posterior fossa mass or brainstem invasion. Two additional findings worth including in this discussion are head tilt and MacEwan's "cracked pot percussion note." The latter is of historical interest more than practical value, yet may be present in an infant with a large, hydrocephalic head without obvious papilledema [23, 35]. Tilting of the head, usually contralateral to the tumor, is often noted by the examiner and may be elicited by questioning the parents. One fifth of our patients were found to have

a head tilt, and this was usually accompanied by a stiff neck [5, 12, 13].

Radiology

High-resolution CT scanning provides accurate localizing capabilities and yields valuable information regarding the structural characteristics of the tumor.

Cerebellar astrocytomas on CT scan have been divided into several groups (table 19-2) [38, 39].

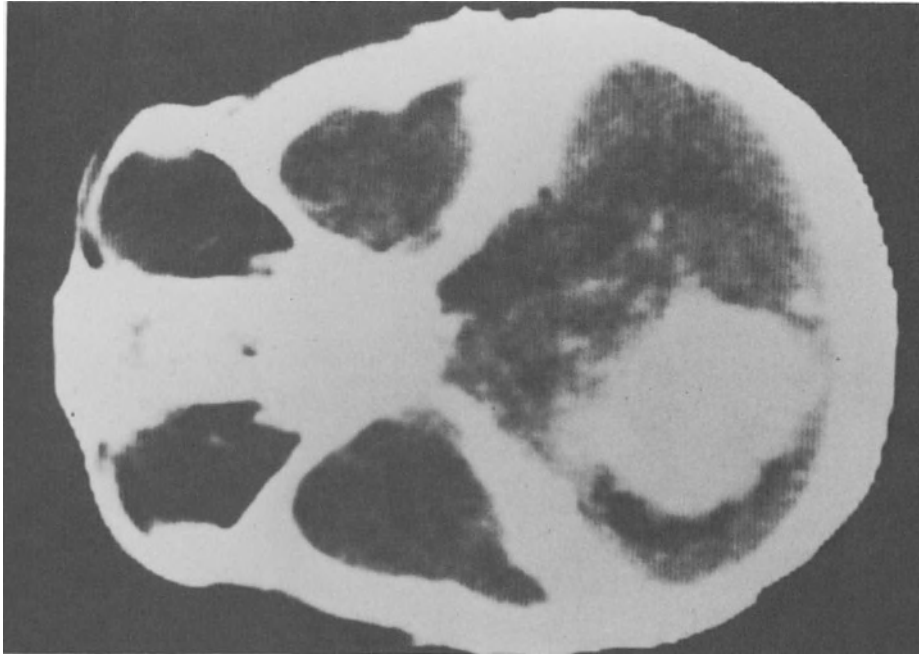
1. *Solid cerebellar astrocytoma*. These are solid enhancing masses that may contain small intratumoral cysts. In our series, about 50% of the solid tumors had small intratumoral cysts (figure 19-1).
2. *"Typical" cystic cerebellar astrocytoma*. These tumors consist of an enhancing tumor nodule in association with a cyst that is usually much larger than the mural nodule. The cyst wall does not enhance (figure 19-2).
3. *"False" cystic cerebellar astrocytoma*. These tumors consist of an enhancing tumor nodule in association with a large cyst with an enhancing cyst wall (figure 19-3A).
4. *Thick-walled cystic cerebellar astrocytoma*. These tumors consist of a neoplastic thick-walled cyst without a mural nodule (figure 19-3B).
5. *Thin-walled cystic cerebellar astrocytoma*. These tumors consist of a neoplastic thin-walled cyst without a mural nodule (figure 19-3C).

The solid portion of the tumor is usually hypodense or isodense in comparison to the adjacent cerebellum, and characteristically enhances with the administration of intravenous contrast agents [40, 41]. Increased density within the tumor indicates calcification and not blood [42, 43]. Cyst fluid demonstrates an increased attenuation value in comparison to cerebrospinal fluid due to its protein content [44]. On occasion, a layering effect has also been noted due to the leakage of contrast material inside the cyst and settling in the dependent portion of the cavity.

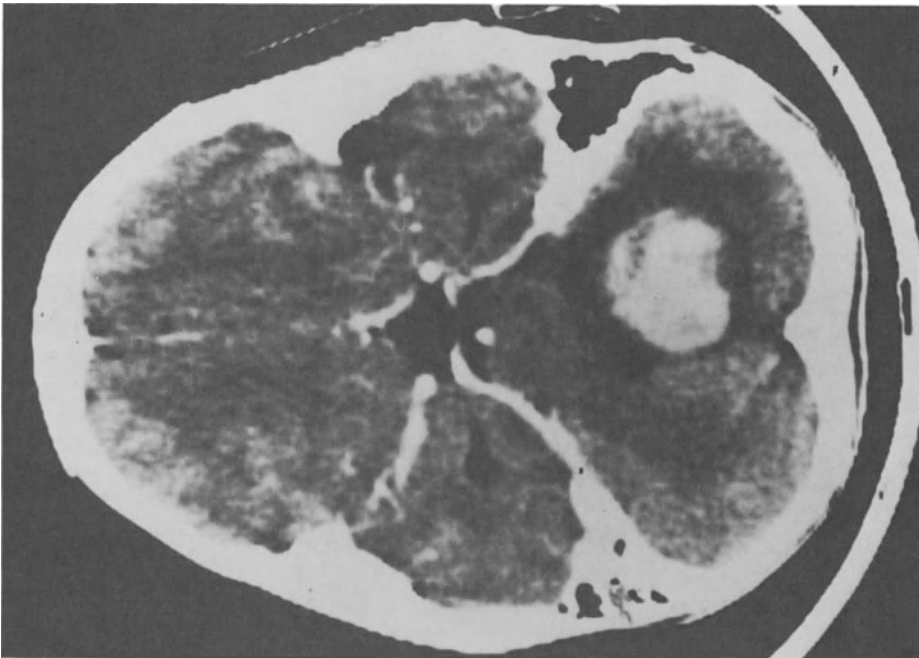
An important CT feature that must always be noted is enhancement of the cyst wall, and

TABLE 19-2. CT characteristics of 42 low-grade cerebellar astrocytomas: Hospital for Sick Children, Toronto, 1975-1986

Tumor type	No.	Hydrocephalus	Calcification	Hemorrhage	Location			Location of mural nodule		% of total
					Cerebellar hemisphere	Cerebellar vermis	Hemisphere and vermis	Medial	Lateral	
Solid	17	15	1	1	3	7	7	-	-	40
"Typical" cystic cerebellar astrocytoma, mural nodule and non-enhancing cyst wall	11	11	-	-	7	2	2	6	5	26
"False" cystic cerebellar astrocytoma, mural and nodular enhancing cyst wall	5	5	1	-	4	1	-	2	3	12
Thick-walled enhancing cyst, no nodule	7	7	2	-	1	1	5	-	-	17
Thin-walled enhancing cyst, no nodule	2	1	1	-	1	1	-	-	-	5
TOTAL	42	39	5	1	16	12	14	8	8	100

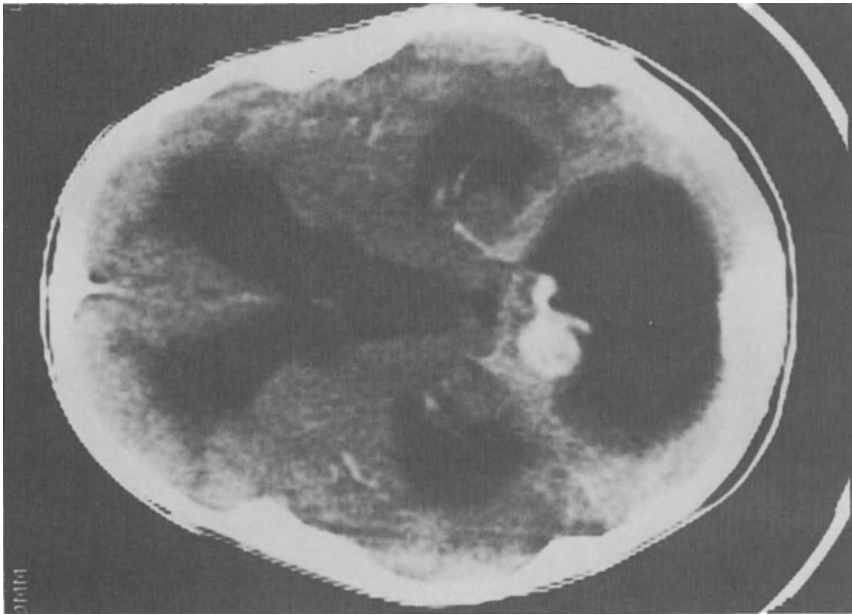


B

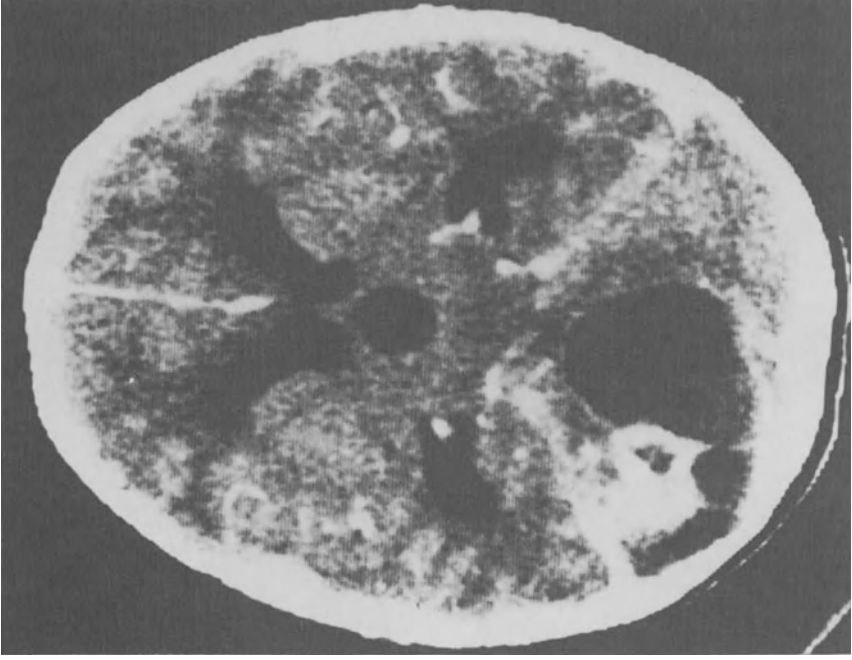


A

FIGURE 19-1. A. Solid cerebellar astrocytoma on enhanced CT scan with small intratumoral cyst. B. Solid cerebellar astrocytoma on enhanced CT scan with peritumoral edema.

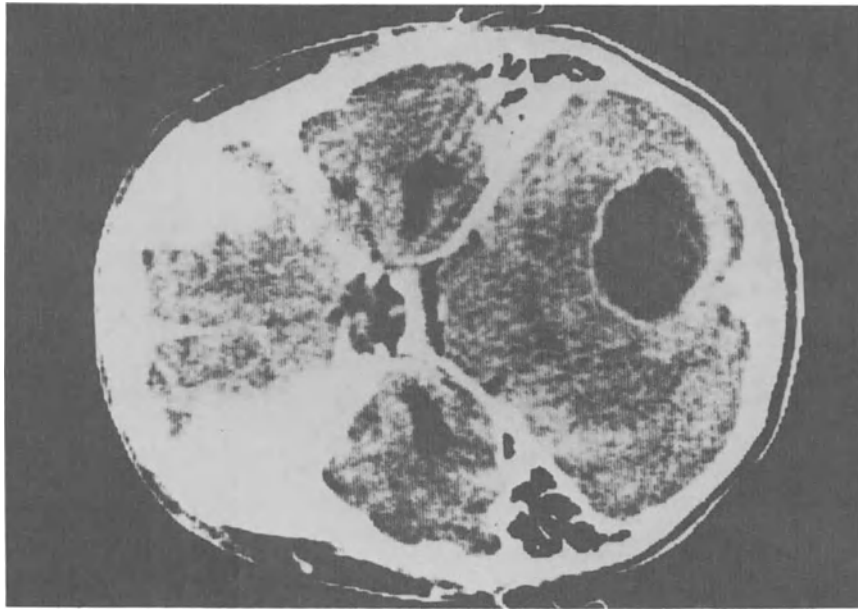


A

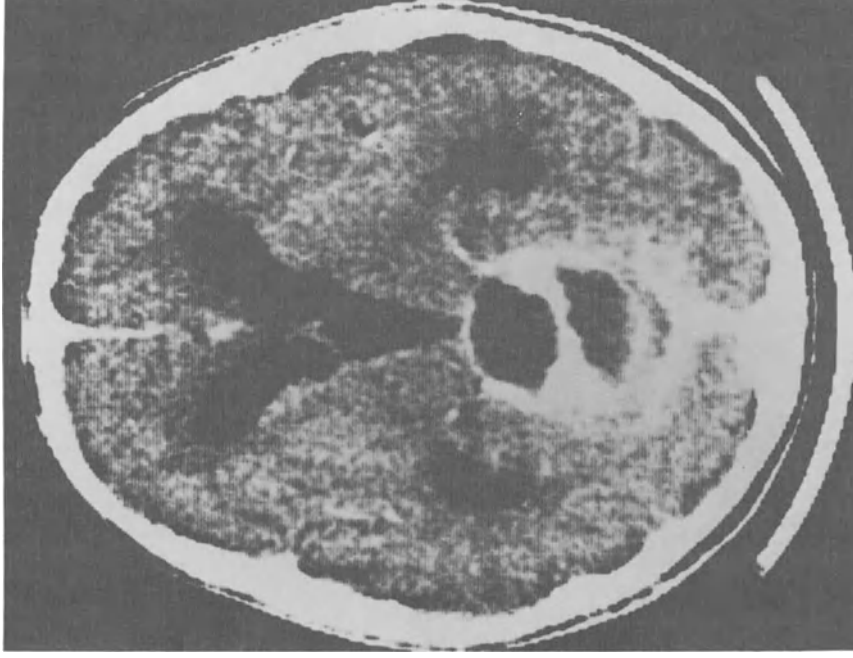


B

FIGURE 19-2. A. Cystic cerebellar astrocytoma with anterior mural nodule on enhanced CT scan. Note lack of enhancement of cyst wall. B. Cystic cerebellar astrocytoma with lateral mural nodule on enhanced CT scan. Note lack of enhancement of cyst wall.



A



B

FIGURE 19-3. A. Cystic cerebellar astrocytoma consisting of mural nodule and enhancing cyst wall on enhanced CT scan. B. Cystic cerebellar astrocytoma consisting of thick-walled multiloculated cyst in superior cerebellar vermis on enhanced CT scan.



FIGURE 19.3. C. Cystic cerebellar astrocytoma consisting of thin-walled enhancing cyst on enhanced CT scan.

the intensity to which this occurs. Contrast accumulation in the cyst wall unequivocally indicates the presence of tumor [43, 45] (figure 19-3). In cases where a mural tumor nodule is identified, the wall of the cyst frequently does not enhance [46]. The perimeter of the cyst cavity may appear irregular, thick, and tortuous, or may be nearly round or oval with a thin but easily detectable rim of contrast enhancement. The interface between the cyst wall and compressed cerebellum may often appear hyperdense or give the impression of faint enhancement (figure 19-2B). This finding must not be interpreted to represent neoplastic tissue. Another misconception is the correlation of the enhancing tumor cavity to higher grade of malignancy [43]. Cyst wall biopsies taken from enhancing cyst walls have confirmed the

presence of low-grade astrocytoma [4], while biopsy of nonenhancing cyst walls have confirmed absence of tumor [44] (figure 19-4).

Table 19-2 summarizes our experience with cerebellar astrocytomas since the availability of CT scanning at the Hospital for Sick Children (1975–1986). The vast majority of all tumors were associated with an obstructive hydrocephalus (93%). Forty percent of the lesions were solid, or nearly so, while the remaining 60% were cystic with or without a mural tumor nodule. Following contrast administration, five distinct patterns emerged: 1) solid or primarily solid with associated intratumoral cysts



FIGURE 19-4. Gliotic cyst wall after excision of mural tumor nodule in patient with cystic cerebellar astrocytoma.

(40%); 2) cyst with mural nodule, cyst wall does not enhance (26%); 3) cyst with mural nodule, cyst wall enhances (12%); 4) thick-walled cyst without a mural nodule (17%); and 5) thin-walled cyst without a mural nodule (5%). Calcification was identified in 12% of the tumors, and evidence of hemorrhage was seen in only one patient.

Although experience with MRI is still in its infancy, rapid technical advances have resulted in exquisite imaging detail of posterior fossa tumors. MRI may soon surpass CT as the primary screening modality in the evaluation of a child with a suspected tumor due to the lack

of ionizing radiation and loss of artifact from the bone enveloping the contents of the infratentorial space. Delineation of cyst fluid and hemorrhage are easily obtained with MRI. Early attempts at predicting histological degrees of malignancy based on comparing different pulse sequences of lesions with various proton densities have been encouraging [46]. One apparent difficulty has been in distinguishing edema from the tumor edge, and for that reason, CT scanning with intravenous contrast agents is superior to MRI for that purpose, i.e., tumor margin versus surrounding edema or tumor within the cyst wall [47]. The development of paramagnetic agents for contrast, i.e., gadolinium-DTPA, may help to define the tumor margin, although some investigators have suggested that heavily weighted T2 images may be as good or better than the paramagnetic compounds [48, 49].

Gross Appearance and Location

Cerebellar astrocytomas may originate from any location within the cerebellum. Tumors that primarily occur in the vermis, i.e., midline, or involve in addition one or both hemispheres are the most common anatomical type [20, 21, 32, 39, 50]. An isolated lateral, i.e., hemispheric, location occurs less frequently than vermian or mixed vermian–hemispheric masses [5, 22, 39]. This has been reflected in our patient population, with 39% of the tumors being located in either hemisphere only. An interesting finding has been that younger patients tend to have a greater number of midline lesions [10, 32]. Multicentric cerebellar astrocytomas are exceedingly rare [20].

Regardless of location, cystic tumors with or without a mural nodule are more frequently encountered than the solid variant [22, 30, 34, 51]. A predominantly hemispheric location is seen when the tumor is cystic, while a midline location is usually associated with solid neoplasms [17, 21, 25, 28]. Of the cystic tumors,

in our series, nearly 64% were associated with a mural tumor nodule and half of these originated medially. This is in keeping with other reports in the literature [36, 37].

However, Mabon et al.'s experience showed that most cystic lesions were without a mural nodule, and thus they questioned what role the solid tumor had in possibly creating the cyst cavity [25]. The site of the nodule may be predominantly medial, or may show no preference for either a vermian or lateral location as in our series [9, 39]. It may also be buried deep in the cyst wall as often as it protrudes into the cavity. The gross appearance of the nodule varies from yellow-brown to grey-red and has a soft suckable consistency [23, 30]. The cyst fluid is similar in color and consistency to tumor cysts located outside the posterior fossa, and reflects the high protein concentration. When exposed to ambient air, it typically clots (Froin's syndrome) [21]. The cyst wall is smooth and glistening (figure 19-4), but may be coated by a fine layer of tumor or raised nodules [21, 25, 50, 52]. The nodule may be plaquelike and occupy the major portion of the cavity [54]. Regardless, the color the texture of the cyst lining should be carefully noted, and the surgical resection planned in accordance with these findings. Unlike Cushing's experience, tumor-lined cysts are not unusual and must be recognized to exist even in the presence of a mural nodule [22] (figure 19-3C).

Pathology

Astrocytomas in the cerebellum in children are low-grade in terms of biological activity, and are readily identified through positive reaction with antisera to glial fibrillary acidic protein (GFAP). As a general rule, they do not create a diagnostic dilemma. However, there have been attempts to subclassify this group of tumors on the basis of pure histological features and on the basis of a clustering of histological features, since those features relate to prognosis [26, 52, 54]. In practice, these tumors are simply called low-grade astro-

cytomas, and unusual features are appropriately noted. Long-term survival with minimal neurologic deficit is characteristic.

It is now rare to receive in surgical pathology an intact circumscribed cerebellar astrocytoma. Small fragments of tumor often removed with the Cavitron are the usual submission to pathology. Because of excellent long-term survival, it is even rarer to encounter a cerebellar astrocytoma at postmortem.

The modification of the World Health Organization (WHO) classification has simplified the histological designation applied to cerebellar astrocytomas [55]. Astrocytomas are called astrocytomas. Modifying terms such as pilocytic, fibrillary, or gemistocytic are used at the discretion of the pathologist.

The common cerebellar astrocytoma described as pilocytic and/or compact and spongy contains compact cellular areas adjacent to less cellular areas in which there may be microcysts [52]. The astrocytic component is readily identified with conventional histology and confirmed by immunoperoxidase or electron microscopy. Antisera to GFAP react with the intracytoplasmic intermediate filaments to produce a dark brown deposit. By electron microscopy, bundles of intermediate filaments are identified in cytoplasmic processes. In most cases Rosenthal fibers can be identified, and in some cases the tumor is all Rosenthal fibers. Focal calcification is frequent. In contrast to astrocytomas in adults, the presence of endothelial proliferation does not denote a worse prognosis. It is also not uncommon to identify variation in nuclear size, shape, and degree of chromaticity. Other characteristic accompaniments of this tumor include nests of oligodendroglial cells and focal outgrowth of astrocytoma into the subarachnoid space. Neither of these observations interferes with the excellent prognosis associated with the diagnosis of cerebellar astrocytoma.

A review of 42 low-grade cerebellar astrocytomas seen at the Hospital for Sick Children over the past decade revealed that 37 were pilocytic ("compact and spongy"), three were

fibrillary, one was gemistocytic, and one was mixed with oligodendroglioma.

Malignant primary cerebellar astrocytomas are exceedingly uncommon in either adults or children [6, 13, 14, 25, 56–58]. During the past decade, we have only encountered one malignant cerebellar astrocytoma. Features indicating malignancy correspond to those listed for the Glioma B group of Winston et al. [59]. However, vascular endothelial hyperplasia and cellular atypia, findings that imply malignancy in other central nervous system neoplasms, may represent degenerative foci without a malignant potential [52]. Rarely, a histologically benign cerebellar astrocytoma will undergo malignant transformation [60] many years after the initial operation. A striking example of this was reported by Kleinman et al. [61] in a patient of Cushing's who 48 years previously underwent a subtotal resection of a benign (juvenile pilocytic) astrocytoma. In reviewing the literature including their case, 4 of the 5 patients undergoing malignant transformation had previously received radiotherapy. Tumors that largely occupy a midline portion may invade the brainstem via the floor of the fourth ventricle or cerebellar peduncles [5, 13, 37, 52]. This can be appreciated at the time of exploration and at autopsy [30, 61]. The microscopic pathology of the cyst wall may confirm the presence of tumor, lining part of or the entire cyst cavity, or will fail to exhibit any neoplastic tissue, showing instead a gliotic membrane [10, 11, 28, 62]. Prior to the advent of CT scanning, preoperative assessment of the histological composition of the cyst wall was impossible. However, correlation of enhancing areas on the CT scan with pathological data confirms the presence of tumor tissue in those portions of the cyst wall that clearly enhance with the administration of contrast agents [39, 41, 46, 63]. Therefore, the presence of a mural nodule cannot always be equated with a adjacent cyst wall of nonneoplastic composition. In our series, five patients had an enhancing cyst wall associated with a mural nodule of tumor. Each

cavity was removed in total, along with the solid tumor, and microscopic inspection revealed evidence of tumor in all five cyst walls.

Surgical Management

Remember the lovely cysts with sparkling, yellow fluid and a nice mural nodule just begging to be taken from its nest.

W.J. German

Stated simply, the cerebellar astrocytoma is the most readily excised tumor with the least attendant morbidity in pediatric neurosurgery. The operative mortality, which varied from 5% to 32% in the older series, has virtually been eliminated due to technical advances in both neuroanesthesia and neurosurgery [14, 20, 23, 30, 35]. The operative morbidity is also minimal, owing to the lack of any major cerebellar dysfunction resulting from removing portions of the cerebellar cortex [24]. Cushing stressed the importance of a complete excision at the first sitting and felt that recurrences were more likely to become embedded in the floor of the fourth ventricle, thereby increasing the morbidity of a subsequent operative procedure [23].

Complete excision is technically more feasible in cystic tumors than in the solid midline variant, which may on occasion be invasive and not amenable to radical removal [5, 32]. This fact notwithstanding, solid tumors can be extirpated completely or radically (greater than 95%) regardless of their location [28]. The goal of surgery should be a gross total resection of all abnormally enhancing tissue demonstrated on the CT scan. Removal of the mural nodule without resection of the enhancing cyst wall must be considered as an incomplete excision. Repeated cyst aspirations without attacking the source of the fluid have no place in the management of cerebellar astrocytomas (figure 19-5).

Hydrocephalus occurred in 93% of our patients, which is consistent with other reports in the literature [39, 44, 64]. Because of this, several investigators have advocated insertion of CSF shunt prior to the definitive posterior

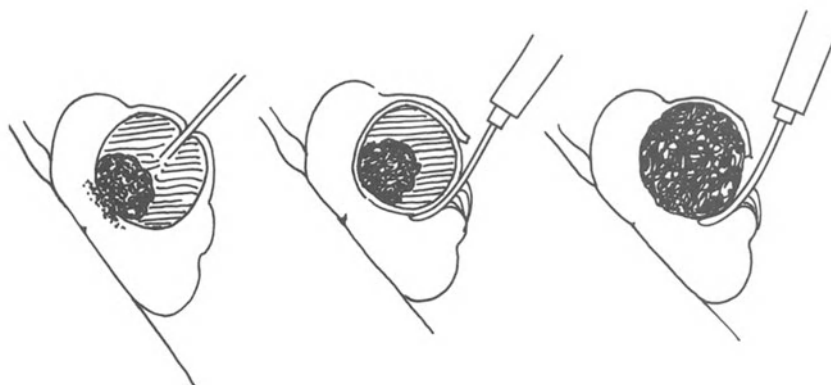


FIGURE 19-5. Diagrammatic depiction of aim of surgery in cerebellar astrocytoma.

Left: "Typical" cyst cerebellar astrocytoma. Only the mural nodule need be removed.

Middle: "False" cystic cerebellar astrocytoma. Both the mural nodule and the cyst wall must be removed.

Right: Solid cerebellar astrocytoma. The entire tumor must be removed.

fossa exploration [12, 18, 64]. However, this maneuver is not without hazard, and as others have pointed out, upward cerebellar herniation, with or without intramural hemorrhage, may occur, although uncommonly [64, 65]. One of 14 patients in our series who underwent preoperative placement of a ventriculoperitoneal (VP) shunt demonstrated this clinical syndrome. We do not insert a VP shunt preoperatively unless the patient is extremely ill and fails to respond to steroid therapy. At the time of surgery, the ventricle may be drained if the posterior fossa is tense. If the fourth ventricle has been opened and CSF is not flowing freely, a catheter may be passed through the aqueduct into the third ventricle and secured distally in the cisterna magna. This obviates the need for external ventricular drainage and avoids the need of a postoperative shunt.

Stein reviewed the cases of children requiring postoperative shunts for hydrocephalus following removal of a cerebellar astrocytoma [66]. The incidence was approximately 20%. He felt that this complication was due to an aseptic meningitis and noted this to be more frequent in those patients undergoing a complete tumor resection. He urged that the dura be closed and steroids administered to try to avoid this complication. Our own practice is to carry out a water-tight dural closure utilizing cadaver freeze-dried dura.

Postoperative Therapy

The indication for radiotherapy in the management of cerebellar astrocytomas continues to be challenged by most investigators. Since the 1930s, several authors have contended that radiation plays no role in the treatment of astrocytomas [14, 15, 20, 21]. There is widespread agreement that postoperative radiation is not necessary, provided that a gross total resection of the tumor is accomplished [64, 67–69]. There are numerous reports of prolonged survival following incomplete resection without radiotherapy that make it difficult to assess the efficacy of this treatment modality [24, 25, 36, 37, 50, 60]. In some cases, despite radiotherapy, a histologically benign astrocytoma has disseminated from its primary site [58, 70]. Nevertheless, there have been several proponents of postoperative radiotherapy when the tumor is only partially excised [14, 27, 28, 69]. Fazekas claimed that the beneficial effect radiation had was more of a palliative one, as opposed to a curative one, since the ten-year survival

rate for low-grade astrocytomas was little affected [67]. Although little morbidity may be expected with focal posterior fossa radiation [71], it is disturbing that 80% of those patients whose cerebellar astrocytomas underwent malignant transformation received radiation therapy.

When the tumor shows microscopic features of anaplasia, or is found to be invading the brainstem at the time of surgery, radiotherapy has been recommended as adjuvant therapy [5, 53, 59]. In the former group, craniospinal irradiation was found to be superior to cranial irradiation alone [56], although in Kopelson's series of patients, spinal subarachnoid metastases were not identified, and he proposed only the need for local radiation to the posterior fossa [58].

We would recommend postoperative therapy only for malignant astrocytomas. Patients with subtotal resection of their tumors should be followed closely with neurological examinations and CT scans. Recurrences in this group of children should be treated with reoperation. Radiation should only be considered if brainstem invasion is demonstrated at the time of reoperation, or if malignant transformation occurs, which has not been seen in our patient population. A patient who has previously undergone radiotherapy and subsequently develops recurrence without brainstem involvement may be a candidate for interstitial brachytherapy using low-activity radioactive sources.

At the present time, there is little evidence to suggest a beneficial effect from chemotherapy for cerebellar astrocytomas. Anecdotal reports using either single agents or multidrug protocols are encouraging [16, 21]. Malignant astrocytomas should be given adjuvant chemotherapy in addition to craniospinal radiotherapy. These patients should undergo staging myelograms with CSF cytology. Spinal metastases should receive local tumor radiation boosts in addition to the standard spinal axis dose. Positive CSF cytology persisting after craniospinal radiotherapy must be treated with intrathecal chemotherapy.

Prognosis and Recurrence Patterns

The cerebellar astrocytoma is conspicuous in pediatric neuro-oncology as having the best prognosis with the greatest chance for cure of any brain tumor [13, 28, 34, 50].

The location of the tumor, i.e., midline versus lateral, has affected the prognosis in some reports [35, 44, 51, 72]. This was also demonstrated in our series of patients (75% of recurrences, midline). Recurrences were equally divided between solid and cystic tumors. Although Elvidge [24, 73] found a greater postoperative survival with the cystic form of cerebellar astrocytoma, other investigators showed that the prognosis was relatively unaffected by the cystic or noncystic nature of the tumor [25, 26, 34]. Therefore, this macroscopic feature has little effect on the pattern of recurrence of cerebellar astrocytomas.

The most important factor that favors long-term survival is the extent of tumor resection [30]. There is no question regarding the efficacy of gross total resection in the outcome of patients with cerebellar astrocytomas [13, 34, 50, 73]. While recurrence following "complete" excision (pre-CT era) has been reported [60], this is the exception rather than the rule. It has even been emphasized that subtotal tumor resection is compatible with a prolonged recurrence-free survival [35–37]. In those cystic tumors with a mural nodule, it has long been recognized that removing the solid tumor from the cyst wall, as opposed to merely aspirating the cyst fluid, is the sine qua non for a cure to result [1, 20, 23, 30]. With the additional information provided by CT scanning, resecting the nodule without the enhancing cyst wall will likely result in a less than optimal result. Every patient in our series who developed a recurrence of their tumor had either a subtotal resection or biopsy. No patient, regardless of tumor location, gross appearance, or microscopic pathology developed a recurrence after initially undergoing a complete resection of all enhancing tumor tissue. Controversy exists regarding

tumor recurrence and prognosis and its relation to histological features. Our data and that of others fail to show a difference in outcome related to microscopic tumor features unless there is frank evidence of malignancy [23, 28, 34, 73]. The group B tumors of Gilles et al. [54] and the diffuse astrocytomas of Gjerris and Klinben and of Russel and Rubinstein are uncommon compared to the pilocytic astrocytomas, and distinctly represent a tumor type with a more aggressive growth potential [26, 52, 54]. However, these tumors are uncommon and were not evident in our recent review of 42 low-grade cerebellar astrocytomas seen at the Hospital for Sick Children.

The extent of resection is the most important factor in determining long-term recurrence-free survival. Location plays a role in outcome only if the surgeon takes a less radical approach, being concerned with the proximity of the deep cerebellar nuclei and the brainstem. Why do some cerebellar astrocytomas that are biopsied or incompletely resected remain dormant for indefinite periods of time? Cushing hypothesized that a certain proportion of these tumors will spontaneously regress [23]. Whether the "single cerebellar cyst" described by Silverberg represents one end of this spectrum is uncertain [62]. We have noticed a similar finding in two patients whose CT scans showed residual tumor six months postoperatively, yet subsequent follow-up scans showed complete regression of the enhancing mass.

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20. BRAIN METASTASES

Jeffrey C. Allen

Central nervous system (CNS) metastases from systemic cancer are usually separated into two distinct anatomic categories depending on whether they arise in the extradural or intradural spaces. The biology of metastasis differs for each of these locations, and each cancer has its own pattern of spread. Extradural or epidural metastases usually arise from a metastasis involving bone adjacent to a neural structure or from venous plexuses or lymph channels in the extradural space (figure 20-1). Intradural metastases may involve the leptomeninges, brain, or spinal cord, and are usually of hematogenous origin. This chapter reviews only the subject of parenchymal brain metastases from systemic solid tumors arising in childhood.

Brain metastases arise more commonly in adults than children, both from an incidence and a numerical perspective. Nearly a million adults will acquire cancer each year in the U.S., compared to only 6000 children. Solid tumors (carcinomas and sarcomas) tend to be relatively and absolutely more common in adults than in children. The most common malignancy in children is leukemia, which composes 40% of all cases of childhood cancer. Primary brain tumors contribute 20% of the childhood cancer population, and the remaining 40% of cases consist of solid tumors such as osteogenic sarcoma, Ewing's sarcoma, neuroblastoma, lymphoma, Wilms' tumor, rhabdomyosarcoma, and germ-cell tumors.

In population-based studies such as the one

from Olmstead County, Minnesota, reported by Percy et al. in 1972, the annual incidence of brain metastases was 11.1/100,000 population, approximately equivalent to the incidence of primary brain tumors (12.5/100,000) [1]. These statistics would predict the annual occurrence of approximately 28,000 new cases of brain metastasis in adults per year. Institutional neurosurgical series tend to underreport the frequency of brain metastases, since only a portion of patients with CNS metastases will have a biopsy or resection. Thus, the frequency of brain metastases in operative brain tumor series may range from 3%–25% [2]. The frequency of brain metastases in autopsy series of cancer patients is approximately 15%–20% [3].

Much of the literature and experience on the subject of brain metastases pertains to the adult situation. Although the knowledge gained from the study of brain metastases in adults can be applied to the pediatric condition, one must be mindful that the most common solid tumors in adults are carcinomas (lung, breast, colon, etc.), while the most common solid tumors in children are sarcomas. The biologic behavior and patterns of metastases may differ considerable.

Review of the Literature

There are only a few large contemporary surveys of brain metastases in children with solid tumors. Three institutional reviews have been



FIGURE 20-1. Extradural metastasis in a child with metastatic neuroblastoma.

published in the last 15 years; these are an autopsy study from Memorial Sloan Kettering Cancer Center (MSKCC) from 1951–1972 [4], another clinical and autopsy study from the same institution from 1973–1982 (ten years later) [5], and a third clinical study from the University Health Center of Pittsburgh accruing patients from 1966–1981 [6]. Another multi-institutional study of brain metastases from Ewing's sarcoma is also available [7]. The clinical incidence of brain metastases in this series was low (2%). These statistics would predict an approximate annual clinical occurrence of 80 cases of brain metastases in children with solid tumors in the U.S.A. The overall incidence in autopsy series is higher, ranging from 6%–13% [4, 5], but varies considerably depending on histology, location, stage, and duration of survival.

Vannucci and Baten were the first to report a large contemporary series of pediatric patients with brain metastases from 1951–1972 [4]. They excluded all patients with leukemia or lymphoma and any case in which brain metastases might have arisen from adjacent bone or dura. The authors presented three clinical and 11 autopsy cases. This review preceded the availability of modern CT scanning, and patients with small or subclinical metastases may not have been diagnosed prior to an autopsy. The overall incidence of brain metastases in their autopsy series was 6% (13 of 217 brains examined). The incidence by histology was as follows: Wilms' tumor, 12.9% (4 of 31); rhabdomyosarcoma, 6.6% (3 of 45); osteogenic

sarcoma, 8.3% (1 of 12); and neuroblastoma, 2.7% (2 of 75). One case of ovarian carcinoma, one of hepatocellular carcinoma, and one of malignant melanoma were also reported.

The most common presenting symptoms in this series included focal neurologic signs (79%) and signs and symptoms of intracranial hypertension (64%). Five of the 14 patients received radiation therapy, but only one patient survived beyond three months. The autopsy examinations revealed common observations in the 11 patients. All had pulmonary metastases, even the two with neuroblastoma. Although pulmonary and brain metastases are unusual in neuroblastoma, these two patients developed pulmonary metastases from local extension of mediastinal tumors. Single brain metastases were observed in 4 of 11 cases and multiple metastases in seven cases.

These authors concluded that brain metastases most likely arose from hematogenously derived tumor emboli emanating from pulmonary metastases. Not enough clinical information was reported in this review to comment on management. There was only one long-term survivor (14 months), and the cause of death was not mentioned.

Deutsch et al.'s series of 12 cases of cerebral metastases is a clinical series [6]. All 12 patients were diagnosed premortem and 11 were treated with brain irradiation. Autopsy data are reported in only one child. This institutional experience spans a period of 15 years at the University Health Center of Pittsburgh and excludes patients with leukemia or lymphoma and with CNS metastases extending from parameningeal sites. One of the children had brain metastases at initial diagnosis of his primary tumor. For the other 11 children, the average interval from primary diagnosis to the clinical onset of brain metastases was 13 months (2–36 months). Eight of 12 (67%) presented with focal signs and 42% had symptoms of raised intracranial pressure. The methods of diagnosis of brain metastases in these 12 patients included surgery or autopsy (6), CT scan alone (3), and

brain scan (3). The histologic diagnoses were Wilms' tumor (3) Ewing's sarcoma (2), rhabdomyosarcoma (2), hepatoblastoma (1), germ-cell tumor (3), and osteosarcoma (1).

Eleven of the 12 patients had active systemic disease involving at least the lungs, while one patient had a brain metastases as the sole evidence of recurrent disease. Nine of the children were receiving chemotherapy prior to the appearance of the brain metastases.

The treatment consisted of surgery plus radiation in five patients and radiation alone in seven patients. One patient did not complete the course of radiotherapy. Eight patients died within two months of detection of brain metastases from either systemic or CNS metastases. Four patients were long-term survivors (2, 3, 6, and 8 years respectively). Three of these patients had resections of their brain metastases in addition to whole-brain irradiation, and their systemic disease was responsive to chemotherapy.

The radiation treatment usually consisted of 3000 rads delivered over 10 fractions to the whole brain. These authors recommended that the radiation dose to the brain metastases approach that used to control the primary sarcoma. They raised the concern that the incidence of brain metastases may rise when systemic chemotherapy more effectively controls systemic disease and promotes longer survival. Once again, the most important risk factor for brain metastases appeared to be the presence of lung metastases. The fact that one third of Deutsch et al.'s patients experienced long-term survival suggests that brain metastases need not become a terminal event if the systemic disease can be controlled and the brain metastases are radiosensitive.

A subsequent institutional review of the brain metastasis experience in children from MSKCC was conducted by Graus, Walker and Allen including the years 1973–1983 [5]. CT scans were available in this institution from 1975 onward. Adjuvant chemotherapy was used more aggressively for the majority of children with malignant solid tumors. Certain

malignancies became potentially readily curable with chemotherapy during this period (Wilms'), and these diseases less often produced brain metastases than in the previous review by Vannucci and Baten [4].

This retrospective review identified 31 patients, age 21 or less, with brain metastases. It also excluded patients with leukemia or lymphoma and those with CNS metastases related to parameningeal disease. Of 139 complete autopsies that included the CNS, 18 patients had brain metastases. Thirteen additional patients with clinically symptomatic brain metastases who did not have postmortem examinations were identified by review of CT files from 1978–1982. Only 3 of these 13 patients had histologic confirmation of brain metastases. The clinical presentation correlated with the CT scan findings and was highly suggestive of brain metastases in the other ten patients.

The autopsy data were analyzed separately from the clinical data. The overall incidence of brain metastases in the autopsy series was 13% (18 of 139). The incidence was highest in patients with germ cell tumors (4 of 8—50%) followed by Ewing's sarcoma (2 of 12—17%), rhabdomyosarcoma (3 of 21—14%), osteogenic sarcoma (5 of 38—14%), and neuroblastoma (0 of 37). Brain metastases were also identified in patients with malignant schwannoma (2 cases), melanoma (1 case), and Wilms' tumor (1 case).

Data on the onset of clinical symptoms from brain metastases were available on 25 patients from both the autopsy and clinical series. Six other patients harbored subclinical metastases that were discovered at autopsy as incidental findings. Pulmonary metastases were present in 22 of the 25 patients (88%) at the clinical presentation of the brain metastases. Systemic disease was evident in 24 of 25 patients, and one had an isolated brain metastases. Excluding patients with osteogenic sarcoma, the diagnosis of pulmonary metastases was made on the average within one month of the original diagnosis, reflecting the aggressive and widespread nature

of the malignancies in this patient population. The median interval to the diagnosis of pulmonary metastases in patients with osteogenic sarcoma was longer (eight months). The average median interval from the diagnosis of pulmonary metastases to brain metastases was ten months for all patients.

Of the 81% (25 of 31) of patients with neurologic symptoms anteceding the diagnosis of brain metastases, 52% had signs or symptoms of raised intracranial pressure, 36% had seizures, and 36% had focal neurologic signs. Five of these patients became symptomatic from spontaneous intratumoral brain hemorrhage. Three died within several days from raised intracranial pressure.

The number, location, and gross and microscopic appearance of the brain metastases were analyzed in the 18 autopsied patients. Seven had solitary metastases. Gross hemorrhagic metastases were present in 50% of cases including patients with germ-cell tumors (4 of 4), osteogenic sarcoma (2 of 2), Ewing's sarcoma (2 of 2) and rhabdomyosarcoma (1 of 3). Thrombocytopenia did not seem to contribute to the hemorrhagic diathesis of these tumors (figure 20-2). Cerebellar metastases were present in 23% of the patients.

With regard to clinical management, 21 of 25 clinically symptomatic patients had therapy with either surgery or radiotherapy or both. The median radiotherapy dose was 3000 rads delivered over 10 elapsed days. Five of these 21 patients died of a recurrent brain tumor despite therapy. Five of the 15 patients whose brain metastases responded completely to radiotherapy alone died of systemic rather than CNS metastases. Germ-cell tumors had a high response to radiotherapy (4 of 5) as opposed to sarcomas (1 of 6).

When this study was compared to the previous institutional survey conducted ten years earlier [4], the incidence of brain metastases in the autopsied population rose from 6% of 217 cases in patients under 15 years of age to 9.8% (10 of 102). Although Wilms' tumor was the

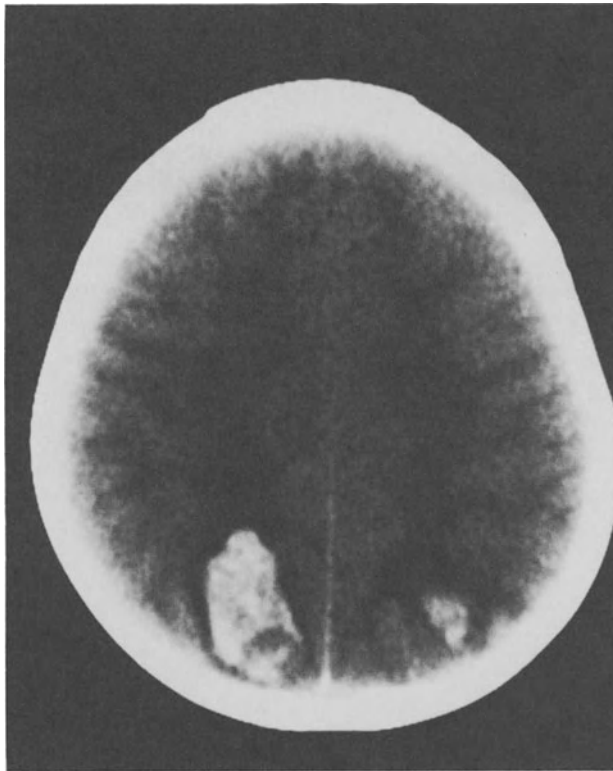


FIGURE 20-2. CT scan without contrast showing hemorrhage in metastatic rhabdomyosarcoma, confirmed by biopsy.

most common diagnosis in the former series, there were no cases in the latter autopsy series. The high frequency of hemorrhagic metastases (50% of autopsy cases and 38% of clinical cases) is a relatively recent observation. There appears to be a high incidence of spontaneous intratumoral hemorrhage in brain metastases from sarcoma patients, including not only germ-cell tumors but also osteogenic sarcoma, Ewing's sarcoma, and rhabdomyosarcoma. This clinical and autopsy observation could not be as well appreciated prior to the availability of CT scanning.

Surgery was recommended for patients with single brain metastases to be followed by whole-brain radiotherapy. Whole-brain irradiation alone was recommended for all patients with multiple metastases. Higher doses may be re-

quired in relatively radioresistant diseases such as sarcomas.

Factors Predisposing to the Development of Brain Metastases

The incidence of CNS metastases may vary considerably according to the histology of the solid tumor and its pattern of systemic metastases. The most important factor predisposing to the occurrence of brain metastases in children appears to be the presence of pulmonary disease related either to the location of the primary tumor or to metastases to the lungs. The incidence of brain metastases is not simply a function of the systemic tumor burden but is more related to its biology and pattern of spread [8].

An illustrative example exists with neuroblastoma, which rarely produces brain metastases from hematogenous origin. Monte et al.

[9] reviewed the pattern of metastases of pediatric neuroblastic tumors in autopsy cases at Johns Hopkins Medical Center. There were 31 cases of systemic neuroblastoma, all of whom had metastatic disease at autopsy. Neuroblastoma rarely produced lung metastases. Sixteen had CNS metastases, which in 15 cases involved the dura, in nine cases the leptomeninges, and in three cases the gray matter. In 15 of 16 cases, CNS metastases arose from adjacent bone metastases and in only one case was there a cortical gray-matter metastasis separate from leptomeningeal disease. No metastases were encountered in cerebral white matter. Thus, true parenchymal brain metastases are rare in neuroblastoma. This observation has been also been confirmed in both the MSKCC series and the Pittsburgh series [5–7].

In another institutional review from the Baltimore Cancer Research Center of the incidence of brain metastases in 114 sarcoma patients, 11 (10%) of patients (predominantly adults) developed clinically significant brain lesions [10]. Two patients had cerebral metastases at diagnosis, while nine developed them, on the average, 75 weeks following diagnosis. Ten of these 11 patients had pulmonary metastases as well, which preceded the diagnosis of brain metastases by 49.5 weeks. The association between antecedent pulmonary metastases and brain metastases was so high in this sarcoma population that the authors suggested utilizing prophylactic brain irradiation in sarcoma patients who developed pulmonary disease. Pulmonary and brain metastases are probably both of hematogenous origin.

With regard to the incidence by histology, brain metastases developed in 26% (4 of 15) of patients with rhabdomyosarcoma and 27% (3 of 4) with malignant fibrous histiocytomas. There two categories included 7 of the 11 cases. These authors believed that the incidence of brain metastases in sarcoma patients was on the increase due to prolonged survival resulting from more effective systemic chemotherapy. They suspected that the CNS was a relative

pharmacologic sanctuary whereby the blood–brain barrier protected small metastatic lesions from the cytotoxic effects of chemotherapy [10].

There is a close association between brain metastases and pulmonary metastases in testicular carcinoma as well. In a large review of 65 complete autopsies from the MSKCC in predominantly young adults, 37% of the patients had brain metastases, and all of these had pulmonary lesions [11]. The authors concluded that the tumor spread to brain hematogenously. The presence of active systemic disease in these patients dissuaded these authors from concluding that the brain was simply a pharmacologic sanctuary, because chemotherapy controlled neither the systemic nor CNS disease in these patients. Curiously, these germ-cell tumors appeared to spare the leptomeninges and developed solely in brain parenchyma. Choriocarcinoma was the histology most frequently associated with brain metastases, and these tumors tended to be hemorrhagic. A CT without IV contrast was a reliable indicator of intratumoral hemorrhage [11].

In this series, brain metastases occurred almost invariably in the context of widespread systemic disease, usually developing within two years of the primary diagnosis. The brain metastases were frequently disabling. Symptoms readily responded to whole-brain irradiation, but patients usually succumbed rapidly to their systemic disease, often without CNS recurrence [12].

In another institutional review of testicular carcinoma with a different perspective regarding the pattern of metastases emanating from testicular carcinoma, a relatively favorable prognosis prevailed in two groups of patients; those who developed brain metastases at the primary diagnosis in the context of widespread systemic disease and those who developed brain metastases in the context of recurrent disease but whose systemic cancer was chemotherapy-responsive. Seventy percent of such patients were able to achieve long-term disease-free

remissions following whole-brain irradiation (5000 rads) and systemic chemotherapy (cisplatin, bleomycin, and vinblastine).

Management

The clinical management of brain metastases falls into two categories: preventive and therapeutic. In conditions with a high predisposition for brain metastases such as lung carcinoma, studies are presently in progress to validate the role of prophylactic whole-brain irradiation, even for patients with normal CT scans at diagnosis [13]. The theory is that micrometastases are present in a high percentage of such patients at diagnosis. Even if chemotherapy produces long-term remissions for the systemic disease, the intact blood-brain barrier will probably limit delivery of chemotherapy agents to these small lesions. In addition, radiotherapy will be more effective with minimal disease. The disadvantages of this approach are that a certain percentage of patients will be irradiated unnecessarily, and radiotherapy may have undesirable late effects on cerebral function in those patients who experience long-term survival.

The first and most important initial therapy for such patients at diagnosis is the administration of high doses of corticosteroids. The subsequent management of symptomatic brain metastases is somewhat controversial. For patients with an undiagnosed primary systemic cancer who present with one or more cerebral lesions, surgical confirmation of the nature of the brain disease is usually indicated followed by whole-brain irradiation [14]. For patients with known progressive or recurrent systemic cancer with a single brain metastasis, surgery is usually indicated, followed by whole-brain irradiation. For patients with multiple cerebral lesions in the context of recurrent systemic disease that is considered to be radiosensitive, whole-brain irradiation is usually administered without surgery. For relatively radioresistant disease or for patients who have previously received whole-brain irradiation to brain tolerance,

surgical resection maybe the treatment of choice [15].

Another novel approach yet to be validated on a large scale is the use of parenteral chemotherapy alone for brain metastases. This approach seems implausible for those patients who develop brain metastases while on systemic chemotherapy, unless other active chemotherapy agents are available. Conte et al. [16] cite a 65% (13 of 20) response rate using combination chemotherapy without surgery or radiotherapy in adults with brain metastases. Responsive tumors included oat-cell and non-oat-cell lung carcinoma and breast carcinoma. The combination chemotherapy consisted of adriamycin, VM-26, and CCNU.

In a much larger study of the use of chemotherapy alone in 100 patients with brain metastases from breast carcinoma, 50% of the patients had objective responses in brain as well as systemic disease. The median duration of remission was 10+ months for 10 patients experiencing a complete response and seven months for 40 patients experiencing a partial response [17]. The chemotherapy regimens included combinations of cyclophosphamide, 5-FU, methotrexate, vincristine, and adriamycin.

Although the long-term prognosis of patients with brain metastases is usually guarded, aggressive therapy is often rewarded by long-term remissions of CNS disease. Often the major challenge is the control of systemic rather than CNS disease, and for this reason as well, chemotherapy has advantages. Although brain metastases are uncommon in children, the clinician must remain vigilant in solid tumor patients who develop new focal neurologic signs or symptoms, especially if pulmonary metastases are present. MRI may be a more sensitive screen for CNS pathology if the metastases are too small to enhance on CT.

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21. RECURRENT CENTRAL NERVOUS SYSTEM TUMORS

Melvin Deutsch

As with most other childhood malignancies, the reappearance of an intracranial tumor either locally or at distant sites after primary therapy implies a dire prognosis. However, retreatment may provide long subsequent survival or even cure of patients with recurrent biologically non-aggressive tumors such as pituitary adenoma, craniopharyngioma, meningioma, and cerebellar astrocytoma. Even the patient with a recurrent biologically aggressive tumor such as medulloblastoma may derive significant palliation and even cure from retreatment. Retreatment is more likely to be beneficial if administered when the recurrent tumor is still localized to a small volume and before apparent dissemination via the cerebral spinal fluid (CSF) pathways has occurred. Also, retreatment will be better tolerated if administered before deterioration in neurological status. In prior years, recurrent intracranial tumor was diagnosed usually after the patient developed symptoms. Nucleotide brain scanning was seldom effective in detecting the small preclinical lesion. Invasive procedures, such as angiography, ventriculography, and pneumoencephalography, were not employed as routine follow-up procedures in the treated child. The advent of computerized tomography (CT) scanning and magnetic resonance imaging (MRI) greatly improved the clinician's ability to detect and localize recurrent intracranial tumor.

In the era prior to CT scanning, once a previously treated child presented with symptoms

suggestive of recurrent tumor, especially if this had been a highly malignant tumor such as medulloblastoma or malignant glioma, frequently very little more was done either diagnostically or therapeutically. Occasionally, repeat courses of radiotherapy were administered on the basis of clinical findings suggestive of recurrent tumor. It is possible that many patients believed to have recurrent intracranial tumor on the basis of clinical findings and a past history of a treated tumor did not indeed have recurrent tumor but rather some other cause, perhaps correctable, for their symptoms, such as radiation necrosis, hydrocephalus from adhesions or shunt blockage, infection, or even nonintracranial disease. Thus, it is possible that some patients reported as being cured after repeat courses of radiotherapy for "recurrent intracranial tumor" were in fact free of tumor at the time of retreatment. There are examples of medulloblastoma patients surviving many years after retreatment for presumed recurrent tumor in whom the recurrent tumor was never histologically verified.

Case History, Patient No. 1. White female underwent subtotal resection of a posterior fossa medulloblastoma at age 11 years and postoperatively had radiotherapy to the posterior fossa, 5080 rads and spinal cord, 2200 rads. Ten years later at age 21 years, the patient presented with a change in neurological status. A previously present ataxia became worse and a nucleotide brain scan showed an abnor-

mality in the posterior fossa. On this basis, the patient was treated with a repeat course of radiotherapy (5000 rads) just to the posterior fossa. Eighteen years later, the patient still has persistent ataxia and a left sixth and seventh cranial nerve palsy. Subsequent CT scans have not indicated any evidence of posterior fossa tumor.

Comment. Recurrent tumor was never histologically verified in this patient. The patient was retreated mainly on the basis of the neurosurgeon's impression that there had been clinical changes attributable to a posterior fossa tumor.

Physical examination with neurological evaluation should be a part of the follow-up of all children treated for intracranial tumors. Any worsening of the patient's neurological status should be investigated with imaging and laboratory studies. The detection and localization of tumor, hydrocephalus, and therapy-related complications has been greatly facilitated by the noninvasive modalities of CT and MRI. The widespread availability of stereotactic surgery permits tissue evaluation of abnormalities detected by these imaging modalities with a minimum of morbidity and mortality.

It is extremely important that all patients with suspected recurrent tumor be evaluated vigorously prior to retreatment in order to be sure that recurrent tumor is indeed present. Likewise, it is important to exclude correctable nonneoplastic causes of neurological symptoms prior to assuming that the patient's outlook is hopeless because of recurrent tumor.

Recurrent tumor may be suspected on the basis of clinical findings, radiographic studies, or laboratory data. Recurrent tumor at the primary site often will be associated with recurrence of symptoms similar to the clinical picture at the initial presentation. In such cases where imaging studies demonstrate a mass lesion at the site of the primary tumor, the diagnosis is almost certainly recurrent tumor, especially if serial studies show an increase in size. However, the possibility of radiation necrosis should be considered if high doses of external radiotherapy have been administered, unusual fractionation

schemes have been employed, neutron or high linear energy transfer (LET) radiation has been used, or the tumor has been treated with an interstitial implant. Radiation necrosis usually does not appear before four months from completion of radiotherapy. The radiographic and clinical signs associated with radiation necrosis often mimic tumor, and biopsy may be the only method of differentiating one from the other.

Radiographic evidence of a mass lesion remote from the primary site or in an area that has received no radiation or a relatively low dose strongly suggests tumor. A tissue diagnosis is still important in order to verify recurrent tumor. If there has been a many-year interval following diagnosis of the initial tumor, the possibility of a second neoplasm must be considered. This is especially pertinent in irradiated patients with a mass lesion appearing many years later.

Case History, Patient No. 2. White male underwent subtotal resection of medulloblastoma at age three years and postoperatively was treated with craniospinal irradiation (posterior fossa dose 4460 rads, supratentorial brain 4060 rads, spinal cord 2500 rads). Three years later he presented with a left pleural effusion, and cytology revealed malignant cells consistent with medulloblastoma. There was no evidence of a primary extra-CNS tumor. The patient was then treated with left hemithorax irradiation and four weekly injections of vincristine. The patient subsequently did well until age 15 years, at which time a CT scan demonstrated an enhancing mass in the right frontal region. Pathology revealed meningioma.

Comment. The long disease-free interval from the initial radiotherapy and the CT scan findings suggested meningioma as opposed to recurrent medulloblastoma.

Case History, Patient No. 3. White female underwent gross total removal of a cerebellar astrocytoma at age four years. Twenty years later she was evaluated because of headache of two or three years duration. A CT scan revealed a tumor in the posterior fossa and the patient underwent subtotal resection of astrocytoma grade II–III. Postoperatively she was treated with radiotherapy to the posterior fossa, 5500 rads/

30 fractions. Nine years later there is no evidence of residual or recurrent tumor.

Comment. Recurrent low-grade cerebellar astrocytoma after an almost 20-year disease-free interval is extremely unusual. Postoperative radiotherapy was administered, since the surgeon believed that there was residual tumor and the patient had never received previous radiotherapy.

Laboratory studies on CSF and serum may confirm the clinical and radiographic impression of recurrent tumor. Malignant cells in the CSF confirm recurrent tumor.

The presence of some types of intracranial tumors can be suspected and even documented with accuracy on the basis of abnormally high levels of tumor-produced compounds, or *markers*. Response to treatment can be assessed by measurements of tumor markers in blood and/or CSF. Likewise, the reappearance of the marker compound may be the first indication of tumor progression or recurrence.

An obvious example of a tumor producing an identifiable marker compound is the hypersecretory pituitary adenoma. The more common hypersecretory pituitary adenomas produce prolactin, growth hormone, and adrenocorticotrophic hormone (ACTH) either alone or in combination. The clinical syndromes associated with these adenomas are well known, and the type of pituitary adenoma can often be identified by measurements of serum hormone levels. Following successful treatment, a drop in serum level of the particular hormone is expected. Resection produces a rapid drop, whereas the return to normal hormone levels is much slower following successful radiotherapy. It may take two or more years for growth hormone levels to return to normal following irradiation of a growth-hormone-secreting adenoma. Measuring serum levels of the various pituitary hormones can be a reliable method to determine failure of therapy or progression of a hypersecretory adenoma.

Intracranial germ-cell tumors, like their gonadal counterparts, may produce abnormal

amounts of human choriogonadotropin (HCG) and alpha-fetoprotein (AFP), which can be detected in serum and CSF. Abnormally high levels of HCG may be produced by choriocarcinoma, germinoma, and the other malignant teratomas. AFP is elaborated only by embryonal carcinoma or endodermal sinus tumor. If present at diagnosis, serum measurements of these compounds provide an indication of response to therapy. Subsequent elevations of these marker compounds in CSF or serum almost always indicate recurrent tumor.

Less specific tumor markers for intracranial tumors are the polyamines, spermadine and putrescine. CSF putrescine levels are frequently elevated in patients with primitive neuroectodermal tumor (PNET), brainstem glioma, ependymoma, and pineal germ-cell tumors, but are used most frequently in the follow-up of patients with medulloblastoma.

There are data to suggest that CSF polyamine determinations may be predictive of recurrent medulloblastoma prior to radiographic and clinical signs of tumor. Marton et al. found a consistent association between elevations in CSF putrescine levels and recurrent medulloblastoma [1]. Among 32 patients, elevations in putrescine levels were predictive of recurrence in 15 patients. There were no false-positive and only three false-negative determinations. However, Phillips et al. reported transient false elevations in several patients, and these were not associated with hydrocephalus or infection [2].

For patients with suspected recurrent tumor in the central nervous system, craniotomy with resection provides a definitive diagnosis. If resection is not considered feasible, at least a stereotactic biopsy should be considered in view of the low morbidity and mortality associated with the procedure. In those cases where further treatment is not feasible for recurrent tumor, tissue confirmation may not be necessary. However, a workup is indicated at least to exclude a nonneoplastic condition that might be correctable. A common situation is the child irradiated for a brainstem glioma in whom

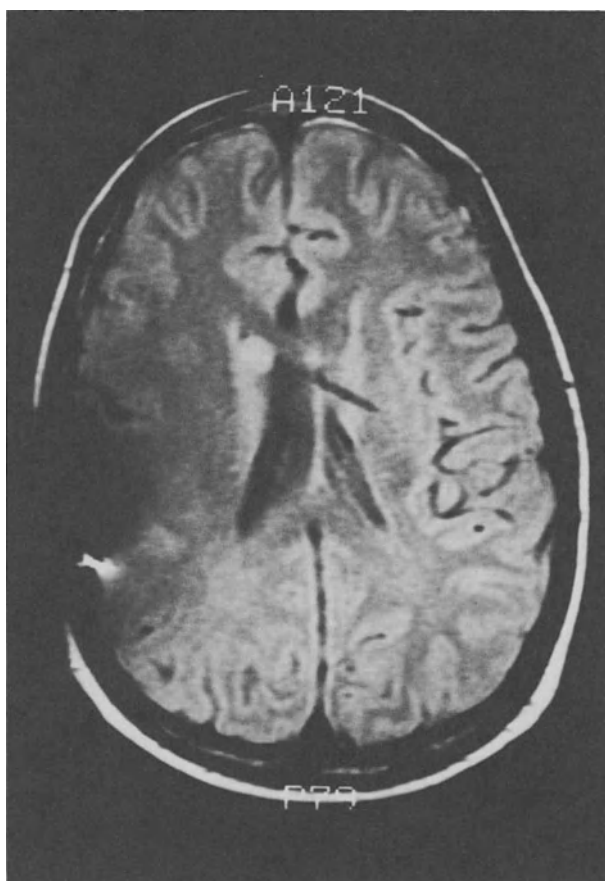


FIGURE 21-1. Recurrent medulloblastoma in right frontal horn in an asymptomatic patient three years, nine months postdiagnosis.

symptoms and radiographic signs of tumor reappear within 12 months. Such cases are not amenable to resection or further radiotherapy, and the benefits of chemotherapy are minimal. Even if radiation necrosis involving the brainstem is present as opposed to tumor, surgical intervention is not likely to be of benefit. For such cases, a trial of corticosteroids may be indicated in addition to general supportive measures.

There are situations where repeat therapy is possible but unlikely to provide long-term benefit. However, significant palliation may be provided. The patient presenting with distressing neurological deterioration secondary to hydrocephalus, regardless of the etiology, may warrant intervention to correct the hydrocephalus. Similarly, the patient presenting with

recurrent tumor and significant peritumor edema may derive short-term benefit from the administration of corticosteroids. Even a repeat course of low-dose radiation for symptomatic recurrence may provide worthwhile short-term palliation. Often, intracranial metastasis can be reirradiated at time of further tumor progression, and the author has also administered repeat courses of low-dose radiation for spinal cord lesions that have already been irradiated to "tolerance." Second- and third-line chemotherapeutic regimens in the context of a phase I or II trial can be justified if there is a possibility of benefit without significant morbidity.

Occasionally, the clinician is confronted with

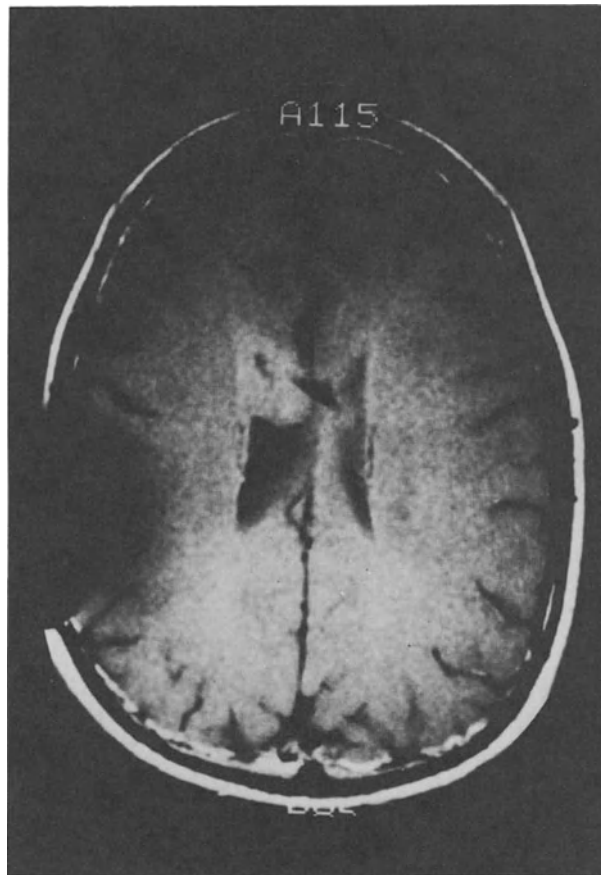


FIGURE 21-2. The same patient as in figure 21-1, five years, seven months postdiagnosis. Patient still asymptomatic.

an asymptomatic patient posttherapy in whom laboratory or imaging studies indicate possible recurrent tumor. For such cases, whether or not to pursue a tissue diagnosis will depend upon the original tumor diagnosis, initial therapy, interval from therapy, and location of the suspected recurrent tumor.

Case History, Patient No. 4. White male at age 21 years underwent resection of medulloblastoma from the posterior fossa. There was no evidence of dissemination, and postoperatively he was treated with craniospinal axis irradiation. Chemotherapy was not administered. Following surgery and radiotherapy, the patient was completely asymptomatic and with-

out evidence of neurological deficits. Three years and nine months from diagnosis, MRI showed a lesion in the right frontal horn (figure 21-1) and also a second one in the suprasellar region. Since the patient was completely asymptomatic, it was elected not to biopsy the lesion or administer therapy. The lesions stayed relatively stable in size until five years, seven months from diagnosis, at which time MRI showed increase in size of the lesions (figure 21-2). Even though the patient was completely asymptomatic, it was elected to biopsy a lesion, which was proven to be medulloblastoma. Myelography and CSF cytology were negative.

Comment. Unusual features of this case are the slow progression of the metastatic lesions once identified and the lack of symptoms. Biopsy and therapy were considered after progression of the metastatic lesions, even though the patient was asymptomatic. It is unknown whether or not the patient's chance for subsequent long-term survival would have been

better if therapy had been carried out at the first indication of recurrence.

As noted above, possible recurrent tumor involving the brainstem is not amenable to further therapy, and a tissue diagnosis would not be of great importance. However, for the patient who has recurrent tumor amenable to further therapy that might be curative, tissue diagnosis and therapeutic intervention obviously are indicated. For all patients, symptomatic or asymptomatic, who present with evidence of extra-CNS tumor, especially in the absence of recurrent CNS tumor, workup with definitive diagnosis should be undertaken to rule out an extraneural second malignancy (see case history 2).

There are situations in which the importance of early diagnosis and intervention cannot be overestimated. For the patient presenting with symptoms of spinal cord involvement, imaging studies are indicated to rule out tumor. If present, therapy should be instituted in order to avoid paralysis and reverse neurological deficits.

Case History, Patient No. 5. White male underwent subtotal resection of a suprasellar germinoma at age seven years. CSF was negative for malignant cells. Postoperatively, radiotherapy was administered just to the area of involvement, 5000 rads in 30 fractions. Two years later, the patient presented with severe low back pain that progressed to weakness of both legs. After three emergency room visits, the child was finally admitted and a myelogram demonstrated cord compression. A CT scan of the head did not show any evidence of tumor in the suprasellar area, but there was a small nodule in the right frontal lobe. Radiotherapy (3000 rads/20 fractions + 900 rads/3 to involved regions) was administered to the craniospinal axis and the patient experienced practically complete reversal of his neurological deficits related to the spinal cord lesions. Subsequent CT scans were negative for intracranial tumor. Patient is currently alive and well five years later.

Comment. Diagnostic evaluation should have been carried out as soon as the patient presented with low back and leg weakness. In view of the previous

TABLE 21-1. Patterns of tumor recurrence

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|--|
| I. Recurrence at primary site or directly contiguous |
| 1. Pituitary adenoma |
| 2. Craniopharyngioma |
| 3. Meningioma |
| 4. Low-grade glioma (astrocytoma, oligodendroglioma, ependymoma) |
| A. Optic chiasm—hypothalamus |
| B. Cerebellum |
| C. Midbrain |
| D. Cerebral hemispheres |
| 5. Supratentorial malignant glioma |
| 6. Brainstem glioma |
| II. Recurrences at primary and distant sites |
| 1. Medulloblastoma |
| 2. Supratentorial PNET |
| A. Ependymoblastoma |
| B. Pinealblastoma |
| 3. Anaplastic ependymoma |
| 4. Germ-cell tumors |
-

diagnosis and the known propensity of suprasellar germinoma to disseminate via the CSF pathways, a biopsy was not considered necessary in this situation.

Intracranial tumors of low biological aggressiveness, if they recur, tend to recur locally or at a directly contiguous site (table 21-1). Some tumors such as pituitary adenomas and craniopharyngiomas never disseminate. Meningiomas and low-grade gliomas also have a very low incidence of dissemination, and for such patients evaluation of the spinal cord by imaging and CSF studies is not indicated in the absence of symptoms. Brainstem gliomas, regardless of their histopathology, tend to recur locally. Supratentorial malignant gliomas have a low incidence of dissemination, and local recurrence at the primary site remains the chief cause of failure. However, the possibility of CSF dissemination of a malignant glioma or brainstem glioma should be considered in the patient presenting with appropriate symptoms.

Case History, Patient No. 6. White female had biopsy confirmation of a brainstem glioblastoma multiforme at age 12 years. Radiotherapy was

administered to the involved region, 6000 rads/35 fractions. Four years later the patient presented with leg weakness, and a myelogram demonstrated subarachnoid nodularity at the lower thecal sac. Biopsy at laminectomy revealed glioblastoma. The patient subsequently had radiotherapy directed to the entire spinal axis and she also received chemotherapy. Tumor subsequently recurred in the upper spinal cord and also intracranially.

Comment. Brainstem gliomas rarely present with clinical evidence of dissemination. The long disease-free interval for glioblastoma of the brainstem is extremely unusual. For this reason, tissue confirmation was obtained to rule out the possibility of a second tumor not related to the previous brainstem glioma.

Case History, Patient No. 7. White male at age three years underwent gross total removal of a malignant oligodendroglioma from the right frontal lobe. Postoperatively he received radiotherapy to the area of initial involvement (5400 rads/30 fractions) and also CCNU, vincristine, and prednisone according to a protocol of the Childrens Cancer Group. Nine months later the child presented with back pain with inability to walk, and a myelogram revealed diffuse involvement of the spinal subarachnoid space. CT scan of the head revealed tumor in the posterior fossa but no evidence of tumor at the original operative site. Biopsy confirmed malignant oligodendroglioma. Further radiotherapy and chemotherapy did not produce a response, and the child expired three months from time of recurrence.

Comment. Supratentorial malignant gliomas rarely disseminate via the CSF pathways. Local recurrence is the main cause of failure for such patients. However, dissemination must be considered in patients presenting with symptoms of tumor distant from the original primary site.

The primitive neuroectodermal tumors (medulloblastoma, supratentorial PNET), germ-cell tumors, and malignant ependymomas have the propensity for dissemination via the CSF pathways. Detection of recurrence at one site should be followed by a thorough evaluation to rule out other sites of recurrent disease within the central nervous system and even beyond the CNS. In most reported series of medulloblastoma, recurrence in the posterior fossa is the

most common cause of failure [3–6]. However, with improvement in survival and local control rates, recurrence in the supratentorial brain and in the spinal cord has become more common. Frequently, supratentorial lesions will be asymptomatic until they reach a formidable size. Thus, prior to the availability of CT scanning, recurrences in the supratentorial brain were rarely noted. McFarland et al., in their review of the literature up to 1968, reported that only 6% of recurrences beyond the posterior fossa occurred in the supratentorial portion of the brain [7]. Similarly, spinal cord lesions may be asymptomatic at diagnosis and also at the time of recurrence. Unless a myelogram is performed on all patients with recurrent intracranial medulloblastoma, the incidence of spinal cord involvement at relapse will be artificially low. In a series reported by Deutsch in which most patients had myelography at time of relapse, if their condition permitted, the incidence of relapse in the spinal cord was about the same as that for the posterior fossa [8].

Prior to the 1970s, extraneural metastases from primary intracranial tumors were rarely detected. In the author's personal series of 70 patients with newly diagnosed medulloblastoma seen in a 19-year period prior to 1974, there was one instance of extra-CNS tumor detected. Since 1974, 45 patients have been treated, and with follow-up greater than two years, five have had extra-CNS recurrences detected. Systemic relapse occurred in 4 of 12 patients with initial cord involvement (M3) and in only 1 of 33 patients with initial M0, M1, or M2 disease (no cord involvement). Other reports have also indicated a relatively high incidence of extraneural metastasis in childhood brain tumors treated in more recent decades. This may reflect improvement in length of survival secondary to improved radiotherapy. Duffner and Cohen reported on 36 children with brain tumors treated with surgery, radiotherapy, and chemotherapy in the 12-year period prior to 1981 [9]. In five patients, metastases beyond the central nervous system were documented. Two had



FIGURE 21-3. Metastatic medulloblastoma involving vertebral body.

medulloblastoma and one each had unclassified glioma, ependymoma, and PNET. Berry et al. reported metastatic tumor beyond the central nervous system in 35% of medulloblastoma patients with relapse [3]. Bone is the most common site of extra-CNS involvement and lesions are often osteoblastic (figure 21-3).

Surgery

Resection should be attempted for those biologically nonaggressive tumors that are accessible to resection. Pituitary adenomas and cranio-pharyngiomas, especially if the primary treatment had been radiotherapy, should be considered for resection. Even a partial resection may provide a long-term symptom-free interval.

Practically all meningiomas will have been treated initially by surgery. In those that recur, repeat resection occasionally will provide a long disease-free interval [10–12]. Chan and Thompson report a patient who had initial resection of a meningioma at age $2\frac{1}{2}$ years and

subsequent resections for recurrence at age 14, 20, 25, 27, and 30 years [12]. Subsequent to the last resection, she was reported as being alive and well 11 years later. Low-grade glioma of the cerebellum recurrent after surgical therapy also may be amenable to further resection. For patients undergoing repeat surgery, radiotherapy should be considered postoperatively if it had not been administered initially and if there is concern about the adequacy of resection or if pathological examination indicates progression to a more malignant phase (see case history 3).

For supratentorial malignant gliomas, debulking recurrent tumor may provide immediate symptomatic improvement. In addition, debulking a malignant glioma may improve the success of a subsequent interstitial implant. Rarely, even a gross total resection may be accomplished for recurrent supratentorial glioma.

TABLE 21-2. Indications for surgery

-
- I. Biopsy—Partial resection
 - A. Verify histopathology
 - B. Debulk to relieve mass effect. Reestablish CSF flow
 - II. Supportive procedures
 - A. Shunt procedures for hydrocephalus
 - B. Reservoir placement for intraventricular chemotherapy
 - C. Cyst drainage
 - III. Extensive resection
 - A. Biologically low aggressive tumors—surgery possibly curative
 - 1. Pituitary adenoma
 - 2. Craniopharygioma
 - 3. Meningioma
 - 4. Cerebellar astrocytoma
 - 5. Cerebral glioma
 - B. Biologically aggressive tumors
 - 1. Medulloblastoma
 - 2. Accessible supratentorial malignant gliomas and PNET
 - IV. Laminectomy for cord compression
 - 1. Diagnosis of metastasis
 - 2. Relieve cord compression
-

Recurrent medulloblastoma in the posterior fossa occasionally can be gross totally resected. A solitary metastatic lesion in the supratentorial brain sometimes can be resected. However, it is certainly doubtful that surgery alone for recurrent medulloblastoma would provide significant prolongation of life. Most patients with recurrent PNET (medulloblastoma or supratentorial PNET) will require subsequent radiation and/or chemotherapy.

Surgical procedures other than resection may be important in the management of the child with recurrent tumor (table 21-2). Stereotactic surgical procedures such as cyst aspiration, intracystic insertion of radioactive nuclides, and

TABLE 21-3. Stereotactic surgery

-
- 1. Biopsy
 - 2. Cyst aspiration
 - 3. Intracystic insertion of radioactive solution
 - 4. Interstitial implant
-

interstitial implants are examples of surgical procedures that may afford long-term benefit (table 21-3). In addition, the placement of reservoirs with cannulas for intracystic or intraventricular chemotherapy is an important contribution to the management of patients with recurrent tumor.

Radiotherapy

For recurrent central nervous system tumors, one can consider radiotherapy in four different contexts:

- 1. The recurrence is in an area that has previously been irradiated to a high dose (4000–6000 rads).
- 2. The recurrence is in an area that has previously been treated with a low dose of radiation as would be administered prophylactically to the craniospinal axis in patients with medulloblastoma (under 4000 rads).
- 3. The recurrence is in an area that has not received any previous radiotherapy, although other parts of the central nervous system have been irradiated.
- 4. The recurrence is in a patient who has not received any prior radiotherapy.

The last situation does not pose any problems in terms of normal tissue tolerance. For patients who have recurrent tumor and who have never

TABLE 21-4. Indications for radiotherapy

-
- I. Aggressive radiotherapy
 - 1. No previous radiotherapy
 - A. Radiotherapy alone for recurrence
 - B. Radiotherapy after repeat excision
 - 2. Recurrence in low-dose region
 - 3. Tumor type with high likelihood of response
 - A. Medulloblastoma
 - B. Germinoma
 - II. Palliative radiotherapy
 - 1. Recurrence in high-dose region after short interval
 - 2. Widely disseminated tumor
 - 3. Poor performance status
-

had previous radiotherapy, therapy should be administered according to the guidelines used for primary untreated tumors and should be considered if there is any question at all as to the adequacy of the repeat resection and if the pathological findings indicate a more aggressive neoplasm (table 21-4).

When considering radiotherapy to a previously irradiated area in terms of risk of radiation-induced damage, it is important to consider such factors as total dose, daily fraction size, volume irradiated, the site to be irradiated, and, very importantly, the interval since the initial course of radiotherapy.

For previously irradiated patients in whom it is decided that repeat radiotherapy will be administered, it is then necessary to determine whether or not to treat just the area of recurrent tumor or the entire central nervous system. For those tumors that do not disseminate via the CSF pathways, it is necessary to just reirradiate the recurrent tumor, and in such situations, radiotherapeutic modalities that effectively limit the dose to just the tumor volume may be preferable over conventional external radiotherapy (table 21-5). In such cases, one hopes to minimize the amount of radiation delivered to normal tissues that have been previously irradiated.

Patients treated with radiotherapy for cere-

bral hemisphere gliomas, low-grade or malignant, will have received high doses to large volumes. The malignant supratentorial gliomas tend to recur within a short interval, and the likelihood of providing benefit with another course of external radiotherapy is very small. Low-grade gliomas, if they recur, tend to have a longer disease-free interval, but they may have a more malignant histology at the time of recurrence, and retreatment with external radiotherapy still would necessitate a high dose to a relatively large volume. Patients with recurrent glioma involving a relatively localized volume not extending into the brainstem may be suitable for retreatment with an interstitial implant.

Gutin et al. reported 40 temporary high-activity I-125 implantations to treat recurrent malignant brain tumors in 37 patients, including children [13]. All tumors had recurred after surgery and radiotherapy. One to three sources were stereotactically placed. Minimum tumor doses to the tumor periphery varied from 3000–12,000 rads at 20–100 rads/hour. Thirteen patients experienced tumor regression for 4–13+ months. Five additional implantations provided “stabilization” for 4–12 months.

All patients with medulloblastoma and many with supratentorial PNET, malignant ependymoma, and germ-cell tumors are treated with craniospinal irradiation. Patients who present with recurrence of such a tumor, which has the propensity for spread via the CSF pathways, require a thorough evaluation to ascertain whether recurrence is solitary or involves multiple sites. Obviously, in patients with multiple sites of recurrent disease, a repeat course of radiotherapy should encompass the entire CNS if there is a likelihood of a long-term beneficial response. Such patients should also have an evaluation to rule out systemic metastasis.

In the author’s experience, patients with medulloblastoma recurrent after initial surgery, radiation, and chemotherapy have a relatively short survival postrecurrence. For patients not

TABLE 21-5. Radiotherapeutic modalities with dose-distribution advantages

1. Interstitial implant
Well-defined tumor in location amenable to implant; cerebral hemispheres
2. Insertion of radioactive isotope
Cystic lesions—craniopharyngioma, cystic glioma
3. Heavy charged particle beam (protons)
Pituitary adenoma
4. Stereotactic radiosurgery (gamma knife)
Well-defined small (< 3 cm) lesions; pituitary adenoma, craniopharyngioma, meningioma.

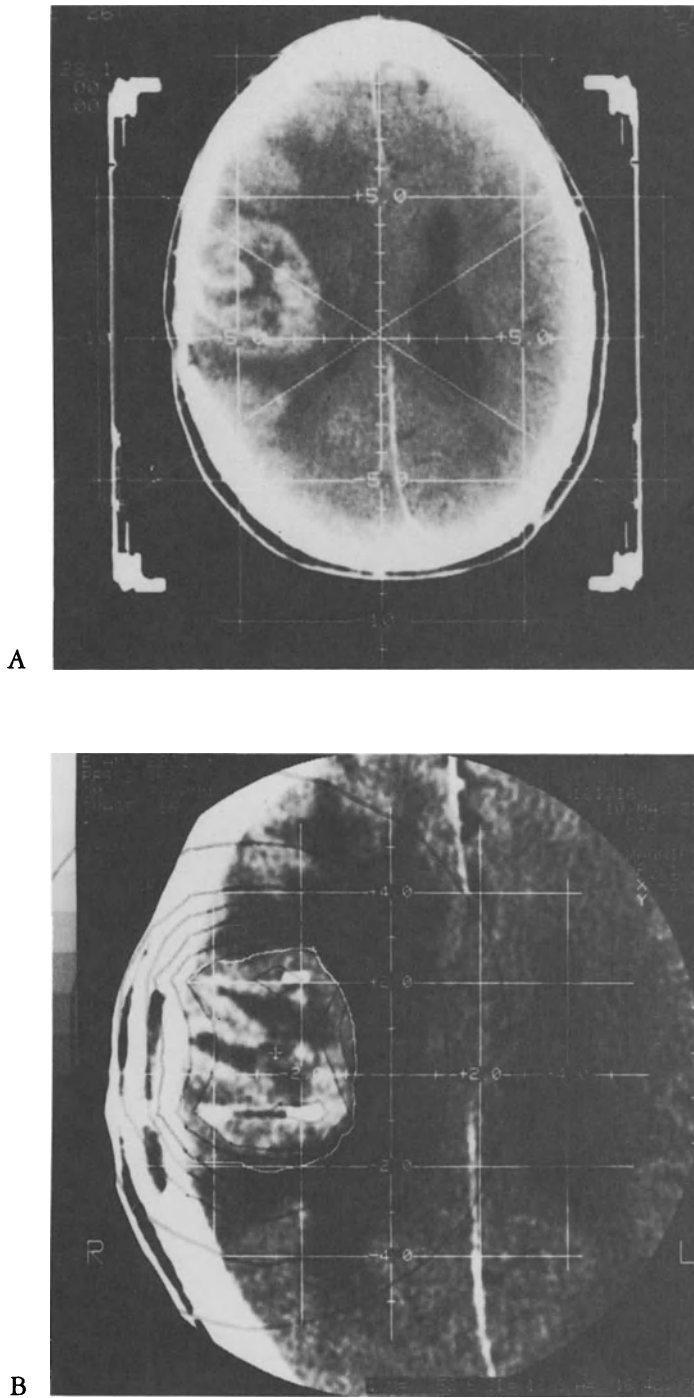


FIGURE 21-4. A. Recurrent glioblastoma multiforme. B. After implant of I-125 seeds. White line is tumor edge. 40 rads/hour isodose line is third black line from inside. (Courtesy M. Eddy.)

having chemotherapy initially, the combination of radiation and chemotherapy at the time of recurrence will occasionally provide long-term disease-free survival. In view of the high incidence of disseminated disease in patients presenting with recurrent medulloblastoma who are subjected to vigorous evaluation, the author recommends that radiotherapy for recurrent medulloblastoma, even if the recurrence appears solitary, be directed to the entire central nervous system. For supratentorial PNET and malignant ependymomas, there simply are not enough data as to patterns of failure to allow a firm recommendation concerning volumes to be irradiated for solitary recurrence. Most medulloblastoma relapses will have occurred by three years following diagnosis and thus the amount of radiation that can be readministered is limited. However, relatively low doses of radiotherapy (3000 rads/15–20 fractions) plus chemotherapy may provide long-term survival.

Case History, Patient No. 8. White male was diagnosed as having medulloblastoma at age 9½ years. There was no evidence of dissemination on CSF examination and myelography. The posterior fossa was irradiated to 5400 rads in 30 fractions, the supratentorial brain received 3450 rads in 22 fractions, and the spinal cord received 3000 rads in 20 fractions. Three years from diagnosis he presented with symptoms of spinal cord involvement, and myelography demonstrated three lesions involving the cord. The CT scan was negative for evidence of intracranial recurrence. CSF cytology was positive for malignant cells. The patient was retreated with craniospinal axis irradiation and chemotherapy. The entire brain received 2505 rads/15 fractions, and the spinal cord received 3000 rads/18 fractions. Involved portions of the cord received an additional 1050 rads/7 fractions. The patient was well for six years following retreatment and then developed further recurrent medulloblastoma involving the spinal cord.

Case History, Patient No. 9. White male underwent resection of a posterior fossa medulloblastoma at age 9½ years. There was no evidence of dissemination (M0). Postoperatively he was treated with craniospinal axis irradiation. He did not receive chemotherapy. At three years from diagnosis, the

patient underwent partial resection of recurrent tumor in the posterior fossa. At that time, there was no evidence of dissemination beyond the posterior fossa. He was then treated with a repeat course of craniospinal axis irradiation. The entire brain received 3000 rads in 10 fractions and the spinal cord received 1800 rads in 10 fractions. He also received concomitant misonidazole. Prior to the repeat course of radiotherapy, and for one additional year, he was treated with vincristine, CCNU, and procarbazine. The patient is currently alive and well nine years from documentation of recurrent tumor in the posterior fossa.

Comment. Occasionally, low-dose reirradiation and chemotherapy will provide long-term control of disease in the patient with recurrent medulloblastoma.

Chemotherapy

For the patient with a recurrent intracranial tumor postsurgery and postradiotherapy, chemotherapy may provide benefit. Recurrent tumors with known responsiveness, such as medulloblastoma, malignant glioma, and germ cell tumors, should be considered for chemotherapy. The potential benefit of chemotherapy for such patients must be weighed against the risk and likelihood of therapy-induced toxicity, especially in the already seriously ill patient. Systemic metastases may respond more favorably than intracranial tumors due to an absence of a blood–brain barrier (table 21-6).

Recently completed Childrens Cancer Group (CCG) adjuvant chemotherapy trials have indicated a benefit for adjuvant chemotherapy (CCNU, vincristine, prednisone) for patients with malignant supratentorial glioma and for the subset of medulloblastoma patients consid-

TABLE 21-6. Indications for chemotherapy

1. Tumors of known responsiveness
A. Medulloblastoma
B. Supratentorial malignant glioma
C. Germ-cell tumors
D. Metastases from non-CNS primary
2. Phase I + II studies
3. Systemic metastases

ered to have a poorer prognosis on the basis of T3B, T4 primary tumors and metastatic disease at diagnosis [14]. Current CCG protocols for supratentorial malignant glioma and advanced-stage medulloblastoma are evaluating this regimen versus the 8-drugs-in-1-day regimen reported by Bleyer et al. [15]. So far, the supratentorial malignant glioma and the subset of poor-risk medulloblastoma are the only common childhood brain tumors beneficially affected by adjuvant chemotherapy. At time of recurrence, patients with these tumors should be considered for treatment with these chemotherapy regimens, especially if they had not received adjuvant chemotherapy. Adjuvant chemotherapy and chemotherapy for recurrence has not proven to be of much benefit for brainstem gliomas. Low-grade gliomas in other sites have not been extensively evaluated in terms of response to chemotherapy.

Because of their slow growth rate, low-grade gliomas are considered unlikely to respond to chemotherapy. However, Bloom reported a definite objective response to chemotherapy (BCNU or CCNU) in 7 of 8 patients with recurrent grade I–II astrocytoma and in 4 of 7 patients with a recurrent oligodendroglioma [16].

The rare intracranial germ-cell tumors are also responsive to chemotherapy. Adjuvant therapy with cis-platinum-containing regimens is advocated for the nongerminoma germ-cell tumors [17–19]. Similarly, intracranial germ cell tumors at recurrence often respond dramatically to chemotherapy [20–22].

The PNETs (medulloblastoma, pineoblastoma, ependymblastoma) and high-grade gliomas are the tumors most often treated with chemotherapy for recurrence or progression. The agents most often used to treat these recurrent childhood brain tumors are the nitrosoureas, vincristine, procarbazine, and methotrexate, either alone or in combination. The number of patients actually treated with chemotherapy for recurrent brain tumors must be high, but the number of similarly treated cases in any reported

series is usually less than 20. Responses and even long-term survivals have been reported.

Rosen et al. reported favorable responses to high-dose methotrexate in 5 of 7 patients with recurrent medulloblastoma [23]. However, Mooney et al. reported no responses to high-dose methotrexate in five patients with medulloblastoma [24].

Allen and Helson used high-dose cyclophosphamide (≥ 80 mg/kg intravenous) to treat 18 children with recurrent brain tumors of various histologies [25]. Responses were obtained in 16 patients. All seven patients with medulloblastoma showed a favorable response.

Cangir et al. treated 23 patients (22 with recurrent or progressive tumor of various histologies) with the MOPP regimen (nitrogen mustard, vincristine, prednisone, procarbazine) [26]. On the basis of neurological and radiographic changes, responses were documented in 17 patients. Six had responses lasting more than one year.

The use of autologous bone marrow rescue following lethal doses of chemotherapy is another approach to the treatment of recurrent brain tumors. Hochberg et al. reported the use of high-dose BCNU (600–1400 mg/M²) followed by autologous bone marrow rescue to treat 11 patients with recurrent glioma [27]. Four patients showed clinical improvement for a median of eight months. Two patients had diminution in size of their tumor as demonstrated by enhancement on CT scan.

The reader is referred to Zeltzer for a more complete compilation of data concerning chemotherapy for recurrent medulloblastoma [28]. While it is clear that favorable responses are occasionally obtained, it is not yet clear that patients with recurrent tumors have been cured by chemotherapy alone. The author has had two patients with recurrent medulloblastoma treated with repeat low-dose irradiation and combination chemotherapy (procarbazine, vincristine, CCNU) who are subsequently alive and free of disease at greater than nine years.

All patients with extra-CNS relapse should be

considered for chemotherapy especially if there is no evidence of recurrent tumor within the central nervous system. The lack of a blood-brain barrier may improve the effectiveness of systemically administered chemotherapy. Occasionally, long-term beneficial responses have been observed (see case history 2).

Allen reported using multiple drug regimens to treat four patients with recurrent extraneural medulloblastoma [29]. Two patients died at 22 and 25 months with recurrent tumors within the central nervous system but without evidence of systemic tumor. Two additional patients with medulloblastoma and pineoblastoma had bone marrow involvement documented at diagnosis. Both were treated with chemotherapy and died three and four months later, respectively, without evidence of extraneural tumor.

Anecdotal reports indicate that extra-CNS metastatic lesions from intracranial primary germ-cell tumors respond to chemotherapy similarly to metastases from primary gonadal tumors [21, 30, 31].

More aggressive therapy for primary intracranial tumors may increase survival long enough for extra-CNS metastasis, present at diagnosis, to become clinically overt. With continued improvements in survival, the clinician must be alert to the possibility of extraneural metastasis, especially in the child with medulloblastoma having evidence of central nervous system dissemination at diagnosis.

Summary

The child with recurrent intracranial tumor certainly has a poor long-term prognosis. However, long-term palliation and even cure is possible with retreatment of many types of recurrent tumor, especially those that are of low biologic aggressiveness. The choice of therapy for recurrent tumor must be determined on the basis of tumor histology, extent of tumor, age and clinical status of the patient, and previous therapy—all factors that impact on subsequent outcome. Whenever possible, retreatment

should be aggressive. Occasionally, unexpected long-term benefit will occur even for highly malignant tumors. Increased salvage of patients with recurrent tumor is likely with further developments in experimental radiotherapy modalities and in the design of effective chemotherapy regimens.

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22. LATE SEQUELAE IN SURVIVORS OF CHILDHOOD BRAIN TUMORS

Melvin Deutsch

For the first half of this century, success in the treatment of childhood brain tumors often was measured just in terms of six-month survival rates. The high operative mortality associated with brain tumor surgery contributed to the overall dismal results. The lack of accurate noninvasive imaging techniques in the years prior to the development of computerized tomography (CT) precluded the accurate localization of many tumor types and also the early diagnosis of tumor and hydrocephalus. In addition, the limitations of orthovoltage radiation equipment precluded the administration of homogeneous high doses of radiation to the cranio-spinal axis and even to localized areas of the brain except with the best of techniques. The occasional long-term survivor usually had a biologically nonaggressive tumor. Keith et al. traced 256 children treated for intracranial tumor between 1920 and 1944 [1]. Only 34 patients (13%) survived five years; 12 were non-gliomas. In this entire series, there were eight ten-year survivors: two meningiomas, two ependymomas, two cerebellar gliomas, one cranio-pharyngioma, and one chromophobe adenoma. Two of these ten-year survivors subsequently died of tumor. Two additional patients had seizures, and one was also blind. An additional patient treated for a chromophobe adenoma was considered to be in good condition but blind.

As the therapeutic results improved with the introduction of megavoltage radiotherapy, improved neurosurgical techniques, and better

perioperative care, reports in the 1960s were optimistic that the majority of survivors were leading normal lives. Bouchard, in 1966, reported a 20-year experience (1939–1958) in the treatment of 119 children under age 15 [2]. Eighty percent (80%) of the five-year survivors were said to have returned to normal and useful life. Partial disability “continued from the time of diagnosis and treatment in 16% of cases.” Similarly, there was very little evidence of endocrine dysfunction detected. Thus, it appeared that most long-term survivors experienced recovery from their tumor and neurological deficits. Persistent disability was considered most likely secondary to effects of tumor.

Bloom et al., reporting in 1967 on 22 children surviving 5–17 years after radiotherapy for medulloblastoma, claimed that 18 (82%) were leading an active life, with only three having a mild disability [3]. Two additional patients were considered partially disabled, and two were totally disabled. These latter two patients had been treated at age 11 months and 15 months, respectively.

Over the past decade it has been appreciated that survivors of childhood brain tumors may have a range of sequelae from mild impairments with little if any impact on quality of survival to profound impairments significantly affecting quality of survival and even causing death. Furthermore, many of the late-appearing deficits appear to be therapy-related—more specifically, associated with radiation. Often, patients will

have deficits persistent from diagnosis in spite of successful ablation of tumor, and these are considered tumor-related. Similarly, deficits appearing in the immediate postoperative period may persist. These surgery-related impairments will not be discussed as “late” sequelae. Complications of chemotherapy are usually acute and occur during or soon after a course of therapy. These side effects are usually reversible if there is dose modification or discontinuation of the drug. However, symptoms of organ dysfunction from chemotherapy may persist and progress in spite of discontinuation of the drug, leading to chronic impairments.

This chapter will be concerned mainly with late-appearing sequelae related to radiation therapy. Two groups of late sequelae are the subjects of separate chapters. Psychointellectual impairments are late effects that are unique to the brain tumor patient and are discussed in chapter 23. With improvements in long-term survival rates and with the use of combined modality therapy, the appearance of second tumors in patients surviving a childhood malignancy is no longer a rare event. Second tumors following treatment of childhood brain tumors will be the subject of chapter 24.

Radiotherapy-Induced Changes

In the early years of radiotherapy for brain tumors, before accurate dose determinations were possible, some of the administered doses must have been very high, since there are reported instances of acute neurologic deterioration following a single treatment [4]. Large daily fractions of 750–1000 rads have occasionally been used in the treatment of patients with intracranial metastasis [5, 6]. However, such large individual fraction sizes occasionally have been associated with a worsening of neurologic symptoms. Currently, in the treatment of childhood central nervous system tumors, radiotherapy is usually administered at 150–200 rads per day. There is no reason at present to use higher daily doses to treat such children.

A subacute or early delayed reaction to radiation manifested by somnolence is well known to clinicians caring for children with acute lymphocytic leukemia who have received prophylactic irradiation of the brain. Freeman et al. in 1973 first called attention to this syndrome in children who received whole-brain irradiation and intrathecal methotrexate or cranio-spinal axis irradiation as central nervous system (CNS) prophylaxis [7]. Eleven of 28 children developed pronounced symptoms of somnolence, anorexia, and lethargy approximately six weeks after completion of cranial irradiation, and an additional 11 children developed a mild form of the syndrome. This symptom complex seldom lasts more than 1–2 weeks. An early delayed reaction following radiation was also observed in 1966 by Boldrey and Sheline in patients receiving high-dose external radiotherapy for intracranial tumors [8]. They described a similar syndrome characterized by a worsening in clinical condition that usually occurred within two months following completion of radiotherapy. In their experience, this period of clinical worsening lasted for a period of several days to as long as six weeks. It was rare in children under age ten years.

Radionecrosis of the brain is the most severe complication of radiotherapy directed to the central nervous system. In 1980, Sheline et al. reviewed the literature and were able to identify 80 cases who received a single course of external radiotherapy and in whom it was possible to make an estimate of the administered dose and fractionation regimen [9]. Eleven patients had been irradiated for cancer of the skin, 17 for other extracranial tumors, 20 for either a pituitary tumor or craniopharyngioma, and 32 for a primary brain tumor. Twenty-six (26) of the 80 patients had received a total dose equal to or greater than 7000 rads. Of 20 patients developing necrosis after treatment with total doses ≤ 5000 rads, 17 received daily fractions ≥ 250 rads. However, there were three patients who had received 170 to 220 rads per fraction, a regimen considered safe. In Sheline et al.’s re-

view of the literature, the interval from radiotherapy to necrosis varied from four months to 12 years, but only one patient developed necrosis after 56 months.

Mikhael reviewed 356 patients irradiated for primary tumors arising within the cranial cavity [10]. Three hundred (300) had primary brain tumors, 37 had pituitary tumors, and 19 had optic gliomas. The patients with primary brain tumors usually were treated with 5000 rads or more. Patients with optic glioma received an average of 6400 rads, which seems rather high. The pituitary tumor group was treated with 5000–6000 rads. The age of the patients at the time of treatment was not given. The overall incidence of symptomatic radiation necrosis was 3.3% in the primary brain tumor group, 10.8% in the pituitary tumor group, and 10.5% in the optic glioma group. It was thus 4.5% (16 of 356) in the overall group. In this series, the latent period varied from 9 to 28 months from treatment. All radionecrotic masses studied by angiography were avascular. In those cases where a mass showed abnormal localized stain and/or neovascularity, there was recurrent tumor. The author emphasized that differentiation of radionecrosis from tumor on a radiographic and clinical basis is difficult but can be suggested when CT abnormalities correlate with volumes that have received high doses.

On gross appearance, radionecrosis may be difficult to distinguish from an intracerebral neoplasm and the edema surrounding it. Microscopically, vessel walls are thickened and endothelial proliferation is common. Demyelination may vary from small patches of myelin loss to large confluent lesions. Coagulation necrosis probably represents the most severe aspect of radiation necrosis and has been frequently described after neutron irradiation [11, 12].

Marks et al. reviewed 152 patients irradiated for primary brain and pituitary tumors between 1974 and 1976 [13]. Seven of 139 patients (5%) who received 4500 rads or more at 180–200 rads per day developed pathologically docu-

mented radionecrosis. Necrosis did not occur in any patient receiving a dose less than or equivalent to 5400 rads in 30 fractions. The median time for development of necrosis after completing radiotherapy was 14 months with a range of 6–22 months. Besides the seven patients with pathologically confirmed radiation necrosis, two additional patients had neurological deterioration without radiologic evidence of tumor.

Aristizabal et al. in 1977 reported a 20-year experience (1952–1971) during which time 122 patients with pituitary adenomas were treated with external radiotherapy [14]. Only 25 patients had craniotomy prior to radiotherapy. Five patients developed severe complications within 10–16 months of completion of radiotherapy. One patient had autopsy-confirmed necrosis of the brainstem, and four other patients developed blindness considered secondary to optic nerve damage. In 106 patients treated with 220 rads or less per fraction, there were only three complications (3%). In 16 patients receiving greater than 220 rads per fraction, there were two complications (12.5%).

In 1980, Edwards and Wilson reviewed the literature concerning treatment of radiation necrosis and selected 92 cases that contained sufficient data concerning site of necrosis, treatment, and outcome [15]. Thirty-eight (38) patients had radiation necrosis following irradiation of an extracranial lesion. Twenty-six (26) patients underwent surgery for focal necrosis and 24 showed improvement. Two died. Of 12 patients who did not have surgery, only one showed improvement with corticosteroids. Nine patients with diffuse necrosis died, as did two with focal necrosis. Patients who developed radiation necrosis after treatment of intracranial extra-axial tumors such as pituitary tumors and craniopharyngiomas also did better if treated with surgery if the necrosis was focal rather than diffuse and did not involve the brainstem. Of 28 patients with radionecrosis following irradiation of primary intracranial intra-axial lesions, surgery for focal necrosis provided improvement in 5 of 7 patients. All

21 patients not undergoing surgery showed progression or death. None of these patients was reported to have been on corticosteroids. Altogether, 15 patients had received corticosteroid therapy, and in 13 there seemed to be a response in terms of at least stabilization of the deficit. Seven patients became steroid-dependent, requiring steroids for more than two months.

Burger et al. reported a postmortem study of 25 cases of intracranial gliomas [16]. Twenty patients had received radiotherapy to the whole brain with or without chemotherapy and corticosteroids. Of 17 patients treated with 5000–6000 rads, four developed “late delayed” radiation necrosis usually occurring in the white matter adjacent to the neoplasm. Changes of diffuse cerebral edema were present in many cases. Interestingly, the cases that developed radiation necrosis had not received corticosteroids during radiotherapy. It is possible that brain tissue in the immediate vicinity of tumor is more vulnerable to radiotherapy, possibly because of the effect of peritumor edema. The authors suggest that corticosteroid therapy during radiotherapy may decrease edema and protect against radiation necrosis.

Radiation necrosis may be more common following interstitial implants than after external radiotherapy. This is due to the high dose adjacent to the sources and also to the fact that most implants are carried out in patients who have already received substantial external radiotherapy. In 1984, Gutin et al. reported results of high-activity iodine-125 sources for recurrent malignant brain tumors in 37 patients [17]. Five patients underwent reoperation 5–12 months after implantation. Necrosis was discovered in three patients, and two other patients also had necrosis but some apparent residual tumor. All five were alive 10–25 months following implantation. Leibel and Gutin have emphasized the importance of surgery in differentiating radiation necrosis from persistent tumor following implant [18]. They also stress that evacuation of necrotic tissue

often produces a markedly beneficial response. The current Brain Tumor Cooperative Group (BTCG) protocol (87–01) that is evaluating interstitial implants with I-125 in the treatment of newly diagnosed malignant gliomas strongly suggests that reoperation be carried out in patients thought to have possible persistent or recurrent tumor following implantation, since clinically and radiographically it is difficult to differentiate necrosis from tumor.

Large-Vessel Injury

There are reports of symptomatic intracranial large-vessel vasculopathy following irradiation for brain tumors in children. Painter et al. described four patients who were treated with radiotherapy at ages eight months to seven years and then developed a strokelike presentation 2–22 years later [19]. In two patients, arteriography demonstrated vascular stenosis. The patient who developed vasculopathy 22 years following therapy was noted at autopsy to have severe atherosclerosis affecting the vertebro-basilar system, especially marked within the portal of irradiation. Brant-Zawadzki et al. also documented stenosis of a large intracranial vessel following radiotherapy [20]. The relatively few reports concerning radiation-induced large-intracranial-vessel occlusive disease suggest that it is an extremely rare sequelae or that it is being overlooked.

Spinal Cord Damage from Radiotherapy

Spinal cord necrosis is not common with the currently recommended doses used for craniospinal axis irradiation for childhood brain tumors. This complication is more likely in patients requiring reirradiation of the spinal cord for recurrent tumor. It is important that the gap-juncture between the two cranial fields and the spinal field, or between two spinal fields when treating the craniospinal axis, be accurately calculated to avoid overlap with overdosage. The symptoms of spinal cord damage

are dependent upon the cord level. Treatment is purely supportive.

Several cases of spinal cord injury following hyperthermia have occurred in patients who had previously received chest irradiation for intrathoracic tumors, suggesting that radiotherapy may sensitize the spinal cord to subsequent hyperthermic therapy [21].

Chemotherapy-Induced Neurologic Injury

Rarely, severe neurologic impairments occur following CNS prophylactic therapy for acute lymphocytic leukemia [22, 23]. A severe form of symptomatic leukoencephalopathy has been described mainly in patients treated with combination whole-brain irradiation along with high-dose intravenous methotrexate and/or intrathecal methotrexate. The risk of a severe complication is greatest with the use of all three modalities and correlates with the total amount of administered chemotherapy.

Chemotherapy regimens containing high-dose intravenous methotrexate or intrathecal methotrexate are not commonly used to treat childhood brain tumors, and therefore there are not much data available about the risk of late complications following prolonged methotrexate therapy following high-dose cranial irradiation.

Recently, Walker et al. have reported encephalopathy secondary to intra-arterial administration of BCNU in patients with malignant glioma [24]. All patients had received radiotherapy. Encephalopathy began 1–6 months from the time of the last BCNU administration with seizures occurring in 6 of 8 patients, confusional state in one, and gait ataxia in one. Seven patients died and one was alive 15 months after onset of the encephalopathy.

Adult patients with malignant glioma treated with radiotherapy and a nitrosurea have a very poor long-term survival rate, and reoperations in such patients are rare. Thus, it is difficult to assess the impact of nitrosurea chemotherapy on the incidence of radiation damage to the central nervous system. Similarly, it is not yet

possible to state whether, and to what extent, chemotherapy regimens containing a nitrosurea and vincristine, as are commonly used in the treatment of childhood brain tumors, will potentiate radiation damage to the brain. Certainly, these regimens do not appear to be as dangerous as the combination of brain irradiation and methotrexate.

Endocrine Dysfunction

Whole-brain irradiation or irradiation of tumors near the floor of the cranium often necessitates inclusion of the pituitary gland in the irradiated volume. With craniospinal axis irradiation, a portion of the thyroid gland is also irradiated by the portal used to treat the spine. The incidence of pituitary dysfunction following radiotherapy varies widely in reported series and probably reflects the extensiveness or adequacy of evaluation (clinical impression versus actual hormone-level measurements), age of the treated population, types of tumors, and administered doses.

Bloom et al. reported that 22 survivors of medulloblastoma did not have endocrine abnormalities, but it is not clear whether evaluation of these survivors included actual hormone level determinations [3]. Similarly, Bouchard also reported no endocrine dysfunction in 30 survivors of various childhood intracranial tumors treated by radiotherapy [2]. Broadbent et al. evaluated eight patients surviving medulloblastoma, and only one failed to show a growth hormone response to exercise [25]. None had clinical evidence of growth hormone deficiency, and all had received 3000–3500 rads to the hypothalamic–pituitary region.

Wara et al. evaluated nine children ages 10 months to 13 years at time of diagnosis who were treated with radiotherapy for tumors not involving the hypothalamus or pituitary region [26]. All received 4054–5730 rads at 160–180 rads/day to the pituitary–hypothalamic area. Growth hormone deficiency—lack of growth hormone response to insulin, arginine, and

L-dopa—was documented in all patients. Six had significant height reduction. One of seven also had a subnormal ACTH response to insulin hypoglycemia. This group of nine may have been a select group, having seen evaluated because of poor growth.

Shalet et al. in 1975 reported 16 children 1–12 years following radiotherapy for intracranial tumors not directly involving the pituitary–hypothalamic region [27]. Age at the time of testing was 7–22 years. Eight had also received either BCNU or vincristine. Eleven children, age 2–14 years, were studied soon after surgery but before more than two weeks of administered radiotherapy, and they had no growth hormone deficiency, but the peak growth hormone response was lower than in a control group with abdominal tumors. This early blunting of the growth hormone response to insulin suggests that tumor and/or the surgical procedure may have some effect on the hypothalamic–pituitary axis. There was no definite evidence of any other pituitary hormone deficiency in the study group, although thyroid-stimulating hormone (TSH) and thyrotropin releasing hormone (TRH) levels were higher in the growth-hormone-deficient children than in those with normal growth hormone production. A subsequent study by Shalet et al. evaluated growth hormone secretion in 39 brain tumor patients and 17 children with acute lymphocytic leukemia who received whole-brain irradiation prophylactically [28]. The acute leukemia patients were all in remission and off chemotherapy at the time of study. Doses were recalculated to an equivalent dose in three weeks. Thirty-seven (37) of 56 patients had an impaired growth hormone response (peak < 20 microunits/liter). Only one had received a dose less than 2900 rads. Five patients receiving more than 2900 rads had normal growth hormone function. Four were over age 13 years at time of treatment.

Dacau-Voucetakis et al. evaluated children treated with 2400 rads to the whole brain prophylactically for acute lymphocytic leukemia

[29]. Growth hormone levels were normal prior to radiotherapy. Soon after completing radiotherapy, growth hormone levels were abnormally low. Six to 12 months later, there was some recovery of pituitary function, indicating suppression but then recovery after low doses of radiotherapy.

Danoff et al. evaluated endocrine function in 23 patients irradiated for brain tumors not involving the pituitary region. Growth hormone deficiency was noted in six, and two of these also had panhypopituitarism [30]. Pituitary deficiency was seen only in patients irradiated before 11 years of age.

Growth hormone production seems to be the pituitary function most sensitive to radiation. The effects of diminished growth hormone secretion will be more obvious in younger children than in older individuals who have already reached adult height. The critical dose level below which growth hormone secretion will not be impaired may be between 2000–3000 rads. Other pituitary functions seem to be less affected by radiation and when present may be secondary to tumor or even surgery. Fortunately, the availability of synthetic growth hormone permits replacement therapy and attainment of normal height if instituted early enough.

The thyroid will be irradiated incidentally in patients treated with craniospinal axis irradiation. The isthmus and medial aspects of the thyroid are in the radiation beam used to treat the spinal cord. Depending upon the energy of the beam and the thickness of the neck, the anterior surface of the thyroid may receive at least 50% of the dose delivered to the spinal cord. The lateral portions of the thyroid will receive lower doses of scattered radiation depending upon the width of the field.

Fuks et al. in 1976 reviewed the reported data on thyroid dysfunction following radiotherapy to the neck [31]. In patients with Hodgkin's disease or head and neck cancer who were receiving radiotherapy, the reported incidence of thyroid dysfunction was 0%–66%,

depending upon the extensiveness of evaluation. The doses of radiation to the thyroid for such conditions would be much higher than the amounts delivered during spinal irradiation. Clinical hypothyroidism secondary to spinal irradiation, if it occurs, must be extremely rare.

There are few data to suggest that chemotherapy as used for brain tumors has an adverse effect on the pituitary–hypothalamic axis. Von Muhlendahl et al. evaluated 22 children with acute lymphocytic leukemia age 2–10½ years at diagnosis who were in remission at intervals 5–12 weeks following all therapy and 2–3 years following cranial irradiation [32]. Ten children had received 850 rads to the neuroaxis, nine received 1800 rads, and three received radiation for reinduction therapy (850, 2400, and 3270 rads). Endocrine function, including growth hormone levels, TSH, thyroxin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), cortisol secretion, and urinary concentrating capacity, was considered normal in all patients, although, borderline levels were noted in a few.

Bone

Retardation of growth of the spinal is a potential sequela of craniospinal axis irradiation. In older teenagers, growth retardation is not a concern, but in a young child, interference with spinal growth from radiotherapy may result in a easily recognizable growth deficit. This could be especially pronounced if, in addition, there is growth hormone suppression from cranial irradiation or tumor. However, many of the spinal changes will be subtle and not easily noticeable.

Bloom in 1969 reported no obvious spine abnormalities in 12 patients treated with craniospinal axis irradiation, 2000 rads/6–8 weeks, at age 2–13 years and observed 3–17 years later [3].

Neuhauser et al. studied 34 survivors of childhood malignancy who had been treated with radiotherapy that included a portion of the spine [33]. All except one patient were six years of

age or less at the time of irradiation. Severe changes in the vertebral bodies were seen only with total doses greater than 2000 rads. Less than 1000 rads resulted in no changes regardless of the age at therapy. One thousand to 2000 rads were associated with mild changes, such as slight diminution in height of the vertebral body. Children under two years of age tended to have more severe changes. The importance of irradiating the entire vertebral body was emphasized in order to prevent scoliosis secondary to damage occurring in only a portion of the epiphyseal plate.

Probert and Parker evaluated 44 children treated with spinal irradiation for Hodgkin's disease, lymphoma, and medulloblastoma before age 15 years [34]. Daily fractions of 200–250 rads were administered. Twenty-nine (29) received greater than 3500 rads to the spine and 15 less than 2500 rads. Twenty-two (22) children also received chemotherapy for Hodgkin's disease or leukemia. Standing and sitting heights of the patients were compared to normal values. Eight of 29 patients receiving greater than 3500 rads had sitting heights greater than two standard deviations below the mean for their age. However, only three had a standing height greater than two standard deviations below the mean, indicating a disproportion between sitting and standing height secondary to the spinal irradiation. Six of 15 children receiving under 2500 rads had a sitting height greater than two standard deviations below the mean. Children treated under age six years or at puberty showed the greatest retardation of spine growth.

Chemotherapy alone as used for brain tumors has not been reported to affect bone growth adversely. Long-term methotrexate can cause osteoporosis with fracture, but such regimens are not used in brain tumor patients [35].

Corticosteroids over long periods can cause osteoporosis, vertebral fracture, growth delay, and aseptic necrosis. Patients successfully treated for brain tumor will not need long-term steroid maintenance in pharmacologic doses, and thus steroid-induced bone changes should be rather

rare. However, aseptic necrosis of the femoral and humeral heads has been reported in seven neurosurgical patients treated with dexamethasone for short periods (15–37 days) [36, 37]. The clinical and radiographic signs of aseptic necrosis appeared 7–30 months following steroid therapy. Surgery was required in all patients. None of the patients had other apparent factors predisposing to aseptic necrosis.

Eye

For almost any intracranial tumor, it should be possible to use a radiotherapy technique that avoids direct exposure of the eyeball. When the brain is irradiated by two lateral portals, the eyeball is shielded by laterally placed lead blocks. The radiation dose delivered to the eyes will depend upon position of the blocks, transmission through the blocks, beam energy, and administered dose. Lead blocks used for shielding are usually five half-value layers thick. Thus, about 3.12% of the beam is transmitted. In addition, there will be scattered radiation from unblocked portions of the beam. It is extremely important that children be properly immobilized during therapy, since just a slight movement may expose a portion of the eyeball to be unblocked beam. Using thermal luminescent dosimetry to measure dose on the upper eyelid during whole-brain irradiation via two lateral fields, the dose at the upper lid varied from 9.4%–14.4% of the dose administered to the midplane of the brain [38]. Thus, with proper technique and blocking, the total dose to the eyeball should be low enough to avoid serious late sequelae. In the course of whole-brain irradiation, the lateral eye blocks have to be positioned low enough so that the medial portion of the anterior cranial fossa is not shielded. This area just above the cribriform plate is occasionally the site of recurrent medulloblastoma [39, 40]. Recurrence in this site is thought to be secondary to the lateral eye blocks shielding the inferior portion of the anterior cranial fossa.

The lens is the most radiosensitive structure in the eye. The clinical and pathological characteristics of radiation-induced cataracts have been well described by Cogan et al. [41]. Subsequently, Merriam and Focht in 1957 [42] and Merriam et al. in 1972 [43] elucidated and reviewed the association between radiation and cataract formation, which can be summarized as follows:

1. The lowest dose associated with any opacity of the lens is 200 rads, regardless of the schedule of fractionation.
2. The lowest dose associated with a progressive cataract is 500 rads.
3. Using fractionated radiation over 3–12 weeks, the minimum cataractogenic dose is 400 rads.
4. Doses greater than 1000 rads to the lens will produce a cataract in 100% of cases.
5. The degree of opacity may vary from stationary opacities with slight if any visual impairment to a progressive lesion causing blindness.
6. The degree of opacity is related to the dose of radiation.
7. The interval from radiation exposure to subsequent cataract development varies from months to many years. The higher the dose of radiation, the shorter the interval for development of cataracts.
8. Younger individuals may be more sensitive to the cataractogenic effects of radiation.
9. Neutrons are about 4–10 times more cataractogenic than low LET radiation.
10. Radiation-induced cataracts can be effectively treated with surgery.

The lacrimal gland may receive a high dose, especially during the irradiation of frontal lobe tumors. A dry eye secondary to irradiation of the lacrimal gland is rare. Secretory glands in the lids and conjunctiva are usually able to function sufficiently, thus preventing chronic dry eye unless the entire eyeball is included in the radiation field.

Radiation-induced injury to the retina has been described mainly in patients irradiated for extensive tumors of the paranasal sinuses infiltrating into the orbit [44, 45]. In such cases, the eyeball has been exposed to doses over 6000 rads. With the doses used for the irradiation of childhood intracranial tumors and with proper technique, radiation injury of the retina should be an extremely rare occurrence.

An association between long-term systemic administration of corticosteroids and posterior subcapsular cataract formation was first described in the early 1960s [46, 47]. This complication is seen mainly in patients on high doses of corticosteroids for protracted intervals, as is the case for nephrotic syndrome, rheumatoid arthritis, and immunosuppression after renal transplant [48–50]. The likelihood of steroid-induced cataract appears to be well correlated with dose and duration of therapy. Fortunately, most children surviving treatment of a brain tumor will not require long-term pharmacologic steroid dose administration.

Ears

In the course of irradiating tumors near the base of skull or the whole brain, the inner- and middle-ear structures can receive a substantial dose. During therapy, symptoms of otitis media may develop, but these usually are self-limiting.

Severe late complications from radiotherapy, such as marked hearing loss and radiation necrosis of the temporal bone or ossicles, should be rare with the doses of radiation currently used to treat childhood tumors. However, in patients receiving repeat courses of radiotherapy for recurrent tumor, the risk of serious sequelae involving the ears increases.

Cis-platinum may cause hearing loss that is related to dose [51]. Audiogram abnormalities are more common than patient complaints of hearing loss. Vestibular dysfunction has also been reported with cis-platinum therapy [52].

Conclusions

The incidence and severity of late complications following radiotherapy for childhood brain tumors depend upon a number of factors. Generally, the younger the child, the more severe the impairment. Higher total doses and daily fraction sizes are also associated with an increased incidence of complications. Thus, it is extremely important, whenever possible, to use radiotherapy techniques that limit the amount of normal tissues included in the high-dose volume. Similarly, it is important to establish minimal effective doses, especially for prophylactic irradiation of the craniospinal axis. Studies exploring the use of chemotherapy in the very young child with an intracranial tumor in hopes of delaying radiotherapy should be supported.

In the author's experience, the majority of long-term survivors lead normal, productive lives. Even some young children irradiated before the age of three years have had subsequent normal development. The most severely handicapped survivors are mostly those in whom deficits are related to the tumor or to surgical complications.

The importance of careful follow-up cannot be overemphasized. Identification and intervention for hormonal dysfunction is obviously important in the treated patient. Similarly, special education and tutorial assistance for intellectual impairments may be extremely valuable in allowing the treated patient to achieve his maximum scholastic potential.

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23. LONG-TERM NEUROPSYCHOLOGIC AND INTELLECTUAL SEQUELAE IN BRAIN TUMOR PATIENTS

Craig L. Silverman
Patrick R.M. Thomas

With increasingly aggressive multimodality treatment, the ability to cure or at least obtain long-term survival for significant numbers of children with primary or secondary brain tumors is becoming more commonplace, with further success on the horizon. With this increasing survival rate comes the responsibility to evaluate closely the subtle and more overt long-term effects on the children themselves—not only physical and functional effects, but behavioral, neuropsychological, and intellectual effects as well. Long-term physical and hormonal effects are easily evaluated and quantitated, and early intervention may modify the long-term effects on the child. Other long-term sequelae, however, are less easily defined and can require a comprehensive range of tests to even establish a general area of deficiency, let alone to determine the cause and effect mechanisms. Such is the case for late neuropsychological and intellectual impairments in children after treatment for central nervous system tumors, whether that treatment is surgery, irradiation, chemotherapy, or any combination of these modalities.

The recent medical literature reveals controversy concerning the potential detrimental

effects of prophylactic and curative cranial irradiation on further intellectual development in children. The issue is complicated by numerous difficulties, such as 1) precise knowledge of prediagnosis neuropsychological function, 2) administering reproducible tests to young children, and 3) the use of control populations for comparison analysis, as well as the undetermined effects of nontreatment-related factors, such as socioeconomic situation. Also, the disease itself and prolonged hospitalization may play a significant role in the child's subsequent development.

Historical Background

The quality of survival of children with primary brain tumors or those requiring prophylactic brain irradiation for acute lymphoblastic leukemia (ALL) has recently become of interest to those specialists directly involved in the treatment and care of the pediatric oncology patient. Realizing that quality of survival was an important endpoint, early investigators attempted to qualify treatment results, but restricted themselves to gross functional descriptions of the patients' quality of life [1–3]. They classified

the survivors of pediatric brain tumors into broad categories that indicated that 70%–80% of patients led an active, useful life with minimal problems (groups I and II) and that only a small percentage was severely disabled or incapacitated. However, the sporadic observation that decreased IQ or delayed academic achievement occurred more commonly than in the general population led to more extensive investigation of children thought to be functionally normal in order to determine if there were significant though subtle intellectual problems. With the help of child psychologists and psychological–intellectual testing [4–8] the oncology community has begun a much more scientific evaluation of the seemingly neurologically intact pediatric brain tumor survivor to determine the etiology of academic delay, behavioral problems, or other difficulties that develop years after treatment.

Acute Lymphoblastic Leukemia Data

The greatest body of literature concerning late intellectual effects after therapy directed to the central nervous system is derived from studies of children afflicted with ALL. Most of these reports stress a comparison of ALL patients receiving a moderate dose of cranial irradiation (18–24 Gy) either with ALL patients not receiving prophylactic cranial irradiation, or with siblings of the ALL patients, or with patients with non-ALL cancer who do not receive prophylactic brain irradiation but may have received similar chemotherapy.

These studies can roughly be grouped into 1) those that show no effect of cranial irradiation on later neuropsychological functioning and 2) studies that show either a trend toward a decrease in a variety of neuropsychological functions or definite and significant neuropsychological problems following prophylactic cranial irradiation.

Whitt et al. [9] noted that the conception that cranial irradiation causes cognitive problems is inferred from:

1. Observations of neuropsychological problems following direct exposure of the brain tissue to cranial irradiation
2. The following assumptions presumed to be true:
 - a. Patients with ALL are normal at initiation of treatment
 - b. Survivors of prior central nervous system (CNS) regimens not containing prophylactic brain irradiation had no cognitive problems
 - c. Children treated for other malignant tumors do not develop cognitive problems

Whitt et al. contend that there are problems with this basic line of reasoning and argue that the brain is not exposed merely to irradiation, but also potentially to the tumor cells, as well as to the administered intrathecal and intravenous medications. They also contend that the use of previously treated nonirradiated ALL cohorts as the control group is suspect, since the fact that they survived without cranial irradiation may indicate a less virulent ALL subtype. Cohorts of patients having other malignant disease but no prophylactic cranial irradiation may not be a valid control group due to differences in drugs and the timing of the drugs. Finally, they note that in their study, socioeconomic factors were much more powerful than the type of therapy in determining post-treatment performance on neuropsychological profile tests, and they claim that other studies have failed to control for this potentially important factor.

Negative Studies

In one of the first published studies on late neuropsychological sequelae, Soni et al. reported on 45 patients treated for ALL and found no noteworthy neurological or psychological effects of craniospinal irradiation either by a prospective or retrospective study [10]. The neuropsychological test data failed to document any specific deleterious effects. Vervoss et al. evaluated 22 patients with ALL after CNS

irradiation and could find no deleterious effects on neuropsychological function [11]. Obetz et al. correlated four independent neurodiagnostic procedures: electroencephalogram (EEG), neurologic examinations, computed tomography (CT) of brain, and neuropsychological testing [12]. Only five patients had abnormal psychological testing; three had received cranial irradiation and two had not. Ivnik et al. did an extensive evaluation of survivors of leukemia treated on Cancer and Acute Leukemic Group B (CALGB) protocols [13]. Patients receiving intrathecal methotrexate alone or intrathecal methotrexate plus intravenous methotrexate were compared to a second group who received intrathecal methotrexate plus prophylactic cranial irradiation. Correlating 75 tested variables, they could find only five that were significantly different between the two groups, which is only slightly more than the four variables expected to differ by chance alone. Performance levels of both groups appeared to be slightly less than expected for healthy and untreated children of similar age. This suggested to the authors that the ALL alone or with treatment may contribute to diminished performance. Deleterious effects did not seem to correlate with age at time of treatment. However, there were some significant differences that did occur in areas similar to those suggested by other researchers, such as memory, performance score, and abstract reasoning. Whitt et al. compared patients who had received 24 Gy prophylactic cranial irradiation to ten patients not treated with cranial irradiation and found no difference in a whole host of tests [9]. They concluded that socioeconomic factors were much more important predictors of neuropsychological functioning than the type of therapy, sex, or age at diagnosis.

Robison et al. found few abnormalities in a group of ALL survivors, all of whom had received 24 Gy to the brain [14]. Younger children did not score differently from older children and, if anything, the 4–6-year-old age group did worse than either younger or older children. Eiser and Lansdown studied ALL

patients in Great Britain; no difference was seen in patients five years of age or older at time of cranial prophylaxis, but some differences were seen in the younger-aged children [15]. In a follow-up publication, they reported that if the radiotherapy were delayed six months or more from diagnosis, few if any effects were seen compared to children who had not received prophylactic brain irradiation [16]. Yet, in the delayed cranial irradiation group, significant changes were seen in younger children. This is a fascinating report, but will probably never be duplicated due to its unique treatment design.

Acute Lymphoblastic Leukemia— Positive Reports

As was seen in the preceding section, even in those reports in which the authors concluded that no significant differences were noticed, there was a mild trend towards worse performance for the irradiated patients, especially the young patients, on those examinations that tested for higher, more complex brain functions such as abstract reasoning and perceptual analysis. There are many reports that have expanded on these trends.

Eiser, in a follow-up publication to her 1977 article, compared patients who had not received prophylactic cranial irradiation to patients who had immediate (within two months of diagnosis) CNS irradiation and those who had delayed (greater than six months) cranial irradiation [16]. She found significant delays in full-scale IQ and especially in performance-scale IQ, arithmetic, and perceptual analysis tests in the group that had received immediate prophylactic cranial irradiation. The groups that had not received cranial irradiation or had received delayed cranial irradiation did approximately equally well on the psychometric testing, although she did note that in the group that received delayed cranial irradiation, the younger the age at time of diagnosis and treatment, the worse the subsequent performance status. Meadows et al. reported similar results in com-

paring the patient population, some of whom had cranial irradiation and some of whom did not [17]. Subsequently, Meadows et al. evaluated 23 children who were tested within one month of diagnosis and then retested 12–30 months later, of whom 18 were retested again some three years later after the initial diagnosis [18]. They compared those children with six patients who had not been irradiated and to another six with Wilms' tumor. They demonstrated that 11 of 18 irradiated children demonstrated a ten-point IQ drop from the initial test to the third test, with those initially aged 2–5 years at time of diagnosis demonstrating the greatest drop in IQ. They also noted that those patients with the highest initial IQ (greater than 110) demonstrated a significant drop (23 points versus 8 points) compared to those with an initial IQ less than 110. They also noted that 13 of 18 demonstrated at least two impaired scores in their subtests. On the subtest analysis, one half demonstrated at least five categories to be significantly impaired, compared to 1 of 6 children who had not received radiotherapy. This latter child was noted to be "slow" prediagnosis.

Jamoun evaluated the effect of age on cognitive development [19]. He compared 43 patients who were less than three years old at time of prophylactic brain irradiation for ALL to 43 patients who were 3–6 years of age and to a group greater than seven years of age at the time of prophylactic irradiation. He noted that the mean distribution of IQ levels for the group as a whole were within normal limits. However, he found that the youngest children again scored worse than the other age groups, and there also seemed to be a correlation with time since treatment. Patients below the age of six years seemed to score significantly worse on the British Ability Scales than their siblings, with short-term memory, nonverbal reasoning, and speed of information processing significantly decreased. He also compared the results of the youngest children with mixed control groups and found significantly decreased scores in all categories. Academically, these children did

extremely poorly compared to the national norms and to their siblings. It was noted that this group of patients had higher IQ scores, were older, and were tested at longer intervals from treatment than the patient population of Eiser [15, 16]. This supports the results found by Meadows et al., namely that the brightest children had the most significant defects and that time from therapy was indeed very important [17, 18]. Patients who had oral methotrexate were compared to those who had intramuscular methotrexate; the latter patients had more significant drops in IQ.

Pfefferbaum-Levine compared 18 ALL survivors who had received prophylactic cranial irradiation to 14 survivors who had not been irradiated and found that for all 39 neuropsychological subtests, the prophylactically irradiated patients scored lower, and these differences were significant in the full-scale IQ, the verbal IQ, arithmetic skills, and memory [20]. Similar results were demonstrated by Rowland et al. [21] Stehbens and Kisker [22], Pavlosky et al. [23], Moss et al. [24], and Twaddle et al. [25].

Primary Brain Tumors

As suggested in the previous sections dealing with acute lymphoblastic leukemia, there exist significant decreases in a variety of neuropsychological and intellectual functions in children who have had prophylactic cranial irradiation, though it may be argued forcefully that there may be other factors at work and that the control groups used for comparison suffer from a variety of potential problems. Nevertheless, there seems to be more or less agreement that performance, memory, abstract reasoning, and arithmetic seem to be most affected in these children and that age at initial diagnosis and treatment is important, as might be expected. There is a suggestion that these problems may persist and worsen, since there seems to be a trend towards increased difficulties with increased intervals from treatment.

Similar arguments can be made for the results

compiled in evaluating neuropsychological and intellectual functions in survivors of primary pediatric brain tumors. Such studies often suffer from a lack of an accurate estimation of prediagnosis IQ, a potential for underestimation of the IQ at the time of initial testing (which is usually done in the immediate postoperative period), and the effects of a neurosurgical procedure, prolonged hospitalization, and having a chronic disease. There are also inherent difficulties in comparing these children to normal groups.

It is important to note that IQ difficulties and academic delay have been noted in children with chronic diseases [26–28], with raised intracranial pressure [29], and after posterior craniotomy or any neurosurgical procedure, especially if there has been increased intracranial pressure [2, 29–31].

There have been several studies looking at the gross IQ and quality of survival in children treated with surgery plus radiation. Danoff et al. evaluated 38 patients who were alive one year or more following radiotherapy for a variety of intracranial tumors, such as craniopharyngioma, optic nerve glioma, cerebellar astrocytoma, etc. [32]. They discovered that almost 50% of the survivors had IQ levels less than 89, whereas in the normal population the incidence should be about 25%. They found no correlation between either the irradiated volume or the tumor type and the incidence of low IQ (< 89). Children under age three years at diagnosis were most likely to have subsequent low IQ scores. This was similarly noted by Spunberg [33]. Similarly, no correlation was found with increased intracranial pressure, but there was a significantly increased number of low IQ scores in those patients who had hypothalamic involvement by tumor. Also, those patients already classified as moderately or severely disabled physically had severe IQ deficiencies as well.

Hirsch et al. compared survivors of medulloblastoma to a group to patients undergoing only surgical resection for cerebellar astrocytoma and found a higher incidence of low IQ scores

(< 89) in the medulloblastoma patient [30]. Most of these patients were functionally intact.

Kun and Mulhern evaluated 30 children, half with posterior fossa tumors and the remainder with supratentorial tumors [34]. Nine children were evaluated postsurgically before the initiation of radiotherapy, and 29 others were evaluated after irradiation. Patients received either entire cranial irradiation or subtotal supratentorial brain irradiation with doses between 40–50 Gy. The number of patients scoring below IQ of 89 was in excess of the normally expected distribution [35] in both the verbal and memory scales. When Kun and Mulhern analyzed for intellectual delay (IQ and memory scores less than 80) it was found that 2 of 9 children evaluated before radiotherapy already had low IQ scores, but 8 of 15 additional children who received either cranial or supratentorial irradiation developed delays. The authors could find no effect on intellectual delay between those who required shunt procedures and those who did not. On serial examination of ten patients, five were noted to be stable and three deteriorated, but two improved, with increases in IQ scores of ten points or more. These same authors subsequently evaluated 18 children, some of whom were reported in the original publication [36]. At initial evaluation, intellectual delays were noted in 4 of 8 children who were less than six years old at diagnosis and treatment, compared to intellectual delays in only 1 of 7 who were greater than six years old. At the time of the second evaluation, they noted improvement in full-scale IQ scores in 3 of 18 children (17%), improvement in the verbal IQ in 2 of 18 (11%), and improvement in performance IQ in 6 of 18 children (33%). Those children exhibiting persistently decreased scores all had concomitant neurological problems. At the time of the third evaluation, the full-scale IQ scores were stable in 8 of 9 patients and improved in 1 of 9. Therefore, improvement was noted in 4 of 18 children, but there was no correlation between improvement and initial IQ score or time elapsed from diagnosis.

Duffner et al. evaluated ten children who were treated with surgery, radiotherapy, and chemotherapy for medulloblastoma, brainstem tumors, or ependymomas [37, 38]. All received 30–38 Gy whole-brain irradiation and 44–64 Gy to the posterior fossa. They noted that 3 of 6 medulloblastoma patients had IQ scores less than 80. Prediagnosis school tests were available in three of the patients, and there were significantly decreased IQ scores in all three. Other abnormalities were noted in the other medulloblastoma patients, although results were muddled by the fact that some had neurological deficits as well.

In a study by Silverman et al., nine medulloblastoma survivors were evaluated and compared to nonirradiated siblings [39]. They found that there were indeed decreased performance IQ scores and decreased academic achievement, especially in arithmetic. There seemed to be an association between decreased performance and younger age at the time of irradiation as well as the interval from irradiation to testing. Those children who were youngest were tested at the greatest interval from irradiation. One of the patient–sibling pairs was identical twins, and the treated patient scored approximately the same as his nonirradiated sibling, although he did have some decrease in his scores. However, he was 18 years old at the time of diagnosis, and severe neuropsychological results were not expected. A follow-up study by Clouse J (personal communication, 1989) demonstrated no improvement or deterioration in this patient.

Conclusions

Based on the results of a multitude of studies, there is no doubt that there can be significant neuropsychological and intellectual problems in survivors of both acute lymphoblastic leukemia and primary brain tumors who have received radiotherapy to the brain with moderate or high doses (table 23-1). However, it is premature to conclude absolutely that radiotherapy

TABLE 23-1. Observed neuropsychological problems after brain irradiation

Nonverbal/abstract reasoning
Perceptual analysis
Arithmetic
Speed of information processing
Full-scale IQ
Verbal IQ
Performance IQ
Memory

TABLE 23-2. Factors affecting development of neuropsychological problems

1. Sequence of radiation therapy following chemotherapy (immediate vs. delayed)
2. Age of patient
3. Interval from irradiation
4. Hypothalamic involvement
5. Chemotherapeutic agents plus administration route
6. Surgery
7. Hippocampal damage?
8. Growth hormone?
9. Cerebral blood flow?
10. Dose of irradiation??
11. Volume of irradiation??
12. Intracranial pressure??

is the sole cause, since there appears to be neither a dose nor a volume response curve, and surgery itself [2, 30, 32, 40], or some other not yet identified factor such as growth hormone deficiency [41], hippocampal damage (Abayomio, personal communication, 1989), hypothalamic involvement [32, 42], or even disturbances in cerebral blood flow [43] may contribute to neuropsychological and intellectual deficits (table 23-2). Better imaging techniques may identify the structural changes associated with the poor performance of these children [44, 45]. The lack of prediagnosis extensive testing is a major pitfall, though academic information from school systems and preschool programs may help assess the true preoperative or prediagnosis neuropsychological function. However, it must be remembered that these test

results may be influenced by prediagnosis subclinical disease. At present, the value of extensive neuropsychological testing may be to diagnose such deficits early and perhaps identify those children who would benefit from aggressive tutorial assistance in order to minimize the effects.

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24. SECOND PRIMARY TUMORS IN TREATED PATIENTS

Melvin Deutsch

Because of improvements in long-term survival rates for many of the common childhood malignancies, there has developed an awareness that such long-term survivors are at substantial risk for developing second malignancies. Several reports have implicated radiation therapy and/or chemotherapy as the probable cause of most second malignancies [1-7]. In addition, possible genetic factors have also been identified in a substantial number of patients who have developed second malignancies [3, 5, 7]. There is still a cohort of patients who develop second primary tumors for whom neither radiotherapy nor genetic predisposition is the apparent etiology.

This chapter will discuss second primary tumors in patients surviving a primary brain tumor treated during childhood and the possible etiologies of such tumors. A comprehensive review of chemotherapy- and radiation-induced tumors is beyond the scope of this work.

There are several possible causes of second primary tumors in patients who have survived a childhood tumor (table 24-1).

Genetic Factors

Retinoblastoma is the only common childhood malignancy for which hereditary transmission has been well delineated. The same factors causing the hereditary retinoblastoma predispose these patients to the development of second primary tumors. Actually, the child treated for

the hereditary or bilateral retinoblastoma has about the same chance of dying from a second malignancy as from recurrent retinoblastoma [8]. At one time, it was believed that the high incidence of second malignancies in retinoblastoma patients was due to administered radiation therapy. While radiotherapy may be a factor in promoting second malignancy in the genetically susceptible patient, a significant percentage of second malignancies arise outside of the radiation fields or in patients who have not had radiotherapy [9, 10]. Osteosarcoma is the most common second malignancy observed in retinoblastoma patients [4, 7]. In irradiated patients, it often occurs within or near the irradiated area. In nonirradiated patients, osteosarcoma involving the skull and facial bones is extremely rare, thus suggesting that radiotherapy does contribute to osteosarcoma formation in the susceptible patient.

A well-defined pattern of genetic transmission has not been determined for childhood brain tumors except for those which occur in patients afflicted with a hereditary disorder such as neurofibromatosis (table 24-1). Such children are at risk for multiple primary tumors whether or not their brain tumor developed as a result of the hereditary disorder. The most common intracranial tumors in children with neurofibromatosis are gliomas of the optic pathways and other astrocytomas [11]. Acoustic neuroma and meningioma are more commonly seen in adults with neurofibromatosis.

TABLE 24-1. Possible factors promoting second tumors

1. Genetic predisposition—hereditary disorders
A. Neurofibromatosis
B. Nevroid basal cell carcinoma syndrome
C. Multiple cancer family
2. Persistence of etiologic agent in patient or in environment
A. Viral
B. Chemical
C. Hormonal
3. Treatment
A. Ionizing radiation
B. Chemotherapy
C. Nonantineoplastic drugs
4. Persistent immunosuppression from therapy
5. Persistent effects on host tissue from original tumor
6. Etiologies unrelated to primary tumor
A. Smoking
B. Diet
C. Environment or occupational exposures
7. Chance

Individuals with the nevroid basal-cell carcinoma syndrome are at a higher risk for developing medulloblastoma. Patients with this syndrome develop basal-cell carcinomas. However, radiotherapy seems to promote the development of subsequent basal-cell carcinoma in these medulloblastoma patients. Meadows et al. reported two cases with multiple basal-cell carcinomas developing within the irradiated fields for medulloblastoma at two and five years from treatment, respectively [3].

In a study of 292 cases of second malignant neoplasms that occurred in individuals who had their first tumor in childhood, Meadows et al. noted that 23 patients had siblings afflicted with childhood cancer [7]. Usually, a sibling had a similar childhood tumor. The most common tumor affecting sibling pairs was retinoblastoma, with nine pairs affected. Four pairs of siblings had brain tumors.

Therapy

The majority of children with brain tumors do not have an apparent genetic predisposition or

concomitant hereditary disorder predisposing to primary tumors. Still, these patients, if they survive their primary brain tumor, are at risk for developing second malignancies. While it is possible that as yet unidentified genetic factors are responsible, it is widely believed that therapy for the primary tumor may be responsible. Ionizing radiation and chemotherapeutic agents may be directly oncogenic or may contribute to oncogenesis indirectly by causing immunosuppression or other alterations in the immune surveillance system. This would be comparable to the situation seen in organ transplant patients, who have a high incidence of subsequent malignancy believed to be secondary to immunosuppressive therapy.

There is no longer any doubt that ionizing radiation is tumorigenic. Similarly, chemotherapy, especially with alkylating agents, has also been recognized as being tumorigenic. Radiation-induced tumors were first observed soon after the discovery of radium and X-rays [12]. Studies of populations exposed to radiation for various reasons have suggested the tumorigenic effect of ionizing radiation (table 24-2).

Populations exposed to ionizing radiation because of occupation, such as radium-dial

TABLE 24-2. Populations at risk for tumorigenesis from ionizing radiation

1. Occupation exposures
A. Early radiation workers (skin cancers, leukemia)
B. Radium-dial painters (bone sarcomas)
2. Diagnostic radiation exposures
A. Multiple fluoroscopies for tuberculosis (breast cancer)
3. Exposures to nuclear weapons
A. Leukemia, solid tumors
4. Patients treated for benign diseases
A. Thymic irradiation (thyroid tumors)
B. Tinea capitis (meningioma, other CNS tumors, thyroid tumors)
C. Acne (skin cancer)
D. Ankylosing spondylitis (leukemia)
E. Benign gynecological diseases (leukemia)
5. Patients treated for malignancy

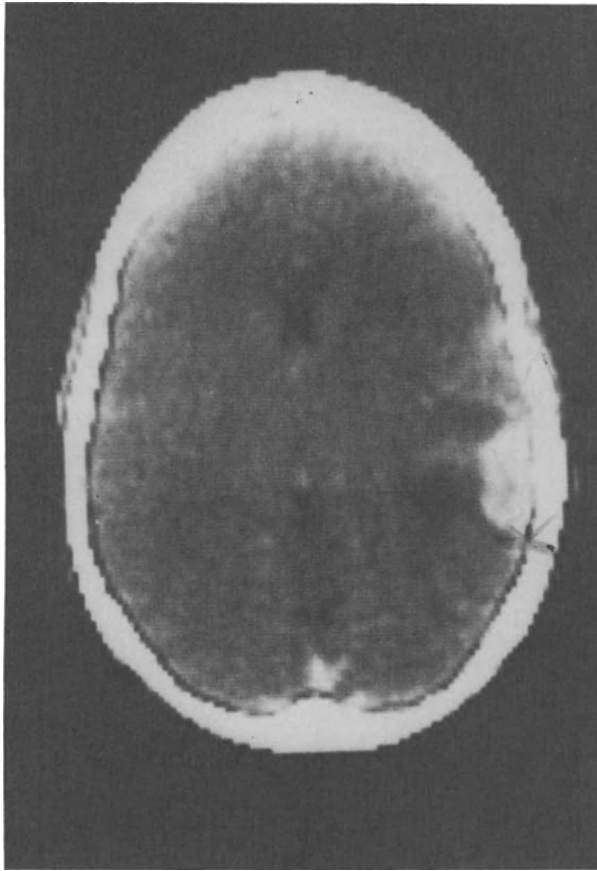


FIGURE 24-1. Thirty-seven-year-old female with recurrent meningioma two years after resection. At age eight years, the patient was treated with radiotherapy to the scalp for tinea capitis. The administered dosages are unknown. The recurrent tumor was excised and treated with postoperative radiotherapy. The patient is well and free of disease seven years later.

painters and the early radiologists, were often exposed over a many-year period — quite unlike the situation in therapeutic radiology. Similarly, populations exposed to ionizing radiation from nuclear weapons also represent a situation quite dissimilar from the patient treated for a malignancy. However, data from patients treated with radiation for benign conditions, often with incidental normal tissue exposures not too dissimilar from those seen in the treatment of intracranial tumors, suggest the oncogenic potential of ionizing radiation.

In the course of irradiating a central nervous system (CNS) tumor, normal tissues that are unavoidably irradiated are skin and subcutaneous tissue, skull bones, and normal intracranial tissues. With craniospinal axis irradiation, additional tissues incidentally exposed are the thyroid gland, esophagus, and portions of the upper respiratory tract and gastrointestinal tract. In addition, a much greater portion of the bone marrow and lymphoid tissue is exposed. Also, there may be scattered radiation to the breasts and lungs.

Data from several different patient groups treated with radiation for benign conditions support the conclusion that ionizing radiation may be tumorigenic (table 24-2). The findings from several of these patient populations are relevant to the child treated for a central nervous system neoplasm.

Of particular relevance are findings that radiation administered to the scalp during childhood is associated with an increased incidence of meningioma (figure 24-1). Until about 1959, superficial radiation was frequently used to cause temporary alopecia in the treatment of tinea capitis. Techniques varied, but usually the entire scalp was divided into five regions, each treated with a single dose of superficial radiation (60–100 KV) [13–15]. Doses to the scalp were thought to have been in the range of 500–800 rads. The underlying brain should have received a much lower dose because of the low penetration of the superficial radiation and the protective effect of the overlying skull bone. However, it is possible that higher doses were administered to parts of the scalp and underlying brain due to overlap of the fields.

Two large series from Israel have reviewed 42 and 43 patients, respectively, with meningioma following scalp irradiation [16, 17]. The first series of 42 patients was matched with a control group of 84 meningioma patients from the same time period (1952–1981) [16]. When compared to the control group, meningiomas in the previously irradiated patients were more likely to be located at the falx, parasagittal area, and convexity. These are the intracranial sites that should have received the highest doses. There were six cases of multiple meningiomas in the previously irradiated group compared to none in the control group. Meningiomas in the irradiated group tended to be more aggressive, and the local recurrence rate was higher.

The second series from Israel included 43 patients with meningioma who had previously received scalp irradiation [17]. Forty-one patients had received low-dose irradiation for tinea capitis, and two had received 1500 rads each for astrocytoma and leukemia, respectively. As in the other large Israeli series, the majority of tumors presented in the falx, parasagittal area, or convexity. Tumors from the previously irradiated patients were more likely to have histologically aggressive characteristics, and the

recurrence rate was also higher. By the authors' calculations, irradiated patients had received about 175 rads at the surface of the brain. However, almost all the irradiated patients showed chronic skin changes and alopecia, indicating that much higher doses may have been delivered.

In both series, the post-scalp-irradiated patients were younger than the control groups, and the number of male and female patients in the irradiated groups were about equal, as opposed to a preponderance of female patients in the nonirradiated control groups.

Spalone et al. also reported two patients who developed meningioma after irradiation of the scalp for tinea during childhood [18]. They also reported a third patient who developed a meningioma at age 25 years after having been irradiated to the scalp for a vascular nevus at the age of six months. The authors reviewed the literature and found three additional cases of meningioma developing 17–47 years after irradiation of vascular nevi on the scalp.

A follow-up study of patients with tinea capitis in the United States showed an increased incidence of tumors and leukemia in irradiated as opposed to nonirradiated patients [19]. In the radiation-treated group of about 2000 patients, there were 14 subsequent malignancies, including four leukemias, three gliomas, two basal-cell carcinomas of the scalp, and one each of the following: carcinoma of the parotid, fibrosarcoma of the mandible, lymphoma of the submandibular lymph nodes, Hodgkin's disease, and carcinoma of the rectum. There were no cases of meningioma in this population. In the nonirradiated cohort of about 1400 patients, there was only one malignancy, a case of Hodgkin's disease. Follow-up of tinea patients irradiated in Israel has also revealed an increased risk of leukemia, thyroid cancer, and malignant CNS tumors [20]. In such patients, Modan et al. estimated the dose to the thyroid from a course of radiotherapy for tinea to be between 4.3 and 16.9 rads [21].

The increased risk of meningiomas, other CNS tumors and other malignancies developing

after irradiation of the scalp for a benign condition suggests that irradiation of CNS neoplasms in children may produce a similar spectrum of postirradiation neoplasms.

In the course of craniospinal axis irradiation for such tumors as medulloblastoma, a portion of the thyroid gland is irradiated by the posterior spinal cord field. Using supervoltage X-ray to irradiate the spinal cord to a dose of 3000 rads, portions of the thyroid gland may receive more than 2000 rads. Follow-up of infants treated with radiation for thymic gland enlargement has revealed an increased risk of thyroid neoplasms, both benign and malignant [22, 23]. Doses to the thyroid varied with techniques and types of equipment used. It seems likely that the thyroid gland was often directly in the treatment portal. The total dose to the thyroid may have been as high as 600 rads. Data from the study of Hempelmann et al. demonstrated a correlation between the dose to the thyroid and subsequent thyroid tumors [22]. Fortunately, radiation-induced thyroid malignancies seem to have the same favorable outcome as those not associated with radiation. Whereas most children treated for thymic enlargement were in a much younger age group than the child treated for a CNS tumor, the data do indicate that incidental irradiation of the thyroid gland in the course of treating children, especially the very young, with spinal axis irradiation may put the patient at an increased risk for subsequently developing thyroid tumors.

The association between irradiation of the skin for benign conditions such as acne and the subsequent development of basal and squamous-cell carcinomas has also been well demonstrated. However, most such patients subsequently developing skin cancers appear to have had large doses of low kilovoltage radiation, and most such radiation-induced skin cancers will develop in areas showing chronic radiation damage [12, 24]. With megavoltage radiation as it is commonly used today in the treatment of childhood brain tumors, skin damage predisposing to second malignancy is highly unlikely.

Patients with ankylosing spondylitis treated with irradiation of the spine are another group that has provided information concerning the possible tumorigenic effects of radiation. Studies on over 14,000 patients from Great Britain treated with radiotherapy in the time period 1935–1954 revealed an increased mortality from leukemia and aplastic anemia [25]. The risk of the irradiated patient developing acute nonlymphocytic leukemia was approximately ten times the expected risk. The risk of death from aplastic anemia was increased approximately 29-fold. There was a very slight increase in deaths from cancers in irradiated sites such as the pharynx, stomach, pancreas, and lung. Interestingly, the risk of developing leukemia appeared to be greater for patients irradiated at an older age. Follow-up of ankylosing spondylitis patients not treated with radiotherapy does not indicate an excess mortality from leukemia or cancer [26]. It is possible that ankylosing spondylitis or other factors associated with the illness may cause an increased susceptibility to leukemogenesis by radiation. However, the data from the radiation-treated ankylosing spondylitis population do indicate another possible tumorigenic effect of spinal axis irradiation.

More relevant to the patient surviving a brain tumor during childhood are those reports concerning an increased incidence of second neoplasms in long-term survivors of childhood malignancies. In 1975, Li reported 19 new malignancies in a group of 414 long-term survivors of childhood malignancies [1]. In addition, there were 11 new benign tumors and two tumors of “indeterminate type.” All children with subsequent second malignancies had been treated with radiotherapy, and the second tumor (including two leukemias) developed within the radiation therapy field in all but two cases. Twelve children also had received chemotherapy. A subsequent update by Li in 1977 identified three children with brain tumors and subsequent leukemia or lymphoma [27]. In two, the leukemia or lymphoma was diagnosed within a year of the original diagnosis

and probably was unrelated to treatment. A third patient with ependymoma developed acute lymphocytic leukemia three years later. A fourth child with acute lymphocytic leukemia at age two years developed an astrocytoma one year later.

Meadows et al. in 1977 identified 102 patients who developed a second malignancy after treatment of a malignancy during childhood [3]. Sixty-nine had received radiotherapy. Fifteen of these patients also had an apparent genetic predisposition to second malignancies, including 11 with the hereditary type of retinoblastoma. Six of 54 children without a known genetic disease had brain tumors treated with radiation. Three developed leukemia or lymphoma, two developed soft-tissue sarcomas, and one developed bone cancer. Three other patients had leukemia or lymphoma with glioma at 2, 4, and 15 months of each other, respectively, without receiving radiation. Interestingly, three children with colon carcinoma, an extremely unusual tumor in children, developed gliomatous tumors 13–53 months later.

Of the 102 patients, 21 children developed a second malignancy without having received radiotherapy and without a known genetic predisposition to second tumors [3].

In 1985, Meadows et al. reported on 292 patients who developed second malignant neoplasms after being treated for a first neoplasm during childhood [7]. Data were collected from 12 pediatric oncology centers throughout the United States, Canada and western Europe as part of the Late Effects Study Group (LESG). The most common primary tumor was retinoblastoma (52 patients) followed by Hodgkin's disease and soft-tissue sarcomas (40 patients each) and Wilms' tumor (36 patients). The initial tumor was a brain tumor in 31 patients.

The most common second malignancy was bone sarcoma, which developed in 67 patients, followed by soft-tissue sarcoma in 59 patients and leukemia–lymphoma in 57 patients. Twenty-nine patients subsequently had a brain tumor as their second malignancy. Bone sarcomas were

considered to be radiation-associated in 52 of the 67 cases. Of 15 patients developing bone sarcoma who did not have radiotherapy, eight had chemotherapy. Similarly, 43 of 59 patients developing soft-tissue sarcoma had received radiotherapy. Of the 29 second tumors that were in the brain, 13 were considered radiation-associated. Fifteen patients did not receive radiotherapy, but of this latter group, 11 had received chemotherapy. Thyroid cancer was the second malignancy in 26 patients and considered to be radiation-associated in 24. Only two patients with subsequent thyroid cancer had a previously treated childhood brain tumor.

Hawkins et al. reported 90 second primary tumors in a group of 10,106 three-year survivors of childhood cancer [4]. This incidence of second malignancies was considered to be about six times the expected rate. The mean follow-up for the total group of three-year survivors was 7.8 years, starting from the time of three-year survival from the first malignancy. The most common second malignancy was osteosarcoma, which occurred in 24 patients (27%). Twenty-four patients who developed a second malignancy had an initial CNS tumor. These 24 children represented 1% of 2343 children who survived three years following diagnosis of a brain tumor. Ten had medulloblastoma. The percentage of medulloblastoma patients surviving three years who subsequently developed a second malignancy was 2.3%. Four second neoplasms in previously treated brain tumor patients were meningioma. Five were soft-tissue sarcoma, seven were carcinomas (including three of the thyroid and two of the colorectal region), four were basal-cell carcinomas, and one was an osteosarcoma. Acute leukemia developed in one patient. Only one medulloblastoma patient subsequently developed a thyroid carcinoma.

Additional cases of thyroid carcinoma appearing 6–11 years after craniospinal axis irradiation for ependymoblastoma [28] and medulloblastoma [29, 30] have been reported.

Kingston et al. identified 161 children who

TABLE 24-3. Second neoplasms in patients with primary childhood brain tumors (Kingston et al. [5])

Type of neoplasm	No. of patients
CNS tumors	12
Carcinomas	9
Skin	7
Soft-tissue sarcoma	6
Leukemia	5
Osteosarcoma	2
Lymphoma	1
Other	3
TOTAL	45

TABLE 24-4. Second neoplasms after chemotherapy for childhood malignancy (Kingston et al. [5])

Type of neoplasm	No. of patients
Osteosarcoma	14
Leukemia	13
CNS tumors	10
Soft-tissue sarcoma	6
Hodgkin's disease	3
Carcinoma	3
Other	1
Total	50

subsequently developed a second primary neoplasm [5]. Ten children developed a second neoplasm within one year of the first, and these children were considered to have simultaneous multiple primary tumors. Six of these patients with simultaneous primary tumors had an initial brain tumor and five also had a recognized genetic disorder predisposing to multiple malignancies. Forty-five patients had a CNS tumor as the primary malignancy (table 24-3). Of the 161 cases, there were 12 patients with multiple primary CNS tumors, and five had neurofibromatosis. In five patients, the second tumor was a meningioma and in four, an astrocytoma. Three of these latter patients had evidence of neurofibromatosis.

Interestingly, there was an association be-

tween CNS tumors and acute leukemia. Six children with acute lymphocytic leukemia treated with chemotherapy and radiotherapy to the brain (2400 rads) developed astrocytoma 3.9–9.2 years later. One additional patient with acute myelogenous leukemia developed a meningeal sarcoma 3.5 years later. He had been treated with chemotherapy and total-body irradiation (1000 rads). Five children with primary brain tumors subsequently developed acute leukemia. Three had acute myelogenous leukemia and two had acute undifferentiated leukemia. The leukemia developed at 1.5–3.8 years in four patients and at 19.2 years following the diagnosis of brain tumor in the fifth patient. All had received radiation and two had also received chemotherapy.

For patients treated prior to 1970, the two tumor types most frequently associated with development of a second malignancy were genetic retinoblastoma and CNS tumors. Since 1970, children with leukemia and lymphoma are the group most commonly developing second tumors. This may be a reflection of both an increase in survival for children with leukemia and the use of intensive chemotherapy regimens. Of 151 patients with nonsimultaneous malignancies, 125 were treated with radiation and in 77, a second tumor developed within or close to the radiation therapy fields. An additional 16 patients developed leukemia.

Fifty children had been treated either with chemotherapy alone (5 cases) or with radiotherapy (45 cases) for the first malignancy. An alkylating agent had been used in 38 patients. Osteosarcoma and leukemia were the most common second tumors in chemotherapy-treated patients (table 24-4). Of 19 leukemias, 13 arose in patients treated with chemotherapy, and all had received an alkylating agent. Ten of the 13 had also received radiotherapy. Six patients developed leukemia as a second malignancy after having received radiotherapy alone for the first malignancy.

In an analysis of the LESG data by Meadows et al., there were 98 patients with second malig-

nancies unassociated with radiotherapy [7]. Forty-nine had received chemotherapy for the first malignancy. Twelve of the second malignancies were acute leukemia. All but 2 of the 49 patients had received an alkylating agent.

Reviewing LESG data on 9170 patients who survived two years following treatment of a childhood malignancy, Tucker et al. concluded that radiotherapy and alkylating agents increased the risk of bone cancer [6]. The risk of bone cancer after radiotherapy correlated with the administered dose. There was no increased risk with less than 1000 rads. The risk of radiation-induced bone cancer increased with dosages up to 8000 rads.

From the same cohort of 9170 patients, Tucker et al. identified an association between chemotherapy with alkylating agents and a significant increase in leukemia, mainly acute nonlymphocytic types, among survivors of childhood tumors [31]. The risk of subsequent leukemia correlated with the total dose of administered alkylating agents.

Schmahl et al. in 1982 published a literature review of 303 cases of second malignancies following chemotherapy [32]. Second malignancies following alkylating agents were usually leukemia. Cyclophosphamide-induced tumors other than leukemia were mainly squamous-cell carcinoma of the skin and carcinoma of the urinary bladder. The mean latent period for development of a urinary bladder carcinoma was 81 months compared to 49 months for leukemia and 18 months for squamous-cell carcinoma. Practically all patients developing urinary bladder carcinoma or squamous-cell carcinoma of the skin following cyclophosphamide therapy were adults at the time of their initial treatment. However, a three-year-old male treated with cyclophosphamide for lymphoma subsequently developed transitional cell carcinoma of the urinary bladder 13 years later [33]. This patient had been on maintenance cyclophosphamide for 13 years.

A possible association between alkylating agent chemotherapy for Hodgkin's disease and

subsequent leukemia has been suggested in several reports [31, 34–36]. There may be an increased risk of solid tumors following chemotherapy for Hodgkin's disease. However, greater follow-up intervals with larger numbers of patients will be necessary to assess accurately the risk of chemotherapy-induced second malignancies in Hodgkin's disease patients. An increased incidence of bone sarcomas in Hodgkin's patients treated with multiagent chemotherapy and radiotherapy was reported by Kushner et al. [36]. The bone malignancy occurred within or at the margin of the radiotherapy field in all patients. Bone malignancies were not seen after radiotherapy or single-agent chemotherapy alone.

Particularly relevant to the childhood brain tumor patient are reports indicating that nitrosureas may be leukemogenic. An increased risk of acute nonlymphocytic leukemia has been reported in adult patients treated with adjuvant chemotherapy regimens containing semustine (Methyl-CCNU) for gastrointestinal cancer [37]. Several cases of acute leukemia have been reported after nitrosurea therapy for glioma in adults [38, 39]. However, some of these patients also received other chemotherapeutic agents, including procarbazine, VM-26, or hydroxyurea. Greene et al. followed 2656 patients entered into seven Brain Tumor Study Group (BTSG) protocols for adult malignant glioma [40]. Because of the poor survival of this group, there were only 2569 person-years of observation, and only 290 patients were observed for more than two years. Among 1628 patients who were treated with BCNU, there were two cases of acute nonlymphocytic leukemia. This represented a 24.6-fold increase over the expected number. There were no leukemias in the 1028 protocol patients receiving other chemotherapy or no chemotherapy for malignant glioma. Most of these patients also received radiation. Since the median survival of patients with malignant glioma on these clinical trials was one year or less, two cases represents a significant number. It is likely that with

increased survival, there would be a greater number of cases of subsequent leukemia.

Conclusions

1. The patient with a childhood brain tumor has an increased risk of being afflicted with a second tumor, benign or malignant. This increased risk is present for decades following therapy.

2. Many patients with a primary brain tumor will have a genetic predisposition to multiple tumors. Among the known hereditary disorders predisposing to multiple tumors are neurofibromatosis and the nevoid basal-cell carcinoma syndrome. As yet unidentified genetic disorders may be responsible for other multiple tumor associations such as glioma-colon carcinoma and glioma-leukemia.

3. Radiotherapy may be the cause of second neoplasms in a large proportion of treated brain tumor patients. Radiotherapy may potentiate the development of tumors in the genetically susceptible individuals. For example, an increased number of basal-cell carcinomas have been noted within irradiated skin in medulloblastoma patients with the nevoid basal-cell carcinoma syndrome. Also the appearance of osteosarcoma involving the skull in patients irradiated for retinoblastoma suggests the tumorigenic potentiating effects of radiation in the genetically susceptible patient.

4. Many chemotherapeutic drugs such as the nitrosureas, procarbazine, and cyclophosphamide, which are used in chemotherapy regimens to treat childhood brain tumors, may be carcinogenic.

5. Continued follow-up of all patients treated for childhood brain tumors is important to detect second malignancies at an early stage when cure is most likely. Attention should be directed to likely sites of second malignancies such as the thyroid gland in patients treated with craniospinal axis irradiation. Similarly, patients should be cautioned to avoid known

carcinogens, which may potentiate radiotherapy tumorigenesis.

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ADDENDUM TO CHAPTER 2: TUMORS OF THE CENTRAL NERVOUS SYSTEM IN CHILDREN

Laurence E. Becker

Venita Jay

Since the completion of the chapter on neuropathology of childhood brain tumors, there have been newer and exciting developments in the field. In the following update, we have incorporated some of the recent and notable developments in the diagnostic approach to brain tumors.

Tumor Markers

There has been more systematic utilization of various immunohistochemical markers and more widespread use of monoclonal antibodies. In updating the current status of various immunohistochemical markers, the glial fibrillary acidic protein (GFAP) antiserum remains a very useful tool in surgical neuropathology [1]. It is well established that the expression of GFAP is not restricted to astrocytes; despite these reservations, the GFAP antisera and monoclonal antibodies are the most commonly used markers for the identification of astrocytes and glia-related neoplasms. They have helped to identify new entities or poorly recognized variants of astrocytomas such as pleomorphic xanthoastrocytoma, lipidizing malignant gliomas, the superficial cerebral astrocytomas of infants and desmoplastic infantile ganglioglioma [2].

In view of the wide range of neoplastic cells of varied histogenesis which are immunoreactive for vimentin, the value of vimentin as a specific diagnostic tool remains limited. Vimentin immunoreactivity may be found in meningiomas, schwannomas, astrocytomas, and choroidomas as well as in a variety of other tumors

such as sarcomas, carcinomas, melanomas, and lymphomas. Vimentin is often coexpressed with other intermediate filament proteins.

The value of anti-S100 antibodies in neuro-oncology is also limited in view of the broad spectrum of their reactivity. Anti-S100 antibodies are useful in the diagnosis of suspected amelanotic melanomas in conjunction with anti-Leu-7-monoclonal antibody and for the distinction of histiocytosis X from juvenile xanthogranulomas of the brain [3]. S100 immunoreactivity may be only occasionally present in anaplastic and malignant nerve sheath tumors. The cells forming the perineurial sheaths and the neoplasms (perineuriomas, also known as hypertrophic neuropathy or localized neurofibrosis) which are thought to arise from these cells are S100 negative [4]. Schwann cells and perineurial cells may be distinguished further with the use of an additional marker, epithelial membrane antigen.

FACTOR VIII-related antigen (FVIIIrAg) and ULEX europeus I lectin (UEA I) are reliable markers for identifying vascular endothelial cells in nervous system tumors [1] and complementary to histopathological analysis, identification of biological differences between tumors.

Tumor Grading

There has also been a resurgence of interest in grading of tumors based on histological parameters. Grading of astrocytomas is a controversial subject. Dumas-Duport et al. [29] described a new grading system for astrocytoma using the presence or absence of four parameters:

nuclear atypia, mitoses, endothelial proliferation, and necrosis. By this grading system, 0 criterion = grade 1, 1 criterion = grade 2, 2 criteria = grade 3 and 3 or 4 criteria = grade 4. By this grading system, survival curve of patients with grade 2 corresponded to grade 1 and 2 of Kernohan and that of grade 4 coincided with the Kernohan grade 3 and 4 survival curves. However, this correlation was not applicable to cerebellar astrocytomas and pilocytic astrocytomas.

Grading of oligodendrogliomas has also been controversial. The Kernohan system of grading adapted for oligodendrogliomas consisted of several parameters: cell density and amount of neuropil, pleomorphism, hyperchromasia, vascular and endothelial proliferation, mitotic rate, necrosis, microcysts, and calcium. Using four features—endothelial proliferation, necrosis, cell density, and pleomorphism, Smith et al. [30] reported that their grading system significantly correlated with survival. The ultimate test of the validity of a grading system is a true correlation of grade with prognosis. The advantage of Smith's grading system is that it reduces the histopathologic features and also simplifies grading by scoring the features in a simple on-off fashion. Kros et al. [31] compared the Smith and Kernohan grading systems in a study of 72 cases and found that the Smith system identified three groups of patients with significantly different survival times. In Smith's grade A and Kernohan's grade 1 the longest survivals were found. Smith's grades B and C as well as Kernohan's grades 2 and 3 were intermediate with respect to survival times while in Smith's grade D and Kernohan's grade 4 the shortest survivals were found.

Specific Tumors

PRIMITIVE NEUROEPITHELIAL TUMOR

While the concept of primitive neuroepithelial tumor (PNET) has gained support, it is not without controversy [32–38]. The use of the

term PNET is an indication that the pathologist cannot tell by examining the tumor by conventional histology whether it arose in the cerebrum, cerebellum, or pineal gland. Therefore, it is suggested that the pathologist be objective and call such tumors PNETs rather than try to give them different names based on the presumed site of origin of the tumor. Variable results of intermediate filament expression in PNETs may be attributed to variations in methodology used e.g., variations in fixation and processing of the samples may destroy or mask epitopes of vimentin, neurofilament protein and other polypeptides. Recently, Gould et al. [38] have reported results of an immunohistochemical study using frozen samples of PNETs employing a wide range of markers including synaptophysin and all classes of intermediate proteins. All cases expressed synaptophysin, while many tumors expressed vimentin, GFAP, and neurofilament. Coexpression of various antigens by individual cells was also noted. The systematic application of molecular markers indicates that PNETs manifest a distinctive but complex phenotypic profile. With application of more specific immunohistochemical markers, subsets of PNET will be identified, some of which will likely become clinicopathological entities in the future.

PLEOMORPHIC XANTHOASTROCYTOMA

The pleomorphic xanthoastrocytoma described by Kepes and colleagues in 1979 is an unusual variant of the supratentorial astrocytoma in young subjects [39–41]. Although the clinicopathologic features of this entity (superficial location, leptomeningeal invasion, pleomorphism, relatively favorable prognosis) have been confirmed in subsequent reports, it now appears that the biological behavior of some of these is less predictable than initially reported. In some cases where death followed shortly after diagnosis, there may have been histologic confusion between this entity and a malignant glioma with heavily lipidized tumor cells.

DESMOPLASTIC INFANTILE GANGLIOGLIOMA

Vandenberg et al. [2] reported an apparently distinct pathological entity which they called desmoplastic infantile ganglioglioma. The tumors occurred in children below 18 months, usually within the first four months of life. The frontal and parietal areas are most often involved. They were composed predominantly of a dense desmoplastic tissue resembling a moderately cellular fibroma. Multiple cysts and firmness were the most visible gross characteristics. The fibroblastic elements were admixed with variable numbers of pleomorphic neuroepithelial cells with divergent astrocytic and neuronal differentiation. In one case where electron microscopy was performed, the astrocytic cells were partly invested by a basal lamina. Successful total or near-total surgical resection was followed by a favorable postoperative course extending in some cases over many years of tumor-free survival.

DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOR

Daumas-Duport and colleagues [42] described a clinicopathologic entity, which they called the "dysembryoplastic neuroepithelial tumor", in patients ranging from 1–19 years who presented complex partial seizures. All tumors were supratentorial, intracortical with a multinodular appearance. A heterogeneous cell population of astrocytes, oligodendrocytes and neurons were found. In addition to the chronic nature of the seizures, one-third of the patients showed radiologic features such as focal cranial deformity indicating an early onset and long standing. Although tumor removal was incomplete or subtotal in 17/39 patients, long term follow-up (range 1–18 years, mean 9 years) showed neither clinical nor radiological evidence of recurrence.

MENINGEAL HEMANGIOPERICYTOMA

Despite the differences in opinion regarding terminology, there is consensus that the

meningeal hemangiopericytoma (also referred to by some as hemangiopericytic type of angio-blastic meningioma) is more aggressive than the conventional meningioma [43]. In contrast to the ordinary meningioma, the tumor has a propensity for both local recurrence and extra-neural metastases. The tumor is extremely vascular and appears to arise in the meninges. The reticulin pattern and cytological appearances of the tumor may vary from field to field [43].

INTRAVENTRICULAR NEUROCYTOMA

In the differential diagnosis of intraventricular oligodendroglioma an entity known as intraventricular neurocytoma has to be considered [44, 45]. Histologically, the tumor is composed of small uniform cells with perinuclear haloes and regular round nuclei. Ultrastructurally, the cells contain occasional microtubules and scattered dense-core vesicles in the cytoplasm and have cell processes containing dense core and clear vesicles.

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