Sickle Cell Anemia

A Medical Dictionary, Bibliography,
and Annotated Research Guide to
Internet References

James N. Parker, M.D.
and Philip M. Parker, Ph.D., Editors

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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with sickle cell anemia is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about sickle cell anemia, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to sickle cell anemia, from the essentials to the most advanced areas of research. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on sickle cell anemia. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to sickle cell anemia, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. For readers without access to Internet resources, a directory of medical libraries, that have or can locate references cited here, is given. We hope these resources will prove useful to the widest possible audience seeking information on sickle cell anemia.

The Editors

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/cancerinfo/ten-things-to-know**.

CHAPTER 1. STUDIES ON SICKLE CELL ANEMIA

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on sickle cell anemia.

The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and sickle cell anemia, you will need to use the advanced search options. First, go to **http://chid.nih.gov/index.html**. From there, select the "Detailed Search" option (or go directly to that page with the following hyperlink: **http://chid.nih.gov/detail/detail.html**). The trick in extracting studies is found in the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Journal Article." At the top of the search form, select the number of records you would like to see (we recommend 100) and check the box to display "whole records." We recommend that you type "sickle cell anemia" (or synonyms) into the "For these words:" box. Consider using the option "anywhere in record" to make your search as broad as possible. If you want to limit the search to only a particular field, such as the title of the journal, then select this option in the "Search in these fields" drop box. The following is what you can expect from this type of search:

- **Sickle Cell Disease: A Review and Update of Current Therapy**

  Source: Journal of Oral and Maxillofacial Surgery. 57(2): 171-178. February 1999.

  Contact: Available from W.B. Saunders Company. Periodicals Department, P.O. Box 628239, Orlando, FL 32862-8239. (800) 654-2452.

  Summary: Sickle cell disease (SCD) is a disorder of the beta hemoglobin chain, characterized by chronic hemolytic anemia and episodes of symptomatic, painful, vasocclusive crises. Patients with SCD are at risk for various perioperative complications. The oral and maxillofacial surgeon should have a reasonable level of understanding of the pathophysiology of this disease, to assure safe perioperative management. This article provides a review of the basic pathophysiology of SCD, the

systemic manifestations of the disease, including the specific SCD complications seen in the oral and maxillofacial region, and prevention of perioperative complications. The author covers six factors involved in the pathophysiology of SCD: deoxygenation, vascular stasis, temperature, acidosis, infection, and dehydration. The author also discusses current modes of therapy and management for this disease. Most minor oral surgical procedures can be done under local anesthesia, without any major complications. Because of the general lack of effective treatments for SCD, traditional therapy has focused on general medical care and appropriate management of complications as they arise. 2 tables. 30 references.

- **Sickle Cell Disease and the Kidney**

  Source: Seminars in Nephrology. 23(1): 66-76. January 2003.

  Contact: Available from W.B. Saunders Company. Periodicals Department. 6277 Sea Harbor Drive, Orlando, FL 32887-4800. (800) 654-2452.

  Summary: Sickle cell disease is a genetic defect in hemoglobin polymerization that results in red blood cell deformities when deoxygenated. This article describes how sickle cell disease (SCD) affects the kidney: by acute mechanisms, as a form of the sickle crisis, and insidiously with renal (kidney) medullary or papillary necrosis, with resulting tubular defects. Glomerular hyperperfusion and hypertrophy results in a chronic sickle cell nephropathy that results in a significant morbidity in the progression to end stage kidney disease. Kidney transplantation offers a major advantage to survival and should be coupled with efforts toward prevention of recurrent disease. 2 figures. 66 references.

- **Dental Management of Patients With Sickle Cell Anemia**

  Source: Journal of the Canadian Dental Association. 59(2): 180-185. February 1993.

  Contact: Available from Canadian Dental Association. 1815 Alta Vista Drive, Ottawa, Ontario, Canada K1G 3Y6. (800) 267-6354 or (613) 523-1770; Fax (613) 523-7736; http://www.cda-adc.ca/.

  Summary: This article outlines the physiology, medical aspects, and dental manifestations of sickle cell anemia, and gives guidelines for its dental management. Topics covered include the epidemiology of sickle cell anemia; its physiology; diagnosis; clinical presentation; dental manifestations; preventive dental care; anesthesia and analgesia issues; and oral surgery in patients with sickle cell anemia. 1 figure. 2 tables. 32 references. (AA-M).

- **Sickle Cell Anemia and Dental Caries: A Literature Review and Pilot Study**

  Source: SCD. Special Care in Dentistry. 22(2): 70-74. March-April 2002.

  Contact: Available from Special Care Dentistry. 211 East Chicago Avenue, Chicago, IL 60611. (312) 440-2660.

  Summary: This article reports on a cohort study undertaken to determine whether individuals with sickle cell anemia (SCA) were more susceptible to dental caries (cavities) than non SCA control subjects. Thirty-five cases of SCA (aged 6 years and older) were identified from a screening of 15,900 current patient files at the Howard University College of Dentistry Dental Clinic. A total of 140 non SCA control subjects was selected. While there was virtually no difference in DMFS (decayed, missing, filled surfaces) between SCA cases and controls for 6 to 19 years olds, for subjects aged 20 and

older, the DMFS was 30.4 percent higher in the SCD cases. For all ages, the M component for SCA cases was 40.7 percent higher, and the D component was 20.0 percent higher, while the F component was only 3.5 percent higher than for controls. Untreated decay was 24.4 percent higher in the SCA cases. The findings from this pilot study suggest that SCA cases have a higher susceptibility to dental caries or that SCA patients may have different treatment pathways once caries is detected. The authors conclude that while none of the observed differences were statistically significant, these findings were of clinical interest and should be pursued in future large scale studies. 3 figures. 2 tables. 24 references.

- **Managing the Dental Patient with Sickle Cell Anemia: A Review of the Literature**

  Source: Pediatric Dentistry. 12(5): 316-320. September-October 1990.

  Summary: This article reviews the literature on the management of dental patients with sickle cell anemia (SCA), a genetic disease that primarily affects the black population. After an introductory section describing the disease and its manifestations (particularly in children), the authors cover the incidence of SCA, diagnosis, morbidity and mortality, medical management of SCA, psychosocial aspects, dental findings associated with SCA, and dental considerations. Mucosal pallor, delayed eruption, dental hypoplasia, and radiographic changes are common oral findings associated with SCA. The dentist's goal should be to treat the SCA patient with a thorough understanding and knowledge of the disease; ramifications of the disease must be considered carefully before dental treatment is initiated. One of the dentist's main goals should be to instill a positive attitude in the patient and parents to maintain good dental health. 25 references. (AA-M).

- **Sickle Cell Anemia: A Review of the Dental Concerns and a Retrospective Study of Dental and Bony Changes**

  Source: SCD. Special Care in Dentistry. 15(1): 38-42. January-February 1995.

  Contact: Available from Special Care Dentistry. 211 East Chicago Avenue, Chicago, IL 60611. (312) 440-2660. Fax (312) 440-2824.

  Summary: This article reviews the medical concerns pertinent to the dental care of patients with sickle cell anemia (SS); a preliminary study of dental findings in these patients is also presented. The dental characteristics observed in 21 dental patients with SS are described. Radiographic findings included 'steplader' trabeculae pattern (70 percent), enamel hypomineralization (24 percent), calcified canals (5 percent), increased overbite (30-80 percent), and increased overjet (56 percent). The authors make comparisons with other studies of the sickle cell patient and suggest areas for further study. The authors also provide detailed guidelines for patient care management of dental patients with sickle cell anemia. 1 table. 25 references. (AA-M).

Federally Funded Research on Sickle Cell Anemia

The U.S. Government supports a variety of research studies relating to sickle cell anemia. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[2] CRISP (Computerized Retrieval of Information on Scientific Projects) is a searchable

[2] Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration

database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions.

Search the CRISP Web site at **http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen**. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to sickle cell anemia.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore sickle cell anemia. The following is typical of the type of information found when searching the CRISP database for sickle cell anemia:

- **Project Title: A COMPARATIVE APPROACH TO GLOBIN REGULATION/THALASSEMIA**

  Principal Investigator & Institution: Zon, Leonard I.; Professor; Children's Hospital (Boston) Boston, Ma 021155737

  Timing: Fiscal Year 2003; Project Start 01-FEB-1998; Project End 31-JAN-2008

  Summary: (provided by applicant): The synthesis of hemoglobin involves globin chain production, heme-biosynthesis and iron utilization. We have undertaken a genetic approach to understanding the process of hemoglobin production using the zebrafish as a model system. Mutagenesis screens have previously identified five complementation groups of zebrafish mutants with defects in hemoglobin production. In the previous grant period, we isolated the sauternes gene, which encodes ALAS2, the first enzyme in the home-biosynthesis pathway. Mutations in ALAS2 cause congenital sideroblastic anemia in humans, and the zebrafish sau mutant represents an animal model of this disease. We also isolated the ferroportin 1 gene as the defect in the weissherbst mutant. Ferroportin 1 proved to act as the basolateral iron transporter of the gut as well as the placental iron transporter in mammals. Subsequently, it was found that mutations in ferroportin 1 are associated with hemochromatosis in humans. Our studies established the fish system as a means to study human disease and to isolate novel genes. During this new grant period, we will further sequence and characterize the zebrafish globins and establish the structure of the globin loci. We plan to isolate and characterize two newly identified hypochromic mutant genes. A dominant suppressor screen will be done to delineate genes that participate in the ferroportin 1 pathway of iron utilization. A chemical genetics approach will be used to understand hemoglobin production. A library of sixteen thousand compounds will be examined for effects on rescue of our hypochromic mutant phenotypes and another screen will look for chemicals that induce fetal globin gene expression in adults. These pharmaceutical compounds may ameliorate disease conditions in other vertebrates. Our studies should provide a better understanding of the basic biology of hemoglobin production and may have a therapeutic impact on patients with thalassemia, **sickle cell anemia,** and hemochromatosis.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ALLOCHIMERISM FOLLOWING HAPLOIDENTICAL STEM CELL TRANSPL**

  Principal Investigator & Institution: Hoffman, Ronald; Professor; Medicine; University of Illinois at Chicago 1737 West Polk Street Chicago, Il 60612

(FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

Timing: Fiscal Year 2002; Project Start 16-AUG-1999; Project End 31-JUL-2004

Summary: Allogeneic stem cell transplantation is the sole curative treatment for patients with hemoglobinopathies. Widespread implementation of transplant strategies in this group of patients has been severely curtailed, because most patients do not have an HLA identical sibling or unrelated matched donor. An alternative approach which is potentially applicable to most patients with **sickle cell anemia** is the use of related haploidentical stem cell donors, provided the morbidity and mortality from graft failure and graft versus host disease (GVHD) can be minimized. Conditioning regimens previously utilized to cross the double immunological barrier of host versus graft and graft versus host reactions have been associated with significant life threatening toxicities. This is especially problematic for patients with advanced hemoglobinopathies who have a limited ability to tolerate myeloablative conditioning regimens as a consequence of multi-organ dysfunction and poor performance status. The development of less toxic regimens which would be capable of eliminating host-derived cytotoxic T lymphocyte precursors for cellular resistance to engraftment and minimizing GVHD is key to the successful implementation of a haploidentical transplantation program for patients with hemoglobinopathies. We plan to develop a non-toxic stem cell conditioning regimen especially suited for hemoglobinopathy patients in a non-human primate model which closely mimics the events and difficulties that will be encountered during human stem cell transplantation. The specific aims of the proposal are: 1) To determine whether the use of a purine analogue (fludarabine) as a component of stem cell transplant conditioning regimen will reduce the need for total body irradiation required to achieve long-term engraftment of haploidentical stem cells; 2) To determine whether large doses of purified hematopoietic stem cells (depleted of T cells) will facilitate long-term engraftment in a haploidentical recipient conditioned with a less toxic regimen, and reduce the risk for severe GVHD; 3) To determine whether additional immunosuppressive therapy is capable of further facilitating long-term engraftment of haploidentical donor stem cells and reduce the need for toxic agents in the conditioning regimen. The development of a transplantation regimen that promotes long-term establishment of mixed chimerism without the use of profound myeloablation is expected to lead to access to this curative therapy by a greater number of hemoglobinopathy patients.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ALLOGENEIC CHIMERISM IN MURINE SICKLE CELL DISEASE**

  Principal Investigator & Institution: Archer, David R.; Assistant Professor; Pediatrics; Emory University 1784 North Decatur Road Atlanta, Ga 30322

  Timing: Fiscal Year 2003; Project Start 08-JUL-2003; Project End 31-MAY-2007

  Summary: (provided by applicant): **Sickle cell disease** is a debilitating inherited hemoglobin disorder that is the most common single-gene disease in the world. Hematopoietic stem cell transplantation is the only curative therapy for SCD; however toxic myeloablative conditioning regimens and barriers to allotransplantation have limited its use to children with major complications and HLA matched donors. New myelosuppressive/immunosuppressive transplant strategies are emerging to reduce morbidity and mortality and to make cell transplantation available to a larger number of patients by intentionally inducing mixed hematopoietic chimerism. However, these protocols raise significant issues that can be best addressed in a preclinical model. Using a murine model of **sickle cell disease** that expresses exclusively human sickle hemoglobin we have defined a non-myeloablative transplant protocol that induces mixed hematopoietic chimerism and tolerance to MHC disparate donors while

correcting hematologic and pathologic manifestations of the disease. In Aim 1, we will extend these studies to determine the levels of donor chimerism that provide hematologic and/or physiologic cure of **sickle cell disease.** We will determine if very low levels of stem cell chimerism can induce and maintain allogeneic tolerance, and whether genetically modified cell populations can be expanded to provide a permanently corrective mixed chimeric state. **Sickle cell disease** is now recognized as having complex inflammatory interactions between multiple cell types that lead to pathological outcomes. These interactions may also be responsible for the increased rate of rejection found in stem cell transplantation for **sickle cell disease.** In Aim 2 we will investigate inflammatory and immunological mechanisms involved in this rejection process. We will investigate co-stimulation blockade resistant rejection, immune effector populations, adhesion molecules and cytokines for their involvement and contribution to allogeneic rejection. These aims provide a comprehensive systematic approach to studying the relationship between mixed chimerism and sickle pathophysiology and the enhanced rejection rate found in transplantation for **sickle cell disease.** Both Aims address basic mechanisms of transplantation tolerance and rejection as well as providing the critical preclinical data that are required for the design of future non-myeloablative transplants protocols.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ARGININE THERAPY IN SICKLE CELL DISEASE**

  Principal Investigator & Institution: Morris, Claudia R.; Children's Hospital & Res Ctr at Oakland Research Center at Oakland Oakland, Ca 94609

  Timing: Fiscal Year 2002; Project Start 04-SEP-2000; Project End 31-AUG-2005

  Summary: The purpose of this proposal is to foster the scientific development and laboratory skills of Dr. Claudia R. Morris, MD, in order that she may become an independent clinical investigator. The comprehensive sickle cell center at Children's Hospital Oakland and its Research Institute will provide the applicant with the ideal setting in which to investigate the impact of oral arginine administration on nitric oxide production in **sickle cell disease** (SCD) at the clinical, biochemical and cellular levels. Through the collaboration with the clinical mentor, Elliott Vichinsky MD, and an extensive network of experienced scientific and clinical researchers, Dr. Morris will obtain the foundation for the development of an independent academic career. Vaso-occlusion is responsible for most of the morbidity in SCD. The etiology of vascular obstruction in SCD is multifactorial, but mechanisms regulating vascular tone are likely to include nitric oxide (NO), as NO is one of the most potent vasodilators known. NO metabolites (NOx) are elevated in SCD patients at baseline, but decrease significantly during vaso-occlusive crisis (VOC) and acute chest syndrome (ACS). L- Arginine (L-Arg) is the precursor to NO, and Dr. Morris has demonstrated that L-Arg levels are also decreased in SCD patients during VOC and ACS. Dr. Morris has also recently demonstrated that oral L- Arg supplementation can increase endogenous NOx levels in SCD patients during VOC, while causing a paradoxical decrease in NOx levels when administered to SCD patients at steady-state. L-Arg therefore has the potential to alter the nature of VOC in SCD by increasing NO production. The specific aims of the proposal are: (1) to institute a blinded, placebo control, phase Il/Ill clinical trial in SCD patients hospitalized with VOC to determine if oral L-Arg therapy will decrease the length of hospitalization, and (2) to characterize some of the biochemical and cellular effects of arginine therapy in SCD patients with VOC. The outcome of this proposal may impact both patient care and clinical assessment. It offers greater insight into the pathophysiology of SCD, and is the foundation for future studies. Dr. Morris has

demonstrated that an L-Arg deficiency may be involve in some of the vaso-occlusive complications of SCD, hence L-Arg supplementation may be a new therapeutic intervention that will improve quality of life for patients with SCD.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ASPIRIN PROPHYLAXIS IN SICKLE CELL DISEASE**

  Principal Investigator & Institution: Lerner, Norma; Pediatrics; University of Rochester Orpa - Rc Box 270140 Rochester, Ny 14627

  Timing: Fiscal Year 2003; Project Start 15-SEP-2003; Project End 31-MAY-2006

  Summary: (provided by the applicant): Neurologic complications secondary to cerebrovascular damage are prevalent in children with homozygous **Sickle Cell Disease.** These patients experience both clinically-overt cerebrovascular accidents and "silent infarctions," demonstrated by Magnetic Resonance Imaging (MRI). They are also at risk for neurocognitive abnormalities. We hypothesize that daily, low-dose, aspirin therapy will safely diminish the incidence and progression of cognitive deficits, as well as the pre-disposition to overt and silent stroke in children with homozygous **Sickle Cell Disease.** In order to optimize the design of a future trial to test this hypothesis, we propose a randomized, placebo-controlled, double-blind pilot study. The trial's primary objective is to evaluate the safety and tolerability of daily low-dose aspirin in children with **Sickle Cell Disease.** The secondary objectives are: 1. To establish the level of compliance with aspirin administration. 2. To identify the most useful assessments in a battery of age-appropriate neurocognitive tests. 3. To assess the feasibility of MRI and Magnetic Resonance Angiography (MRA) studies, and the utility of classification systems for use in group comparisons. 5. To establish trends in Transcranial Doppler (TCD) ultrasound velocities over time, and the validity of using trends in group comparisons. 6. To obtain preliminary data regarding the effect of aspirin on the incidence of cognitive deficit, imaging abnormalities, overt stroke, painful crises, and Acute Chest Syndrome. 7. To establish the feasibility of recruiting patients. A minimum of 60 patients will be enrolled. Subjects will include children between the ages of 3 and 10 years, with documented homozygous **Sickle Cell Disease** who are currently followed at the Galisano Children's Hospital (University of Rochester Medical Center, Rochester, New York), and at Saint Luke's-Roosevelt Hospital Center (Columbia University, New York, New York). Subjects will be randomized to one of two treatment groups, daily aspirin (1-2.5 mg./kg./day), or placebo. Patients will receive therapy for 18 months. There will be careful laboratory and clinical monitoring every 3 months, and more frequently as needed. Group comparisons regarding pre- and post-treatment clinical complications, neurocognitive testing, MRI, MRA, and TCD studies will be made.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: BETA-3 INTEGRINS IN PLATELET AND VASOOCCLUSIVE DISORDERS**

  Principal Investigator & Institution: Coller, Barry S.; Head; Lab/Blood & Vascular Biology; Rockefeller University New York, Ny 100216399

  Timing: Fiscal Year 2003; Project Start 01-SEP-1976; Project End 31-AUG-2008

  Summary: (provided by applicant): The broad long-term objectives of this grant proposal are to enhance our understanding of blood cell adhesion phenomena and to translate that knowledge into improved diagnosis, treatment and prevention of disease. In previous grant periods, the biology of the beta3 integrin receptors GPIIb/llla

(alphaIIbbeta3) and alphaVbeta3 was studied using monoclonal antibodies and analysis of patients with Glanzmann thrombasthenia, including the role of alphaIIbbeta3 in platelet function [which led to the development of monoclonal antibody c7E3 Fab (abciximab) as a new antiplatelet therapy] and the role of the alphaVbeta3 receptor in sickle cell adhesion. In addition, studies in a mouse model of **sickle cell disease** identified a potential direct role of leukocytes in microvascular obstruction. The recent availability of the crystal structure of alphaVbeta3, in conjunction with the P.l.'s studies on the epitope of 7E3, and advances in computer modeling of protein structure and murine embryonic stem cell biology, open new possibilities for understanding integrin structure and function. Thus, in Specific Aim 1, studies will be performed to: A. Define the 7E3 epitope on alphaIIbbeta3 and alphaVbeta3 using multiple techniques and to assess the alphaIIbbeta3 activation mechanism by studying the binding of 7E3 to receptors locked in various states of activation, B. Engineer the 7E3 epitope into mouse alphabbeta3 and alphaVbeta3 by modifying mouse beta3 and produce a mouse expressing the 7E3 epitope for preclinical studies of new indications for abciximab. C. Use a new computer model of alphaIIb to understand better alphaIIbbeta3 structure and function, and the abnormalities in select patients with Glanzmann thrombasthenia, and D. Express select beta3 Glanzmann thrombasthenia mutations in megakaryocytes derived from murine ES beta3-/- cells for functional analysis. In Specific Aim 2, important aspects of **sickle cell disease** will be studied, focusing on the poorly understood biology of large vessel arterial stenosis and thrombosis as well as the potential roles of P-selectin and beta3 integrins in microvascular occlusion and organ damage. These will include: A. The acute and chronic response of "Berkeley" sickle cell mice and appropriate controls to arterial injury. B. The impact of breeding either P-selectin deficiency or beta3 deficiency into Berkeley sickle cell mice on erythrocyte survival, organ damage, and microvascular occlusion.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: BIRMINGHAM SCIENCE EDUCATION PARTNERSHIP (BSEP) PHASE I**

  Principal Investigator & Institution: Hajduk, Stephen L.; Professor; Biochem & Molecular Genetics; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

  Timing: Fiscal Year 2002; Project Start 29-SEP-2000; Project End 31-AUG-2005

  Summary: (Adapted from the applicants abstract): The University of Alabama at Birmingham, McWane Science Center and the Birmingham City Schools (BCS) propose a highly coordinated program to provide high school science teachers and their students with a laboratory-based learning experience in genetic and molecular biology and the application of these fields to advances in modern medicine. While all of the programs described here are based on providing a high level of science content training to the participating teachers and students the primary goal will be to provide them with an opportunity to explore, by experimentation, the molecular world. The Birmingham Science Education Partnership (BSEP) integrates five highly successful existing programs with three new initiatives. To achieve the greatest impact these programs are highly interrelated and will provide maximum flexibility so that all BCS high school students will gain a better knowledge of new and exciting advances in health sciences. The combined programs will: 1) train BCS teachers in molecular biology during a summer course, BioTeach, taught by the UAB faculty and students; 2) provide BioTeach graduates with five molecular biology laboratory modules in their classrooms; 3) provide BCS teachers the opportunity to bring their classes to the GENEius program at

McWane Science Center to conduct day-long experiments in DNA fingerprinting and the genetic basis for **sickle cell anemia;** 4) develop and build exhibits at McWane Center to help the public better appreciate experiments conducted by students in the GENEius program; 5) expand the development and dissemination of inquiry-based Genetics and Microbiology courses in the BCS; 6) strengthen existing high school science club curricula by offering long-term projects including genome analysis and infectious diseases; 7) expand the current summer internship program for high school students to include training in basic molecular concepts and laboratory skills; 8) recruit and train undergraduate Outreach fellows to serve as facilitators in high school classroom programs. Several factors contribute to the likely success and sustainability of the BSEP. First, the partners are the major contributors to biomedical research and science education in Birmingham. Second, substantial commitment of resources in the form of State funds, private and federal grants and physical facilities are available to the programs described in this proposal. Third, the partner institutions have a track record of working effectively together, drawing from their varied expertise, to provide exciting and innovative science education programs.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CLINICAL RESEARCH IN PEDIATRIC SICKLE CELL DISEASE**

  Principal Investigator & Institution: Mueller, Brigitta U.; Pediatrics; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

  Timing: Fiscal Year 2002; Project Start 01-SEP-2000; Project End 31-AUG-2005

  Summary: Clinical research in cell disease (SCD) has reached a new developmental milestone. Ironically, the recent success of hydroxyurea and other new treatments makes the work of clinical investigation harder. In order to move the field forward, we now need to develop clinical investigators who excel in the arenas of clinical investigation and **sickle cell disease.** Dr. Brigitta U. Mueller is an ideal person to grow into this role. She is a pediatric hematologist/oncologist who early on focused on clinical trials related to pediatric HIV disease at the National Cancer Institute's (NCI) intramural program. We have recruited her to Children's Hospital so that she can shift her attention to **sickle cell disease** while expanding her training and experience in clinical investigation. The goal of our five-year development plan is for her to become an independent investigator - lead sickle cell clinical research at our institution, and direct multi-institutional studies. Dr. Mueller will pursue her career development under the mentorship of Dr. Orah S. Platt, an experienced investigator in **sickle cell disease,** and Dr. Carlo Brugnara, an expert in design of innovative therapies in **sickle cell disease.** She will focus her efforts in four major areas: 1) Throughout the 5 years she will see and discuss patients with Dr. Platt, and meet with Dr. Brugnara to discuss research ideas and review data. 2) She will conduct and analyze the proposed clinical trial - evaluating the effect of Mg, a known inhibitor of K-Cl cotransport, in patients with Hb SC disease. Our hypothesis is that oral Mg will block K- Cl cotransport, prevent cell dehydration, and reduce polymerization-induced vasoocclusive complications. 3) She will design and implement a research infrastructure that will be used as a resource for future proposals. 4) She will do course work at the Harvard School of Public Health and obtain the MPH degree, concentrating on research design, implementation; and analysis. The trial of Mg for the prevention of pain crises in patients with Hb SC disease that we propose, will serve as a template for bringing a variety of treatments designed in basic laboratories to clinical trial.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: COMPARATIVE APPROACHES TO BIO-KNOWLEDGE DISCOVERY**

  Principal Investigator & Institution: Kim, Junhyong; Professor; Biology; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104

  Timing: Fiscal Year 2003; Project Start 01-AUG-2003; Project End 31-JUL-2006

  Summary: (provided by applicant): In this planning grant to establish a Program of Excellence in Biomedical Computing, the University of Pennsylvania and the Children's Hospital of Philadelphia propose to develop a new organization that will serve as a central conduit of biomedical computing research tying together the activities of three schools and six research institutes. The organization will consist of a scientific steering committee with internal and external members to oversee research activities, an oversight committee to provide institutional support, an executive committee to govern day-to-day activities, and an office of education to coordinate the training activities. The organizational structure will be generated under the umbrella of the Penn Genomics Institute and the Penn Center for Bioinformatics to leverage existing resources. Interdisciplinary research interactions will be promoted by funding 12 new seed grants (made possible by matching funds) focusing on comparative approaches to biomedical knowledge discovery. In the first year, four projects will be funded: (1) pattern discovery in comparative genomics; (2) computational phylogeny reconstruction; (3) comparative text mining for cancer research; and (4) comparative informatics approach to sickle-cell disease. In subsequent years, new projects will be added to the first four through an internal solicitation for proposals. The Scientific Steering Committee will review these proposals and four new projects will be funded in Years 2 and 3. Each year, existing projects will be reviewed and at the end of the planning grant, all projects will be reviewed for consolidation into a small number of high impact projects. New interactions between existing computational faculty and biomedical faculty will be encouraged by holding opportunity presentation retreats to introduce researchers from complementary fields to biological problems and computational methods. Faculty basic education seminars will be held monthly where basic concepts like "transcription" will be discussed in a highly interactive format. The existing core facility for bioinformatics will be augmented with additional high-performance computing hardware, support for teaching basic computational biology tools, and a facility to coordinate dissemination of software tools developed from this grant. An existing PhD level training program in biomedical computing will be supplemented to provide research experience for undergraduates and masters students.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: COMPREHENSIVE SICKE CELL CENTER**

  Principal Investigator & Institution: Joiner, Clinton H.; Professor; Children's Hospital Med Ctr (Cincinnati) 3333 Burnet Ave Cincinnati, Oh 45229

  Timing: Fiscal Year 2002; Project Start 10-APR-1998; Project End 31-MAR-2004

  Summary: This proposal is submitted by the Cincinnati Comprehensive Sickle Cell Center, one of the first comprehensive programs in the country. The CCSCC is based in the Division of Hematology/Oncology at Children's Hospital Medical Center and its affiliated institution, the University Hospital of the University of Cincinnati College of Medicine, which provide a full range of clinical services to people affected by **sickle cell disease.** The proposal contains four interactive basic science projects focused on globin gene regulation (Project 1), erythropoietin receptor gene expression in early hematopoiesis (Project 2), mechanism of dehydration of sickle cells and the therapeutic potential for inhibiting this process (Project 3), and the hydration state and survival in

vivo of sickle cells (Project 4). A clinical research project is focused on the treatment of sickle cell vaso-occlusive episodes employing behavioral, pharmacological, and physiological approaches (Project 5). Educational (Project 6) initiatives include the development of a Transition Program for young adults transferring from pediatric to adult medical care, and educational programs from a patient/patient perspective for patients, families, and professionals. These educational activities will be carried out in collaboration with two community agencies, the Sickle Cell Awareness Group and the Sickle Cell Parent and Family Network. The Sickle Cell Research Scholars Program (Project 7) provides an important opportunity to contribute to the development of a new generation of investigators focused on **sickle cell disease.** Pediatric and Adult Clinical Program (Cores A and B) provide organization of the clinical services for patients and essential support for the basic science and clinical research projects. An Administrative Core (C) provides overall fiscal and programmatic management, and serves as a focal point for Center activities, programs, and communication. The projects and cores in this proposal will be integrated with ongoing, independently funded programs of follow-up of newborn hemoglobinopathy screening, education and counseling, a Hemoglobin Diagnostic Laboratory, and other basic science research projects. With this integrated program, the Cincinnati Comprehensive Sickle Cell Center will contribute to the national effort to optimize care for those affected by **sickle cell disease,** and ultimately to find a cure for patients with this disorder.

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- **Project Title: COMPREHENSIVE SICKLE CELL CENTER**

  Principal Investigator & Institution: Johnson, Cage S.; Professor of Medicine; Medicine; University of Southern California 2250 Alcazar Street, Csc-219 Los Angeles, Ca 90033

  Timing: Fiscal Year 2002; Project Start 01-APR-1993; Project End 31-MAR-2004

  Summary: The current projects represent the continuing development and expansion of our research program into the pathophysiology of vaso-occlusion and builds upon the historical strengths of our Center. With this proposal, we now move forward into two novel directions that explore new questions in **sickle cell disease** and strengthen collaborations between existing projects. Dr. Kohn will address an entirely new research objective for this Center in vitro and in vivo models of human erythropoiesis. Dr. Donald Kohn, one of the leading pediatric gene therapy investigators in this country, has developed a new method to expand stem cells from patients with **sickle cell disease** into mature erythrocytes or granulocytes in quantities sufficient to allow Dr. Meiselman to make biorheologic measurements of these cells prior to exposure to the in vivo environment and to allow Dr. Coates to study the intrinsic properties of sickle neutrophils. This approach will not only allow Dr. Meiselman to determine if b-globin related differences in sickle RBC rheologic properties are present in virginal sickle RBC, but also to measure the direct rheologic consequences of the genetic manipulations of the RBC proposed by Dr. Kohn. The novel model of human sickle erythropoiesis in the bnx-mouse will provide an in vivo environment for future exploration of hypothesis posed in other Projects. From the collaborations between Drs. Coates, Kalra and Meiselman, we have strong evidence that sickle erythrocytes specifically activate leukocytes which can then participate in endothelial damage. Dr. Coates Project will address the role that the reticuloendothelial systems, a major target in this disease, plays in disease manifestations. Two projects explore the intrinsic properties of the sickle RBC whole two other projects explore those characteristics of the vascular endothelium and reticuloendothelial system which contribute to vaso-occlusion. This closely knit ensemble of project directors have extensive histories of prior NIH support and bring

expertise from wide-ranging backgrounds in basic research to bear on the problem of vaso-occlusion.

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- **Project Title: COMPREHENSIVE SICKLE CELL CENTER**

  Principal Investigator & Institution: Stuart, Marie J.; Professor; Pediatrics; Thomas Jefferson University Office of Research Administration Philadelphia, Pa 191075587

  Timing: Fiscal Year 2002; Project Start 08-JUN-1998; Project End 31-MAR-2004

  Summary: Although **Sickle Cell Anemia** (SCA) has been characterized at the molecular level, the pathophysiology of its protein manifestation the vasocclusive crisis (VOC) still remains obscure. The exact events that lead to microcirculatory impairment and obstruction by sickled erythrocytes involve a complex and dynamic sequence of events that dependent presumably as much on microcirculatory tone, the activation state of the endothelium, white cells, platelets, and the fluid phases of coagulation as it does on the surface and internal characteristics of the red cell and its content of sickle and fetal hemoglobin. This Center grant will attempt to address the areas enumerated above in a unique and prospective fashion with focus on the crucial window of time during which a watershed change occurs in the erythrocyte's internal characteristics i.e.-its hemoglobin content of S and F. We will meticulously correlate how these physiologic changes in hemoglobin content during the first few years of life will affect the state of activation of the other cellular elements of blood, coagulation factors and endothelium, and how these changes effect the protein clinical manifestations of the disease-VOC and the occurrence of pain. The incidence and the attributes of sickle pain in these infants and young children will be assessed in a comprehensive and prospective longitudinal study. Additionally, our research program will explore at the cellular and molecular level the rationale for potential use of interventional strategies directed at one of the life threatening complications of **Sickle Cell Disease,** the acute chest syndrome, and also investigate a second and interventional program designed for our children in late childhood and early adolescence which will increase their resilience and perceived control over their lives and illness. Thus, this Center Grant seeks to address various aspect of basic and translational research besides providing the support our patients require to lead independent and productive lives. The research projects will be supported by the traditional aspects of a Comprehensive Sickle Cell Center including education and counseling services, a diagnostic and laboratory core, and appropriate statistical and administrative support.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: COMPREHENSIVE SICKLE CELL CENTER PROGRAM**

  Principal Investigator & Institution: Haynes, Johnson Jr.; Professor; Comprehensive Sickle Cell Ctr; University of South Alabama Mobile, Al 366880002

  Timing: Fiscal Year 2002; Project Start 01-APR-1988; Project End 31-MAR-2004

  Summary: (Adapted from the Applicant's Abstract) The current proposal includes five basic research projects, four clinical research projects, educational and community support projects, and the Laboratory Core. Clinical diagnosis is handled by the physicians within the Adult Sickle Cell Clinic (Drs. Haynes and Hunter) and Pediatric Sickle Cell Clinic (Drs. Yang, Little, Pace, Gremse) and laboratory diagnosis within the Community Projects Blood Screening Laboratory and the Laboratory Core A at USA. Counseling is provided by the Community Project. Dr. Steven R. Goodman serves as Director of the USA Comprehensive Sickle Cell Center is responsible for all operations

with specific oversight of all research projects. Dr. Johnson Haynes serves as Associate Director of Clinical Programs with oversight of the clinical care of 600 children and adults with **sickle cell disease** who are cared for within USA Sickle Cell clinics and hospital wings. Ms. Rose Peterson is Associate Director for Community Programs.

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- **Project Title: CORE CLINICAL CENTER FOR NHLBI TM/H RESEARCH NETWORK**

  Principal Investigator & Institution: Ness, Paul M.; Pathology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-AUG-2007

  Summary: (provided by applicant): This proposal is to participate in a Transfusion Medicine/Hemostasis Clinical Research Network. The proposal is submitted by the Transfusion Medicine Division of the Johns Hopkins Medical Institutions (JHMI) with specific collaborations from the Hematology divisions of the Departments of Medicine and Pediatrics (responsible for the management of **sickle cell anemia** and hemostatic disorders), the Department of Anesthesia and Critical Care Medicine, the Hematopoietic and Therapeutic Support service (HATS) (a joint program of the Departments of Pathology and Oncology), and the Advanced Transfusion Practices (ATP) Center at JHMI. The JHMI core clinical center will coordinate the activities of individuals with expertise in transfusion medicine/hemostasis, taking advantage of pre-existing links between the JHMI departments and programs, and utilizing a large and diverse patient base whose therapy is highly dependent upon transfusion and hemostatic therapies. The Hopkins team will participate with other institutions and the coordinating center of the network, proposing study protocols and amending protocols suggested by collaborating institutions. The proposal describes two clinical protocols that could be selected by the clinical research network. One study will focus upon the transfusion needs of patients with **sickle cell anemia** in the perioperative setting using hemoglobin based oxygen carriers as one therapeutic option compared to transfusions. A second protocol will study a widely used but incompletely evaluated alternative to transfusion, acute normovolemic hemodilution (ANH), whose efficacy and adverse event profile is unclear. If the ANH procedure is efficacious, and important element is its provision of fresh autologous blood elements to reduce bleeding in perioperative patients, an important hemostasis endpoint.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CORE--ANIMAL FACILITY**

  Principal Investigator & Institution: Nolta, Jan A.; Associate Professor; University of Southern California 2250 Alcazar Street, Csc-219 Los Angeles, Ca 90033

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 31-MAR-2008

  Summary: It is proposed to establish an Animal Core to support Project 4 (Dr. Malik) and Project 5 (Dr. Kalra). The Animal Core will develop a breeding colony of sickle transgenic mice (Tg HbS) to be used in both of these projects, and will breed immunodeficient beige/nude/xid mice for globin gene lentiviral vector biosafety testing in Project 4. The Animal Core will optimize methods for breeding, transplantation, and post-procedure maintenance of the fragile Tg HbS mice. The Animal Core will assist in development of a model for acute chest syndrome and will perform X-rays for Project 5 using the Tg HbS mice. The Animal Core will perform sequential blood and serum testing of the mice for engraftment and biosafety assays for Project 4. The Animal Core

will perform organ harvest from the Tg HbS and immunodeficient mice, and will process serum and tissues, including banking, cell sorting, cryopreservation, and cryosectioning, for further detailed studies by the basic science investigators and by the Laboratory Core.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CORE--ANIMAL MODELS**

  Principal Investigator & Institution: Sorrentino, Brian; Associate Member; St. Jude Children's Research Hospital Memphis, Tn 381052794

  Timing: Fiscal Year 2002; Project Start 01-SEP-2002; Project End 31-AUG-2003

  Summary: The development of successful gene therapy for **sickle cell disease** will rely heavily upon animal experimentation in order to establish the clinical feasibility of this approach. These animal models are critical for assessing new approaches for transduction of human hematopoietic stem cells, for evaluating gene therapy approaches for modulating hemoglobin switching, and for designing clinical strategies for the selective amplification of genetically-modified hematopoietic stem cells. Repopulating of non-obese diabetic immunodeficient mice with human hematopoietic cells has proven to be an important assay for human stem cell function. This model system will be used to evaluate various retroviral vectors and transduction pro protocols. This system will also be used to directly evaluate potentially therapeutic vectors by targeting repopulating hematopoietic cells derived directly from normal patients and those with **sickle cell anemia.** A second system that will be provided by this core is transgenic mice that contain the human beta-globin cluster on a yeast artificial chromosome. These mice provide an in vivo model to study the transcriptional switching of fetal to adult globin synthesis. Various transcription factors and modulators thereof will be studied in this models to determine if fetal globin synthesis can be reactivated in the adult developmental stage. The third model provided by this core is a Rhesus macaque transplant model provided by our collaborators at the National Heart Lung and Blood Institute. This non-human primate model will be utilized to study novel approaches for efficient stem cell gene transfer to evaluate the efficacy of using drug selection to amplify a minority of genetically-altered stem cells (Project 4), and to test various sickle cell therapeutic vectors in a stringent and clinically relevant model. This core provides centralized access to these animal models, and provides standardized assays for evaluating gene transfer endpoints in these systems. Furthermore, the common gene therapy objectives that converge in this core will continue to serve as an important source of collaborative interactions between the investigations in the program project.

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- **Project Title: CORE--CLINICAL FACILITIES**

  Principal Investigator & Institution: Benjamin, Lennette J.; Associate Professor of Medicine & Clinic; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2002; Project Start 20-MAY-2002; Project End 31-MAR-2003

  Summary: (Adapted from Applicant's Abstract) Cost containment trends are leading to major cutbacks and downsizing in health care facilities nationwide. Under these circumstances, it is particularly encouraging that the Institution (Montefiore Medical Center of the Albert Einstein College of Medicine) has seen fit to expand (with additional space and hospital paid personnel) the Sickle Cell Clinical Facilities developed by this Core in the previous period. This is a testament that the investigators

have accomplished prudent but innovate quality care for the patients, and in a manner that has satisfied Hospital Administrators as being fiscally responsible and beneficial for the mission of this non-profit but financially solvent private Hospital. The investigators also feel that the investigators have accomplished what funded clinical activities should be: a pilot effort that needs to become self supportive through its own success. In this proposal the expansion of the Day Hospital to two daily cycles instead of the original one, the increase of personnel supplied by the hospital as well as the new physical facility will allow the proposed Clinical core to move to another level of activity. This Core is now in a position to provide better patient support to the research efforts of several of the Projects proposed in this application. The investigators also intend to extend the principles and practices of the Center to other sections of the Hospital and health care new that Montefiore has created in the Bronx and lower Westchester County. The investigators intend to improve the data management to facilitate clinical research. Finally, the investigators are now in a position of sharing the success with other Institutions (including other Centers) in this country and abroad. The investigators have already hosted health workers from the Boston and Philadelphia Comprehensive Sickle Cell Centers. The investigators expect that the next cycle will be a banner five years for the activities of the clinical core.

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- **Project Title: CORE--CLINICAL FACILITY**

  Principal Investigator & Institution: Jeng, Michael; St. Jude Children's Research Hospital Memphis, Tn 381052794

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 31-MAR-2008

  Summary: The purpose of the Center's clinical core is to provide comprehensive clinical care for patients with **sickle cell disease** who reside in the catchment area of western Tennessee, northern Mississippi, and eastern Arkansas and to provide an infrastructure for investigators to complete clinical and basic science research studies. The Center has developed a comprehensive system of patient care, which involves the collaboration of several institutions, with St. Jude and LeBonheur Children's Medical Center as the primary institutions. St. Jude is the central institution provides personnel, outpatient space, a unit, laboratory and clinical and research clinical translational trials facilities, and institutional support to the center: LeBonheur Children's Medical Center and the Department of Pediatrics of the University of Tennessee provide inpatient facilities, emergency room care, pediatric subspecialists, transfusion services, laboratory facilities, and access to a Clinical Research Center and Pediatric Pharmacy Research Unit. This collaboration provides an astounding array of facilities for the care of sickle cell patients and creates an optimal venue to implement clinical research projects, both local and collaborative/network (inter-center).

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CORE--PATIENT SERVICE**

  Principal Investigator & Institution: Day, Sarah; St. Jude Children's Research Hospital Memphis, Tn 381052794

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 31-MAR-2008

  Summary: The overall purpose of the patient services core is to provide education, genetic counseling, hemoglobinopathy diagnosis, and community outreach related to **sickle cell disease** for persons residing in the Mid-South area. These services provide a foundation for the application for a Comprehensive Sickle Cell Center. Patient services

are currently supported by SJCRH and by grants from the Tennessee Department of Health, Mississippi Department of Health and United Way. The St. Jude Sickle Cell Center is a recognized leader in patient service activities involving education and genetic counseling. The center has a multi-phase education program for parents of newborns with **sickle cell disease,** an education and support program for teens with **sickle cell disease,** and an education program for the use of Desferal. In addition, the center has worked with health departments throughout western Tennessee to establish a program for the provision of **sickle cell trait** counseling. All of the center's education and counseling protocols have been published in peer-reviewed nursing journals, presented at national meetings and provided upon request to over 40 sickle cell programs throughout the country.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DEFERIPRONE THERAPY FOR SICKLE CELL DISEASE**

  Principal Investigator & Institution: Olivieri, Nancy F.; Director, Hemoglobinopathy Program; Uhn Toronto General Hospital 200 Elizabeth St, Ccrw1-800 Toronto,

  Timing: Fiscal Year 2001; Project Start 30-SEP-1996; Project End 31-AUG-2004

  Summary: (Adapted from applicant's abstract) This research study is designed to determine if administration of the orally active iron chelator deferiprone can ameliorate the chronic hemolytic anemia of **sickle cell disease** by inhibiting iron-induced oxidative damage to the sickle erythrocyte membrane and decreasing red cell destruction. The cytoplasmic surface of sickled cells has been shown to carry abnormal deposits of free iron, capable of generating free hydroxyl radicals that induce protein thiol oxidation and lipid peroxidation leading to cation leak, cell dehydration, reduced erythrocyte deformability, and premature red cell destruction. Removal of iron from the red cell membrane would be expected to reduce the generation of hydroxyl radical, and represents a novel approach to the therapy of **sickle cell disease.** Preliminary studies with the orally active iron chelating agent deferiprone (L1) have demonstrated the utility of this agent in the removal of free iron deposits from membranes of red blood cells in vitro and in vivo. In the proposed studies the dose, schedule of administration, and pharmacokinetic profile of deferiprone that will be most effective in the removal of erythrocyte membrane free iron and that which achieves maximal sustained plasma drug concentrations of deferiprone will be established, and improvement in biotin red cell survival, ferrokinetic measurements of erythron transferrin uptake, and abnormalities associated with oxidative denaturation of hemoglobin and lipid peroxidation within red cells in patients with **sickle cell disease** treated with an extended period of deferiprone under the optimal dosing regimen will then be examined. The combination of determinations of red cell survival using biotinylated erythrocytes and of ferrokinetic measurements of erythron transferring uptake will provide a comprehensive assessment of red cell production and destruction in patients with **sickle cell disease,** before and after extended therapy with deferiprone.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DIPYRIDAMOLE/MAGNESIUM TO IMPROVE SICKLE CELL HYDRATION**

  Principal Investigator & Institution: Kalinyak, Karen A.; Medical Director; Children's Hospital Med Ctr (Cincinnati) 3333 Burnet Ave Cincinnati, Oh 45229

  Timing: Fiscal Year 2003; Project Start 11-JUL-2003; Project End 31-MAR-2008

Summary: Vaso-occlusivc episodesare common among patients with **sickle cell anemia** (SCA), causing pain and chronic organ damage. SCA is characterized by the presence of dense, dehydrated sickle red blood cells (SS RBC), which are rheologically abnormal and are selectively trapped during vaso-occlusion. Strategies to prevent cellular dehydration would offer important therapeutic options that might decrease vaso-occlusive episodes. SS RBC dehydration results from cation depletion mediated by two cation transport systems, a sickling-induced (SI) leak pathway and the KCI cotransporter (KCC). Previous work at this Center has shown that di-pyridamole inhibits the SI fluxes of Na, K and Ca in vitro. Increasing cellular magnesium inhibits KCC activity and increases cellular hydration in animal models of SCA. A small clinical study in SCA patients demonstrated that Mg supplementation increased cellular Mg, reduced KCC activity and improved red cell hydration. This study will test the hypothesis that significant reduction in SS RBC dehydration will be seen in patients with SCA treated with either dipyridamole or magnesium. An additive, and possibly synergistic, effect on dense cell formation is hypothesized in patients treated simultaneously with both agents. A prospective, randomized, crossover, repeated measures design will be conducted among 48 patients with SCA, ages 12 years and older. Patients will be recruited from the Cincinnati Comprehensive Sickle Cell Center and the Sickle Cell Program at Wayne State University in Detroit. This design will allow for efficient comparison of the three treatment options; dipyridamole alone, magnesium alone or a combination of both. We anticipate that these therapies will be well tolerated by the patients. Primary outcome measures include the number of dense cells, assessed by automated cell counting and phthalate density gradients, cellular cation content, cell volume and hemoglobin concentrations. Using the biotin label technique pioneered in Cincinnati, measurements of red cell survival and rate of dense cell formation will be made in six patients in each treatment group, and will shed light on the mechanisms underlying SS RBC dehydration and its postulated inhibition by dipyridamole and Mg.

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- **Project Title: DNA METHYLATION, CHROMATIN, AND GLOBIN GENE SILENCING**

  Principal Investigator & Institution: Desimone, Joseph; Geneticist; Medicine; University of Illinois at Chicago 1737 West Polk Street Chicago, Il 60612

  Timing: Fiscal Year 2003; Project Start 18-APR-2003; Project End 31-MAR-2007

  Summary: (provided by applicant): Increased level of fetal hemoglobin (HbF) is clinically beneficial ill patients with **sickle cell anemia.** Experiments performed in the baboon model demonstrated that HbF levels could be elevated using pharmacologic agents such as 5-aza-2'-deoxycytidine (decitabine), butyrates, and hydroxyurea. The usefulness of these drugs in patients with **sickle cell disease** was confirmed in a number of clinical trials. The MSH study demonstrated that hydroxyurea therapy reduced the number of pain crises, incidence of acute chest syndrome, and transfusion requirements in patients. A significant number (10-40%) are refractory to treatment as evidenced by minimal changes in HbF levels. Furthermore, because the increased HbF is distributed heterogeneously among red cells, a large percentage of erythrocytes remain unprotected from intracellular polymerization of deoxy-HbS molecules. New and improved agents and therapies must therefore be developed which increase HbF to higher levels in a greater proportion of patients and maximize the number of F cells produced. It is our goal to develop a better therapeutic regimen for patients with **sickle cell disease** based upon the use of the demethylating drug decitabine, histone deacetylase inhibitors, and growth factors. We intend to investigate the mechanism of action of these agents by

determining the role of DNA methylation and histone acetylation in both the development regulation of globin gene expression and the reactivation of HbF expression in the adult. Analysis of the methylation and histone acetylation status of genes in small numbers of highly purified hematopoietic progenitor cells is now possible using FACS, bisulfite sequencing and immunoprecipitation of formaldehyde-fixed chromatin fragments (CHIP) in combination with PCR. We propose to follow changes in gamma-globin gene expression, DNA methylation, and histone acetylation during fetal development and normal erythroid differentiation, and following augmentation of HbF production induced by administration of decitabine and histone deactylase inhibitors. We will use an in vitro culture system and an in vivo baboon model system that we have used for the past 20 years to study these mechanisms. These studies will define the mechanisms of gamma-globin gene silencing, and will aid in the development of new procedures to augment HbF production in patients with **sickle cell disease.**

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- **Project Title: DRED REPRESSION OF EMBRYONIC/FETAL GLOBIN GENE TRANSCRI***

  Principal Investigator & Institution: Engel, James D.; Professor and Chair; Cell and Developmental Biology; University of Michigan at Ann Arbor 3003 South State, Room 1040 Ann Arbor, Mi 481091274

  Timing: Fiscal Year 2003; Project Start 01-APR-2003; Project End 31-MAR-2007

  Summary: (provided by applicant): One attractive, efficacious strategy for reducing both the pain and morbidity associated with **sickle cell disease** (SCD) would be to induce fetal gamma-globin synthesis in adult erythroid cells. Such a strategy could be executed, in theory, either by forcing fetal gene-specific transcriptional activators to be inappropriately activated during adult erythropoiesis or by inhibiting the activity of adult stage fetal globin gene repressors. Using a combination of molecular genetics and biochemistry, we recently identified a potential definitive stage gamma-globin gene repressor (which we named DRED, for direct repeat erythroid-definitive). We cloned the DNA binding subunits of the repressor by purifying them from adult murine erythroid tissue culture cells, and the summary of our current evidence suggests that the large DRED repressor complex binds to direct repeat (DR1) sites in the epsilon- and gamma-globin gene promoters using two nuclear orphan receptors, TR2 and TR4, as the molecular scaffold upon which the larger DRED complex is assembled. Since TR2/TR4 heterodimers have been shown to repress other cellular genes, DRED could constitute an excellent target for therapeutic intervention in the treatment of SCD. Here we experimentally address five questions that will either confirm or refute the hypothesis that DRED might be an appropriate target for therapeutic intervention in the treatment of SCD and/or Cooley's anemia (beta-thalassemia). First, can we provide further evidence, using modified transgenic human beta-globinYACs, that the DR1 element in the gamma-globin gene promoter is the direct target of DRED repression? Second, can we provide additional biochemical evidence that the TR2/TR4 heterodimer is the basis for that repression? Third, will tissue-specific gain of function experiments (forced transgenic expression of TR2 and TR4 in erythroid cells) lead to precocious silencing of the endogenous murine or transgenic human embryonic/ fetal globin genes? Fourth, will conditional, erythroid tissue-specific loss of function of TR2 and TR4 (by either germ line inactivation or dominant negative repression) lead to ectopic synthesis of embryonic/fetal globin genes in definitive erythroid cells? Fifth, what are the

components, other than TR2 and TR4, that constitute the 0.5 MDa DRED repression complex.

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- **Project Title: ENU MUTAGENESIS OF GAMMA GLOBIN SILENCERS IN SICKLE MICE**

  Principal Investigator & Institution: Ryan, Thomas; Biochem & Molecular Genetics; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

  Timing: Fiscal Year 2003; Project Start 01-APR-2003; Project End 31-MAR-2007

  Summary: (provided by applicant): Gamma globin silencer gene(s) will be identified in an animal model of **sickle cell disease** (SCD) after global mutagenesis. N-ethyI-N-nitrosourea (ENU) will be used to induce point mutations that will inactivate or alter random sets of genes throughout the mouse genome in individual embryonic stem (ES) cells. Mice that are cloned from these cells will be screened for dominant and recessive mutations that affect gamma globin gene silencing by quantifying the persistent expression and synthesis of fetal hemoglobin in the founder animals and their progeny. This phenotype driven approach will utilize a knockout-transgenic mouse model of SCD that reproduces most if not alt of the pathology of the disorder (Science 278: 873-876). The model was created by targeted deletion of the adult mouse alpha and beta globin genes followed by introduction of human alpha, gamma, and beta sickle globin transgenes into the germline. During fetal and adult life these animals synthesize only human hemoglobin in their red blood cells. Similar to man, these SCD mice switch from human fetal hemoglobin, HbF, to adult sickle hemoglobin, HbS, at the time of birth. SCD mouse ES cell lines will be established from developing blastocysts isolated from sickle cell females that were mated with sickle males. Sickle ES cells will be treated with ENU and thousands of individual subclones established. Hundreds of SCD founder mice will be produced annually from these randomly mutated ES cell subclones by tetraploid embryo complementation. Alterations of heterocelluiar gamma globin chain levels in circulating erythrocytes will be assessed in founder animals and their offspring to discover potential cell lines containing gamma globin silencer mutations. Microsatellite linkage analysis of mutant offspring outcrossed to congenic SCD mice and direct sequence comparison to the routine genome will allow the positional cloning of gamma globin silencer genes. Finally, putative silencing factors will be positively confirmed by replicating the exact germline modification discovered during the ENU screen into SCD and beta thalassemic ES cells, followed by direct examination of the phenotype in mice generated from the modified cells by cloning. Successful completion of these studies will define the gene(s) responsible for gamma globin silencing. By experimental design, the in vivo therapeutic benefits associated with increasing HbF levels due to modification of these gone(s) on the pathophysioiogy of **sickle cell anemia** and Cootey's anemia will be tested directly in animal models of these disorders.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: FUNCTIONAL GENOMICS OF INFLAMMATION**

  Principal Investigator & Institution: Hawiger, Jack J.; Distinguished Chair and Professor; Microbiology and Immunology; Vanderbilt University 3319 West End Ave. Nashville, Tn 372036917

  Timing: Fiscal Year 2002; Project Start 10-DEC-2001; Project End 30-NOV-2006

  Summary: Inflammation is the major mechanism of diseases mediated by blood cells and plasma proteins. Inflammatory responses underlies a variety of human diseases

including atherosclerosis, coronary and peripheral arterial disorders exemplified by Kawasaki disease and systemic lupus (SLE), acute and chronic lung diseases (asthma, acute respiratory distress syndrome, interstitial lung disease), and a variety of vascular diseases including vasooclusive crises in **sickle cell anemia.** The overall goals of the proposed Program are (i) to conduct genome-wide mutagenesis to select novel genes involved in inflammatory response; (ii) to analyze novel genes at the level of blood lineage specific expression and stimulus-response coupling; (iii) to analyze novel genes in animal models and stimulus-response coupling; (iii) to analyze novel genes in animal models of systemic and localized inflammatory response; and (iv) to determine the function of novel genes in development and signaling of phagocytic and mast cells, T lymphocyte subsets, and B lymphocytes. The currently available resources such as the library of the murine embryonal stem (ES) cell clones with disrupted genes (approximately 600) will be expanded using a new generation of vectors. The Program is a tightly knit organization of highly interactive and cohesive projects and cores: Genetic & Proteomic Analysis of Inflammation; Phagocytosis-Based Functional Genomics of Inflammation; T Lymphocyte-Based Functional of Inflammation; B Lymphocyte-Based Functional Genomics; the Microarrays Core to develop a mutant library microarrays and a new pro-inflammatory gene expression microarrays; the Animal Models Core to screen and analyze phenotype of mutant mice; the Bioinformatics Core to develop a new inflammatory gene database; and the Administrative Core will coordinate this Program to generate, analyze, and share new quality data on genetics and proteomics of inflammation to advance new diagnostic and therapeutic approaches to the diseases of cardiovascular, pulmonary, and blood systems mediated by inflammatory response.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GENE THERAPY STRATEGIES FOR SICKLE CELL DISEASE**

  Principal Investigator & Institution: Kan, Yuet W.; Professor of Medicine; Cardiovascular Research Institute; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747

  Timing: Fiscal Year 2002; Project Start 30-SEP-1994; Project End 31-AUG-2005

  Summary: Sickle cell anemia is one of the most common genetic diseases worldwide, estimated to affect on in six-hundred African American births. During the past decade, great strides have been in management of patients by treatment modalities that are primarily directed towards and treatment of complications. Important advances have been made on the prevention of early death from pneumonia and other infections with early diagnosis and prophylactic antibody therapy. Frequent transfusions have also reduced incidence of recurring cerebrovascular episodes. Concerted efforts are being made to find agents that stimulate fetal hemoglobin synthesis. Hydroxyurea is found to decrease the frequency of painful crisis and hospitalization, and recent studies with butyrates appear to be promising. This program project is a continuation of our research on gene therapy strategies of **sickle cell disease.** It utilizes several approaches to improve the possibility of gene therapy in **sickle cell anemia.** From work of the past project years, we have succeeded in building an improved mouse model of **sickle cell anemia** that may more closely mimic the human condition Because these mice have difficulty in surviving in utero and neonatal period, we are planning various strategies to improve their survival. We also plan experiments to test the in utero delivery of genes, as the liver hematopoiesis in the fetus is accessible. We will test viral vectors using the fetal mice and fetal monkey models. For transplantation of hematopoietic cells in utero or in the neonatal period without cytoabelation of the host, we will explore using the erythropoietin receptor to impart proliferative advantage to donor's

hematopoietic cells. Finally, homologous recombination will be used to correct the sickle mutations. This program project will be supported by four cores, to provide administrative support, stem cells, viral vectors, and mouse breeding for the projects. The University of California at San Francisco has a long standing commitment to **sickle cell anemia** research, patient care, and education. This program project will work closely with the Northern California Comprehensive Sickle Cell Center, now in its twenty-second year of NHLBI funding.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GENE TRANSFER INTO STEM CELLS BY FOAMY VIRUS VECTORS**

  Principal Investigator & Institution: Josephson, Neil C.; Medicine; University of Washington Grant & Contract Services Seattle, Wa 98105

  Timing: Fiscal Year 2002; Project Start 01-APR-2001; Project End 31-DEC-2005

  Summary: (adapted from the application) This research project is designed to provide the applicant, Neil Josephson, with training in the areas of retroviral vector development and gene transfer into hematopoietic stem cells. Dr. Josephson is a board certified hematologist with an interest in stem cell disorders and gene therapy. Stem cell gene therapy offers the promise of treating hereditary disorders such as **sickle cell anemia** and thalassemia. It also may play a role in the therapy of acquired diseases such as cancer and HIV. This promising technology has not yet yielded clinical results because current retroviral vectors do not efficiently transfer genes into hematopoietic stem cells. The work proposed in this application will develop and test a new retroviral gene transfer system based on the human foamy virus (HFV). HFV vectors have many qualities that make them good candidates for use in stem cell gene transfer. They are non-pathogenic, have a wide host range, and can transduce quiescent cells. Aim 1 focuses on vector development. Using currently available HFV vector backbones, new constructs will be generated with a variety of different internal promoters and reporter genes. Current HFV vector production methods rely on transient transfection of vector constructs and yield a crude stock contaminated with toxins. Density centrifugation techniques for purifying HFV stocks will be investigated. To allow for easier and more pure vector production an HFV packaging line will be developed. Aim 2 looks at the ability of HFV vectors to transduce human hematopoietic cells. The impact of multiplicity of infection and length of exposure to vector stock on hematopoietic cell transduction will be explored. The role of cell cycle in transduction efficiency will also be explored. Conditions that are found to most efficiently transduce progenitor cells will be applied to marking studies of human pluripotent repopulating cells in the NOD/SCID xenotransplantation model. Aim 3 outlines work that will take the best HFV vectors produced in aim 1 and the optimal transduction protocols from work in aim 2 and apply them to a pre-clinical marking study of nonhuman primates. Non-human primates are the most biologically similar animal model to humans. Therefore, it is essential to use this model for testing the efficacy and safety of HFV vectors before applying them to clinical studies. Most primates kept in captivity are infected with the simian foamy virus (SFV) which is very similar to HFV. The presence of SFV in HFV vector transduced animals could complicate the interpretation of marking and toxicity results. Therefore, in vitro analysis of HFV effects on SFV will be explored. Transduction protocols from studies in aim 2 will be applied to marking studies of non-human primate hematopoietic progenitor cells. Once optimal transduction protocols have been determined, in vivo transplantation and marking studies will be performed. Marked animals will be followed for the presence of transduced cells by evaluation of reporter

gene expression and proviral copy numbers. Animals will be evaluated for any potential toxic effects of the transduction and transplantation.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GENE TRANSFER TO FETAL AND NEONATAL HSC POPULATIONS**

  Principal Investigator & Institution: Gaensler, Karin L.; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747

  Timing: Fiscal Year 2002; Project Start 01-SEP-2002; Project End 31-AUG-2003

  Summary: Despite intensive efforts to develop effective therapy for **sickle cell anemia** (SCA), this disease continues to be associated with significant morbidity and mortality. SCA affects 0.2% of African American children and young adults. In order for future gene therapy-based strategies for SCA to be successful: 1) transduction of self-renewing stem cells must be highly efficient, 2) transduced cells must have a selective or proliferative advantage, and 3) gene delivery vectors must produce stable, therapeutic levels of globin gene expression over the lifetime of the individual. Our goal is to develop procedures for efficient gene transfer into fetal liver and have already shown that high-level gene expression may be achieved following either intraperitoneal or direct intrahepatic injection of viral or non-viral vectors. We will focus on the transduction of highly proliferative HSC in the murine fetal liver. Our first hypothesis is that direct in utero delivery of gene transfer vectors will result in the transduction of higher numbers of HSCs than can be achieved in vitro, and without disrupting either the microenvironment or biology of these early HSC. We will determine the most efficient vector system for gene transfer into totipotent fetal HSC using MLV- and HIV-based retroviral vectors, and adeno-associated viral vectors. We will focus on the transduction of highly proliferative HSC in the murine fetal liver. Our first hypothesis is that direct in utero delivery of gene transfer vectors will result in the transduction of higher numbers of HSCs than can be achieved in vitro, and without disrupting either the microenvironment or biology of these early HSC. We will determine the most efficient vector system for gene transfer into totipotent fetal HSCs using MLV- and HIV-based retroviral vectors, and adeno-associated viral vectors. Our second hypothesis is that transuterine injection provides an efficient model for rapidly screening novel globin gene vectors. We will deliver human gamma or beta gene expression. The therapeutic efficacy of gamma or beta globin vectors that direct high-level expression of globin will be tested in murine models of beta thalassemia and **sickle cell anemia.** Vectors that produce high-level globin gene expression will reduce red cell sickling and confer a survival advantage of transduced red cells. These studies will also define the fate of transduced hematopoietic stem cells and their progeny during ontogeny.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GENETIC MODIFIERS OF SEVERITY IN SICKLE CELL ANEMIA**

  Principal Investigator & Institution: Platt, Orah S.; Associate Professor of Pediatrics; Children's Hospital (Boston) Boston, Ma 021155737

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 31-JUL-2006

  Summary: (provided by applicant): Despite the fact that all individuals with **sickle cell anemia** (SS) have the identical genetic defect (homozygous beta 6 glu to val), there is a wide variation in clinical severity. While clinicians have long been aware of this variability, it was the epidemiologic data amassed by the NHLBI's Cooperative Study of **Sickle Cell Disease** (CSSCD) that allowed objective measurement of this variability and identification of key risk factors for severity. In this proposal we focus on one of the key

risk factors for severity identified by the CSSCD - baseline white blood cell count (baseline WBC). This initially unanticipated risk factor is becoming more obviously relevant as new investigations into the pathophysiology of the disease increasingly emphasize the importance of white cells and inflammation. At the same time, baseline WBC and other markers of inflammation are emerging as risk factors for mortality in the general population, making the exploration of genetic determinants of baseline WBC of interest not only to the SS population, but also to the population at large. Our strategy for locating the genes that are responsible for the variability in baseline WBC involves three unique populations: inbred strains of mice (Jackson Labs, Bar Harbor), baboon pedigrees (Southwest Foundation for Biomedical Research, San Antonio), and nuclear and extended families of ~300 probands with SS (Boston, Creteil). The animals will be useful in determining quantitative trait loci (QTLs) and ultimately individual genes that influence baseline WBC. The SS probands and their families will allow quantification of the relative importance of genetic and environmental modifiers of baseline WBC in the probands (SS), as well as their normal heterozygous (AS) and unaffected (AA) relatives. Genotyping, and phenotyping using baseline WBC and more specific markers of inflammation (e.g. cytokines, adhesion molecules, hematopoietic growth factors) in these families will allow not only QTL mapping and gene identification, but also an analysis of how genetically interrelated the inflammatory markers are. We anticipate that these studies will provide new insights into the genetics of inflammation that will be of benefit to patients with SS as well as the general population of African heritage. In addition, the data and sample resource we will create is designed to continue to answer questions well beyond the inflammation issue that we focus on in this proposal.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GENETIC MODULATION OF SICKLE CELL ANEMIA**

  Principal Investigator & Institution: Steinberg, Martin H.; Professor of Medicine and Pediatrics; Medicine; Boston University Medical Campus 715 Albany St, 560 Boston, Ma 02118

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 31-JUL-2006

  Summary: (provided by applicant): Endothelial cell genes are likely to be differentially expressed among patients with **sickle cell disease.** Variable expression of selected genes may, by modulating the response of the endothelium to sickle cells, leukocytes, growth factors, chemokines, cytokines, adhesion molecules and hemostasis, account for some heterogeneity of vasoocclusive disease. In addition, polymorphisms in genes expressed in endothelial cells and other tissues may alter gene expression or the gene product. Single nucleotide polymorphisms (SNPs) that segregate with selected features of the disease may mark important genes for further study. We plan a twofold approach to the question of genetic modulation of defined phenotypes of **sickle cell disease.** First, using microarrays containing cDNA of human microvascular endothelial cell expressed genes, we will profile the pattern of gene expression in endothelial cells obtained from patients with **sickle cell anemia** and HbSC disease who have defined phenotypes; we will also ascertain if there is enhanced responsiveness of their endothelial cells to biological stimuli such as TNF , IL1 or LPS. Second, using genomic DNA, we will search for SNPs in genes we hypothesize could play a role in phenotypic heterogeneity of **sickle cell anemia** and in genes whose endothelial cell expression differs in patients with and without designated phenotypes. In the first phase of our SNP studies, we will use banked DNA from more than 2000 patients with **sickle cell disease** who participated in the NHLBI-supported Cooperative Study of **Sickle Cell Disease** and study pooled DNA from patients with defined phenotypes to establish an association between a SNP and a

phenotype. In a second phase, we will confirm positive findings in individual samples from these pools. A third phase will involve a search for SNPs in an independent population of family triads with a **sickle cell disease** proband having a defined phenotype to establish association and linkage of a SNP and phenotype. Our prime objectives are to learn if endothelial cell gene expression or polymorphisms in endothelial cell-expressed genes correlate with phenotypes of **sickle cell disease** and discover SNPs that segregate with defined phenotypes of **sickle cell anemia.** We hope to develop insights into the relationships of endothelial-expressed genes and clinical features of **sickle cell disease** and find SNPs that mark modifiers of disease severity.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GENETIC RISK FACTORS FOR CVA IN CHILDREN WITH HB SS**

  Principal Investigator & Institution: Kutlar, Abdullah; Medicine; Medical College of Georgia 1120 15Th St Augusta, Ga 30912

  Timing: Fiscal Year 2002; Project Start 28-SEP-2001; Project End 31-AUG-2005

  Summary: (provided by applicant): **Sickle cell anemia** is a single gene disorder affecting the beta globin chain of human adult hemoglobin. Varying phenotypic expressions of this disease have led to studies of genetic factors contributing to this diversity. Factors that lead to stroke and the development of cerebrovascular disease in children with **sickle cell disease** are not fully understood. This study will determine if common genetic polymorphisms associated with thrombophilia are important risk factors for the development of cerebrobvascular disease and stroke in these children. The genetic polymorphisms to be studied include MTHFR (methylenetetrahydrofolate reductase) variant (C677T mutation), ACE (angiotensin converting enzyme), ID (insertion/deletion) polymorphism, prothrombin 20210 G to A mutation, and mutations in the Factor V gene (Factor V Leiden, Rsa I polymorphisms; in exon 13 of the factor V gene known as R2 and R3 haplotypes, and Factor V R485K polymorphism). Hb SS patients randomized to the STOP study as well as patients screened in STOP II will provide the basis for this study.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GENETIC THERAPY FOR SICKLE CELL DISEASE**

  Principal Investigator & Institution: Malik, Punam; Assistant Professor of Pediatrics and Pa; University of Southern California 2250 Alcazar Street, Csc-219 Los Angeles, Ca 90033

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 31-MAR-2008

  Summary: Sickle cell anemia (SCA) is characterized by repeated vascular occlusions and hemolysis, primarily resulting from the sickle-shaped RBCs formed under hypoxia. Treatment for the disease is mainly symptomatic. Bone marrow transplantation, a curative modality, is limited to a few with matched donors and has potential side effects. Increasing expression of the "anti-sickling" gamma-globin in the RBCs by long-term administration of hydroxyurea reduces the frequency of sickling events. Gene therapy using the "gamma-globin gene in hematopoietic stem cells (HSCs) can improve the survival of RBCs derived from the genetically modified HSCs permanently. Gene therapy for hemoglobinopathies with onco-retroviral vectors has suffered from problems of vector instability, low titers and variable expression. With the advent of better vectors, improved gene transfer techniques and a better understanding of stem cell and vector biology, gene therapy is going from the bench to the bedside, in disorders like SCID and hemophilia B. The recently developed, lentiviral vectors transduce the non-dividing HSCs and stably export large genomic fragments required

for high-level regulated "globin' gene expression. Self-inactivating (SIN) lentiviral vectors are even more advantageous: the viral long terminal repeat is deleted upon integration into cells, completely inactivating viral transcription, a feature ideal for the expression of a highly lineage-restricted gene, and additionally improves the bio-safety. We have recently shown remarkably lineage-specific and long-term expression of GFP and a therapeutic correction of the murine erythropoietic porphyria in primary and secondary mice with SIN-lentiviral vectors. We would like to extend these results and examine the properties of SIN-lentiviral vectors in carrying the human gamma-globin gene and erythroid regulatory elements for gene transfer into HSCs, resulting in high-level, stable and sustained expression of gamma-globin in RBCs. The aims of the study are: 1) Develop SIN-lentiviral vectors carrying the human y-globin gene and erythroid regulatory elements, and screen them in MEL cells for stable transmission and high-level expression. 2) Determine the efficacy, lineage-specificity and long term expression of these vectors in transgemc sickle mice. 3) Determine gene transfer and efficacy of these vectors in the RBC progeny of human SCA progenitor cells, using the unique model of human RBC production from normal and SCA progenitors developed in our laboratory. Together, these aims comprise a focused research to produce sustained and therapeutic levels of gamma-globin in human SCA RBCs, and form the basis of future preclinical studies.

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- **Project Title: GLOBIN GENE TRANSFER FOR THERAPY OF SICKLE CELL ANEMIA**

  Principal Investigator & Institution: Sadelain, Michel; Associate Professor & Director; Sloan-Kettering Institute for Cancer Res New York, Ny 10021

  Timing: Fiscal Year 2002; Project Start 30-SEP-1996; Project End 31-MAY-2005

  Summary: (Applicant's Description Verbatim): **Sickle cell anemia** is one of the commonest inherited diseases in humans, characterized by a severe chronic hemolytic anemia with an unpredictable course. While current forms of chemotherapy do not represent a radical treatment, the use of bone marrow replacement is limited by complications of allogeneic transplantation and the need for aggressive conditioning regimens. Thus, the goal of this proposal is to develop a treatment for severe hemoglobinopathies that integrates a genetic correction in autologous hematopoietic stem cells (HSC) with a reasonable transplantation strategy. The approach we propose is based on efficient lentiviral-mediated transfer of a wild-type globin gene in cord blood or peripheral blood stem cells, together with a selection for genetically modified cells that is applied in vivo after transplantation. In vivo selection is useful for two purposes: (1) to increase the relative representation of genetically corrected blood cells and (2) to decrease the toxicity associated with the transplantation conditioning regimen. Our recent results establish that efficient gene transfer of a modified beta-globin gene and large elements of the beta-globin LCR can be achieved using recombinant lentiviruses. We have demonstrated that (1) a large LCR greatly increases mean globin expression compared to the core elements of the LCR that were previously investigated and (2) incorporation of an insulator element into a retroviral vector increases the probability of expression at random integration sites and decreases vector silencing. The major goals of this project are: (a) to improve erythroid-specific gene expression from a virally encoded beta-globin transcription unit; (b) to compare the betaAand gammaAglobin genes in terms of their level of expression in bone marrow chimeras and their therapeutic activity in mouse models of **sickle cell disease;** (c) to confer a competitive advantage to the transduced HSC for repopulation of the host marrow using resistance to methotrexate

as a model. We propose a detailed analysis of the function of the LCR and of the chicken globin insulator in stringent in vitro and in vivo assays that are relevant to the critical evaluation of their therapeutic potential. These studies are based on investigations in murine models of **sickle cell disease** and in primary human CD34+ cells of normal subjects and patients. To analyze globin gene expression and the effectiveness of drug resistance in selecting out corrected cells that express therapeutic levels of the globin transgene, we will capitalize on our ability to efficiently derive erythroid progeny from long-term cultured CD34+ cells and our mouse/human xenochimeras based on NOD-scid/scidmice. We ultimately aim to establish by direct experimental evidence that expression of the lentivirus-encoded human globin gene is sustained over time in murine and human cells in vivo and that expression of the mutant dihydrofolate reductase permits efficient in vivo selection with methotrexate/trimetrexate.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GLUTATHIONE HOMEOSTASIS IN SICKLE CELL DISEASE**

  Principal Investigator & Institution: Jahoor, Farook; Professor; Pediatrics; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

  Timing: Fiscal Year 2002; Project Start 01-JUN-2001; Project End 31-MAY-2004

  Summary: Homozygous **sickle cell disease** (HbSS) is characterized by increased hemolytic rate of "sickle shaped" erythrocytes. In addition, individuals with HbSS also have lower erythrocyte concentrations of the endogenously produced antioxidant glutathione (GSH), suggesting that they have impaired antioxidant capacity. It has been proposed that the generation of superoxide free radical by hemichromes, iron atoms and released haem groups, leads to peroxidation of the erythrocyte lipid membrane, which contributes to the sickling process. However, the extent to which antioxidant capacity is actually impaired, the mechanism(s) underlying such an impairment, and the relationships to oxidant damage and to the degree of in vivo sickling in HbSS have not been determined. The research proposed addresses the following hypotheses: i) HbSS subjects have lower erythrocyte GSH concentrations than control subjects because they synthesize GSH at a slower rate. ii) The slower rate of GSH synthesis is due to reduced availability of glycine and cysteine because of slower de novo synthesis of these two amino acids. iii) Supplementing the diets of the HbSS subjects with either cysteine, glycine, or cysteine plus glycine will stimulate GSH synthesis to a higher rate than its rate of consumption thereby replenishing the GSH pool size. iv) The higher oxidative load of the HbSS subject is directly related to the decreased synthesis and availability of GSH, hence stimulation of GSH synthesis rate will result in a decreased oxidative stress. Using biochemical and stable isotope tracer methods, these hypotheses will be tested in 32 subjects with HbSS and 8 control subjects matched for age, gender and usual dietary intakes. The experimental protocol will determine differences in 1) the rates of synthesis of erythrocyte GSH, cysteine and glycine, 2) whole body protein breakdown rate, 3) the plasma concentrations of lipid hydroperoxides, 4) the resistance of erythrocyte to oxidative stress at baseline and after a 4 weeks of dietary supplementation. The data obtained will provide insight into the relationship between oxidant capacity and sickling and whether dietary intervention can improve the metabolic status of subjects with HbSS.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HEMOSTASIS**

  Principal Investigator & Institution: Bach, Ronald; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

Timing: Fiscal Year 2002; Project Start 01-APR-2002; Project End 31-MAR-2003

Summary: This abstract is not available.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HOMOCYSTEINE AND COAGULATION IN SICKLE CELL DISEASE**

  Principal Investigator & Institution: Balasa, Vinod; Children's Hospital Med Ctr (Cincinnati) 3333 Burnet Ave Cincinnati, Oh 45229

  Timing: Fiscal Year 2003; Project Start 11-JUL-2003; Project End 31-MAR-2008

  Summary: The coagulation system and endothelial cells are believed to contribute to the vascular pathology of **sickle cell disease** (SCD). Elevated plasma homocysteine (Hcy) is associated with vascular disease and thrombosis in the general population and is believed to induce endothelial cell dysfunction and activate the coagulation system. Patients with SCD exhibit activation of coagulation and an increase in activated circulating endothelial cells (CEC). Preliminary data demonstrate that hyperhomocysteinemia (HHcy) is present in 38% of patients with SCD and that a majority (62%) of these individuals have pyridoxine deficiency, compared to race and age-matched controls. It is hypothesized that HHcy is associated with activation of coagulation and CEC in SCD and that a lowering of Hcy with pyridoxine supplementation will reduce this activation. Therefore, the aims of this study are to determine the following in patients with SCD: (1) prevalence of HHcy and its association with vitamin cofactor deficiencies (2) correlation of HHcy with activation of CEC and coagulation (3) responsiveness of HHcy to pyridoxine supplementation (4) correlation of a decrease in Hcy levels with reduction in the activation of CEC and coagulation. The following laboratory determinations will be made in patients with SCD and in race and age-matched controls: fasting and post-methionine load Hcy, levels of red cell folate, serum vitamin B12, pyridoxal 5'-phosphate, the C677T MTHFR genotype; markers of activation of coagulation (prothrombin fragment 1.2, thrombin:antithrombin complexes), and fibrinolysis (plasmin:antiplasmin complexes, D-dimer); enumeration of CECs and the presence of activation markers VCAM-1 and tissue factor on CECs. SCD patients with HHcy will be randomized to receive a 6-week trial of pyridoxine supplementation or placebo and levels of Hcy, pyridoxine, and determination of markers of activation of coagulation and CECs will be repeated. This study is a collaborative trial open to all the sickle cell centers and at least 248 SCD patients and 248 controls will be recruited. Hey levels will be regressed on age in the controls and 95% confidence intervals will be determined. The chi-square statistic will be used to test the difference. Linear regression will be used to determine the relationship between Hcy and the activation markers. Paired t-tests will be used to test the other hypotheses. Pyridoxine supplementation is a simple therapy with the potential to reduce thrombotic complications of **sickle cell disease.**

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HUMAN GLOBIN GENE TRANSFER AND EXPRESSION**

  Principal Investigator & Institution: Bank, Arthur; Professor; Genetics and Development; Columbia University Health Sciences New York, Ny 10032

  Timing: Fiscal Year 2002; Project Start 01-APR-1998; Project End 31-MAR-2003

  Summary: The long-term goal of the project is to ameliorate or cure **sickle cell disease** and beta-thalassemia (thal) by retroviral gene transfer of normally functioning human beta or gamma globin genes into the hematopoietic progenitor cells (HPC) including stem cells of patients with these disorders. Retroviral vectors containing these globin

genes and their control elements such as the locus control region (LCR) will be used to transduce human HPC from bone marrow or peripheral blood progenitor cell (PBPC) harvests. Ultimately, the goal is to cure the patients by autotransplantation by harvesting of HPC from patients with **sickle cell disease** and beta-thal, transducing these cells to restore high level gamma- or beta-globin expression, and then re-infusing the gene-corrected cells back into the patients. Progress has been made over the past five years in 1) the construction of beta and gamma globin gene containing retroviral vectors that are stably transmitted into target murine HPC; and 2) the conditions or transferring and expressing human genes such as the human multiple drug resistance (MDR) gene in murine and human HPC. In studies in this grant, improved human globin gene containing vectors will be constructed and tested in murine and human HPC, and more efficient methods of transferring and expressing these genes while maintaining their long-term repopulating ability will be explored. These methods will include the use of long-term marrow culture, and purified HPC with stroma and/or new growth factor combinations. In addition, the human MDR CDNA will be added to globin gene containing vectors to provide a selectable marker that can be used to enrich for globin gene transduced HPC in vitro and in vivo. Conditions which favor the engraftment and expression of globin gene transduced HPC without marrow ablation in murine models of **sickle cell disease** and beta-thal will be sought as well. Lastly, when the PI has obtained appropriate human globin gene containing vectors and culture conditions for their transduction and expression in murine and human HPC, we plan to design and initiate phase 1 clinical trials in sickle cell and beta-thal patients to test the safety and efficacy of retroviral globin gene transfer as an approach to the treatment of these disorders.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: IN VIVO SICKLE CELL VASOOCCLUSION: ADHESION MECHANISMS**

  Principal Investigator & Institution: Frenette, Paul S.; Assistant Professor; Medicine; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 10029

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 31-JUL-2005

  Summary: (provided by applicant): The overall objective of this proposal is to understand the adhesive mechanisms mediating vaso-occlusion in **sickle cell disease.** Although several studies have documented roles for a number of adhesion molecules in sickle cell adhesion in vitro, there is very little in vivo data. The recent development of a mouse strain that exclusively expresses human globins provides us with the opportunity to study the adhesive mechanisms in vivo using intravital microscopy. Our preliminary studies indicate that cytokine-induced inflammation produces severe vasoocclusion in post-capillary venules in the cremaster muscle of sickle cell mice. Our results indicate that adherent leukocytes play a key role in this process since they can bind circulating sickle cell erythrocytes (SS RBCs) and initiate venular occlusion. Endothelial selectin-deficient mice, which display defects in leukocyte recruitment in venules, show few SS RBC-leukocyte interactions and no vasooclusion. In this proposal, we wish to further investigate the hypothesis that vasooclusion in **sickle cell disease** is initiated by the adhesive interaction between SS RBCs and adherent leukocytes. In specific aim I, we will identify the type of leukocyte (mononuclear vs polymorphonuclear) that interacts with SS RBCs in vivo, and we will further evaluate the roles of leukocyte and endothelial adhesion molecules in vasoocclusion using adhesion molecule knockout mice and inhibitory antibodies; we will also develop a model to investigate vasoocclusion in the bone marrow microvasculature, an important

target in **sickle cell disease.** In specific aim II, we will develop adhesion assays to dissect the molecular mechanisms mediating SS RBC-leukocyte interactions and, in parallel, we will conduct intravital experiments to confirm putative adhesion pathways. In specific aim III, we propose to evaluate the in vivo functions of three adhesion molecules previously shown to participate in sickle cell adhesion (von Willebrand factor, beta3 integrins and thrombospondin), using adhesion molecule knockout mice and sickle cell animals. The proposed studies should shed new light on the in vivo mechanisms of sickle cell vasoocclusion and may lead to novel ways to treat sickle cell crises and other complications of this disease.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INCREASING GAMMA GLOBIN EXPRESSION IN SICKLE CELL DISEAS**

  Principal Investigator & Institution: Blobel, Gerd A.; Associate Professor; Children's Hospital of Philadelphia 34Th St and Civic Ctr Blvd Philadelphia, Pa 19104

  Timing: Fiscal Year 2003; Project Start 22-JUL-2003; Project End 31-MAR-2008

  Summary: Sickle cell disease is caused by a point mutation in the beta-globin gene. Under hypoxic conditions, hemoglobin containing mutant beta-globin protein (HbS) forms insoluble polymers, leading to defects in red cell shape, flexibility and adhesion. Elevated levels of gamma-globin reduce hemoglobin polymerization and improve the clinical manifestation of the disease. Therefore, treatment of patients is aimed at raising expression of the gamma globin gene, which is normally silent in adult life. This application proposes to explore two approaches to raise gamma-globin levels. Specific Aim I focuses on the use of synthetic DNA ligands, called polyamides, to raise the gamma to beta-globin ratio. Polyamides are low molecular weight, cell permeable polymers consisting of pyrrole and imidazole derivatives that bind to predetermined DNA sequences with specificities and affinities approaching those of natural DNA binding proteins. In collaboration with Dr. Peter Dervan whose laboratory is at the forefront in developing polyamides, we synthesized and purified several polyamides designed to inhibit transcription factor binding to essential regulatory sites in the b-globin gene promoter. We will examine these polyamides in primary human bone marrow and umbilical cord erythroid cells for their effectiveness in inhibiting beta-globin expression in vivo. In addition, we will design new polyamides with the goal to activate gamma globin gene expression directlv. Studies in Specific Aim II will test a novel viral vector for its capacity to express a transgene in a fashion that is resistant to gene silencing. One major limitation of viral vectors is that they are often subject to gene silencing, especially in hematopoietic (HS) and embryonic stem (ES) cells and their differentiated progeny. Virally induced gene silencing is associated with deacetylation of histones, and treatment of cells with deacetvlase inhibitors leads to reactivation of viral gene expression. We have produced a viral vector that contains a modified histone acetyltransferase that binds specifically to the viral DNA sequence. The proposed studies wil! test this vector's ability to express a transgene at high levels and in a fashion resistant to gene silencing in HS and ES cells. The long term goal of this Specific Aim is to use this vector for gamma-globin gene expression in HS cells of test animals and ultimately patients with **sickle cell disease.**

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INDUCTION OF STABLE CHIMERISM FOR SICKLE CELL ANEMIA**

  Principal Investigator & Institution: Walters, Mark C.; Director; Children's Hospital & Res Ctr at Oakland Research Center at Oakland Oakland, Ca 94609

Timing: Fiscal Year 2002; Project Start 25-AUG-2001; Project End 31-JUL-2005

Summary: Hematopoietic cell transplantation (HCT) has curative potential for individuals with **sickle cell disease.** While the results of conventional HCT have been good, this treatment carries risks of significant short- term and longterm toxicities. For this reason, HCT has been reserved for children who have experienced severe symptoms that predict a poor outcome. Of interest, some patients developed stable donor-host hematopoietic chimerism after conventional HCT. Due to a natural enrichment of donor erythrocytes in the blood, those who developed stable chimerism had a significant clinical benefit, even when there was a minority of donor cells. These observations have paralleled efforts to develop less-toxic, non-myeloablative preparative regiments for transplantation, proved first in a canine model of transplantation, and subsequently translated successfully in a clinical trial for older adults with hematological malignancies. Thus, this proposal, based on these supporting pre-clinical and clinical investigations, aims to investigate a modified transplant procedure for **sickle cell disease** that significantly reduces the toxicity of HCT, yet retains its therapeutic benefit. This is a novel approach, conducted in the outpatient setting, which will rely upon the ability to establish and maintain donorhost chimerism. It will be achieved by combining less toxic, non-myeloablative pre-transplant therapy with modulated post-grafting immuno-suppression aimed at controlling host-versus-graft and graft-versus-host reactions. This investigation will employ an existing network of collaborative sickle cell and transplant centers to identify and enroll eligible patients. The primary endpoint of stable donor cell engraftment will be determined and secondary endpoints to measure the impact on sickle cell-related symptoms and end-organ damage will be followed. If successful, this novel approach will expand the availability of HCT for patients with clinically significant hemoglobinopathies.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INFLAMMATION IN SICKLE DISEASE**

  Principal Investigator & Institution: Vercellotti, Gregory M.; Senior Associate Dean for Education; Medicine; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2002; Project Start 01-APR-2001; Project End 31-MAR-2005

  Summary: (Investigator's abstract) **Sickle cell anemia** patients suffer end organ damage due to vaso-occlusion. Over the past two decades investigations of red blood cell/vessel wall interactions have led to a revised paradigm for the understanding of vaso-occlusive phenomena in **sickle cell disease.** Clinical conditions associated with inflammation such as infections, surgery and others exacerbate crises in **sickle cell anemia** patients. Preliminary data demonstrate that patients with **sickle cell disease** have markers of inflammation including elevated C-reactive protein levels and activated monocytes. In vitro these monocytes activate human endothelial cell NF-kB and adhesion molecule expression. Transgenic mouse models of human **sickle cell disease** also have markers of inflammation, including elevated white blood cell counts and activated monocytes. This proposal posits that an inflammatory phenotype augments tissue injury through worsened vasoocclusion. Thus, inflammation augments vaso-occlusion while anti-inflammatory agents may minimize vaso-occlusion. The project will examine these hypotheses in transgenic mouse models of human sickle cell disease: (1) Anti-inflammatory agents decrease vascular inflammation and improve blood flow. (2) Pro-inflammatory agents such as murine cytomegalovirus, lipopolysaccharide and hypoxia/reoxygenation, increase vascular inflammation and worsen vaso-occlusion. (3) TNF-alpha, IL-1 beta and CD18 transgenic knockout mice that express human betaS

hemoglobin have decreased vascular inflammation and improved blood flow parameters. These studies will provide information for understanding the role of the inflammatory response and its relationship to vaso-occlusion in **sickle cell disease** and serve as an important foundation for developing new and novel therapies to prevent organ dysfunction.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INFLAMMATORY CONTROL OF ERYTHROPOIESIS IN SICKLE DISEASE**

  Principal Investigator & Institution: Means, Robert T.; Medicine; Medical University of South Carolina 171 Ashley Ave Charleston, Sc 29425

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 31-JUL-2005

  Summary: (provided by applicant): The anemia of chronic disease (ACD) is one of the most common hematologic syndromes encountered in clinical medicine. Over the last decade, studies have clearly established that ACD is a consequence of the cytokines which mediate the immune and inflammatory process. In contrast, **sickle cell anemia** is the result of a genetic defect producing a single amino acid change which alters the solubility of deoxygenated hemoglobin. Over the same period of time, it has become recognized that the clinical manifestations of the sickle syndromes result from a constellation of processes, including activation of inflammation. A heightened inflammatory state with consequent cytokine production can be demonstrated in patients with **sickle cell disease.** However, the unique characteristics of the sickle erythrocyte (including the persistent expression of CD36) alter the characteristics of the erythroid response to cytokines. Review of the literature suggests that CD36 persistence at high levels is unique to sickle erythrocytes, and contributes to their adhesive properties. In our preliminary data, we have demonstrated that CD36 is a positive regulator of erythropoiesis. As discussed above, the cytokine mediators of the inflammatory response produce ACD, and similar mechanisms can be implicated in sickle disease. Based on data in the literature and on our preliminary results reported below, it is hypothesized that CD36 expression protects sickle erythroid progenitors against cytokine suppression, and that those progenitors which persistently express CD36 have a selective growth advantage in the presence of inhibitory cytokines. This would result in the preferential production of CD36-expressing erythrocytes, which are then more likely to participate in intravascular adhesion. The cytokines involved in the inflammatory response would therefore enhance the frequency of vascular sickling events by increasing the frequency of potentially adherent erythrocytes. This hypothesis will be tested through the following Specific Aims: Specific Aim 1 will identify the differences in CD36 expression between progenitors from sickle cell patients and precursors, and those from controls. In Specific Aim 2, the differences in sensitivity to cytokine inhibition between sickle and control CFU-E, and the extent to which these differences can be attributed to differences in CD36 expression, will be defined. In Specific Aim 3, FA6-152will be used to characterize the response of CFU-E from sickle patients to CD36 activation, and to determine how CD36 activation alters the pattern of progenitor suppression by inhibitory cytokines, as well as the contribution of rhEPO to these processes; and Specific Aim 4 will characterize local cytokine production in the marrow of sickle cell patients, and how it relates to erythroid CD36 expression and to clinical phenotype.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INTRACELLLAR PATHWAYS THAT SILENCE THE FETAL GLOBIN GENE**

  Principal Investigator & Institution: Ikuta, Tohru; Human Genetics; Boston University Medical Campus 715 Albany St, 560 Boston, Ma 02118

  Timing: Fiscal Year 2003; Project Start 07-APR-2003; Project End 31-MAR-2007

  Summary: (provided by applicant): Considerable concerns and efforts have been directed to the development of new fetal hemoglobin (Hb F) inducers. Hydroxyurea (HU) is being used for treating **sickle cell anemia** (SCA), but the magnitude of response to HU significantly varies between SCA patients. The clinical efficacy of HU for beta-thalassemia remains unclear. Rather than studying cis-acting regulatory elements, our research has been focusing on clarifying intracellular pathways that regulate globin gene expression. We recently showed that an intracellular pathway comprising soluble guanylate cyclase (sGC) and cGMP-dependent protein kinase (PKG) plays an important role in gamma-globin gene expression in primary erythroblasts. Our hypothesis that the sGC-PKG pathway plays an important role in Hb F expression was recently substantiated by a discovery of Italian brothers who have no mutations in beta-globin locus but express 25 to 30 % Hb F. They were found to have high levels of protoporphyrin IX, which is a strong activator of sGC. To study "with fresh eyes" the molecular mechanisms for gamma-globin gene silencing, we were concerned with a phenomenon that expression of the gamma- and beta-globin genes is regulated "in a reciprocal manner" at the perinatal period. This has led us to speculate that the gamma-globin gene is silenced in the adult stage by the mechanisms required for activating the beta-globin gene. We will test this hypothesis in this application. Our preliminary studies suggested that 1) cAMP-dependent protein kinase (PKA) activity is necessary for the induction of the beta-globin gene in adult erythroid cells such as MEL cells and primary erythroblasts, that 2) expression of the gamma-globin gene is decreased by activating cAMP-dependent pathways in K562 cells, and that 3) activity of HS2 and a gamma-globin gene promoter is markedly increased by suppressing PKA activity. These results suggest that cAMP-dependent pathways might play a negative role in gamma-globin gene expression. This application has three specific aims. In the first aim, we will characterize intracellular pathways that are required for activating beta-globin gene expression. The second aim will focus on the molecular mechanisms by which intracellular pathways for beta-globin gene expression silence the gamma-globin gene, In the third aim, we will examine whether expression of the gamma-globin gene is induced in primary erythroblasts of the beta-globin disorders and adult mice which have low activities of intracellular pathways for beta-globin gene expression. This application should not only shed much light on the mechanisms that silence the gamma-globin gene, but also provide a clue to the mechanisms underlying the developmental regulation of beta-like globin genes. Furthermore, important information to develop novel Hb F inducers will be disclosed by this study.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: LIVE MICROSCOPY AND CYTOMETRY IN VASCULAR BIOLOGY**

  Principal Investigator & Institution: Lin, Charles P.; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2002; Project Start 01-SEP-2002; Project End 31-AUG-2007

  Summary: (provided by applicant): This is a multidisciplinary, collaborative research program bringing together investigators from several institutions to work across technology and disciplinary boundaries. The group shares a common interest in

vascular biology, particularly in the eye, and specifically in the application of modern optical technology to answer critical questions related to vascular biology. The technology platform will be based on the scanning laser ophthalmoscope and the real-time in vivo confocal microscope previously developed at Schepens Eye Research Institute and at the Wellman Laboratories of Photomedicine. The existing technology will be enhanced with new development to improve image resolution, contrast, sensitivity, methods for quantification, and flexibility of imaging in living animals. Specific questions to be addressed include: 1. What are the cellular processes governing normal vascular development and stabilization? 2. What are the factors governing angiogenesis, Iymphangiogenesis, and immune cell trafficking? 3. What are the cellular mechanisms for the development of sickle cell and diabetic retinopathy? 4. Can we visualize early changes in the retinal pigment epithelium noninvasively in vivo? 5. Can we detect circulating cells in vivo without drawing blood? Is the number of circulating tumor cells a good predictor for tumor burden and response to therapy? Imaging at the cellular level will enable biologists to study problems in living animals over time, gaining physiological insights beyond what can be obtained by classic static measurement (histology, immunocytochemistry, etc.), substantially reducing the number of animals required to answer these critical questions.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MIXED CHIMERISM TO TREAT SICKLE CELL DISEASE**

  Principal Investigator & Institution: Ildstad, Suzanne T.; Director; None; University of Louisville University of Louisville Louisville, Ky 40292

  Timing: Fiscal Year 2002; Project Start 16-AUG-1999; Project End 31-JUL-2004

  Summary: Sickle cell disease (SCD) is one of the most frequent of inherited hemoglobinopathies. Although the genetics and pathophysiology of the disease are well characterized, it was recently described as a "simple disease with no cure". Three percent of all African-Americans have SCD. Fifteen percent of patients die by age 20 and 50 percent by age 40. Bone marrow transplantation (BMT) has been demonstrated to cure SCD. However, the morbidity and mortality associated with conventional BMT, especially graft versus host disease (GVHD) and lethal conditioning, have limited the widespread application of BMT to treat SCD. Only 20 percent of patients with SCD have an HLA-identical family member donor. For the remainder of patients who do not have a matched family member donor, a substantial risk for GVHD exists, since the incidence and severity of GVHD is directly correlated with the degree of genetic disparity between donor and recipient. It would be of significant impact if a nonlethal approach to achieve a mixed chimeric state in patients with SCD, with partial replacement of the defective RBC, could be achieved without substantial risk of GVHD. This study addresses the problems of (1) high toxicity; (2) fear of early mortality; and (3) lack of suitably matched donors, using a new approach to BMT. The goal is to reverse the risk/benefit ratio for BMT for patients with SCD. A novel donor bone-marrow-derived cell, separate from the hematopoietic stem cell (HSC), has been identified that facilitates engraftment of purified donor HSC in allogeneic recipients without producing GVHD. Because BMT has been demonstrated to cure SCD when an HLA-identical sibling donor is available, in AIM I we will APPLY THE FACILITATING CELL PROTOCOL TO CONVENTIONAL BMT FOR **SICKLE CELL DISEASE.** By processing the marrow to remove all undesired cells, we hope to enhance engraftment and avoid GVHD. In AIM II we will ESTABLISH A PARTIAL CONDITIONING APPROACH To MIXED CHIMERISM IN CHILDREN WITH **SICKLE CELL DISEASE** WHO DO NOT HAVE A SUITABLY MATCHED DONOR. We will MONITOR CHIMERISM AND

IMMUNOLOGIC RECONSTITUTION in both cohorts of patients (AIM III). SCID is a chronic ailment with significant morbidity including painful crises, bacterial infections, missed school or work days, and frequent hospitalizations. In AIM IV, we will ASSESS QUALITY OF LIFE in patients who engraft as chimeras. Our overall objective is to apply BMT to treat SCD, yet avoid the morbidity and mortality of lethal conditioning, GVHD, and lack of suitably matched donors.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MOLECULAR CONTROL OF FETAL G-GLOBIN GENE EXPRESSION**

  Principal Investigator & Institution: Peterson, Kenneth R.; Associate Professor; Biochem and Molecular Biology; University of Kansas Medical Center Msn 1039 Kansas City, Ks 66160

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 31-JUL-2005

  Summary: (provided by applicant) Developmental regulation of human beta-like globin gene switching is controlled by several parameters, primarily the trans-acting transcriptional milieu and cis-acting DNA elements. Molecular control of globin gene switching provides a paradigm for understanding the dynamics of mammalian gene expression during ontogeny. Unraveling the mechanisms underlying beta-like globin gene switching, particularly those involved in fetal hemoglobin F (Hb F) induction, will have enormous benefit to patients suffering from a variety of hemoglobinopathies, since the general consensus within the scientific community is that sustained expression of the gamma-globin genes in adults will be palliative to these diseases. Transactivation of fetal gamma-globin gene expression has important therapeutic application for the treatment of **sickle cell anemia** and Cooley's anemia, as well as certain beta-thalassemias. The Specific Aims of this research are to (1) validate the fetal specificity of already identified trans-acting proteins that activate fetal globin synthesis using novel erythroid cell lines derived from human beta-globin locus yeast artificial chromosome (beta-YAC) transgenic mice, (2) verify the fetal specificity of the same transactivators during development in an animal model by over-expression of these proteins in beta-YAC transgenic mice, (3) develop an assay system to identify new, or test existing, pharmacologic compounds that induct fetal gamma-globin gene expression without activating adult beta-globin gene expression using simultaneous measurement of both globin gene products, and (4) clone new transcriptional activators of gamma- globin gene expression from human fetal liver or GM 979 cell cDNA libraries.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MOLECULAR MECHANISM OF HUMAN G-GLOBIN GENE SILENCING**

  Principal Investigator & Institution: Li, Qiliang; Medicine; University of Washington Grant & Contract Services Seattle, Wa 98105

  Timing: Fiscal Year 2003; Project Start 01-APR-2003; Project End 31-MAR-2007

  Summary: (provided by applicant): The goals of this research application are a) to test the hypothesis that the variable human gamma-globin gene silencing in the adult is the consequence of a dynamic equilibrium between euchromatin originating in the LCR and heterochromatin originating in the gamma gene promoter, b) to identify gamma-globin gene specific repressors and corepressors. Our specific aims are i) To test the hypothesis that the gamma gene silencing in the adult is the consequence of a dynamic balance between euchromatin originating in the LCR and heterochromatin originating in the gamma gene promoter. This will be tested in transgenic mice carrying the human beta-

globin locus yeast artificial chromosome (betaYAC) and various mutated betaYACs by examining changes of the histone code specific for heterochromatin and euchromatin. This hypothesis can be validated if changes of the histone code are correlated with the phenotypes induced by the various mutations, ii) To test whether the gammaCACCC box causes heterochromatinization in the gamma gene promoter in the adult. This will be done by relocating the gammaCACCC box in the different locations in the beta-globin locus and examining formation of heterochromatin induced by the gammaCACCC box. iii) To develop an oligonucleotide-mediated chromatin immunoprecipitation approach and using this approach to search for gamma gene specific repressors/corepressors. It is expected that these studies will lead to a unifying model explaining variable silencing of human gamma-globin gene in the adult, and will identify gamma gene specific repressors/corepressors. These studies will facilitate designing of a feasible strategy for human gamma-globin gene reactivation. Such a development will have important consequences for the treatment of patients with **sickle cell disease** or beta thalassemia syndromes.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MOLECULAR MECHANISM OF TRANSDUCING CARDIAC ISCHEMIC PAIN**

  Principal Investigator & Institution: Mc Cleskey, Edwin W.; Senior Scientist/Professor; None; Oregon Health & Science University Portland, or 972393098

  Timing: Fiscal Year 2002; Project Start 01-JUN-2001; Project End 31-MAY-2006

  Summary: provided by applicant) Sensory neurons that innervate the heart (cardiac afferents) detect cardiac ischemia, the condition when the heart receives insufficient oxygen. They trigger chest pain-either the acute pain of a heart attack or angina, an intermittent pain caused by coronary artery disease. They also contribute to damaging cardiac reflexes that accompany artery disease. Although it is clear that cardiac afferents transduce cardiac pain, the molecular mechanism(s) is uncertain. The driving hypothesis of this proposal is that cardiac ischemia releases a set of chemical mediators that activate ion channels and receptors on cardiac afferents, thereby triggering pain. The proposal relies heavily on a novel method we developed to fluorescently tag cardiac afferents so they can be distinguished from other kinds of sensory neurons. This is an essential step for identifying molecules that are necessary for cardiac pain but not for other sensations. Our initial work fmds that cardiac afferents have a unique molecular fmgerprint: they express an extremely Sensitive acid-sensing ion channel at grossly high levels. The result underscores the importance of protons created during ischemia as a mediator of cardiac pain. Our specific aims will: 1) definitively identify the particular clone of acid-sensing ion channel used by cardiac afferents; 2) fmd whether other putative mediators of cardiac pain act by modulating this channel; 3) explore why there is different expression of channels in the two different populations of cardiac afferents. The experimental methods are single cell electrophysiology and immunocytochemistry. The clinical significance of the project lies in the suppression of angina, which is suffered by some 6 million Americans, is debilitating in some, and which triggers damaging cardiac reflexes in all. The results might also be relevant to other forms of vaso-oclusive pain, notably that of **sickle cell anemia.** We will identify molecules that trigger cardiac pain, thereby providing new pharmaceutical targets for its treatment.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MOUSE MODEL FOR SICKLE CELL DISEASE & GENETIC THERAPIES**

  Principal Investigator & Institution: Townes, Tim M.; Professor and Chairman; Biochem & Molecular Genetics; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

  Timing: Fiscal Year 2002; Project Start 30-SEP-1996; Project End 31-AUG-2004

  Summary: (Investigator's abstract) This is the competitive renewal of a grant funded approximately three years ago to develop a mouse model of **sickle cell disease.** During the funding period we produced transgenic mice that switch from human fetal hemoglobin to human sickle hemoglobin around three weeks after birth. These animals were bred with our beta-thalassemic mice containing a knockout mutation of the beta-maj and beta-min globin genes and with Paszty et al's alpha-thalassemic mice containing a knockout mutation of the alphal and alpha2 globin genes. The resulting animals synthesize only human hemoglobin in adult red blood cells. Similar to many human patients with **sickle cell disease,** the mice develop a severe hemolytic anemia and extensive organ pathology. Numerous sickled erythrocytes are observed in peripheral blood. Although chronically anemic, most animals survive for 2 to 9 months and are fertile. We now propose to correct **sickle cell disease** in these mice by transduction of hematopoietic stem cells with viral vectors containing anti-sickling genes under control of human beta-globin Locus Control Region (LCR) sequences. One limitation in this strategy has been the inefficiency of transduction into quiescent stem cells. We have now demonstrated that Sca-1+, c-Kit+, Lin- bone marrow stem cells that are isolated without cytokine prestimulation are efficiently transduced with modified lentiviral vectors carrying a GFP gene. The transduced cells fully reconstitute hematopoiesis in lethally irradiated mice and 10-15 percent of all cell lineages examined express GFP after 3 months. These results suggest that quiescent, hematopoietic stem cells are efficiently transduced by lentiviral vectors and that infection does not impair self renewal and lineage specification in stem cells which mediate long term reconstitution of lethally irradiated animals. Since the life span of sickle red cells is significantly shorter than normal., we speculate that correction of 10-15 percent of erythroid precursors in the marrow will translate to a major fraction in the peripheral blood because genetically corrected erythrocytes have a selective survival advantage. The anti-sickling gene we have developed will significantly reduce morbidity and mortality if the gene is expressed at 10 percent of betaS. If expression of the transduced gene is low, we propose to introduce a modified transcription factor (delta-EKLF) that will efficiently activate the human delta-globin gene. We have demonstrated that low levels of a modified EKLF activate the delta-globin gene at high levels, and HbA2 (alpha2 delta2) has powerful anti-sickling properties.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: NEWBORN SCREENING BY MULTIPLEX MOLECULAR ANALYSIS**

  Principal Investigator & Institution: Naylor, Edwin W.; Neo Gen Screening, Inc. Box 219, Abele Business Park Bridgeville, Pa 15017

  Timing: Fiscal Year 2002; Project Start 01-MAR-1999; Project End 31-MAR-2003

  Summary: (Scanned from the Applicant's Description): A primary newborn screening protocol based on multiplex PCR and analysis of PCR products by low-density oligonucleotide arrays is being developed. The assay is based on DNA obtained from the universally collected neonatal blood card. The following disorders are detected through analysis of their common mutations: 1). Sickle Cell Hemoglobinopathy S allele

(A173T), C allele (G172A), and E allele (G232A); 2). Heriditary Hemochromatosis G845A and C187G; 3). Alpha-1-Antitrypsin Deficiency Z allele (G9989a) and S allele (A7677T); 4). Hereditary Thrombophilia (Factor V Leiden G1691A, Prothrombin G20210A, Methylenetetrahydrofolate reductase C677T); 5). MELAS Syndrome A3243G; 6) Long Chain 3-hydroxy Acyl Co-A Dehydrogenase Deficiency T919C, C1024T, G1528C, C1570T, 675insC, IVS3 +1 G>A,VVS3 +3 A>G; 7)Nephropathic cystinosis 63 kb del, G753A, 357-360 delGACT, 537-557 del 21 bp, 1035 incC, G1261A, G1354A. Automation and/or multiplexing is employed at every stage from punching blood spots to data reduction, enabling a primary molecular system suitable for population screening and economically viable for the laboratory. The assay expands the number of disorders detected by newborn screening thus providing an improved public health service. PROPOSED COMMERCIAL APPLICATION: Not Available

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: NINTH ANNUAL OXYGEN SOCIETY MEETING**

  Principal Investigator & Institution: Grisham, Matthew B.; Professor; Molecular and Cellular Physio; Louisiana State Univ Hsc Shreveport P. O. Box 33932 Shreveport, La 71103

  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-AUG-2003

  Summary: (provided by applicant): We request partial funding for the 9th Annual Meeting of the Oxygen Society to be held on Nov 20-24, 2002 at the San Antonio Marriott Rivercenter, San Antonio, TX. Funds will support the travel, lodging and registration fees of invited speakers so that funds from The Oxygen Society operating budget and annual meeting income can be directed toward supporting the travel and participation of students, fellows and young investigators, as well as members lecturing in an optional workshop on "Back to the Basics: Measurement of reactive oxygen and nitrogen species and their biological effects". This workshop will provide lectures by experts to young or new investigators on the concepts, approaches, interpretations and various techniques applied in quantification of reactants and products of oxidant/free radical-mediated reactions in vitro and in vivo. The body of the meeting will then begin for four days, with four invited plenary lectures delivered in the morning and two parallel afternoon sessions. The themes of the four invited plenary lectures in the morning are: Reactive Oxygen and Nitrogen Species in **Sickle Cell Disease,** Free Radicals and the Biology of Aging, Biological and Antioxidant Activities of Flavanoids, and Nitrative Stress and Neurodegeneration. The lectures delivered in the afternoon sessions will be selected from abstracts submitted at large by members of the Program Committee. Each afternoon session will be chaired by selected young investigators in the field. From 8-9:30 am, The Sunrise Free Radical School, a distinct characteristic of the Oxygen Society Meeting, will be held each day featuring senior scientists or experts in the field addressing fundamental aspects of free radical chemistry and biology to an audience consisting of students, fellows and young investigators. Poster sessions will be displayed all day and will be open for discussion between 4:30-6:30 pm. Overall, sessions will address a broad range of research endeavors surrounding the diverse roles that reactive oxygen and nitrogen species play in biology and disease. Research presented will have an impact on our understanding of aging as well as cardiovascular, neoplastic, inflammatory and neurodegenerative diseases and may provide new insight into mechanisms by which novel antioxidants and therapeutics may attenuate some of these diseases. In summary, the conference provides a forum for exchange of recent basic and applied research on free radical chemistry, biology & medicine as well as an opportunity for scientists to discuss new collaborative arrangements.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: NITRIC OXIDE DIFFUSION AND REACTION WITH ERTHROCYTES**

  Principal Investigator & Institution: Liao, James C.; Professor; Chemical Engineering; University of California Los Angeles 10920 Wilshire Blvd., Suite 1200 Los Angeles, Ca 90024

  Timing: Fiscal Year 2002; Project Start 27-SEP-2000; Project End 31-JUL-2004

  Summary: The broad, long-term goal of this project is to investigate the diffusion and reaction of nitric oxide (NO) in blood, particularly its interaction with red blood cells (RBCs). It is hypothesized that RBCs possess specific mechanisms that regulate the NO consumption rate through modulation of membrane permeability to NO. Specifically the following aims will be pursued. Specific Aim 1: Is NO consumption by RBC regulated by transmembrane diffusion? Specific Aim 2: Do any specific intra-erythrocytic molecules participate in the regulation of NO quenching? Specific Aim 3: How does the regulation of NO consumption by RBCs affect vessel regulation? The first two aims will be addressed by use of a competitive experiment and a differential membrane bioreactor specifically designed to measure the NO-RBC reaction rate. Kinetic models will be used to analyze the data. Biophysical (EPR and fluorescence) and biochemical (characterization of enzymes, metabolites, and lipids) techniques will be applied to RBCs, RBC ghosts, and synthetic liposomes in order to answer these questions. The last aim will be addressed using isolated porcine coronary microvessels as a bio-assay to determine the functional role of NO quenching and its regulation. The hypotheses proposed above are a significant departure from the current understanding that NO consumption is not regulated and that the RBC membrane is "completely permeable" to NO. In addition to its contribution to fundamental physiology, the proposed work directly impacts multiple aspects of clinical medicine, including NO inhalation therapy and the design of blood substitutes. Furthermore, the proposed mechanism might contribute to the pathology of several diseases, such as essential and pulmonary hypertension, peripheral vascular disease associated with diabetes mellitus, **sickle cell anemia,** and other hereditary RBC disorders. In these situations, altered RBC membrane consumption by RBCs is essential to the development of clinical intervention and understanding of the complex roles that NO plays under physiological and pathological conditions.

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- **Project Title: NORTHERN CALIFORNIA COMPREHENSIVE SICKLE CELL CENTER**

  Principal Investigator & Institution: Mentzer, William C.; Professor; Pediatrics; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747

  Timing: Fiscal Year 2002; Project Start 01-APR-1978; Project End 31-MAR-2004

  Summary: The objectives of the Northern California Comprehensive Sickle Cell Center (NCCSCC) are 1) to sponsor and facilitate hemoglobinopathy research at both fundamental and clinical levels and 2) to provide hemoglobinopathy detection, counseling, and education to affected populations using the most modern methods. To pursue these objectives, we have established a CORE hemoglobin structure and diagnosis laboratory at Childrens' Hospital Oakland Research Institute (CHORI) and CORE clinical research programs in the West Bay (UCSF/San Francisco General Hospital) and in the East Bay (Childrens' Hospital Oakland, Highland Hospital). These programs provide hemoglobinopathy detection, counseling and education as well as a

stable, well characterized group of over 500 patients with **sickle cell disease** (SCD) who participate in NCCSCC research projects. Clinical research projects aim to a) test the efficacy of core decompression in the management of aseptic necrosis of bone, b) see whether an acute rise in serum secretory phospholipase AD heralds the acute chest syndrome and justifies early therapeutic intervention, and 3) evaluate the efficacy of potential new therapies (hydroxyurea + phenyl butyrate or clotrimazole, isobutyramide, oral magnesium, oral chelation and various forms of stem cell transplantation). More basic cell and molecular biology research projects will a) exploit our newly developed transgenic mouse model of SCD (which completely lacks mouse globin chains) to explore the pathophysiology of SC and evaluate potential new treatments, b) employ a genome a genome-wide scan to identify genes unlinked to the globin cluster that alter SCD severity and globin chain switching in inbred strains of mice, c) use a human b globin YAC specific transgenic mouse model to define the role of cis-acting regulatory sequences that direct tissue-and stage-specific expression of the human b globin gene family, and d) establish a collaborative research venture to explore the effects of complement, thrombin, and other agonists on the adherence of sickle RBC to vascular endothelium with the ultimate goal of defining a potential role for these interactions in sickle vaso-occlusion. These projects will be carried out at the 2 CORE clinical facilities, CHORI, and laboratories at UCSF and Lawrence Berkeley National Laboratory. Programs will be coordinated by Center staff and evaluated by both internal and external review bodies.

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- **Project Title: NOVEL FUNCTIONS OF RED CELL PROTEINS LU AND LW**

  Principal Investigator & Institution: Chasis, Joel A.; Staff Scientist; Division of Life Sciences; University of Calif-Lawrenc Berkeley Lab Lawrence Berkeley National Laboratory Berkeley, Ca 94720

  Timing: Fiscal Year 2002; Project Start 01-SEP-2000; Project End 31-JUL-2004

  Summary: (Adapted from investigator's abstract) This is a modified and resubmitted application based on the hypothesis that the erythrocyte membrane proteins Lutheran (Lu) and LW function in cell-cell and cell-extracellular matrix interactions in the bone marrow. Based on preliminary results that LW is expressed early in erythropoiesis and binds to alpha4beta1 and alphav integrins, the application proposes that LW may mediate interactions of erythroblasts with one another and with macrophages to form the erythroblastic island structure. Lu glycoprotein is known to bind laminin and the applicant has obtained evidence that it is not expressed until late in erythropoiesis. The timing of the appearance of Lu on the cell surface suggests a role in erythroblast enucleation or release of precursors from the marrow. Additionally, preliminary results indicate that Lu and LW may contribute to the pathophysiology of **sickle cell disease** by mediating the adhesion of sickle red cells to vascular endothelial cells. To test these hypotheses the applicant proposes to: (1) Generate knockout mice lacking the murine homologues of Lu and LW by homologous recombination. (2) Characterize the structure-function of Lu and LW by identifying the domains of Lu and LW involved in ligand binding and employing domain-deletion mutants and site-directed mutagenesis; developing blocking antibodies and peptides and testing their effects on macrophage-erythroblast and erythroblast interactions, erythroid progenitor cell growth, and nuclear extrusion using in vitro assays and micromechanical techniques; and by analyzing erythropoiesis in the knockout mice including the degree of ineffective erythropoiesis, capacity to form erythroblastic islands, process of erythroblast enucleation, and ability to generate reticulocytes during stress erythropoiesis. (3) Examine roles of Lu and LW in

sickle cell disease by studying the effect on vascular blood flow of infusing transgenic/knockout sickle mice with antibodies directed against Lu and LW which block adhesion of sickle red cells to endothelial cells.

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- **Project Title: OPIOID ACTIVITY IN ENDOTHELIUM IN SICKLE CELL DISEASE**

  Principal Investigator & Institution: Gupta, Kalpna; Medicine; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2002; Project Start 01-APR-2002; Project End 31-MAR-2006

  Summary: (provided by the applicant): Our preliminary data show that opioid drugs, administered to sickle patients promote growth of microvascular endothelial cells. This opioid effect on endothelium is accompanied by MAPK/ERK activation and promotion of in vitro (tube formation) and in vivo (in Matrigel implants in mice) angiogenesis. We hypothesize that administration of opioids to sickle patients may increase their risk for retinopathy by pro-angiogenic signaling of opioids in endothelium. We will test this via 4 Specific Aims. I Aim#1 Characterize opioid induced endothelial proliferation, by testing specific hypotheses that endothelial growth response to opioids is, [a] exaggerated for human dermal microvascular endothelial cells (HDMEC) and retinal EC vs. HUVEC, [b] influenced by pro-inflammatory cytokines and VEOF, [c] accompanied by EC activation, cell adhesion molecule and NOS expression, Ed] caused by both a stimulation of growth and inhibition of apoptosis. Aim#2 Identify mechanism of endothelial growth stimulation by opioids via 4 specific hypotheses, that [a] opioid stimulated growth involves specific opioid receptors in both presence and absence of pro-inflammatory cytokines, [b] pro-inflammatory cytokines and growth factors regulate mu opioid receptor (MOR) expression on human microvascular EC, [c] opioid signaling in endothelium involves MAPK/ERK phosphorylation via Gi coupled receptors and NO, Ed] opioid induced proliferation is I dependent upon above signaling pathway. Aim#3 Determine if pro-inflammatory cytokine induced MOR. expression and opioid-induced endothelial growth actually promotes angiogenesis in vitro (tube formation in Matrigel) and in vivo (in Matrigel implants in mice). Aim #4 Use sickle mice to determine if opioids exert biologically important effects in vivo, by testing specific hypotheses that administration of opioids to sickle mice [a) causes increased endothelial activation and cell adhesion molecule and NOS expression, [b] accelerates and/or exaggerates development of retinopathy, [c] improves rate of healing of skin wounds; (longer-term goal). Mostly HDMEC and some retinal microvascular EC will be used, since it is critical for angiogenesis studies to use microvascular not large vessel EC. If our hypotheses are true, this Project may lead to several implications of opioid signaling, resulting in altered, clinical decision making and perhaps even to development of novel therapeutics.

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- **Project Title: PLEIOTROPIC AND EPISTATIC EFFECTS IN SICKLE CELL ANEMIA**

  Principal Investigator & Institution: Nagel, Ronald L.; Professor and Head; Medicine; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 31-JUL-2006

  Summary: (provided by applicant): **Sickle cell anemia** (SCA) is the paradigmatic monogenic disease, but the sickle mutation is not sufficient to define the phenotype. Pleiotropic effects influence complications. Secondly, SCA exhibits an intense inter-individual variability, which is likely to be the effect of epistatic genes, since heritability

of major determinants of severity exhibit high concordance in monozygote twins (89%). The aim of this project is to define the epistatic/pleiotropic genes involved in sickle-cell mediated vaso-occlusion in different organs, building on our years of working on the genetics and pathophysiology of this problem in mice and men. We will engage in the detection of genes involved in sickle cell-mediated vaso-occlusion in animal models, in the detection of genes involved in sickle cell-mediated vaso-occlusion in patients with **sickle cell anemia** and in the detection of genes involved in vaso-occlusive and vaso-proliferative processes in sickle cell retina and choroid and in cerebrovascular complications in **sickle cell anemia,** which our previous work has defined as a special case. The experimental design is the following: Approach 1: Appropriate tissues in sickle transgenic mice and other animal models -+ RNA -+ expression chips -> select the higher express genes and the lower expressing genes vs control -+ BLAST --> the selected human genes will be analyzed for potential epistatic effects by SNP arrays and by sequencing to define polymorphism in appropriately defined human **sickle cell anemia** DNA samples. Approach 2: In the complications without animal models, but candidate genes based on human pathophysiological data, SNPs and sequencing analyzes will be performed in **sickle cell anemia** patients with a particular complication vs **sickle cell anemia** patients without it. Of course, appropriate matching age groups will be selected to assure that the complication is no longer possible in the control group. Genes defined by these two approaches will be followed in animal models when available (KO or over expression, or generated for further confirmation. Members of this proposal have special expertise in retinal, cerebro-vascular problems and statistical analysis. Our institution has well established expertise in transgenic mice, microcirculatory preparations, hemopoiesis and patient follow-up, as a well as experienced SNP, sequencing and CHIP expression facilities.

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- **Project Title: POLYMER-COATED RED BLOOD CELL FOR SICKLE CELL DISEASE**

  Principal Investigator & Institution: Fisher, Timothy C.; Physiology and Biophysics; University of Southern California 2250 Alcazar Street, Csc-219 Los Angeles, Ca 90033

  Timing: Fiscal Year 2002; Project Start 28-SEP-2000; Project End 31-AUG-2004

  Summary: (Investigator's abstract) Although red blood cell (RBC) transfusion is an essential component in the management of acute complications of **sickle cell disease** (SCD), and the recent "STOP" study has demonstrated that chronic blood transfusion can prevent stroke in high-risk SCD children, transfusion in SCD has associated problems: 1) high alloimmunization rates (up to 30 percent) and iron accumulation; 2) limitation of post-transfusion hematocrit to less than 35 percent to avoid blood hyperviscosity which may precipitate a vaso-occlusive event. However, we have recently developed a technique which has the potential to mitigate these problems: covalent bonding of a thin coating of polyethylene glycol (PEG) or related polymers to the RBC surface. Results to date indicate that consequent to coating, the RBC surface is inaccessible to antibodies (i.e., the RBC blood group antigens are "masked") and RBC interactions, such as RBC aggregation, are minimized; the latter effect results in greatly reduced low-shear blood viscosity even when the hematocrit of SS blood is increased with coated RBC. The ultimate objective of this Research Program is the development of safe and effective RBC polymer coating methods which achieve antigen masking and viscosity reduction and which offer therapeutic benefits for **sickle cell disease** subjects. Specific aims include: 1) optimizing polymer coating techniques via evaluating linear, branched, star and dendrimer PEG molecules and various bonding chemistries and crosslinking strategies; 2) evaluation of the functional status of polymer-coated RBC in

terms of RBC morphology, rheological behavior (i.e., deformability), membrane transport and oxygen binding, identification of membrane proteins affected (e.g., C-14 labeled PEGs), the storage ability of coated-cells, and in vivo survival in mice and rabbit systems; 3) evaluation of polymer-coated RBC as therapeutic agents in SCD via in vitro rheologic studies of M and SS RBC mixtures at various hematocrits and oxygen tensions, and via in vivo flow studies using rat mesocecum and cat skeletal muscle preparations; 4) evaluation of polymer coating as a means to prevent alloimmunization and/or to protect transfused RBC in alloimmunized subjects by utilizing both in vitro (e.g., antibody/complement binding, complement lysis, monocyte monolayer assay) and in vivo approaches (e.g., alloimmunized rabbit model, xenotransfusions) methods. An interactive approach to these aims is proposed; their successful achievement should yield important new data and improved health care in SCD.

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- **Project Title: POTASSIUM CHLORIDE COTRANSPORTER GENE EXPRESSION**

  Principal Investigator & Institution: Anderson, Kathleen P.; Associate Professor; Children's Hospital Med Ctr (Cincinnati) 3333 Burnet Ave Cincinnati, Oh 45229

  Timing: Fiscal Year 2003; Project Start 11-JUL-2003; Project End 31-MAR-2008

  Summary: HbS polymerization is the basis for sickle cell pathophysiology, but disease severity and clinical course are influenced by other factors, including cellular dehydration, which markedly accelerates HbS polymer formation. The KCI cotransporter (KCC) normally regulates cation and water content in reticulocytes. However, in sickle red blood cells (SS RBC), high expression of KCC and abnormal response to cell volume may both contribute to SS reticulocyte dehydration. Thus, KCC plays a role in sickle cell pathology, and a potential therapeutic strategy is to reduce KCC activity to improve RBC hydration. One approach to this end would be the genetic manipulation of KCC expression. A comprehensive understanding of the regulated expression of the KCC gene in RBC is the focus of the three specific aims of this project. Recent data indicates that the KCCl isoform and several splicing isotypes are present in erythroid cells. The goal of Specific Aim 1 is to characterize the temporal sequence and level of expression of KCCl and its isotypes during erythroid differentiation, comparing AA and SS cells. Bone marrow samples from AA and SS patients will be analyzed using in situ hybridization teehrdques to assess KCCI mRNA levels in various erythroid precursors. Parallel studies will examine KCCl mRNA levels by RT-PCR and RNase protection assays in differentiating erythroid cells in culture. Protein levels will also be assessed by immunocytochemistry and Western blot analysis. Studies in Specific Aim 2 will determine the critical cis elements regulating transcription of the human gene encoding KCC isoform 1. We have identified at least one functional promoter for this gene, with preliminary evidence suggesting a second promoter as well. These studies will involve transient and stable transfections of erythroid and control cell lines with various reporter gene constructs derived from these promoter regions. Experiments in Specific Aim 3 will characterize the trans-acting factors that bind the genetic elements identified in aim 2. These studies will include electrophoretic mobility shift assays, antibody supershifts to confirm known factors, and protein purification of uncharacterized factors. Together, these experiments will produce a clearer understanding of the mechanisms of KCC gene regulation and its possible abnormalities in **sickle cell disease,** with the ultimate goal of developing new therapies for altering red cell hydration to augment the treatment of **sickle cell disease.**

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- **Project Title: PROTEIN REQUIREMENTS IN ADOLESCENTS W/SICKLE CELL ANEMIA**

  Principal Investigator & Institution: Buchowski, Maciej S.; Associate Professor; Meharry Medical College 1005-D B Todd Blvd Nashville, Tn 37208

  Timing: Fiscal Year 2003; Project Start 01-AUG-2003; Project End 31-JUL-2007

  Summary: Homozygous **sickle cell disease,** known also as **sickle cell anemia** (SCA), results from inheritance of the sickle cell betas-globin gene from both parents and is characterized usually by marked clinical severity. Some children with **sickle cell disease** have delayed growth and sexual development. The reason for the delayed growth and associated poor weight gain is not well understood but it might be associated with the increased requirement for protein and energy. The underlying physiological mechanism of this increase, in addition to chronic anemia, could be explained in part by the accelerated synthesis of new red blood cells and the altered catabolism of sickled red blood cells. However, how these metabolic events develop and progress during the accelerated growth in SCA adolescents is unknown. The central hypothesis of this application is that increased whole-body protein turnover diverts protein from normal growth pathways in SCA adolescents. The rationale for the proposed research is that quantifying protein needs and finding the underlying mechanism(s) for stunting will lead us to establishing nutritional recommendations and designing specific supplementation for SCA children and adolescents. The specific aims are: 1) to determine how much protein is needed in growing SCA adolescents using breakpoint analysis of variables derived from 24-h leucine oxidation and balance, whole body protein turnover, and nitrogen balance, and 2) to determine how much protein requirements are changing during pubertal growth in adolescents with SCA. In the proposed longitudinal study of SCA adolescents, protein requirements will be established using stable isotope tracer techniques, body composition assessment, and indirect calorimetry. Healthy adolescents matched initially for Tanner stage of sexual development, sex, and ethnicity will serve as controls in these experiments. The proposed research is significant, because it is expected to result in new guidelines for nutritional management of adolescents with SCA that will significantly improve their growth rate and attendant weight gains. In addition, we will explain how growth rate in SCA adolescents is altered by increased demands for energy caused by higher whole-body protein turnover and chronic hemolytic anemia. Finally, what is learned from this research will contribute to broader understanding of how SCA affects protein and energy metabolism, how these changes alter growth in SCA adolescents, and what underlying physiological mechanism(s) are involved.

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- **Project Title: RATIONAL DESIGN OF ANTISICKLING AGENTS**

  Principal Investigator & Institution: Safo, Martin K.; Assistant Professor; Medicinal Chemistry; Virginia Commonwealth University Richmond, Va 232980568

  Timing: Fiscal Year 2002; Project Start 01-SEP-2000; Project End 31-AUG-2004

  Summary: (Adapted from applicant's abstract) The applicant's career goal is to seek a research position in a reputable Institution. His primary goal would be to establish rigorous research programs involving structure-based drug design to find the origin, causes, treatment and prevention of tropical diseases, such as **sickle cell anemia,** malaria, and sleeping sickness. Furthermore, it is anticipated that molecular modeling techniques unique to the problems to be encountered will be developed to improve the efficiency of the drug development process. To reach these goals, would require

considerable experience and skills in drug designing process. Therefore, under the direction of his mentor, he intends to initiate a career development research program involving rational development of compounds to treat **sickle cell anemia.** This would help him gain the necessary skills and experience to develop his career as an independent researcher. Below is a brief description of the proposal research. A group of halogenated aromatic compounds are known to bind to hemoglobin and show potential as antisickling agents. These compounds bind to the surface of the protein and may explain the antisickling properties. The long term-goal of this research project is to utilize the above information to design and develop stereospecific agents to bind with high affinity to the surface of the hemoglobin for more potent antisickling agents. In addition, both the T and R-state hemoglobins will be used to study structure-function activities. Therefore, the specific aims are: 1) determine and refine the crystal structures of the deoxygenated hemoglobin co-crystallized with halogenated aromatic acids; 2) determine and refine the crystal structures of carbonmonoxy hemoglobin bound with halogenated aromatic acid; 3) rational design of new stereospecific compounds to bind to known binding sites at the surface of the hemoglobin, and other newly identified binding sites; and 4) biological evaluation of the designed compounds for antisickling, antigelling and allosteric activities.

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- **Project Title: RED CELL AQUAPORIN-1 WATER TRANSPORT PROTEIN**

  Principal Investigator & Institution: Agre, Peter C.; Professor; Biological Chemistry; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 01-APR-1985; Project End 31-MAR-2005

  Summary: The human red cell membrane is the model upon which our general understanding of plasma membranes is based. Several membrane transport proteins have first been identified in red cells, and during previous years of this project, a 28kDa protein was discovered, purified, cloned, expressed and functionally defined in Dr. Agre's laboratory. Now designated AQP1, this protein is the first recognized membrane water transport molecule. While multiple homologous aquaporins are now becoming recognized in other tissues, physical studies of human red cell AQP1 are revealing its structure at subnanometer resolution and are providing advanced insight into the biophysical transport function of the molecule. Here Dr. Agre proposes studies to establish the molecular structure of AQP1 at near-atomic resolution and to define the behavior of AQP1 in membranes. Aim I. Structure and function of purified AQP1 protein. High resolution cryoelectron microscopic analysis of membrane crystals containing red cell AQP1 will be undertaken to elucidate the 3D structure of AQP1 at better than 3 resolution. Yeast and other heterologous systems will be developed to express mutagenized AQP1 molecules with specific epitopes for affinity-purifications, metal binding, definition of the aqueous pore, identification of the sites of ion repulsion and assembly of individual subunits into tetramers. Functional analysis of mutagenized forms of AQP1 will be determined by direct measurement of the water permeability of AQP1 proteins in yeast microsomal vesicles and in reconstituted proteoliposomes. Aim II. AQP1 protein in cell membranes. The Colton blood group antigens result from a polymorphism in the first extracellular loop of the AQP1 protein. Using fluorescently labeled-anti-Co, Dr. Agre plans to characterize the surface equilibrium distributions of AQP1 on normal red cells by immunofluorescence, immunoprecipitations, and flow sorting. Kinetic distributions of AQP1 in red cell membranes will be undertaken with anti-Co by measurement of fluorescence recovery after photobleaching. Similar studies will be performed on enzymatically modified red cells and red cells from patients with

sickle cell anemia and other congenital hemolytic states. These abnormal red cells and AQP1 deficient red cells will also be examined for membrane water permeabilities. To fully define the molecular determinants of the Co antigen, nonerythroid cells will be studied for Co expression by transfection with mutagenized forms of AQP1.

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- **Project Title: REDUCING THE TOXICITY OF BMT IN SICKLE CELL ANEMIA**

  Principal Investigator & Institution: Iannone, Robert; Children's Hospital of Philadelphia 34Th St and Civic Ctr Blvd Philadelphia, Pa 19104

  Timing: Fiscal Year 2003; Project Start 15-AUG-2003; Project End 31-JUL-2008

  Summary: (provided by applicant): The main objective of the research proposal is to reduce the toxicity of bone marrow transplantation (BMT) for **sickle cell disease** (SCD) in order to extend this potentially curative therapy to more patients. Despite current therapies, SCD is associated with substantial morbidity and mortality. Myeloablative BMT can cure SCD but its application is limited by a 5-10% mortality risk, a 10% failure rate, graft-versus-host disease (GVHD) and the risk of gonadal and endocrine dysfunction. Nonmyeloablative BMT (NST) can result in mixed hematopoietic chimerism, stable co-existence of host and donor marrow, and may be less toxic than myeloablative BMT. Because normal red blood cells (RBCs) survive much longer than sickle RBCs, a low-level of normal donor chimerism may substantially reduce the fraction of sickle cells in the circulation and prevent their pathologic effects. There is limited experience, however, with NST in patients with SCD. We have studied animal models of mixed chimerism to treat SCD, tested novel NST regimens for inducing donor-specific tolerance and reducing GVHD, and piloted a clinical trial of NST in patients with SCD. Six of seven patients treated had initial donor engraftment and toxicities were mild and reversible, however, all patients experienced late graft failure. We now hypothesize that HLA-identical sibling bone marrow will engraft in >80% of patients with SCD who receive pre-transplantation fludarabine and low-dose total body irradiation, with or without cyclophosphamide (Cy), followed by post-transplantation Cy, tacrolimus and mycophenolate mofetil. We will study in-vitro anti-donor reactivity as a predictor of rejection, track other factors associated with engraftment and GVHD, assess immune reconstitution after NST, and evaluate the effect of this treatment on multiple clinical parameters. I was recently recruited to the Children's Hospital of Philadelphia to establish a clinical research program in BMT for non-malignant diseases, emphasizing SCD. My objective is to become an independent clinical scientist by obtaining formal instruction and conducting mentored patient-oriented research on reducing the toxicity of BMT for SCD. I have a strong mentoring committee composed of scientists with expertise in clinical trial development, SCD, BMT, biostatistics, bioethics and transplant biology. As part of my training, I will obtain a Master's Degree in Clinical Research through the Center for Clinical Epidemiology and Biostatistics.

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- **Project Title: REGULATION AND FUNCTION OF A HUMAN EMBRYONIC GLOBIN**

  Principal Investigator & Institution: Russell, J Eric.; Assistant Professor; Medicine; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104

  Timing: Fiscal Year 2003; Project Start 01-APR-1999; Project End 31-MAR-2008

  Summary: (provided by applicant): This proposal extends an ongoing research program that is committed to defining the latent therapeutic value of epsilon-globin gene

reactivation in adults with disorders in beta-globin expression. The potential benefit of epsilon-globin in these individuals derives from its incorporation into Hb heterotetramers that display physiologically appropriate O2-binding and antisickling properties. As post-transcriptional mechanisms play essential roles in the regulated expression of other globin genes, it is likely that similar processes affecting the stability and translational efficiency of epsilon-globin mRNA are equally important to its expression. Pilot studies carried out in intact animals and in vitro implicate specific cis sequences and defined trans-acting factors as participants in regulated epsilon-globin mRNA stability, several of which are highly similar to well-described determinants of adult-stage beta-globin mRNA stability. The current proposal extends these pilot studies in three Specific Aims that investigate independent aspects of regulated epsilon-globin mRNA stability. The Aims utilize well-established techniques that draw upon the applicant's experience, as well as several novel methods that have been validated in preliminary studies. Aim I will define specific cis-acting elements that dictate the stability of epsilon-globin mRNA, through novel cell culture analysis of epsilon-globin mRNA variants containing defined site-specific 3'UTR mutations. The physiological importance of these determinants will subsequently be validated in a well-established transgenic mouse model system. Aim II will identify the specific cytoplasmic factors that effect the characteristic stability of epsilon-globin mRNA and may also participate in co-regulating the stabilities of beta- and gamma-globin mRNAs. These experiments will be carried out in vitro and in vivo using familiar analytical methods. Aim III will investigate the effect of regulated epsilon-globin mRNA stability on crucial physiological and molecular processes, including its developmental stage-restricted expression and its translational efficiency in definitive erythroid cells. These experiments will capitalize on several unusual but highly informative methods that have been developed for this specific purpose in the applicant's laboratory. The results from all three Aims will integrate to provide a solid understanding of the fundamental molecular processes regulating the stability of epsilon-globin mRNA, the manner in which these processes may affect the stability of other globin mRNAs, and the physiological consequences--both desirable and undesirable--that result from their targeted dysregulation. The proposed research comprises a crucial step in evaluating the promise of developmentally silenced globin genes for individuals with beta-thalassemia and **sickle cell anemia.**

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- **Project Title: REGULATION OF THE MURINE BETA-GLOBIN LOCUS**

  Principal Investigator & Institution: Fiering, Steven N.; Assistant Professor; Microbiology and Immunology; Dartmouth College 11 Rope Ferry Rd. #6210 Hanover, Nh 03755

  Timing: Fiscal Year 2003; Project Start 12-SEP-1997; Project End 31-MAY-2007

  Summary: (provided by applicant): Transcriptional regulation of the beta-globin locus is a historically important system for the study of tissue and developmentally regulated transcription in mammals. In addition to its importance for fundamental insights into mammalian transcription, understanding how this locus is regulated holds the potential for developing novel therapies for **sickle cell anemia** and beta-thalassemia, two very common human genetic disorders. Regulation of the beta-globin locus is analyzed predominantly in transgenic mice that carry transgenes from the human beta-globin locus. This system has been productive but suffers from problems that are inherent to studying human transgenes in mice, where the randomly generated integration site has powerful effects and the murine transcription factors have not coevolved with the cis

regulatory elements of the transgene. Results from human locus transgenes have been complemented and clarified by analysis of the murine beta-like globin locus through mutation of the murine locus using homologous recombination in ES cells. Comparisons of the human transgene studies and the murine locus studies have formed a baseline of definitive studies that underlies general conclusions concerning the regulation of this locus regardless of species. This proposal continues with the mutational analysis of the routine beta-like globin locus and definitively tests the following hypotheses that have been suggested by studies of human beta-globin locus transgenes in transgenic mice: Aim 1 tests the hypothesis that expression of one gene at the locus quantitatively suppresses expression of another gene at the locus which is expressed at the same developmental stage. This will clarify specific aspects of models of how the locus control region influences gene expression. Aim 2 tests the hypothesis that expression of the embryonic genes suppresses expression of the fetal/adult genes in the embryo. This will prove or disprove the consensus hypothesis concerning the mechanism by which the genes expressed later in development are kept silent early in development. Aim 3 tests the hypothesis that deletion of the core part of a hypersensitive site in the locus control region will have stronger suppressive effects than deletion of the entire site. Unexpected findings using human transgenes have suggested this hypothesis and the experiments proposed in aim 3 will demonstrate the generality of this hypothesis and develop a facile system to dissect the effect if it is also seen in the murine locus.

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- **Project Title: RETROVIRAL TRANSFER OF ANKYRIN FOR SPHEROCYTOSIS**

  Principal Investigator & Institution: Becker, Pamela S.; Associate Professor of Medicine and Chie; Medicine; Univ of Massachusetts Med Sch Worcester Office of Research Funding Worcester, Ma 01655

  Timing: Fiscal Year 2002; Project Start 01-JUL-1999; Project End 31-MAY-2004

  Summary: The current challenges in gene therapy with the hematopoietic stem cell as target include achievement of high transduction efficiency, long-term engraftment of transduced cells, and long-term expression of the transgene. Toward development o methods to achieve these aims, we plan to study stem cell transduction by a retroviral vector containing the ankyrin gene as a model for gene therapy and correction of hereditary hemolytic anemias. We-will use the nb/nb mouse as our hemolytic anemia model and study the impact of stem cell cycle status and low dose (100 cGy) host irradiation (minimal myeloablation) on engraftment of transduced cells. Hereditary hemolytic anemias, including thalassemia and **sickle cell anemia,** affect large populations worldwide, and result in significant morbidity and reduced survival. There are several naturally occurring inherited hemolytic anemias in mice which are analogous to the human disorder, hereditary spherocytosis. One such mutant, the nb/nb mouse, exhibits marked deficiency in ankyrin, a 210 kDa protein that anchors the red cell membrane skeleton to the lipid bilayer. This application proposes to transfer by retroviral vector the cDNA for normal ankyrin to marrow progenitor cells from nh/nb mice to correct the erythrocyte defect and improve the anemia. The murine/human hybrid cDNA consists of the human ankyrin gene promoter, most of the coding sequence of the murine domains for band 3 and spectrin binding, and the alternatively spliced (band 2.2) version of the human regulatory domain. The following objectives will be pursued: 1) to compare expression obtained with pG1-Ank to pG1-Ank/rev that contain ankyrin cDNA in the forward or reverse orientations between the LTRs, 2) to examine differentiating erythroid cells derived from both normal and nb/nb transduced marrow progenitors, 3) to engraft the transduced marrow progenitors in minimally

myeloablated normal recipients with modification of the cytokine incubation time to optimize engraftment, and 4) to transduce bone marrow cells from the nb/nb mouse and engraft these cells in minimally myeloablated nh/nb recipients to improve the hemolytic anemia. The methods developed, including insertion of the cDNA encoding a large protein, the use of non-myeloablative procedures for transplant of genetic diseases, the ability to incubate stem cells in cytokines yet preserve engraftment, and the achievement of tissue-specific gene expression have direct relevance to the development of gene therapy approaches to inherited human disorders.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: RHEOLOGIC & VASCULAR MODULATORS IN SICKLE VASOOCCLUSION**

  Principal Investigator & Institution: Kaul, Dhananjay K.; Professor; Medicine; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2003; Project Start 01-APR-2003; Project End 31-MAR-2007

  Summary: (provided by applicant): We hypothesize that in **sickle cell anemia,** the source of hemodynamic abnormalities is not only abnormal red cell rheology (sickling and adhesion to endothelium), but a derangement of microvascular controls secondary to endothelial dysfunction. This proposal focuses on two potential modulators of microvascular flow and vasoocclusion in **sickle cell anemia.** First, endothelial dysfunction in response to hypoxia, mechanical injury (red cell sickling and adhesion), and oxidative stress (secondary to transient ischemic episodes) would affect the ability of microvasculature to respond to rheological challenge. Second, abnormal adherence of red cells to vascular endothelium would not only result in endothelial injury, but also in a prosickling environment. The objective of this revised proposal is to examine the relationship between abnormal rheology, oxidative stress and vascular tone under in vivo conditions in the sickle context, using transgenic and knockout sickle mouse lines. We will test the following specific hypotheses: 1) Test the hypothesis that sickling and attendant flow abnormalities (e.g., transient vasoocclusive events) will cause oxidative stress, microvascular injury and vascular tone abnormalities. To test this hypothesis, we will investigate the effect of enhanced sickling (hypoxia), examine the effect of arginine supplementation, and evaluate the effect of selected anti-oxidants; 2) Test the hypothesis that genetic and experimental modulations of red cell density and polymer formation will impact endothelium and thereby microvascular function. To test this aspect, we will determine the effects of anti-sickling fetal hemoglobin and experimental modulations of red cell density; 3) Test the hypothesis that red cell adhesion in vivo not only contributes to endothelial injury but plays a crucial role in microvascular obstruction. To test this hypothesis, we will focus on the role of endothelial activation, specific adhesion molecules, hypoxia, NO, anti-oxidants, and use DNA microarray technology to identify genes regulated by adhesion inducing factors. The proposed research involves participation of scientists with expertise in microcirculation, hematology, biochemistry, cell biology and molecular biology. These studies are expected to elucidate new mechanisms with relevance to human **sickle cell disease** and with potential therapeutic implications.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: RHEOLOGICAL AND ADHERENCE PROPERTIES OF SICKLE CELLS**

  Principal Investigator & Institution: Narla, Mohandas; Vice President, Research; New York Blood Center 310 E 67Th St New York, Ny 10021

Timing: Fiscal Year 2002; Project Start 01-OCT-1989; Project End 31-MAR-2006

Summary: (Applicant's Description Verbatim): The research objective is to develop a detailed understanding of the molecular and structural basis for the abnormal rheological and adherence properties of sickle red blood cells and define the in vivo pathologic sequelae of these cellular changes. To achieve our objective we propose the following series of studies: 1) Using novel experimental strategies, determine the relative contributions of the Gardos channel and the K-Cl cotransporter to the morphologic and rheologic heterogeneity of dense sickle red cells. Using intravital microscopy, document effects of the observed rheological heterogeneity on flow behavior in vivo. Generate sickle mice in which the Gardos channel and/or K-CL cotransporter are inactivated to directly establish the relative contributions of these two transport proteins to cell dehydration and compromised blood flow. 2) To develop a mechanistic understanding of premature sickle red cell destruction, distinct populations of mouse sickle cells will be isolated based on differences in their cellular and membrane characteristics and their in vivo life span will be determined. The surface characteristics and surface area of these different cell sub-populations will be documented. Data from these in vitro and in vivo studies will be used to define the contribution of surface area loss and associated membrane changes to the decreased life span of sickle cells. 3) As it is likely that the dynamic strength of a specific adhesive complex will determine its impact on in vivo flow, we will measure the dynamic strength for various specific adhesive interactions identified in mediating sickle red cell adherence to vascular endothelial cells. These data should enable us to define the physiologically relevant adhesive interactions. We will validate the in vitro studies by performing in situ studies on sickle mice in which genes encoding specific adhesive receptors are inactivated. For the proposed studies, we will use multiple techniques in biophysics, molecular biology, cell biology, mouse genetics and circulatory physiology. The sickle mice that we developed expressing exclusively human sickle hemoglobin and exhibiting many clinical features of human disease are a key component of our experimental strategy. These mice should enable us to perform deliberate and specific perturbations for defining the determinants of adherence and flow, which would not be possible in human studies. Our application of these refined systems offers great promise for elucidating the cause of painful vaso-occlusion and identifying potential targets for future therapy.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: SIBLING DONOR CORD BLOOD BANKING AND TRANSPLANTATION**

  Principal Investigator & Institution: Lubin, Bertram H.; Director of Medical Research; Children's Hospital & Res Ctr at Oakland Research Center at Oakland Oakland, Ca 94609

  Timing: Fiscal Year 2002; Project Start 15-JAN-1999; Project End 31-AUG-2005

  Summary: (provided by applicant): Hematopoietic stem cell transplantation (HSCT) has become an important treatment option for patients with **sickle cell anemia** or thalassemia. While the source of HSCT is usually bone marrow from an HLA identical sibling, cord blood (CB) may prove to be an important resource. CB can contain sufficient numbers of hematopoietic stem cells for engraftment post myeloablative therapy, can be used without a complete HLA match, and CB has less chance of inducing graft-versus-host disease (GVHD) than bone marrow. To increase the availability of CB for these purposes, a number of CB banks have been developed. However, none have focused on sibling donor cord blood (SDCB) collection, a process

which requires a unique set of procedures to accommodate collection at remote sites, and none have extensive experience working with families who have a child with **sickle cell anemia** or thalassemia. This revised application contains two specific aims: (1) to collect sibling-donor CB in families that currently have a child with **sickle cell anemia** or thalassemia and (2) to use these CBs to conduct the first multi-center prospective pilot study of CB transplantation in children with these two diseases. The SDCB Program at CHORI will follow procedures that comply with standards for cord blood banking. The success of our feasibility study has demonstrated that our program can collect a sufficient number of Cbs to conduct the pilot transplantation study. Scientific questions regarding engraftment failure, disease recurrence, HLA compatibility, and the requirement for a critical number of HSCs are addressed in the application. We will test the hypothesis that a novel immunosuppressive conditioning regimen (fludarabine, cyclophosphamide and busulfan) and post transplant therapy (mycophenalate mofetil and cyclosporine) will improve engraftment rates and prevent disease recurrence. The effect of SDCB transplantation on hematologic parameters and GVHD will be monitored. Information for this pilot study will be used to design new approaches employing SDCB transplantation for patients with hemoglobinopathies. In summary, the ultimate goal of our proposal will be to focus our SDCB program on collection of CBs from families that have a child with a hemoglobinopathy and to use these CBs to evaluate the role of CB transplants in these children. We anticipate that our project will advance the field of SDCB transplantation from case reports to clinical investigation and, will provide a rational basis for further studies of CB transplantation in children with hemoglobinopathies.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: SICKLE CELL PERSONAL MEDICAL INFORMATION CARD**

  Principal Investigator & Institution: Pringle, Steve; Point Vista Software, Llc 633 Everett St , Ca 94530

  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 31-MAR-2004

  Summary: (provided by applicant): We propose to develop a Personal Medical Information Card (PMIC) to provide an accurate and up-to-date, individualized point-of-care, medical history and treatment plan for patients with **sickle cell anemia.** This wallet sized "smart card" will be carried by patients and contain information on a microchip viewable on a standard PC. The treating physician will enter information onto the PMIC following each visit. Information from the hospital/clinic information system databases as well as information regarding treatment guidelines will be placed on the PMIC. Our specific aims are: (1.) To develop a secure medical information system encoded microchip embedded in a standard wallet sized plastic card for patients with **sickle cell anemia,** (2.) To develop a user-friendly interface between the data management system in the primary care setting and the microchip embedded in the PMIC and, (3.) To place a card reader in the emergency room and primary care setting to evaluate the use of the PMIC by the treating physician and its acceptability to the patient. We anticipate that this application will be applied to many complex, chronic medical conditions, that it will improve the care of patients with **sickle cell anemia** and that it will have considerable commercial value.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: SICKLE RED CELL K+ TRANSPORTER GENETICS IN S. CEREVISIAE**

  Principal Investigator & Institution: Alper, Seth L.; Professor; Beth Israel Deaconess Medical Center St 1005 Boston, Ma 02215

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 31-AUG-2004

  Summary: (provided by applicant): The dehydrated state of the densest erythrocytes in **sickle cell disease** accelerates deoxygenation-induced polymerization of HbS and consequent, preferential sickling of these dense cells. Activity of the KCC K-Cl cotransporters and the IK1 K(ca) channel mediates nearly all of this dehydration. Pharmacological blockade of these K efflux pathways inhibits cellular dehydration in vitro in mouse models of **sickle cell disease,** and in patients, may bring clinical benefit. Understanding the mechanisms of ion transport by K-Cl cotransporters and of K ion permeation through the IK1 K(ca) channel is critical to development of safe pharmacological blockers of higher potency and specificity. Structure-function relationship studies using site-directed mutagenesis are underway for KCC K-Cl cotransporters and for the K(ca) IK1. Though productive, these studies are relatively slow. Experiments proposed in this R21 application will utilize strains of S. cerevisiae deficient in high-affinity K ion uptake in order to perform extensive, unbiased structure-function studies of K-Cl cotransporters and the IK1 K(ca) channel. A selection system has already been validated for KCC1. A selection system for IK1 is under development. The proposed experiments will accelerate production and selection of mutants exhibiting loss-of-function and gain-of-function phenotypes. In addition, the system should permit development of a high throughput screen for inhibitors of K ion uptake by these pathways. These goals will be achieved through pursuit of the following Specific Aims: 1) To validate, characterize, and standardize growth rescue of trk1delta/trk2delta S. cerevisiae in nonpermissive growth conditions by expression of cDNAs encoding KCC K-Cl cotransporters. 2) To define structural regions of KCC1 important to ion transport, to cation and anion selectivity, to inhibitor sensitivity, to a recently discovered dominant negative phenotype, and to acute regulation. This will be achieved by saturation mutagenesis of defined subregions of KCC K-Cl cotransporters, and screening mutants for their ability to rescue growth of trk1delta/trk2delta S. cerevisiae. Select mutants will be further studied in Xenopus oocytes and mammalian cells. 3) (Provisional Aim): Time permitting, to improve, validate, and standardize growth rescue of trk1delta/trk2delta S. cerevisiae by expression in nonpermissive conditions of cDNA encoding the mammalian IK1 K(ca) channel.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: SICKLING MECHANISMS AND RED CELL MEMBRANES**

  Principal Investigator & Institution: Bookchin, Robert M.; Professor; Medicine; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2002; Project Start 01-JUL-1981; Project End 31-MAY-2004

  Summary: The main long-term goal is a thorough understanding of the molecular and cellular pathophysiology of sickle cell (SS) disease. We now focus on the mechanisms by which Hb S interacts with the RBC membranes to alter cell functions, leading clinically to widespread microvascular occlusion and hemolytic anemia. Our immediate aims are: I. To characterize the functional properties and possible molecular nature of the sickling-induced ion permeability pathway(s), "P-sickle", generated by interaction of deoxy-Hb S polymers with the cytosolic membrane surface of SS cells. P-sickle -mediated Ca2+ influx is a critical step in SS cell dehydration. We address several fundamental questions

about P-sickle: is there a single poorly selective permeability pathway or different pathways for the different cations? How does the extent of P-sickle vary among SS cells? How does it vary with pO2 and [Ca2+]0? Is the single pathway conductance high or low, constant or variable? Does a mean P-sickle value reflect tens or thousands of polymer-membrane contacts? Is the stochastic event the number of P-sickle units per cell or their unit conductance? Identifying agents that stimulate or inhibit P-sickle may point to membrane components involved and clues to its molecular nature. II. To investigate the mechanism(s) of generation of the high-Na+, low-K+, low-density, cation-leaky SS and normal RBCs we discovered, and test the hypotheses (i) that many of these cells are derived from dense irreversibly sickled cells (ISCs); (ii) that they comprise the very rapid-turnover K pool we found among low density SS cells; and (iii) that they represent a major final pathway of cell death for sickle cells, and perhaps for normal RBCs. III. To pursue our hypothesis that the marked heterogeneity of volume and density (or cell Hb concentration) among circulating SS and variant RBCs results from heterogeneity of transport systems in the reticulocytes, with the direct and indirect effects of Hb-membrane interactions. These studies employ our newly available flow cytometric technology (modified H*3) in an experimental design in which the transporter distribution among cells is expressed in their rates of volume change. Our integrated RBC and reticulocyte models will be used to test alternative mechanisms of reticulocyte volume control (and decontrol in SS cells). We aim to characterize in detail the transport heterogeneity of SS and normal retics/RBCs, with particular emphasis on the contribution of retics to cell dehydration. IV. To characterize the Hb-polymerization properties and RBC ion-transport functions of a variety of transgenic sickle mouse models to identify those most suitable to test various pathophysiological mechanisms and therapeutic maneuvers in **sickle cell disease.** Once characterized, these will serve investigations within the above three aims.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: SINGLE MOLECULE ANALYSIS OF ERYTHROCYTE ADHESION IN SICKLE CELL DISEASE**

  Principal Investigator & Institution: Golan, David E.; Professor; Boston Medical Center Gambro Bldg, 2Nd Fl, 660 Harrison Ave, Ste a Boston, Ma 02118

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 31-MAR-2008

  Summary: Adhesive interactions involving sickle erythrocytes are critically important in the pathophysiology of vaso-occlusive crisis, hemolytic anemia, and other clinical manifestations of **sickle cell disease.** These interactions appear to be mediated by the abnormal expression and/or function of adhesion molecules on the surface of sickle erythrocytes. Recent studies in model membranes and intact biological systems have begun to elucidate the biochemical and biophysical properties of adhesion molecules that are necessary for stable adhesion; these properties include adhesion molecule expression, size, lateral mobility, surface density, surface distribution, and affinity for the molecule's cognate ligand. Although a number of molecular interactions involved in sickle lerythrocyte adhesion to vascular endothelial cells and T lymphocytes have been identified, the properties of these molecular interactions that are important for stable adhesion remain to be characterized. We have developed a unique set of biophysical and imaging techniques to study, at the level of individual adhesion molecules, the molecular interactions involved in cell-cell adhesion. The methods include fluorescence photobleaching recovery, polarized fluorescence depletion, single particle tracking, laser optical tweezers, glass-supported planar bilayer membranes, fluorescence resonance energy transfer, and dynamic in vitro and in vivo (intravital) adhesion assays. Here we

propose to apply these methods to the study of (1) membrane protein iand lipid dynamics in sickle erythrocytes, (2) adhesive interactions between sickle erythrocytes and activated vascular endotheliai cells, and (3) adhesive interactions between sickle erythrocytes and activated T lymphocytes. We shall use these methods to study adhesive interactions involving the adhesion molecules VLA-4 (alpha4beta1integrin), CD36, and CD2 on sickle erythrocytes, VCAM-1 and alpha-v, beta3 integrin on activated vascular endothelial cells, CD58 on activated T lymphocytes, and the adhesive plasma protein thrombospondin. Results from these studies are expected to lead to a quantitative understanding of important molecular and cellular events in the pathophysiology of **sickle cell disease,** and, ideally, to point the way to targeted therapies that interrupt the most critical aspects of these molecular and cellular events.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: STATISTICS AND DATA MANAGEMENT CENTER-CSCC**

  Principal Investigator & Institution: Helms, Ronald W.; Director of Statistics; Rho Federal Systems Division, Inc. 100 Eastowne Dr Chapel Hill, Nc 27514

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 31-MAR-2008

  Summary: (provided by applicant): Rho Federal Systems Division, Inc. (RhoFED), located in Chapel Hill, North Carolina, proposes to continue to serve as the Statistics and Data Management Center (SDMC) for the Comprehensive Sickle Cell Centers (CSCC) program. The SDMC will act as a coordinating center in support of collaborative clinical studies, local basic and clinical research, and activities to promote optimal communication among CSCC participants and the NHLBI Project Office. These studies will focus on the most promising therapeutic modalities for **sickle cell disease.** The primary goals of the coordinating center are to act as central point of communication for the day-to-day activities of the study group, provide epidemiological and statistical collaboration in the scientific elements, and provide the tools and support to ensure that the data generated by the clinical sites are of highest quality. RhoFED considers the following four aims to be essential in meeting the operational and scientific requirements of the project: a) Provide data management, statistical leadership, and clinical operations management support for common clinical protocols for the CSCC program; b) provide statistical support for all research projects within the CSCC program; c) develop, implement, and maintain web-based information technology to facilitate communication across facilities within the CSCC program and secure data entry and data management for the collaborative clinical studies; d) maintain, expand, and improve the existing CSCC program common patient database with particular emphasis on incorporating data on the social and financial burden of living with **sickle cell disease** and data related to health services utilization, health outcomes, and quality of life.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: STEM CELL EXPANSION USING CHEMICAL INDUCERS OF DIMERIZATION (CID)**

  Principal Investigator & Institution: Blau, C Anthony.; Associate Professor; University of Washington Grant & Contract Services Seattle, Wa 98105

  Timing: Fiscal Year 2002; Project Start 01-SEP-2002; Project End 31-AUG-2003

  Summary: In this application we propose to develop a new system for the in vivo section of genetically modifier hematopoietic cells, based on the use of chemical inducers of dimerization (CIDs). The system used has two components: a fusion protein

and a drug. The fusion protein contains a cytokine receptor signaling domain linked to a protein that provides a high affinity binding site for the CID. Addition of the CID results in dimerization of the fusion protein, thereby activating the receptor signaling domain. In recent studies we have shown that this system can be used as a pharmacologically-activatable "cell growth switch" for genetically modifier primary murine bone marrow cells. T of this application is to carry these in vitro observations into the in vivo setting. The specific aims of this proposal are: 1) To test whether CID-mediated activation of mpl allows for the in vivo selection of transduced murine stem and progenitor cells; 2) To identify and eliminate mpl maturational signaling domains to produce a derivative that is capable of proliferative signaling but incapable of maturational signaling; 3) To test whether CID-mediated activation of mpl allows for the selection and expansion of transduced human CD34+ cells in vitro and in vivo; 4) To test in vivo section in a large animal model using CIDs; 5) To test vectors that contain both a CID-selectable gene and a gamma globin gene for studies of selection in normal mice and in a mouse model of **sickle cell anemia.**

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: TRANSACTIVATORS OF HB F: IDENTIFICATION AND VALIDATION**

  Principal Investigator & Institution: Surrey, Saul; Medicine; Thomas Jefferson University Office of Research Administration Philadelphia, Pa 191075587

  Timing: Fiscal Year 2003; Project Start 01-DEC-2002; Project End 30-NOV-2006

  Summary: (provided by applicant): **Sickle cell disease** (SCD) and Cooley's anemia (CA) are disorders ameliorated by continued expression of fetal hemoglobin; first shown in patients with continued expression of fetal globin due to deletional or nondeletional hereditary persistence of fetal hemoglobin (HFPH). However, others express high fetal globin in the absence of mutation, and therapeutic agents, such as hydroxyurea, induce expression of Hb F. If the rate-limiting factors involved in the regulation of fetal hemoglobin were elucidated, targeted drug discovery could succeed in developing agents with this specific effect. Our proposal focuses on three areas: 1) identify new candidate modifiers using unbiased, genome-wide microarray-based expression profiling to define genes critical to induction of Hb F in cultured human erythroid progenitors. The candidates will be assessed for identification of genes that fall into several categories, including transcription factors, signaling and chromatin remodeling molecules. 2) examine suspected regulators of Hb F expression as well as a subset of differentially-expressed transcripts comparing cord to adult erythroid cultures for functionally relevant genetic variation associated with elevated Hb F levels. Known regulators (KLFs, NFE-4 and soluble guanylate cyclase) and the most promising of the candidate transactivators identified by expression profiling will be explored to identify putative coding region and proximal promoter sequence allelic variants using both public databases and SNP discovery methods. Those with allele frequencies of 10% or more in a small group of SCD patients, will be tested in sequential cohorts of adult and pediatric patients with SCD with and without elevated Hb F. Significant QTL loci will then be examined in a group of parent-child trios and followed with a third population of SCD patients. 3) functional validation of candidate modifiers will be accomplished by knockdown technology employing morpholino antisense oligos and/or interference RNA (iRNA) using K562 cells containing a fetal globin promoter-driven GFP readout from a beta-like globin gene cluster BAC. We are confident that our strategy to identify critical regulatory molecules for Hb F regulation and our ability to quickly and reliably

screen for candidate gene variants will have significant impact on the development of therapeutic intervention strategies for patients with SCD and CA.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ULTRASONIC METHOD FOR TESTING ANTI SICKLING AGENTS**

  Principal Investigator & Institution: Baruch, Martin C.; Empirical Technologies Corporation 3050-A Berkmar Dr Charlottesville, Va 22906

  Timing: Fiscal Year 2002; Project Start 01-SEP-1999; Project End 31-AUG-2003

  Summary: (provided by applicant): The results of the Phase I effort, during the course of which the blood samples of 7 HbSS patients were examined, established the feasibility of using phase-sensitive acoustic detection techniques to quantitatively monitor the polymerization of HbSS. The effects of introducing anti-sickling agents were also clearly resolved in the results. In addition, the acoustic measurements performed on 5 normal blood samples revealed the techniques sensitivity by demonstrating the reproducible resolution of the minute acoustic response to de-oxygenation of normal blood. With the basic response question settled, the primary aim of the Phase II effort will be to develop a laboratory prototype that can be used by a third party to support anti-sickling drug research efforts, general sickle cell research, as well as be potentially used as a potential diagnostic tool in clinical settings. In order to accomplish this goal, the following specific aims will be pursued under Phase II: 1. An improved experimental prototype will be designed. 2. A stable and repeatable test substrate (cell suspension) will be developed. 3. The device will be characterized extensively with regard to calibration, sensitivity, and sample variability. 4. The effects of an extensive number of anti-sickling agents will be measured. PROPOSED COMMERCIAL APPLICATION: Not Available

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: UNIV OF TX SOUTHWESTERN COMPREHENSIVE MED SICKLE CELL CT**

  Principal Investigator & Institution: Buchanan, George R.; Pediatrics; University of Texas Sw Med Ctr/Dallas Dallas, Tx 753909105

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 31-MAR-2008

  Summary: In recent years, treatments for **Sickle Cell Disease** (SCD) have significantly decreased the frequency and duration of sickle cell crises and significantly lengthened the life expectancy of patients. These improvements have been due to clinical, genetic and molecular advances that have revealed basic aspects of the pathophysiology of SCD. In spite of these advances, SCD remains associated with significant mortality and morbidity. The large body of data for autologous stem cell bone marrow transplantation has shown it to be effective for a minority of patients with SCD, but early mortality, the availability of suitable donors and factors involved in patient selection remain limiting factors. As an alternative, genetic correction of SCD offers hope as a potential curative approach for the majority of patients. Recent progress in the development of mouse models of hemoglobin disorders and in lentivirus-based vector design have provided strong rationale and impetus for preclinical implementation of gene therapy approaches for SCD. In this proposal, we address three important challenges to the successful genetic correction of SCD. First, we develop lentivirus-based vectors for the transduction of human gamma-globin genes. These vectors include regulatory elements that are critical for high-level single copy gene expression and are evaluated both in transgenic mice and model cell lines. Second, we evaluate their transduction efficiency into bone marrow-derived hematopoietic stem cells from SCD patients. And third, we

evaluate these transduced cells in vivo using a human/mouse xenograft model of bone marrow transplantation. The preclinical data obtained from these experiments will serve as the rational basis for the implementation of future clinical gene therapy protocols aimed at the genetic correction of SCD.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: USE OF MODIFIED EKLF FOR GAMMA GLOBIN AUGMENTATION**

  Principal Investigator & Institution: Manwani, Deepa G.; Pediatrics; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 10029

  Timing: Fiscal Year 2002; Project Start 30-SEP-2000; Project End 31-AUG-2005

  Summary: (adapted from the application) **Sickle cell anemia** and related hemoglobinopathies are among the most common genetic disorders in this country. Reactivation of fetal globin by pharmacologic agents provides therapeutic benefits in these patients by interfering with the polymerization of the mutant hemoglobin. This proposal outlines an alternative approach for augmentation of fetal hemoglobin. All vertebrate animals switch hemoglobins during development from fetal to adult type. The molecular mechanisms that mediate this process are complex. Erythroid Kruppel like factor (EKLF) is an erythroid specific transcription factor that plays a crucial role in activating beta globin expression and in consolidating the switch from fetal to adult globin. In its absence not only is adult beta globin expression abolished, but there is a competitive increase in gamma globin expression. This has led us to consider whether manipulating EKLF's molecular properties so that it acts as a transcriptional repressor might further augment and stabilize gamma globin gene expression. The above hypothesis will be tested by: (1) Constructing repressor EKLF constructs and testing them by transient transfection assays in cell lines. (2) Monitoring the functional importance of repressor constructs in differentiating embryonic stem cells and transgenic mice.(3) Analyzing the effect of repressor constructs on sickle erythropoiesis in liquid cultures. The end result of these aims will be to provide a transcriptional reagent for gene therapy approaches that will augment fetal hemoglobin levels in patients with **sickle cell disease.** Amelioration of the debilitating effects of this disease provides a considerable clinical rationale for pursuing this goal.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: VASCULAR PATHOBIOLOGY OF SICKLE CELL DISEASE**

  Principal Investigator & Institution: Hebbel, Robert P.; Professor and Vice-Chairman; Medicine; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2002; Project Start 30-SEP-1995; Project End 31-MAR-2006

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: VASO-OCCLUSIVE PROCESSES IN SICKLE CELL RETINOPATHY**

  Principal Investigator & Institution: Lutty, Gerard A.; Associate Professor; Ophthalmology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2003; Project Start 30-SEP-1990; Project End 31-MAR-2007

  Summary: (provided by applicant): **Sickle cell disease** has the highest incidence for a population at risk of any genetically-derived disease. Three in every 1000 African Americans born have **sickle cell anemia** (SS disease). Vaso-occlusions from sickling of

erythrocytes (RBCs) occur in most organs and are the initiating event in sickle cell retinopathy, which occurs in 15-30% of African Americans (depending on genotype) with **sickle cell disease.** We have identified three possible mechanisms of vaso-occlusion in the sickle cell retina in our prior studies with a rat model for sickle erythrocyte (RBC)-mediated vaso-occlusion: 1) tumor necrosis factor alpha (TNFa) stimulated adherence of sickle reticulocytes to vascular endothelium; 2) retention of dense sickled RBCs in hypoxic conditions; and 3) transient retention of sickled RBCs in normal rats as observed with the Rodenstock Scanning Laser Ophthalmoscope (SLO). Retention of sickled RBCs by Mechanism 1 was inhibited by antagonists of VLA-4, an integrin present on some sickled reticulocytes, and by antibodies against fibronectin administered intravenously. One of the proposed studies will determine the effect of TNFa on endothelial cells that stimulates reticulocyte adherence using parallel flow chambers, confocal microscopy, and scanning electron microscopy. Nitric oxide will be evaluated as a therapy for dense, irreversibly sickled cells mediated occlusions (Mechanism 2). The Proposal will also evaluate sites of sickled RBC-mediated vaso-occlusions for injury to endothelial cells, changes in the retinal milieu, and production of cytokines in the retina. Finally, all three mechanisms will be investigated in real time using the Rodenstock SLO. Therapies for prevention of vaso-occlusion or disruption of formed vaso-occlusions will be evaluated for their ability to shorten retention time or eliminate retention of sickled RBCs in real time using the SLO. In summary, this proposal will further investigate the mechanisms of vaso-occlusion in sickle cell retinopathy and will suggest strategies to prevent this initiating event in sickle cell retinopathy and necrosis in other organ systems.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

E-Journals: PubMed Central[3]

PubMed Central (PMC) is a digital archive of life sciences journal literature developed and managed by the National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM).[4] Access to this growing archive of e-journals is free and unrestricted.[5] To search, go to **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Pmc**, and type "sickle cell anemia" (or synonyms) into the search box. This search gives you access to full-text articles. The following is a sample of items found for sickle cell anemia in the PubMed Central database:

- **A human embryonic hemoglobin inhibits Hb S polymerization in vitro and restores a normal phenotype to mouse models of sickle cell disease.** by He Z, Russell JE.; 2002 Aug 6;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=124997
- **Aged garlic extract therapy for sickle cell anemia patients.** by Takasu J, Uykimpang R, Sunga MA, Amagase H, Niihara Y.; 2002;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=117242

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[3] Adapted from the National Library of Medicine: **http://www.pubmedcentral.nih.gov/about/intro.html**.

[4] With PubMed Central, NCBI is taking the lead in preservation and maintenance of open access to electronic literature, just as NLM has done for decades with printed biomedical literature. PubMed Central aims to become a world-class library of the digital age.

[5] The value of PubMed Central, in addition to its role as an archive, lies in the availability of data from diverse sources stored in a common format in a single repository. Many journals already have online publishing operations, and there is a growing tendency to publish material online only, to the exclusion of print.

- **Allele-specific enzymatic amplification of beta-globin genomic DNA for diagnosis of sickle cell anemia.** by Wu DY, Ugozzoli L, Pal BK, Wallace RB.; 1989 Apr; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=286997
- **Experiences of hospital care and treatment seeking for pain from sickle cell disease: qualitative study.** by Maxwell K, Streetly A, Bevan D.; 1999 Jun 12; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=28137
- **Genetic risk factors for cerebrovascular disease in children with sickle cell disease: design of a case-control association study and genomewide screen.** by Adams GT, Snieder H, McKie VC, Clair B, Brambilla D, Adams RJ, Kutlar F, Kutlar A.; 2003; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=183831
- **Oxygen radical inhibition of nitric oxide-dependent vascular function in sickle cell disease.** by Aslan M, Ryan TM, Adler B, Townes TM, Parks DA, Thompson JA, Tousson A, Gladwin MT, Patel RP, Tarpey MM, Batinic-Haberle I, White CR, Freeman BA.; 2001 Dec 18; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=65009
- **Partially Oxygenated Sickled Cells: Sickle-Shaped Red Cells Found in Circulating Blood of Patients with Sickle Cell Disease.** by Asakura T, Mattiello JA, Obata K, Asakura K, Reilly MP, Tomassini N, Schwartz E, Ohene-Frempong K.; 1994 Dec 20; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=45484
- **Phase angle correlates with n-3 fatty acids and cholesterol in red cells of Nigerian children with sickle cell disease.** by VanderJagt DJ, Trujillo MR, Bode-Thomas F, Huang YS, Chuang LT, Glew RH.; 2003; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=156645
- **Reaping of nitric oxide by sickle cell disease.** by Lancaster JR Jr.; 2002 Jan 22; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=117341
- **Recombinant Human Hemoglobins Designed for Gene Therapy of Sickle Cell Disease.** by McCune SL, Reilly MP, Chomo MJ, Asakura T, Townes TM.; 1994 Oct 11; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=44915
- **Retroviral Transfer of a Human [beta]-Globin/[delta]-Globin Hybrid Gene Linked to [beta] Locus Control Region Hypersensitive Site 2 Aimed at the Gene Therapy of Sickle Cell Disease.** by Takekoshi KJ, Oh YH, Westerman KW, London IM, Leboulch P.; 1995 Mar 28; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=42349
- **Role of free radicals in the pathogenesis of acute chest syndrome in sickle cell disease.** by Klings ES, Farber HW.; 2001; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=59517
- **Structural analysis of the 5' flanking region of the beta-globin gene in African sickle cell anemia patients: further evidence for three origins of the sickle cell mutation in Africa.** by Chebloune Y, Pagnier J, Trabuchet G, Faure C, Verdier G, Labie D, Nigon V.; 1988 Jun; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=280443

- **Transgenic knockout mice exclusively expressing human hemoglobin S after transfer of a 240-kb [beta]s-globin yeast artificial chromosome: A mouse model of sickle cell anemia.** by Chang JC, Lu R, Lin C, Xu SM, Kan YW, Porcu S, Carlson E, Kitamura M, Yang S, Flebbe-Rehwaldt L, Gaensler KM.; 1998 Dec 8;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=24545

The National Library of Medicine: PubMed

One of the quickest and most comprehensive ways to find academic studies in both English and other languages is to use PubMed, maintained by the National Library of Medicine.[6] The advantage of PubMed over previously mentioned sources is that it covers a greater number of domestic and foreign references. It is also free to use. If the publisher has a Web site that offers full text of its journals, PubMed will provide links to that site, as well as to sites offering other related data. User registration, a subscription fee, or some other type of fee may be required to access the full text of articles in some journals.

To generate your own bibliography of studies dealing with sickle cell anemia, simply go to the PubMed Web site at **http://www.ncbi.nlm.nih.gov/pubmed**. Type "sickle cell anemia" (or synonyms) into the search box, and click "Go." The following is the type of output you can expect from PubMed for sickle cell anemia (hyperlinks lead to article summaries):

- **A case of Peutz-Jeghers syndrome associated with duodenal carcinoma and sickle cell anemia.**
  Author(s): Avendano-Garcia M, Mercado U, Marin ME.
  Source: The American Journal of Gastroenterology. 2002 March; 97(3): 762-3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11922580&dopt=Abstract

- **A comparative study of the morbidity associated with sickle cell anemia among patients in Ibadan (Nigeria) and Oakland (U.S.A.).**
  Author(s): Oyejide OC, Adeyokunnu AA, Kraus JF, Fanti C.
  Source: Trop Geogr Med. 1982; 34(4): 341-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7168003&dopt=Abstract

- **A modified life table method to study congenital genetic disorders: an application in sickle cell anemia.**
  Author(s): Chan LS, Powars D, Lee J, Weiss J.
  Source: J Chronic Dis. 1982; 35(5): 401-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7068813&dopt=Abstract

[6] PubMed was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The PubMed database was developed in conjunction with publishers of biomedical literature as a search tool for accessing literature citations and linking to full-text journal articles at Web sites of participating publishers. Publishers that participate in PubMed supply NLM with their citations electronically prior to or at the time of publication.

- **A randomized trial of captopril for microalbuminuria in normotensive adults with sickle cell anemia.**
  Author(s): Foucan L, Bourhis V, Bangou J, Merault L, Etienne-Julan M, Salmi RL.
  Source: The American Journal of Medicine. 1998 April; 104(4): 339-42.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9576406&dopt=Abstract

- **A trauma patient with sickle cell anemia.**
  Author(s): Ross C.
  Source: Journal of Emergency Nursing: Jen : Official Publication of the Emergency Department Nurses Association. 1997 June; 23(3): 211-3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9283355&dopt=Abstract

- **Abnormal phospholipid molecular species of erythrocytes in sickle cell anemia.**
  Author(s): Connor WE, Lin DS, Thomas G, Ey F, DeLoughery T, Zhu N.
  Source: Journal of Lipid Research. 1997 December; 38(12): 2516-28.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9458275&dopt=Abstract

- **Abnormalities of the central nervous system in very young children with sickle cell anemia.**
  Author(s): Wang WC, Langston JW, Steen RG, Wynn LW, Mulhern RK, Wilimas JA, Kim FM, Figueroa RE.
  Source: The Journal of Pediatrics. 1998 June; 132(6): 994-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9627592&dopt=Abstract

- **Acute myocardial infarction in sickle cell anemia.**
  Author(s): Assanasen C, Quinton RA, Buchanan GR.
  Source: Journal of Pediatric Hematology/Oncology : Official Journal of the American Society of Pediatric Hematology/Oncology. 2003 December; 25(12): 978-81.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14663284&dopt=Abstract

- **Adenotonsillar hypertrophy: a precipitating factor of cerebrovascular accident in a child with sickle cell anemia.**
  Author(s): Wali YA, al-Lamki Z, Soliman H, al-Okbi H.
  Source: Journal of Tropical Pediatrics. 2000 August; 46(4): 246-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10996992&dopt=Abstract

- **Alpha Thalassemia is associated with decreased risk of abnormal transcranial Doppler ultrasonography in children with sickle cell anemia.**
  Author(s): Hsu LL, Miller ST, Wright E, Kutlar A, McKie V, Wang W, Pegelow CH, Driscoll C, Hurlet A, Woods G, Elsas L, Embury S, Adams RJ; Stroke Prevention Trial (STOP) and the Cooperative Study of Sickle Cell Disease (CSSCD).
  Source: Journal of Pediatric Hematology/Oncology : Official Journal of the American Society of Pediatric Hematology/Oncology. 2003 August; 25(8): 622-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12902915&dopt=Abstract

- **alpha-thalassemia in Bantu population from Congo-Brazzaville: its interaction with sickle cell anemia.**
  Author(s): Mouele R, Pambou O, Feingold J, Galacteros F.
  Source: Human Heredity. 2000 March-April; 50(2): 118-25.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10799970&dopt=Abstract

- **Alveolar bone patterns in sickle cell anemia and non-sickle cell anemia adolescent Nigerians: a comparative study.**
  Author(s): Arowojolu MO, Savage KO.
  Source: J Periodontol. 1997 March; 68(3): 225-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9100197&dopt=Abstract

- **An extension of stochastic curtailment for incompletely reported and classified recurrent events: the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH).**
  Author(s): McMahon RP, Waclawiw MA, Geller NL, Barton FB, Terrin ML, Bonds DR.
  Source: Controlled Clinical Trials. 1997 October; 18(5): 420-30.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9315425&dopt=Abstract

- **Anti-beta s-ribozyme reduces beta s mRNA levels in transgenic mice: potential application to the gene therapy of sickle cell anemia.**
  Author(s): Alami R, Gilman JG, Feng YQ, Marmorato A, Rochlin I, Suzuka SM, Fabry ME, Nagel RL, Bouhassira EE.
  Source: Blood Cells, Molecules & Diseases. 1999 April; 25(2): 110-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10389593&dopt=Abstract

- **Anti-s antibody-associated delayed hemolytic transfusion reaction in patients with sickle cell anemia.**
  Author(s): Kalyanaraman M, Heidemann SM, Sarnaik AP, Meert KL, Sarnaik SA.
  Source: Journal of Pediatric Hematology/Oncology : Official Journal of the American Society of Pediatric Hematology/Oncology. 1999 January-February; 21(1): 70-3. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10029818&dopt=Abstract

- **Ascorbate levels in red blood cells and urine in patients with sickle cell anemia.**
  Author(s): Westerman MP, Zhang Y, McConnell JP, Chezick PA, Neelam R, Freels S, Feldman LS, Allen S, Baridi R, Feldman LE, Fung LW.
  Source: American Journal of Hematology. 2000 October; 65(2): 174-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10996838&dopt=Abstract

- **Aspartame effect in sickle cell anemia.**
  Author(s): Manion CV, Howard J, Ogle B, Parkhurst J, Edmundson A.
  Source: Clinical Pharmacology and Therapeutics. 2001 May; 69(5): 346-55.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11372003&dopt=Abstract

- **Asymmetrical closure of epiphyses in a patient with sickle cell anemia.**
  Author(s): Collett-Solberg PF, Ware RE, O'Hara SM.
  Source: J Pediatr Endocrinol Metab. 2002 September-October; 15(8): 1207-12.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12387521&dopt=Abstract

- **Autoimmune liver disease and sickle cell anemia in children: a report of three cases.**
  Author(s): Chuang E, Ruchelli E, Mulberg AE.
  Source: Journal of Pediatric Hematology/Oncology : Official Journal of the American Society of Pediatric Hematology/Oncology. 1997 March-April; 19(2): 159-62.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9149749&dopt=Abstract

- **Automated oxyhemoglobin dissociation curve construction to assess sickle cell anemia therapy.**
  Author(s): Young RC Jr, Rachal RE, Del Pilar Aguinaga M, Nelson BL, Kim BC, Winter WP, Castro O.
  Source: Journal of the National Medical Association. 2000 September; 92(9): 430-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11052456&dopt=Abstract

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  Author(s): Rao SP, Desai N, Miller ST.
  Source: Journal of Pediatric Hematology/Oncology : Official Journal of the American Society of Pediatric Hematology/Oncology. 1996 May; 18(2): 175-7.
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  Author(s): Klein P, McMeeking A, Goldenberg A.
  Source: The American Journal of Medicine. 1997 April; 102(4): 416.
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- **Barriers to bone marrow transplantation for sickle cell anemia.**
  Author(s): Walters MC, Patience M, Leisenring W, Eckman JR, Buchanan GR, Rogers ZR, Olivieri NE, Vichinsky E, Davies SC, Mentzer WC, Powars D, Scott JP, Bernaudin F, Ohene-Frempong K, Darbyshire PJ, Wayne A, Roberts IA, Dinndorf P, Brandalise S, Sanders JE, Matthews DC, Appelbaum FR, Storb R, Sullivan KM.
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- **Beta S-gene-cluster haplotypes in sickle cell anemia patients from two regions of Brazil.**
  Author(s): Costa FF, Arruda VR, Goncalves MG, Miranda SR, Carvalho MH, Sonati MF, Saad SO, Gesteira F, Fernandes D, Nascimento ML, et al.
  Source: American Journal of Hematology. 1994 January; 45(1): 96-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8250018&dopt=Abstract

- **Beta-S gene cluster haplotypes modulate hematologic and hemorheologic expression in sickle cell anemia. Use in predicting clinical severity.**
  Author(s): Powars DR, Meiselman HJ, Fisher TC, Hiti A, Johnson C.
  Source: Am J Pediatr Hematol Oncol. 1994 February; 16(1): 55-61.
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  Author(s): Goncalves MS, Bomfim GC, Maciel E, Cerqueira I, Lyra I, Zanette A, Bomfim G, Adorno EV, Albuquerque AL, Pontes A, Dupuit MF, Fernandes GB, dos Reis MG.
  Source: Brazilian Journal of Medical and Biological Research = Revista Brasileira De Pesquisas Medicas E Biologicas / Sociedade Brasileira De Biofisica. [et Al.]. 2003 October; 36(10): 1283-8. Epub 2003 September 16.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14502357&dopt=Abstract

- **Blalock-Taussig shunt for tetralogy of Fallot in a patient with sickle cell anemia. A case report.**
  Author(s): O'Keefe JD, LePere R, Britton HA.
  Source: Jama : the Journal of the American Medical Association. 1967 April 17; 200(3): 252-4.
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  Author(s): Jaja SI, Ikotun AR, Gbenebitse S, Temiye EO.
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  Author(s): Wong WY, Powars DR, Operskalski EA, Hassett J, Parker JW, Sarnaik S, Pegelow CH, Hilgartner MW, Johnson CS, Zhou Y, et al.
  Source: Blood. 1995 April 15; 85(8): 2091-7.
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  Author(s): Ferster A, Bujan W, Corazza F, Devalck C, Fondu P, Toppet M, Verhas M, Sariban E.
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  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8427992&dopt=Abstract

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  Author(s): Vermylen C, Cornu G.
  Source: Current Opinion in Hematology. 1996 March; 3(2): 163-6. Review.
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  Author(s): Abboud MR, Jackson SM, Barredo J, Beatty J, Laver J.
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  Source: The Journal of Pediatrics. 1994 February; 124(2): 329-30.
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  Author(s): Gupta P.
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  Author(s): Kalinyak KA, Morris C, Ball WS, Ris MD, Harris R, Rucknagel D.
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  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11224704&dopt=Abstract

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  Author(s): Platt OS, Guinan EC.
  Source: The New England Journal of Medicine. 1996 August 8; 335(6): 426-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8663876&dopt=Abstract

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  Author(s): Hallowell MJ, Smith DP, Petronis J.
  Source: Clinical Nuclear Medicine. 1993 December; 18(12): 1083-5.
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  Author(s): Brinker MR, Thomas KA, Meyers SJ, Texada T, Humbert JR, Cook SD, Gitter R.
  Source: Am J Orthop. 1998 January; 27(1): 43-9.
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  Author(s): Njamkepo E, Delisle F, Hagege I, Gerbaud G, Guiso N.
  Source: Clinical Microbiology and Infection : the Official Publication of the European Society of Clinical Microbiology and Infectious Diseases. 2000 March; 6(3): 131-6.
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  Author(s): Nagel RL.
  Source: The Journal of Clinical Investigation. 1999 October; 104(7): 847-8.
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- **Cardiac abnormalities in children with sickle cell anemia.**
  Author(s): Batra AS, Acherman RJ, Wong WY, Wood JC, Chan LS, Ramicone E, Ebrahimi M, Wong PC.
  Source: American Journal of Hematology. 2002 August; 70(4): 306-12.
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  Author(s): Vocelka CR, Lindley GG, Mulligan MS.
  Source: J Extra Corpor Technol. 2001 December; 33(4): 243-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11806437&dopt=Abstract

- **Cardiopulmonary responses to exercise in women with sickle cell anemia.**
  Author(s): Callahan LA, Woods KF, Mensah GA, Ramsey LT, Barbeau P, Gutin B.
  Source: American Journal of Respiratory and Critical Care Medicine. 2002 May 1; 165(9): 1309-16.
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  Author(s): Gates A, Rogers MA, Puczynski M.
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- **Tissue factor expression by endothelial cells in sickle cell anemia.**
  Author(s): Solovey A, Gui L, Key NS, Hebbel RP.
  Source: The Journal of Clinical Investigation. 1998 May 1; 101(9): 1899-904.
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- **Tissue factor expression in sickle cell anemia.**
  Author(s): Hammerschmidt DE.
  Source: The Journal of Laboratory and Clinical Medicine. 2001 June; 137(6): 440.
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  Source: Am J Pediatr Hematol Oncol. 1982 Summer; 4(2): 213-5. No Abstract Available.
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  Author(s): Robertson PB, Danielson CF, McCarthy LJ.
  Source: Transfusion Science. 1997 June; 18(2): 195-8.
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  Author(s): Garbutt GJ, Wilson JT, Schuster GS, Leary JJ, Ward DC.
  Source: Clinical Chemistry. 1985 July; 31(7): 1203-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2988824&dopt=Abstract

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  Author(s): Eluwa EO, Obidoa O, Obi GO, Onwubiko HA.
  Source: Biochemical Medicine and Metabolic Biology. 1987 October; 38(2): 142-8.
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  Author(s): Koren A, Zalman L, Levin C, Abu Hana M, Mader R, Shalev S.
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  Author(s): Pianosi P, D'Souza SJ, Esseltine DW, Charge TD, Coates AL.
  Source: Am Rev Respir Dis. 1991 February; 143(2): 226-30.
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  Author(s): Chiu D, Vichinsky E, Ho SL, Liu T, Lubin BH.
  Source: Am J Pediatr Hematol Oncol. 1990 Fall; 12(3): 262-7.
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- **Water sports and sickle cell anemia.**
  Author(s): Ratner SJ, Athanasian EA.
  Source: Annals of Internal Medicine. 1986 December; 105(6): 971.
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  Author(s): Hibbeln J, Tarver D.
  Source: Ohio Nurses Rev. 1997 October; 72(9): 12. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9385174&dopt=Abstract

- **What the school health team should know about sickle cell anemia.**
  Author(s): Walker JE.
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  Author(s): Blei F, Puder DR.
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  Author(s): Alayash AI, Dafallah A, Al-Quorain A, Omer AH, Wilson MT.
  Source: Acta Haematologica. 1987; 77(2): 87-9.
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  Author(s): Alayash AI.
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  Author(s): Prasad AS.
  Source: Prog Clin Biol Res. 1981; 55: 99-122.
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- **Zinc in the treatment of homozygous sickle cell anemia: studies in an animal model.**
  Author(s): Schoomaker EB, Brewer GJ, Oelshlegel FJ Jr.
  Source: American Journal of Hematology. 1976; 1(1): 45-57.
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CHAPTER 2. NUTRITION AND SICKLE CELL ANEMIA

Overview

In this chapter, we will show you how to find studies dedicated specifically to nutrition and sickle cell anemia.

Finding Nutrition Studies on Sickle Cell Anemia

The National Institutes of Health's Office of Dietary Supplements (ODS) offers a searchable bibliographic database called the IBIDS (International Bibliographic Information on Dietary Supplements; National Institutes of Health, Building 31, Room 1B29, 31 Center Drive, MSC 2086, Bethesda, Maryland 20892-2086, Tel: 301-435-2920, Fax: 301-480-1845, E-mail: ods@nih.gov). The IBIDS contains over 460,000 scientific citations and summaries about dietary supplements and nutrition as well as references to published international, scientific literature on dietary supplements such as vitamins, minerals, and botanicals.[7] The IBIDS includes references and citations to both human and animal research studies.

As a service of the ODS, access to the IBIDS database is available free of charge at the following Web address: **http://ods.od.nih.gov/databases/ibids.html**. After entering the search area, you have three choices: (1) IBIDS Consumer Database, (2) Full IBIDS Database, or (3) Peer Reviewed Citations Only.

Now that you have selected a database, click on the "Advanced" tab. An advanced search allows you to retrieve up to 100 fully explained references in a comprehensive format. Type "sickle cell anemia" (or synonyms) into the search box, and click "Go." To narrow the search, you can also select the "Title" field.

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[7] Adapted from **http://ods.od.nih.gov**. IBIDS is produced by the Office of Dietary Supplements (ODS) at the National Institutes of Health to assist the public, healthcare providers, educators, and researchers in locating credible, scientific information on dietary supplements. IBIDS was developed and will be maintained through an interagency partnership with the Food and Nutrition Information Center of the National Agricultural Library, U.S. Department of Agriculture.

The following information is typical of that found when using the "Full IBIDS Database" to search for "sickle cell anemia" (or a synonym):

- **A comparison of two regimens of patient-controlled analgesia for children with sickle cell disease.**
  Author(s): Children's Hospital, Medical Center of Central GA, Macon 31208, USA.
  Source: Trentadue, N O Kachoyeanos, M K Lea, G J-Pediatr-Nurs. 1998 February; 13(1): 15-9 0882-5963

- **Alterations in sensitivity to calcium and enzymatic hydrolysis of membranes from sickle cell disease and trait erythrocytes.**
  Author(s): Department of Physiology and Developmental Biology and Neuroscience Center, Brigham Young University, Provo, Utah 84602, USA.
  Source: Judd, A M Best, K B Christensen, K Rodgers, G M Bell, J D Am-J-Hematol. 2003 March; 72(3): 162-9 0361-8609

- **Blood pressure, hematologic and erythrocyte fragility changes in children suffering from sickle cell anemia following ascorbic acid supplementation.**
  Author(s): Department of Physiology, College of Medicine, University of Lagos, Nigeria. sjaja4@yahoo.com
  Source: Jaja, S I Ikotun, A R Gbenebitse, S Temiye, E O J-Trop-Pediatr. 2002 December; 48(6): 366-70 0142-6338

- **Combined effects of in vitro penicillin and sickle cell disease sera on normal lymphocyte functions.**
  Author(s): Department of Pediatrics, Charles R. Drew University of Medicine and Science, King/Drew Medical Center, Los Angeles, California 90059, USA.
  Source: Taylor, Stephen C Shacks, Samuel J Qu, Zengwei Bryant, Psyhra J-Natl-Med-Assoc. 2002 August; 94(8): 678-85 0027-9684

- **Divergent nitric oxide bioavailability in men and women with sickle cell disease.**
  Author(s): Critical Care Medicine Department, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Md 20892-1662, USA. mgladwin@nih.gov
  Source: Gladwin, M T Schechter, A N Ognibene, F P Coles, W A Reiter, C D Schenke, W H Csako, G Waclawiw, M A Panza, J A Cannon, R O 3rd Circulation. 2003 January 21; 107(2): 271-8 1524-4539

- **Effect of anti-IL-6 and anti-10 monoclonal antibodies on the suppression of the normal T lymphocyte mitogenic response by steady state sickle cell disease sera.**
  Author(s): Department of Pediatrics, Charles R. Drew University of Medicine & Science, King/Drew Medical Center, Los Angeles, California 90059, USA.
  Source: Taylor, S Shacks, S Qu, Z Immunol-Invest. 2001 August; 30(3): 209-19 0882-0139

- **Effect of hydroxyurea therapy on resting energy expenditure in children with sickle cell disease.**
  Author(s): The Children's Hospital of Philadelphia, Department of Pediatrics, University of Pennsylvania School of Medicine, 19104, USA.
  Source: Fung E, B Barden E, M Kawchak D, A Zemel B, S Ohene Frempong, K Stallings V, A J-Pediatr-Hematol-Oncol. 2001 December; 23(9): 604-8 1077-4114

- **Efficacy of nalbuphine as a parenteral analgesic for the treatment of painful episodes in children with sickle cell disease.**
  Author(s): Department of Pediatrics, Children's Mercy Hospital, University of Missouri-Kansas City School of Medicine 64108.
  Source: Woods, G M Parson, P M Strickland, D K J-Assoc-Acad-Minor-Phys. 1990; 1(3): 90-2 1048-9886

- **Endothelial dysfunction in patients with sickle cell disease is related to selective impairment of shear stress-mediated vasodilation.**
  Author(s): Service de Physiologie-Explorations Fonctionnelles and the Centre de la Drepanocytose, Hopital Henri Mondor, APHP et Universite Paris XII, France. laurent.belhassen@hmn.ap-hop-paris.fr
  Source: Belhassen, L Pelle, G Sediame, S Bachir, D Carville, C Bucherer, C Lacombe, C Galacteros, F Adnot, S Blood. 2001 March 15; 97(6): 1584-9 0006-4971

- **Energy expenditure and intake in children with sickle cell disease during acute illness.**
  Author(s): Department of Pediatrics, University of Pennsylvania School of Medicine and Divisions of Gastroenterology & Nutrition and Hematology, Children's Hospital of Philadelphia, PA 19104, USA.
  Source: Fung, E B Malinauskas, B M Kawchak, D A Koh, B Y Zemel, B S Gropper, S S Ohene Frempong, K Stallings, V A Clin-Nutr. 2001 April; 20(2): 131-8 0261-5614

- **Energy intake and resting metabolic rate in preschool Jamaican children with homozygous sickle cell disease.**
  Author(s): MRC Childhood Nutrition Research Center, Institute of Child Health, London, United Kingdom. a.singhal@ich.ucl.ac.uk
  Source: Singhal, Atul Parker, Stephany Linsell, Louise Serjeant, Graham Am-J-Clin-Nutr. 2002 June; 75(6): 1093-7 0002-9165

- **Epidural analgesia in a child with sickle cell disease complicated by acute abdominal pain and priapism.**
  Author(s): Departement d'Anesthesie et Reanimation, Centre Hospitalier Universitaire de Bicetre, Le Kremlin Bicetre, France.
  Source: Labat, F Dubousset A, M Baujard, C Wasier A, P Benhamou, D Cucchiaro, G Br-J-Anaesth. 2001 December; 87(6): 935-6 0007-0912

- **Equation to estimate resting energy expenditure in adolescents with sickle cell anemia.**
  Author(s): Center for Nutrition and Department of Family and Community Medicine, Meharry Medical College, Nashville, TN 37208, USA. maciej.buchowski@mcmail.vanderbilt.edu
  Source: Buchowski, M S Chen, K Y Byrne, D Wang, W C Am-J-Clin-Nutr. 2002 December; 76(6): 1335-44 0002-9165

- **Hydroxyurea therapy associated with declining serum levels of magnesium in children with sickle cell anemia.**
  Author(s): Division of Hematology-Oncology, Columbus Children's Hospital and Ohio State University, 43205, USA.
  Source: Altura, Rachel A Wang, Winfred C Wynn, Lynn Altura, Burton M Altura, Bella T J-Pediatr. 2002 May; 140(5): 565-9 0022-3476

- **Hyperhomocysteinemia is associated with low plasma pyridoxine levels in children with sickle cell disease.**
  Author(s): Cincinnati Comprehensive Sickle Cell Center of the Division of Hematology/Oncology, Children's Hospital Medical Center, Ohio 45229, USA. balav0@chmcc.org
  Source: Balasa, Vinod V Kalinyak, Karen A Bean, Judy A Stroop, Davis Gruppo, Ralph A J-Pediatr-Hematol-Oncol. 2002 Jun-July; 24(5): 374-9 1077-4114

- **Low adjusted-dose acenocoumarol therapy in sickle cell disease: a pilot study.**
  Author(s): Department of Internal Medicine, the Red Cross Bloodbank Curacao, the Public Health Laboratory, St. Elisabeth Hospital, Curacao, Netherlands Antilles.

Source: Schnog, J B Kater, A P Mac Gillavry, M R Duits, A J Lard, L R van Der Dijs, F P Brandjes, D P ten Cate, H van Eps, L W Rojer, R A Am-J-Hematol. 2001 November; 68(3): 179-83 0361-8609

- **Management of sickle cell disease; lessons from the Jamaican Cohort Study.**
  Author(s): Medical Research Council Laboratories (Jamaica), University of the West Indies, Kingston.
  Source: Serjeant, G R Serjeant, B E Blood-Revolume 1993 September; 7(3): 137-45 0268-960X

- **Massive fat and necrotic bone marrow embolization in a previously undiagnosed patient with sickle cell disease.**
  Author(s): Institute of Forensic Sciences, San Juan, Puerto Rico.
  Source: Garza, J A Am-J-Forensic-Med-Pathol. 1990 March; 11(1): 83-8 0195-7910

- **Myocardial bridge in a patient with sickle cell anemia.**
  Author(s): Centro de Cardiologia Nao Invasiva, Sao Paulo, Brazil.
  Source: de Seixas, M A Franchin Junior, C A Silva, C E Leal, S M Ortiz, J Arq-Bras-Cardiol. 1999 February; 72(2): 191-200 0066-782X

- **Neutrophil activation in sickle cell disease.**
  Author(s): Department of Immunochematology, CLB, Amsterdam, The Netherlands.
  Source: Lard, L R Mul, F P de Haas, M Roos, D Duits, A J J-Leukoc-Biol. 1999 September; 66(3): 411-5 0741-5400

- **New therapies in sickle cell disease.**
  Author(s): Department of Hematology/Oncology, Children's Hospital Oakland, Oakland, CA 94609, USA. evichinsky@mail.cho.org
  Source: Vichinsky, E Lancet. 2002 August 24; 360(9333): 629-31 0140-6736

- **No effect of acenocoumarol therapy on levels of endothelial activation markers in sickle cell disease.**
  Author(s): Department of Internal Medicine, Slotervaart Hospital, Amsterdam, The Netherlands. jschnog@hotmail.com
  Source: Schnog, J B Mac Gillavry, M R Rojer, R A Meijers, J C Fijnheer, R ten Cate, H Brandjes, D P Duits, A J Am-J-Hematol. 2002 September; 71(1): 53-5 0361-8609

- **Nutritional problems in sickle cell disease patients.**
  Source: Mankad, Vipul N. Suskind, Robert M. Nutr-and-M.D. Van Nuys : PM, Inc. December 1983. volume 9 (12) page 1-2.

- **Optimization of folic acid, vitamin B(12), and vitamin B(6) supplements in pediatric patients with sickle cell disease.**
  Author(s): Analytic Diagnostic Center, Curacao, The Netherlands Antilles.
  Source: van der Dijs, Fey P L Fokkema, M Rebecca Dijck Brouwer, D A Janneke Niessink, Bram van der Wal, Thaliet I C Schnog, John John B Duits, Ashley J Muskiet, Fred D Muskiet, Frits A J Am-J-Hematol. 2002 April; 69(4): 239-46 0361-8609

- **Pentoxifylline (Trental) has no significant effect on laboratory parameters in sickle cell disease.**
  Author(s): Department of Medicine, Albert Einstein College of Medicine, Bronx, NY 10461.
  Source: Billett, H H Kaul, D K Connel, M M Fabry, M E Nagel, R L Nouv-Rev-Fr-Hematol. 1989; 31(6): 403-7

- **Phase angle and n-3 polyunsaturated fatty acids in sickle cell disease.**
  Author(s): Department of Biochemistry and Molecular Biology, University of New Mexico, School of Medicine, Albuquerque, NM 87131, USA.

Source: VanderJagt, D J Huang, Y S Chuang, L T Bonnett, C Glew, R H Arch-Dis-Child. 2002 September; 87(3): 252-4 1468-2044

- **Placebo controlled double-blind study of pentoxifylline in sickle cell disease patients.**
  Author(s): Dante Pazzanese Institute of Cardiology, Sao Paulo, Brazil.
  Source: Manrique, R V J-Med. 1987; 18(5-6): 277-91 0025-7850

- **Plasma-vitamin E and low plasma lipoprotein levels in sickle cell anemia patients.**
  Author(s): Department of Pediatrics, James H. Quillen College of Medicine, East Tennessee State University, Johnson City 37614.
  Source: Stone, W L Payne, P H Adebonojo, F O J-Assoc-Acad-Minor-Phys. 1990; 1(2): 12-6 1048-9886

- **Protection of erythrocyte membrane amino groups from reaction with methyl acetimidate by pyridoxal 5'-phosphate Schiff base formation [Sickle cell anemia, vitamin B6].**
  Source: Chao, T.L. Berenfeld, M.R. Gabuzda, T.G. Biochim-Biophys-Acta-Biomembranes. Amsterdam : Elsevier Biomedical Press. April 11, 1984. volume 771 (2) page 183-187. 0006-3002

- **Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival.**
  Author(s): Center for Sickle Cell Disease and Division of Cardiology, Department of Medicine, Howard University College of Medicine, Washington, DC 20059, USA. olcastro@aol.com
  Source: Castro, O Hoque, M Brown, B D Blood. 2003 February 15; 101(4): 1257-61 0006-4971

- **Random assignment and patient choice in a study of alternative pain relief for sickle cell disease.**
  Author(s): Yale University School of Nursing, USA. Leslie.Nield-Anderson@yale.edu
  Source: Nield Anderson, L Dixon, J K Lee, K West-J-Nurs-Res. 1999 April; 21(2): 266-74 0193-9459

- **RBC survival, zinc deficiency, and efficacy of zinc therapy in sickle cell disease.**
  Author(s): Doctor's Quarters, Medical College Campus, Nagpur, India.
  Source: Gupta, V L Choubey, B S Birth-Defects-Orig-Artic-Ser. 1987; 23(5A): 477-83 0547-6844

- **Reduced vitamin E antioxidant capacity in sickle cell disease is related to transfusion status but not to sickle crisis.**
  Author(s): Department of Haematology, City Hospital Trust, Birmingham, United Kingdom. sukhjinder.marwah@cityhospbham.wmids.nhs.uk
  Source: Marwah, S S Blann, A D Rea, C Phillips, J D Wright, J Bareford, D Am-J-Hematol. 2002 February; 69(2): 144-6 0361-8609

- **Reduction of pain episodes and prothrombotic activity in sickle cell disease by dietary n-3 fatty acids.**
  Author(s): Department of Hematology and Oncology, Winship Cancer Institute, Emory University School of Medicine and Georgia Sickle Cell Center of Grady Memorial Hospital, Atlanta 30303, USA.
  Source: Tomer, A Kasey, S Connor, W E Clark, S Harker, L A Eckman, J R Thromb-Haemost. 2001 June; 85(6): 966-74 0340-6245

- **Responses of normal and sickle cell hemoglobin to S-nitroscysteine: implications for therapeutic applications of NO in treatment of sickle cell disease.**
  Author(s): Nicholas School of the Environment and Earth Sciences, Duke University Marine Laboratory, Beaufort, NC 28516, USA. bona@duke.edu
  Source: Bonaventura, C Godette, G Ferruzzi, G Tesh, S Stevens, R D Henkens, R Biophys-Chem. 2002 July 10; 98(1-2): 165-81 0301-4622

- **Serum zinc, copper and magnesium in sickle cell disease at Ibadan, south western Nigeria.**
  Author(s): Department of Chemical Pathology, University College Hospital, Ibadan, Nigeria.
  Source: Akenami, F O Aken'Ova, Y A Osifo, B O Afr-J-Med-Med-Sci. 1999 Sep-December; 28(3-4): 137-9 0309-3913

- **Sickle cell anemia in the pediatric intensive care unit: novel approaches for managing life-threatening complications.**
  Author(s): Pediatric Critical Care, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, MD 20892-1664, USA. tjenkins@nih.gov
  Source: Jenkins, Tammara L AACN-Clin-Issues. 2002 May; 13(2): 154-68 1079-0713

- **Sickle cell anemia. Pathophysiological role of increased intracorpuscular calcium and changes during treatment with pentoxifylline.**
  Author(s): Instituto Dante Pazzanese de Cardiologia, Sao Paulo.
  Source: Manrique, R Ric-Clin-Lab. 1987 Oct-December; 17(4): 355-62 0390-5748

- **Sickle cell disease and nitrous oxide-induced neuropathy.**
  Author(s): Departments of Haematology and Neurology, St. Thomas' Hospital, London, UK.
  Source: Ogundipe, O Pearson, M W Slater, N G Adepegba, T Westerdale, N Clin-Lab-Haematol. 1999 December; 21(6): 409-12 0141-9854

- **Sickling in vitro of reticulocytes from patients with sickle cell disease at venous oxygen tension.**
  Author(s): Children's Hospital of Philadelphia, Department of Pediatrics, University of Pennsylvania School of Medicine 19104, USA.
  Source: Horiuchi, K Onyike, A E Osterhout, M L Exp-Hematol. 1996 January; 24(1): 68-76 0301-472X

- **Sickling of nucleated erythroid precursors from patients with sickle cell anemia.**
  Author(s): Laboratory of Chemical Biology, NIDDK, National Institutes of Health, Bethesda, MD 20892-1822, USA.
  Source: Hasegawa, S Rodgers, G P Dwyer, N Noguchi, C T Blanchette Mackie, E J Uyesaka, N Schechter, A N Fibach, E Exp-Hematol. 1998 April; 26(4): 314-9 0301-472X

- **Studies on the vasoocclusive crisis of sickle cell disease IV. Mechanism of action of pentoxifylline (Trental).**
  Author(s): Roswell Park Memorial Institute, Buffalo, NY 14263.
  Source: Ambrus, J L Meky, N Stadler, S Sills, R H Gastpar, H Raposa, T J-Med. 1988; 19(2): 67-88 0025-7850

- **Testosterone induced priapism in two adolescents with sickle cell disease.**
  Author(s): Department of Pediatrics, University of Florida College of Medicine, Gainesville 32610-0296, USA.
  Source: Slayton, W Kedar, A Schatz, D J-Pediatr-Endocrinol-Metab. 1995 Jul-September; 8(3): 199-203

- **The comprehensiveness care of sickle cell disease.**
  Author(s): Department of Haematology, Guy's & St Thomas' Hospitals Trust, London, UK. Iheanyi.Okpala@gstt.sthames.nhs.uk
  Source: Okpala, Iheanyi Thomas, Veronica Westerdale, Neil Jegede, Tina Raj, Kavita Daley, Sadie Costello Binger, Hilda Mullen, Jean Rochester Peart, Collis Helps, Sarah Tulloch, Emense Akpala, Mary Dick, Moira Bewley, Susan Davies, Mark Abbs, Ian Eur-J-Haematol. 2002 Mar; 68(3): 157-62 0902-4441
- **The Effect of sodium intake on zinc excretion in patients with sickle cell anemia.**
  Source: Matustik, M. Cassandra. Chausmer, Arthur B. Meyer, Walter J. III. J-Am-Coll-Nutr. New York : Alan R. Liss, Inc. 1982. volume 1 (4) page 331-336. charts. 0731-5724
- **The presentation, management and prevention of crisis in sickle cell disease in Africa.**
  Author(s): Wellcome Tropical Institute, London, U.K.
  Source: Fleming, A F Blood-Revolume 1989 March; 3(1): 18-28 0268-960X
- **The red cell distribution width in sickle cell disease--is it of clinical value?**
  Author(s): Department of Child Health, University of the West Indies, Mona, Kingston Jamaica.
  Source: Thame, M Grandison, Y Mason, K Thompson, M Higgs, D Morris, J Serjeant, B Serjeant, G Clin-Lab-Haematol. 1991; 13(3): 229-37 0141-9854
- **Vitamin B6 status of children with sickle cell disease.**
  Author(s): Division of Gastroenterology and Nutrition, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104-4399, USA.
  Source: Nelson, M C Zemel, B S Kawchak, D A Barden, E M Frongillo, E A Jr Coburn, S P Ohene Frempong, K Stallings, V A J-Pediatr-Hematol-Oncol. 2002 Aug-September; 24(6): 463-9 1077-4114
- **Zinc deficiency in sickle cell disease.**
  Source: Prasad, A.S. Trace elements in man and animals : TEMA 5 : proceedings of the fifth International Symposium on Trace Elements in Man and Animals / editors C.F. Mills, I. Bremner, & J.K. Chesters. Farnham Royal, Slough : Commonwealth Agricultural Bureaux, c1985. page 754-757. ISBN: 085198553X

Federal Resources on Nutrition

In addition to the IBIDS, the United States Department of Health and Human Services (HHS) and the United States Department of Agriculture (USDA) provide many sources of information on general nutrition and health. Recommended resources include:

- healthfinder®, HHS's gateway to health information, including diet and nutrition: **http://www.healthfinder.gov/scripts/SearchContext.asp?topic=238&page=0**
- The United States Department of Agriculture's Web site dedicated to nutrition information: **www.nutrition.gov**
- The Food and Drug Administration's Web site for federal food safety information: **www.foodsafety.gov**
- The National Action Plan on Overweight and Obesity sponsored by the United States Surgeon General: **http://www.surgeongeneral.gov/topics/obesity/**

- The Center for Food Safety and Applied Nutrition has an Internet site sponsored by the Food and Drug Administration and the Department of Health and Human Services: **http://vm.cfsan.fda.gov/**
- Center for Nutrition Policy and Promotion sponsored by the United States Department of Agriculture: **http://www.usda.gov/cnpp/**
- Food and Nutrition Information Center, National Agricultural Library sponsored by the United States Department of Agriculture: **http://www.nal.usda.gov/fnic/**
- Food and Nutrition Service sponsored by the United States Department of Agriculture: **http://www.fns.usda.gov/fns/**

Additional Web Resources

A number of additional Web sites offer encyclopedic information covering food and nutrition. The following is a representative sample:

- AOL: **http://search.aol.com/cat.adp?id=174&layer=&from=subcats**
- Family Village: **http://www.familyvillage.wisc.edu/med_nutrition.html**
- Google: **http://directory.google.com/Top/Health/Nutrition/**
- Healthnotes: **http://www.healthnotes.com/**
- Open Directory Project: **http://dmoz.org/Health/Nutrition/**
- Yahoo.com: **http://dir.yahoo.com/Health/Nutrition/**
- WebMD®Health: **http://my.webmd.com/nutrition**
- WholeHealthMD.com: **http://www.wholehealthmd.com/reflib/0,1529,00.html**

The following is a specific Web list relating to sickle cell anemia; please note that any particular subject below may indicate either a therapeutic use, or a contraindication (potential danger), and does not reflect an official recommendation:

- **Vitamins**

  Folic Acid
  Source: Healthnotes, Inc.; www.healthnotes.com

  Riboflavin
  Source: Integrative Medicine Communications; www.drkoop.com

  Vitamin A
  Source: Healthnotes, Inc.; www.healthnotes.com

  Vitamin B12
  Source: Healthnotes, Inc.; www.healthnotes.com

  Vitamin B2
  Source: Healthnotes, Inc.; www.healthnotes.com

Vitamin B2 (riboflavin)
Source: Integrative Medicine Communications; www.drkoop.com

Vitamin B6
Source: Healthnotes, Inc.; www.healthnotes.com

Vitamin C
Source: Healthnotes, Inc.; www.healthnotes.com

Vitamin E
Source: Healthnotes, Inc.; www.healthnotes.com

- **Minerals**

  Iron
  Source: Healthnotes, Inc.; www.healthnotes.com

  Magnesium
  Source: Healthnotes, Inc.; www.healthnotes.com

  Zinc
  Source: Healthnotes, Inc.; www.healthnotes.com

- **Food and Diet**

  Garlic
  Alternative names: Allium sativum
  Source: Healthnotes, Inc.; www.healthnotes.com

CHAPTER 3. ALTERNATIVE MEDICINE AND SICKLE CELL ANEMIA

Overview

In this chapter, we will begin by introducing you to official information sources on complementary and alternative medicine (CAM) relating to sickle cell anemia. At the conclusion of this chapter, we will provide additional sources.

The Combined Health Information Database

The Combined Health Information Database (CHID) is a bibliographic database produced by health-related agencies of the U.S. federal government (mostly from the National Institutes of Health) that can offer concise information for a targeted search. The CHID database is updated four times a year at the end of January, April, July, and October. Check the titles, summaries, and availability of CAM-related information by using the "Simple Search" option at the following Web site: **http://chid.nih.gov/simple/simple.html**. In the drop box at the top, select "Complementary and Alternative Medicine." Then type "sickle cell anemia" (or synonyms) in the second search box. We recommend that you select 100 "documents per page" and to check the "whole records" options. The following was extracted using this technique:

- **Foods that Fight Pain: Revolutionary New Strategies for Maximum Pain Relief**

  Source: New York, NY: Harmony Books. 1999. 347 p.

  Contact: Available from Harmony Books. 231 Broad Street, Nevada City, CA 95959. (530) 265-9564. PRICE: $14.00. ISBN: 0609804367.

  Summary: This book is intended to help people fight pain by using common foods, traditional supplements, and herbs. It explains which foods contribute to pain and how to avoid them, which foods are pain-safe but high in nutrition, and which foods can actively soothe pain by improving blood circulation, relieving inflammation, and balancing hormones. An introduction describes how food can fight pain at any of the stages of the pain process: the initial injury, the inflammatory response, the pain message traveling through the nerves, and the brain's perception of pain. Part 1 discusses conditions related to poor circulation, such as backaches and chest pain. Part 2

addresses conditions caused by food sensitivities and inflammation, including migraines, other headaches, joint ailments, stomach aches and digestive problems, and fibromyalgia. Part 3 discusses hormone-related conditions such as menstrual pain, breast pain, and cancer pain. Part 4 discusses metabolic and immune problems, including carpal tunnel syndrome, diabetes, herpes and shingles, **sickle cell anemia,** kidney stones, and urinary infections. Part 5 discusses the roles of exercise, rest, and sleep in pain relief; describes several stress-reducing exercises; and explains why the body rebels against certain foods. The book includes menus and recipes, a glossary of ingredients, a list of resources, a list of suggested readings, and an index.

National Center for Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (**http://nccam.nih.gov/**) has created a link to the National Library of Medicine's databases to facilitate research for articles that specifically relate to sickle cell anemia and complementary medicine. To search the database, go to the following Web site: **http://www.nlm.nih.gov/nccam/camonpubmed.html**. Select "CAM on PubMed." Enter "sickle cell anemia" (or synonyms) into the search box. Click "Go." The following references provide information on particular aspects of complementary and alternative medicine that are related to sickle cell anemia:

- **Acetazolamide in the treatment of sickle cell anemia.**
  Author(s): KHANDELWAL MK.
  Source: Indian J Pediatr. 1961 November; 28: 460-2. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14455551&dopt=Abstract

- **Aged garlic extract therapy for sickle cell anemia patients.**
  Author(s): Takasu J, Uykimpang R, Sunga M, Amagase H, Niihara Y.
  Source: Bmc Blood Disorders [electronic Resource]. 2002 June 19; 2(1): 3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12086586&dopt=Abstract

- **An intervention to increase coping and reduce health care utilization for school-age children and adolescents with sickle cell disease.**
  Author(s): Broome ME, Maikler V, Kelber S, Bailey P, Lea G.
  Source: J Natl Black Nurses Assoc. 2001 December; 12(2): 6-14.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11902023&dopt=Abstract

- **Autologous bone marrow transplant in a patient with sickle cell disease and diffuse large B-cell lymphoma.**
  Author(s): Onitilo AA, Lazarchick J, Brunson CY, Frei-Lahr D, Stuart RK.
  Source: Transplantation Proceedings. 2003 December; 35(8): 3089-92.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14697986&dopt=Abstract

- **Blood pressure, hematologic and erythrocyte fragility changes in children suffering from sickle cell anemia following ascorbic acid supplementation.**
  Author(s): Jaja SI, Ikotun AR, Gbenebitse S, Temiye EO.

Source: Journal of Tropical Pediatrics. 2002 December; 48(6): 366-70.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12521281&dopt=Abstract

- **Cardiac abnormalities in children with sickle cell anemia.**
  Author(s): Batra AS, Acherman RJ, Wong WY, Wood JC, Chan LS, Ramicone E, Ebrahimi M, Wong PC.
  Source: American Journal of Hematology. 2002 August; 70(4): 306-12.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12210812&dopt=Abstract

- **Cobaltous chloride therapy in sickle cell anemia.**
  Author(s): STOHLMAN F Jr, RATH CE.
  Source: Bull Georgetown Univ Med Cent. 1953 November; 7(2): 54-9. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=13106576&dopt=Abstract

- **Coenzyme Q10 in plasma and erythrocytes: comparison of antioxidant levels in healthy probands after oral supplementation and in patients suffering from sickle cell anemia.**
  Author(s): Niklowitz P, Menke T, Wiesel T, Mayatepek E, Zschocke J, Okun JG, Andler W.
  Source: Clinica Chimica Acta; International Journal of Clinical Chemistry. 2002 December; 326(1-2): 155-61.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12417107&dopt=Abstract

- **Does a clinical pathway improve the quality of care for sickle cell anemia?**
  Author(s): Co JP, Johnson KB, Duggan AK, Casella JF, Wilson M.
  Source: Jt Comm J Qual Saf. 2003 April; 29(4): 181-90.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12698808&dopt=Abstract

- **Effect of zinc supplementation on growth and body composition in children with sickle cell disease.**
  Author(s): Zemel BS, Kawchak DA, Fung EB, Ohene-Frempong K, Stallings VA.
  Source: The American Journal of Clinical Nutrition. 2002 February; 75(2): 300-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11815322&dopt=Abstract

- **Effect of zinc supplementation on serum testosterone level in adult male sickle cell anemia subjects.**
  Author(s): Prasad AS, Abbasi AA, Rabbani P, DuMouchelle E.
  Source: American Journal of Hematology. 1981; 10(2): 119-27.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6786094&dopt=Abstract

- **Eight children with coexistent sickle cell anemia and plumbism.**
  Author(s): Seeler RA.

Source: Clinical Pediatrics. 1974 June; 13(6): 499-501.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=4209022&dopt=Abstract

- **Erythrocytic ecdysis in smears of EDTA venous blood in eight patients with sickle cell anemia.**
  Author(s): Rao KR, Patel AR.
  Source: Blood Cells. 1987; 12(3): 543-53.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3115341&dopt=Abstract

- **Evaluation of Fagara zanthoxyloides root extract in sickle cell anemia blood in vitro.**
  Author(s): Honig GR, Farnsworth NR, Ferenc C, Vida LN.
  Source: Lloydia. 1975 September-October; 38(5): 387-90.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1202311&dopt=Abstract

- **Exciting new treatment approaches for pathyphysiologic mechanisms of sickle cell disease.**
  Author(s): Mankad VN.
  Source: Pediatric Pathology & Molecular Medicine. 2001 January-February; 20(1): 1-13. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12673841&dopt=Abstract

- **Excretion of iron in response to deferoxamine in sickle cell anemia.**
  Author(s): Cohen A, Schwartz E.
  Source: The Journal of Pediatrics. 1978 April; 92(4): 659-62.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=633013&dopt=Abstract

- **Folate status assessment and folic acid supplements in sickle cell disease.**
  Author(s): Schnog JB, van der Dijs FP, Fokkema MR, Muskiet FD, Muskiet FA.
  Source: Journal of Pediatric Hematology/Oncology : Official Journal of the American Society of Pediatric Hematology/Oncology. 2001 November; 23(8): 548.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11878785&dopt=Abstract

- **Folate supplementation in sickle cell anemia.**
  Author(s): Hoffer LJ.
  Source: The New England Journal of Medicine. 2003 August 21; 349(8): 813; Author Reply 813.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12930937&dopt=Abstract

- **Frequent and prolonged hospitalizations: a risk factor for early mortality in sickle cell disease patients.**
  Author(s): Houston-Yu P, Rana SR, Beyer B, Castro O.

Source: American Journal of Hematology. 2003 March; 72(3): 201-3.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12605392&dopt=Abstract

- **Further studies in the use of hyperbaric oxygen in retinal detachment with sickle cell anemia.**
Author(s): Freilich DB, Seelenfreund MH.
Source: Mod Probl Ophthalmol. 1975; 15: 313-7.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1160909&dopt=Abstract

- **Hepatic iron stores and plasma ferritin concentration in patients with sickle cell anemia and thalassemia major.**
Author(s): Brittenham GM, Cohen AR, McLaren CE, Martin MB, Griffith PM, Nienhuis AW, Young NS, Allen CJ, Farrell DE, Harris JW.
Source: American Journal of Hematology. 1993 January; 42(1): 81-5.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8416302&dopt=Abstract

- **Homocysteine levels and sickle cell anemia: response to Rana et al.**
Author(s): Wang WC.
Source: Journal of Pediatric Hematology/Oncology : Official Journal of the American Society of Pediatric Hematology/Oncology. 2000 March-April; 22(2): 186-7.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10779040&dopt=Abstract

- **Hyperbaric oxygen, retinal detachment, and sickle cell anemia.**
Author(s): Freilich DB, Seelenfreund MH.
Source: Archives of Ophthalmology. 1973 August; 90(2): 90-3.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=4721212&dopt=Abstract

- **Hypnotically induced pain control in sickle cell anemia.**
Author(s): Zeltzer L, Dash J, Holland JP.
Source: Pediatrics. 1979 October; 64(4): 533-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=492819&dopt=Abstract

- **Iron chelation therapy in sickle cell anemia.**
Author(s): Cohen A, Schwartz E.
Source: American Journal of Hematology. 1979; 7(1): 69-76.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=507048&dopt=Abstract

- **Malevolent ogbanje: recurrent reincarnation or sickle cell disease?**
Author(s): Nzewi E.
Source: Social Science & Medicine (1982). 2001 May; 52(9): 1403-16.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11286364&dopt=Abstract

- **Optimization of folic acid, vitamin B(12), and vitamin B(6) supplements in pediatric patients with sickle cell disease.**
  Author(s): van der Dijs FP, Fokkema MR, Dijck-Brouwer DA, Niessink B, van der Wal TI, Schnog JJ, Duits AJ, Muskiet FD, Muskiet FA.
  Source: American Journal of Hematology. 2002 April; 69(4): 239-46.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11921017&dopt=Abstract

- **Oral L-glutamine therapy for sickle cell anemia: I. Subjective clinical improvement and favorable change in red cell NAD redox potential.**
  Author(s): Niihara Y, Zerez CR, Akiyama DS, Tanaka KR.
  Source: American Journal of Hematology. 1998 June; 58(2): 117-21.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9625578&dopt=Abstract

- **Pernicious anemia with neuropsychiatric dysfunction in a patient with sickle cell anemia treated with folate supplementation.**
  Author(s): Dhar M, Bellevue R, Carmel R.
  Source: The New England Journal of Medicine. 2003 May 29; 348(22): 2204-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12773647&dopt=Abstract

- **Phase angle and n-3 polyunsaturated fatty acids in sickle cell disease.**
  Author(s): VanderJagt DJ, Huang YS, Chuang LT, Bonnett C, Glew RH.
  Source: Archives of Disease in Childhood. 2002 September; 87(3): 252-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12193445&dopt=Abstract

- **Plasma homocysteine levels and folate status in children with sickle cell anemia.**
  Author(s): Rodriguez-Cortes HM, Griener JC, Hyland K, Bottiglieri T, Bennett MJ, Kamen BA, Buchanan GR.
  Source: Journal of Pediatric Hematology/Oncology : Official Journal of the American Society of Pediatric Hematology/Oncology. 1999 May-June; 21(3): 219-23.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10363855&dopt=Abstract

- **Prevention of the painful crises of sickle cell anemia with prothrombinopenic anticoagulants: report of a case.**
  Author(s): RODMAN T, MYERSON RM, PASTOR BH.
  Source: The American Journal of the Medical Sciences. 1961 December; 242: 707-11.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14493136&dopt=Abstract

- **Random assignment and patient choice in a study of alternative pain relief for sickle cell disease.**
  Author(s): Nield-Anderson L, Dixon JK, Lee K.
  Source: Western Journal of Nursing Research. 1999 April; 21(2): 266-74.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11512181&dopt=Abstract

- **Reduction of pain episodes and prothrombotic activity in sickle cell disease by dietary n-3 fatty acids.**
  Author(s): Tomer A, Kasey S, Connor WE, Clark S, Harker LA, Eckman JR.
  Source: Thrombosis and Haemostasis. 2001 June; 85(6): 966-74.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11434703&dopt=Abstract

- **Reticulocytosis following ACTH in sickle cell anemia; case report.**
  Author(s): BISGEIER GP.
  Source: J Med Soc N J. 1953 January; 50(1): 24-5. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=13023352&dopt=Abstract

- **Role of spirituality in patients with sickle cell disease.**
  Author(s): Cooper-Effa M, Blount W, Kaslow N, Rothenberg R, Eckman J.
  Source: The Journal of the American Board of Family Practice / American Board of Family Practice. 2001 March-April; 14(2): 116-22.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11314918&dopt=Abstract

- **Self-regulation and assessment approaches for vaso-occlusive pain management for pediatric sickle cell anemia patients.**
  Author(s): Hall H, Chiarucci K, Berman B.
  Source: Int J Psychosom. 1992; 39(1-4): 28-33.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1428615&dopt=Abstract

- **Sickle cell anemia.**
  Author(s): ADAMS RC.
  Source: Phys Ther Rev. 1955 April; 35(4): 185-7. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14370978&dopt=Abstract

- **Sickle cell anemia.**
  Author(s): JAMES GW 3rd, PORTER WB.
  Source: Postgraduate Medicine. 1952 April; 11(4): 357-62.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14920314&dopt=Abstract

- **Sickle cell anemia: a potential nutritional approach for a molecular disease.**
  Author(s): Ohnishi ST, Ohnishi T, Ogunmola GB.
  Source: Nutrition (Burbank, Los Angeles County, Calif.). 2000 May; 16(5): 330-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10793299&dopt=Abstract

- **Sickle cell disease: current clinical management.**
  Author(s): Ballas SK.

Source: Semin Hematol. 2001 October; 38(4): 307-14. Review.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11605165&dopt=Abstract

- **Support for A&E nurses caring for patients with sickle cell disease.**
  Author(s): Thomas VN, Ellis C.
  Source: Nursing Standard : Official Newspaper of the Royal College of Nursing. 2000 October 18-24; 15(5): 35-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11971509&dopt=Abstract

- **The comprehensiveness care of sickle cell disease.**
  Author(s): Okpala I, Thomas V, Westerdale N, Jegede T, Raj K, Daley S, Costello-Binger H, Mullen J, Rochester-Peart C, Helps S, Tulloch E, Akpala M, Dick M, Bewley S, Davies M, Abbs I.
  Source: European Journal of Haematology. 2002 March; 68(3): 157-62. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12068796&dopt=Abstract

- **The fatty acid composition of the serum phospholipids of children with sickle cell disease in Nigeria.**
  Author(s): Glew RH, Casados JK, Huang YS, Chuang LT, VanderJagt DJ.
  Source: Prostaglandins, Leukotrienes, and Essential Fatty Acids. 2002 October; 67(4): 217-22.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12401435&dopt=Abstract

- **The role of red blood cell exchange transfusion in the treatment and prevention of complications of sickle cell disease.**
  Author(s): Danielson CF.
  Source: Therapeutic Apheresis : Official Journal of the International Society for Apheresis and the Japanese Society for Apheresis. 2002 February; 6(1): 24-31. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11886573&dopt=Abstract

- **Transfusion therapy: a coming-of-age treatment for patients with sickle cell disease.**
  Author(s): Reed W, Vichinsky EP.
  Source: Journal of Pediatric Hematology/Oncology : Official Journal of the American Society of Pediatric Hematology/Oncology. 2001 May; 23(4): 197-202. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11846294&dopt=Abstract

- **Transfusional hemosiderosis in sickle cell anemia: another cause of an echogenic pancreas.**
  Author(s): Flyer MA, Haller JO, Sundaram R.
  Source: Pediatric Radiology. 1993; 23(2): 140-2.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8516039&dopt=Abstract

- **Treatment of sickle cell anemia with cobalt chloride.**
  Author(s): WOLF J, LEVY IJ.
  Source: Ama Arch Intern Med. 1954 March; 93(3): 387-96. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=13123563&dopt=Abstract

- **Treatment of sickle cell anemia.**
  Author(s): LEAVELL BS.
  Source: Ama Arch Intern Med. 1954 November; 94(5): 801-5. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=13206460&dopt=Abstract

- **Zinc deficiency and effects of zinc supplementation on sickle cell anemia subjects.**
  Author(s): Prasad AS.
  Source: Prog Clin Biol Res. 1981; 55: 99-122.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7291206&dopt=Abstract

Additional Web Resources

A number of additional Web sites offer encyclopedic information covering CAM and related topics. The following is a representative sample:

- Alternative Medicine Foundation, Inc.: **http://www.herbmed.org/**
- AOL: **http://search.aol.com/cat.adp?id=169&layer=&from=subcats**
- Chinese Medicine: **http://www.newcenturynutrition.com/**
- drkoop.com®: **http://www.drkoop.com/InteractiveMedicine/IndexC.html**
- Family Village: **http://www.familyvillage.wisc.edu/med_altn.htm**
- Google: **http://directory.google.com/Top/Health/Alternative/**
- Healthnotes: **http://www.healthnotes.com/**
- MedWebPlus:
  http://medwebplus.com/subject/Alternative_and_Complementary_Medicine
- Open Directory Project: **http://dmoz.org/Health/Alternative/**
- HealthGate: **http://www.tnp.com/**
- WebMD®Health: **http://my.webmd.com/drugs_and_herbs**
- WholeHealthMD.com: **http://www.wholehealthmd.com/reflib/0,1529,00.html**
- Yahoo.com: **http://dir.yahoo.com/Health/Alternative_Medicine/**

The following is a specific Web list relating to sickle cell anemia; please note that any particular subject below may indicate either a therapeutic use, or a contraindication (potential danger), and does not reflect an official recommendation:

- **General Overview**

  Anemia
  Source: Integrative Medicine Communications; www.drkoop.com

  Hypochondriasis
  Source: Integrative Medicine Communications; www.drkoop.com

  Male Infertility
  Source: Healthnotes, Inc.; www.healthnotes.com

  Night Blindness
  Source: Healthnotes, Inc.; www.healthnotes.com

  Sickle Cell Anemia
  Source: Healthnotes, Inc.; www.healthnotes.com

  Sickle Cell Anemia
  Source: Integrative Medicine Communications; www.drkoop.com

- **Herbs and Supplements**

  Beta-carotene
  Source: Healthnotes, Inc.; www.healthnotes.com

  Carotenoids
  Source: Healthnotes, Inc.; www.healthnotes.com

General References

A good place to find general background information on CAM is the National Library of Medicine. It has prepared within the MEDLINEplus system an information topic page dedicated to complementary and alternative medicine. To access this page, go to the MEDLINEplus site at **http://www.nlm.nih.gov/medlineplus/alternativemedicine.html**. This Web site provides a general overview of various topics and can lead to a number of general sources.

CHAPTER 4. DISSERTATIONS ON SICKLE CELL ANEMIA

Overview

In this chapter, we will give you a bibliography on recent dissertations relating to sickle cell anemia. We will also provide you with information on how to use the Internet to stay current on dissertations. **IMPORTANT NOTE:** When following the search strategy described below, you may discover non-medical dissertations that use the generic term "sickle cell anemia" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on sickle cell anemia, we have not necessarily excluded non-medical dissertations in this bibliography.

Dissertations on Sickle Cell Anemia

ProQuest Digital Dissertations, the largest archive of academic dissertations available, is located at the following Web address: **http://wwwlib.umi.com/dissertations**. From this archive, we have compiled the following list covering dissertations devoted to sickle cell anemia. You will see that the information provided includes the dissertation's title, its author, and the institution with which the author is associated. The following covers recent dissertations found when using this search procedure:

- **An Investigation of the Effects of Counseling on Adolescents with Diagnosed Sickle Cell Anemia** by Huntley, Ola Mae, EDD from University of San Francisco, 1983, 141 pages
  http://wwwlib.umi.com/dissertations/fullcit/8404364
- **Differential Perceptions of Sickle Cell Anemia Patients** by Battle, Stanley Fred, PhD from University of Pittsburgh, 1980, 189 pages
  http://wwwlib.umi.com/dissertations/fullcit/8018278
- **Drawing Blood: Medical Conceptions of Disease in 20th Century America, from Chlorosis to Sickle Cell Anemia (Twentieth Century, Blood Diseases)** by Wailoo, Keith, PhD from University of Pennsylvania, 1992, 425 pages
  http://wwwlib.umi.com/dissertations/fullcit/9308675

- **Identification of the Areas of Knowledge and Behavioral Skills for Sickle Cell Anemia Patient Education Program Development** by Graumlich, Sally Elizabeth, EDD from University of Cincinnati, 1989, 347 pages
  http://wwwlib.umi.com/dissertations/fullcit/9003236
- **Impact of Sickle Cell Anemia on Attitudes and Relationships among Particular Family Members.** by Sellers, Frank, Jr., PhD from University of Pittsburgh, 1974, 128 pages
  http://wwwlib.umi.com/dissertations/fullcit/7419522
- **Law, Medicine and Public Policy: The Sickle Cell Anemia Control Act of 1972. A Case Study** by Schmidt, Robert Milton, PhD from Emory University, 1982, 269 pages
  http://wwwlib.umi.com/dissertations/fullcit/8214059
- **Life, Ethics, and Sickle Cell Anemia: a Single Gene Disorder in a Contingent World (Senegal)** by Fullwiley, Duana Clarice, PhD from Univ. of Calif., Berkeley with the Univ. of Calif., San Francisco, 2002, 388 pages
  http://wwwlib.umi.com/dissertations/fullcit/3082612
- **Maximal Oxygen Uptake of Male Sickle Cell Anemia Trait Subjects.** by Robinson, Joe Richard, EDD from Arizona State University, 1975, 150 pages
  http://wwwlib.umi.com/dissertations/fullcit/7516258
- **Neuropsychological Functioning in Children with Sickle Cell Anemia** by Swift, Andrea Veruki, PhD from University of Georgia, 1987, 110 pages
  http://wwwlib.umi.com/dissertations/fullcit/8712695
- **Psychosocial Characteristics and Scholastic Performance of Children with Sickle Cell Disease** by Nettles, Arie Luticia Quinn, PhD from Peabody College for Teachers of Vanderbilt University, 1987, 127 pages
  http://wwwlib.umi.com/dissertations/fullcit/8722552
- **Relationships of Zinc, Copper, Cholesterol and Erythrocyte Oxidant Stress in Sickle Cell Anemia** by Bereza, Ulana Lydia, PhD from The University of Michigan, 1985, 207 pages
  http://wwwlib.umi.com/dissertations/fullcit/8520868
- **Respiratory Function in Children with Sickle Cell Anemia.** by Borden, Michael Douglas, PhD from Temple University, 1977, 149 pages
  http://wwwlib.umi.com/dissertations/fullcit/7713543
- **Sickle Cell Disease and Its Effect on Parental Relations, Family Environment and Self-Perceptions of Black Adolescents** by Nevergold, Barbara Seals, PhD from State University of New York at Buffalo, 1986, 165 pages
  http://wwwlib.umi.com/dissertations/fullcit/8619347
- **Sociomedical Investigation of Sickle Cell Anemia: Screening and Coping.** by Oke, Ezekiel Adewale, PhD from University of Kentucky, 1977, 173 pages
  http://wwwlib.umi.com/dissertations/fullcit/7815760
- **The Concept of Genetic Disease and Theories of Medical Progress. (Volumes I and II) (Sickle Cell Anemia)** by Juengst, Eric Thomas, PhD from Georgetown University, 1985, 459 pages
  http://wwwlib.umi.com/dissertations/fullcit/8613937

- **The Expectations for the Future of Children with Hematologic Disorders and Their Mothers (Sickle Cell Anemia, ITP)** by Schiller, Marilyn, PhD from New York University, 1989, 182 pages
  http://wwwlib.umi.com/dissertations/fullcit/9004322
- **The Impact of Selected Internal and External Influences on Successful Coping among Mothers of Children with Sickle Cell Disease** by Smith, Virginia Ware, PhD from Saint Louis University, 1980, 235 pages
  http://wwwlib.umi.com/dissertations/fullcit/8120648
- **The Psychoeducational Effects of Sickle Cell Anemia: Analysis of School Success/Nonsuccess in a Group of Children with Sickle Cell Anemia** by Allen, Patrick Lawrence, EDD from University of Cincinnati, 1983, 172 pages
  http://wwwlib.umi.com/dissertations/fullcit/8323183
- **The Signifying Disease: Difference, Discrimination and the Discourse of Sickle Cell Anemia** by Tapper, Melbourne Ximines, PhD from The University of Connecticut, 1990, 388 pages
  http://wwwlib.umi.com/dissertations/fullcit/9102040
- **The Social Support Needs of Parents of Children with Sickle Cell Anemia (Natural, Helping Networks, System)** by Lester, Bernadette Maria Fitts, DSW from The University of Alabama, 1985, 137 pages
  http://wwwlib.umi.com/dissertations/fullcit/8519400

Keeping Current

Ask the medical librarian at your library if it has full and unlimited access to the *ProQuest Digital Dissertations* database. From the library, you should be able to do more complete searches via **http://wwwlib.umi.com/dissertations**.

CHAPTER 5. CLINICAL TRIALS AND SICKLE CELL ANEMIA

Overview

In this chapter, we will show you how to keep informed of the latest clinical trials concerning sickle cell anemia.

Recent Trials on Sickle Cell Anemia

The following is a list of recent trials dedicated to sickle cell anemia.[8] Further information on a trial is available at the Web site indicated.

- **Arginine Treatment of Acute Chest Syndrome (Pneumonia) in Sickle Cell Disease Patients**

  Condition(s): Anemia, Sickle Cell; Pneumonia

  Study Status: This study is currently recruiting patients.

  Sponsor(s): FDA Office of Orphan Products Development

  Purpose - Excerpt: This is a study to determine if oral arginine will increase nitric oxide in **sickle cell disease** (SCD) patients with acute chest syndrome (ACS). It will also assess the effects of arginine in the body and how the body uses nitric oxide in ACS.

  Phase(s): Phase II

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00029731

- **Atorvastatin Therapy to Improve Endothelial Function in Sickle Cell Disease**

  Condition(s): Hemoglobin SC Disease

  Study Status: This study is currently recruiting patients.

  Sponsor(s): Warren G Magnuson Clinical Center (CC)

[8] These are listed at **www.ClinicalTrials.gov**.

Purpose - Excerpt: This study will examine the effects of oral atorvastatin on the linings of blood vessels in patients with **sickle cell disease,** plus the agent's effect on blood markers of inflammation and blood vessel function. **Sickle cell disease** is a recessive genetic disorder and the most common genetic disease affecting African Americans. Inherited are abnormal genes that make hemoglobin, the substance within red blood cells that carries oxygen from the lungs to the body. In the disease, sickle hemoglobin leads to rigidity or hardness of the red cells, causing obstruction in small blood vessels, inflammation, and injury to organs when the flow of blood to them is blocked. Some medications already prescribed for other diseases, such as atorvastatin, which is used for lowering cholesterol levels, can improve blood flow. Patients 18 to 65 years of age who have **sickle cell disease,** who have not had an acute pain episode within the previous week, and who are not pregnant or lactating may be eligible for this study. They will undergo a complete medical history; physical examination; baseline blood tests; and echocardiogram, in which an ultrasound wand is placed against the chest wall to get images inside the heart and blood vessels. In addition, patients will have blood flow studies. During the procedure, they will lie in an adjustable reclining chair for 5 to 6 hours. There will be 20- to 30-minute rests between specific activities and blood samples will be drawn intermittently for testing. Small tubes will be placed in the artery of the forearm at the inside of the elbow. Normal saline will be infused into one tube. A small pressure cuff will be applied to the wrist and a larger cuff to the upper arm. Both cuffs will be attached to an inflation device. A device like a rubber band, a strain gauge, will be placed around the widest part of the forearm. When the pressure cuffs are inflated, blood will flow into the arm, stretching the gauge proportion to blood flow, and information will be recorded. Then light reflected from the patients' hand and the blood flow in the forearm will be measured. Activity of the genes in the white blood cells will be measured as well. Small amounts of sodium nitroprusside, widely used to reduce blood pressure in people with dangerously high blood pressure, will be injected and blood flow will be measured. Later, small amounts of acetylcholine will be injected. It usually causes blood vessels to expand. After that, small amounts of L-NMMA will be injected. It usually decreases local blood flow by blocking the production of nitric oxide in the cells lining the arm's blood vessels. Then acetylcholine combined with L-NMMA will be injected. After that, oxypurinol, an agent taken by many patients to prevent gout, will be injected. The procedures will be repeated, with oxypurinol given along with each of the agents, and the measurement of blood flow in the forearm will be measured after each drug combination. Afterward, patients will be treated for 4 weeks at home with oral atorvastatin. They will be asked to visit the Clinical Center every 2 weeks for collection of blood samples and an examination. After 4 weeks of taking atorvastatin orally, they will be asked to return to repeat the blood flow studies, but only the first half will be conducted. The part using oxypurinol will not be needed. Regarding some of the blood samples collected during the study, there will be an examination of the genes found in the white blood cells. Specific attention will go to those genes that make proteins for cell-to-cell interaction and inflammation, plus those that cause blood cells to stick to the lining of blood vessels.

Phase(s): Phase I

Study Type: Interventional

Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00072826

- **Bone Marrow Transplantation in Treating Children With Sickle Cell Disease**

  Condition(s): Sickle Cell Anemia

  Study Status: This study is currently recruiting patients.

  Sponsor(s): Fred Hutchinson Cancer Research Center

  Purpose - Excerpt: RATIONALE: **Sickle cell disease** is an inherited disorder in which abnormal, crescent-shaped red blood cells interfere with the ability of the blood to carry oxygen through the body and can cause severe pain, stroke, and organ damage. Bone marrow transplantation, is a procedure in which the soft, sponge-like tissue in the center of bones producing white blood cells, red blood cells, and platelets is replaced by bone marrow from a another person. Bone marrow transplantation may be an effective treatment in relieving the symptoms of **sickle cell disease.** PURPOSE: Phase I/II trial to study the effectiveness of bone marrow transplantation in treating children who have **sickle cell disease.**

  Phase(s): Phase I; Phase II

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00004485

- **Collection and Storage of Umbilical Cord Stem Cells for Treatment of Sickle Cell Disease**

  Condition(s): Healthy; Sickle Cell Anemia

  Study Status: This study is currently recruiting patients.

  Sponsor(s): National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

  Purpose - Excerpt: This study will determine the best ways to collect, process and store umbilical cord blood from babies with **sickle cell disease, sickle cell trait** and unaffected babies. **Sickle cell disease** is an abnormality of the hemoglobin in red blood cells that causes the cells to change shape and clump together, preventing their normal flow in the bloodstream. This impairs blood flow to various organs, and the resulting oxygen deprivation causes organ damage. Cord blood is rich in stem cells (cells produced in the bone marrow that mature to different types of blood cells), which may prove useful in new sickle cell therapies. However, cord blood from babies with **sickle cell trait, sickle cell disease** and normal babies may act differently under laboratory conditions, so it is important to learn how best to work with blood from all three groups of babies for future use in possible treatments. Pregnant women between 18 and 45 years of age who are at risk of having an infant with **sickle cell disease** and normal volunteers who are pregnant and not at risk for this disease may be eligible for this study. Potential participants will be counseled about donating her infant's blood in order to make an informed choice. All women who participate in the study will provide a medical history and have blood collected from the umbilical cord and placenta (afterbirth) after the baby's delivery. The blood will be tested for various infectious diseases, processed, frozen and stored for research purposes. In addition, blood from women with babies at risk for **sickle cell disease** will be tested for the presence of the sickle cell gene, tissue typed, and used for research as follows: - **Sickle cell disease** - If cord blood tests show the baby has **sickle cell disease,** the blood will be frozen for an indefinite period of time for possible use in future treatment of the child. This treatment could include stem cell transplantation or gene therapy, treatments are not currently considered routine for **sickle cell disease.** - **Sickle cell trait** or normal hemoglobin - If

cord blood tests show the baby has **sickle cell trait** or is unaffected, the blood will be processed and stored for up to 3 years, during which time it may possibly be used to treat a currently living or future sibling with **sickle cell disease.** After 3 years, the participant may agree to either have the blood discarded, given to research or moved to another facility for continued storage at the participant's expense, if there is a storage fee. Alternatively, if there is no anticipated future need for the collected blood, or if it does not meet standards needed for future treatment, it will be used in NIH-approved research studies. Participants and their family doctor or the baby's pediatrician will be contacted twice a year for information about changes in the baby's health. Participants may also be asked permission to perform new tests developed by researchers.

Study Type: Observational

Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00012545

- **Development of a Hospital-Based Home Program for the Use of Inhaled Nitric Oxide in the Chronic Management of Severe Cardiopulmonary Diseases**

  Condition(s): Pulmonary Hypertension; Lung Disease; Sickle Cell Disease; Cardiac transplant; Lung transplant

  Study Status: This study is currently recruiting patients.

  Sponsor(s): INO Therapeutics

  Purpose - Excerpt: The purpose of this program is to evaluate the logistic issues and patient requirements for chronic pulsed INOmax delivery in ambulatory, home-care patients. To understand patient needs, patients with a variety of underlying diseases will be included. Safety of chronic therapy will be monitored by serial measurements of methemoglobin, platelet function assay and reported adverse events.

  Phase(s): Phase II

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00041574

- **Evaluation of Hydroxyurea Plus L-arginine or Sildenafil to Treat Sickle Cell Anemia**

  Condition(s): Sickle Cell Anemia

  Study Status: This study is currently recruiting patients.

  Sponsor(s): Warren G Magnuson Clinical Center (CC)

  Purpose - Excerpt: Patients with sickle cell disease have abnormal hemoglobin (the protein in red blood cells that carries oxygen to the body). This abnormality causes red blood cells to take on a sickle shape, producing disease symptoms. Fetal hemoglobin, a type of hemoglobin present in fetuses and babies, can prevent red cells from sickling. The drug hydroxyurea increases fetal hemoglobin production in patients with sickle cell disease by making a molecule called nitric oxide. The drugs L-arginine and Sildenafil (Viagra) increase the amount or the effect of nitric oxide. This study will evaluate: - The safety of giving L-arginine or Sildenafil together with hydroxyurea in patients with sickle cell disease; - The effectiveness of L-arginine plus hydroxyurea or Sildenafil plus hydroxyurea in increasing fetal hemoglobin in patients with sickle cell disease; and - The effectiveness of L-arginine plus hydroxyurea or Sildenafil and hydroxyurea in lowering blood pressure in the lungs of patients with sickle cell disease. (Pulmonary

blood pressure is elevated in about one-third of patients with sickle cell disease, and this condition increases the risk of dying from the disease.) Patients with hemoglobin S-only, S-beta-thalassemia, or other sickle cell disease genotype may be eligible for this study. Before starting treatment, patients will have a complete medical history and physical examination. All patients will take hydroxyurea once a day every day by mouth for at least 2 months. They will be admitted to the NIH Clinical Center to take their first dose of hydroxyurea, and will have blood drawn through a catheter (plastic tube placed in a vein) every hour for 6 hours for tests to determine nitric oxide levels. After discharge, they will return to the clinic once every 2 weeks to check for treatment side effects and for blood tests to monitor hemoglobin and fetal hemoglobin levels. After fetal hemoglobin levels have been stable for 2 months, patients will be admitted to the Clinical Center for their first dose of L-arginine (for men) or Sildenafil (for women). Again, blood samples will be collected through a catheter once an hour for 6 hours. If there are no complications, patients will be discharged and will continue taking hydroxyurea once a day and L-arginine or Sildenafil three times a day for at least 3 months until fetal hemoglobin levels have been stable for at least 2 months. Patients will return to the clinic for blood tests every week for 2 weeks and then every 2 weeks to monitor hemoglobin and fetal hemoglobin levels and to check for treatment side effects. Patients will have eye examinations before and during treatment. Some patients with sickle cell disease develop abnormalities in the blood vessels of the eye. Also, Sildenafil can cause temporary changes in color vision. Rarely, more serious eye problems can occur, such as bleeding from the eye blood vessels or damage to the retina-a layer of tissue that lines the back of the eye. Patients will also have an echocardiogram (ultrasound of the heart) before beginning treatment, after hydroxyurea treatment, and after 1 and 3 months of combined treatment with hydroxyurea and L-arginine or Sildenafil to help measure blood pressure in the lungs. Patients who develop complications from L-arginine or Sildenafil may continue in the study on hydroxyurea alone. Patients whose fetal hemoglobin levels increase with the combination therapy of hydroxyurea and L-arginine or Sildenafil may continue to take them.

Phase(s): Phase I

Study Type: Interventional

Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00056433

- **Home Based Massage and Relaxation for Sickle Cell Pain**

  Condition(s): Sickle Cell Disease

  Study Status: This study is currently recruiting patients.

  Sponsor(s): National Center for Complementary and Alternative Medicine (NCCAM)

  Purpose - Excerpt: The purpose of this study is to compare the effects of in-home, family-administered massage and in-home relaxation training on measures of physical status and health care utilization in a sample of African American adolescents age 15 years and older and adults with chronic pain associated with **sickle cell disease** who have been randomly assigned to six sessions of either family-administered massage or progressive muscle relaxation training.

  Phase(s): Phase II

  Study Type: Interventional

  Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00066079

- **Induction of Stable Chimerism for Sickle Cell Anemia**

  Condition(s): Blood Disease; Hematopoietic Stem Cell Transplantation; Anemia, Sickle Cell

  Study Status: This study is currently recruiting patients.

  Sponsor(s): National Heart, Lung, and Blood Institute (NHLBI)

  Purpose - Excerpt: To investigate a modified hematopoeitic cell transplantation (HCT) procedure for sickle cell disease that significantly reduces the toxicity of HCT, yet retains its therapeutic benefit.

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00029393

- **Inhaled Nitric Oxide and Transfusion Therapy for Patients with Sickle Cell Anemia and Secondary Pulmonary Hypertension**

  Condition(s): Sickle Cell Anemia; Pulmonary Hypertension

  Study Status: This study is currently recruiting patients.

  Sponsor(s): National Heart, Lung, and Blood Institute (NHLBI)

  Purpose - Excerpt: This study will test whether inhaling nitric oxide gas mixed with room air can improve pulmonary hypertension (high blood pressure in the lungs) in patients with sickle cell anemia. It is estimated that 20 to 30 percent of patients with sickle cell anemia have moderate to severe pulmonary hypertension, a disease complication associated with higher rates of illness and death. Patients with sickle cell disease 18 years of age or older may be eligible to participate in one or more parts of this three-stage study. Candidates will be screened with a medical history, physical examination, electrocardiogram, echocardiogram and blood tests. Those enrolled will undergo the following tests and procedures: Stage 1: Patients will be tested to determine the cause of pulmonary hypertension. They will have an echocardiogram (ultrasound study of the heart); a test for asthma, with measurement of arterial blood oxygen levels; oxygen breathing study with measurement of arterial blood oxygen levels; chest X-ray; computed tomography (CT) scans of the lung with and without contrast material; magnetic resonance imaging (MRI) of the heart; 6-minute walk to measure the distance covered in that time at a comfortable pace; night-hawks oxygen measurement while sleeping; blood tests for HIV, hepatitis virus, lupus and arthritis and pregnancy; pulmonary ventilation/perfusion scan with evaluation of shunt fraction to the brain and kidney; and exercise studies will be performed to determine oxygen and carbon dioxide consumption and production and to measure the anaerobic threshold. Stage 2: Patients who proceed with stage 2 will have a detailed MRI evaluation of the heart and will be admitted to the Clinical Center intensive care unit for the following procedure: A small intravenous (IV) catheter (plastic tube) is placed in the patient arm and a longer tube, called a central line, in a deeper neck or leg vein. A long thin tube is then inserted through the vein into the heart and the lung artery to measure all blood pressures in the heart and lungs directly. Following baseline measurements the following medications will be delivered for two hours each, separated by a 30 minute wash-out period. The patients is then given oxygen to breathe for 2 hours, followed by infusion of prostacyclin, a blood pressure-lowering drug, for 2 hours; and finally inhaled nitric

oxide for 2 hours. A small blood sample (3 tablespoons) of blood is drawn during the nitric oxide administration. Stage 3: For patients who complete stage II or III and do not respond to NO gas as determined by a decrease in mean or systolic pulmonary artery pressure of greater than 10% from baseline or a 10% increase in 6 minute walk distance, or are unable to receive it due to technical, regulatory (no free standing home structure for storage of NO gas, etc.) or personal lifestyle issues (some patient do not want to carry two tanks of gas - oxygen and NO - or have difficulty learning how to use the NO gas system), we will offer regular exchange transfusions and home oxygen for three months with a goal of maintaining hemoglobin levels of 8-10 and hemoglobin S levels of less than 40%. The monitoring of patients receiving exchange transfusions will be the same as for the patients receiving NO gas: Measurements will include pulmonary artery pressure measured by repeat right heart catheterization, other hemodynamic parameters, exercise tolerance by 6-minute walk, plasma adhesion molecule levels, neutrophil and monocyte mRNA gene profiles, and circulating erythroid progenitor cell a/a hemoglobin message and protein levels. This portion of the study is to be undertaken as an outpatient. Clinical follow-up will involve bi-weekly clinic visits with the principal investigator, associate investigators, or study nurse. At these clinic visits venous blood will be obtained for hemoglobin electrophoresis (including hemoglobin F and A2), CBC, ESR, C-reactive protein and standard chemistries. Research blood, for plasma and erythrocyte reactive nitrogen species and plasma adhesion molecule levels, will be collected with total blood drawn per day not to exceed 30 mL. Protocol nurse or principal investigator will record total weekly symptoms, emergency room visits, hospital admissions, and narcotic use. Echocardiograms and 6-minute walk will be repeated at two-week intervals. 32 mL of blood will be drawn prior to the exchange transfusion and a 4 and 8 weeks for neutrophil and monocyte mRNA expression chip profiling. Patients who develop any complication of their disease (i.e. vaso-occlusive crisis, acute chest syndrome, let ulcers, priapism, avascular necrosis of the femoral hip, asthma, etc.) will be strongly encouraged to directly come to the Clinical Center's 10D ICU for evaluation and direct admission by the 10D ICU physician on-call. If they are very ill they will be instructed to either call and ambulance or go to the nearest emergency room. If they are relatively stable, patients will be instructed to call the 10D ICU and speak with the physician on-call. We will follow patients according to the NO protocol with right heart catheterization at 3 months of therapy and serial echocardiograms. The effects of exchange transfusion will be statistically analyzed separately but in a similar fashion as delineated for NO treatment. All patients will complete Stage I and II of the study prior to entering into Exchange Transfusion therapy. Patients with greater than a 10% increase in six-minute walk distance or a 10% reduction in mean or systolic pulmonary artery pressures, who want to continue Exchange Transfusion therapy will have the option of continuing therapy. In these cases, blood draws and clinical follow-up will be reduced to bi-monthly intervals and when clinically indicated. The Clinical Center will continue to pay for these clinic visits and urgent care at the Clinical Center. The Transfusion Therapy and the Clinical Center care will continue until the study has terminated (anticipated three year study duration). Our physicians and social workers will work with patients to help them obtain appropriate insurance to cover Exchange Transfusion therapy. However, it is possible that circumstances may arise that prevent the patient from continuing this therapy after the study is terminated. Alternative Therapies Patients who have enrolled in the NO or transfusion treatment arm of the study who do not respond to the treatment (defined by a 10% reduction in mean or systolic pulmonary artery pressure measured by right heart catheterization or a 10% increase in 6-minute walk distance) will be eligible to receive the alternative therapy (NO or transfusion) or other FDA approved medications. These medications may include oxygen, prostacyclin (flolan or remodulin), L-arginine,

bosentan or sidenafil. We will limit the number of patients who are treated with medication other than NO or exchange transfusion to 10 subjects. Such patients will be managed at the NIH, in collaboration with their primary medical providers, according to accepted current standards of care using only FDA approved medication. The effect of such treatments on estimated pulmonary artery pressures, measured by echocardiogram, and on 6-minute walk distance will be assessed at regular intervals (every 1-3 months while on protocol) and all adverse events reported to the IRB and DSMB as defined by the current protocol. Patients maintained on alternative therapies will not have research bloods drawn, all laboratory testing will be obtained only for clinical indications. Such patients may be managed on this protocol until the protocol is terminated, the medication used becomes FDA approved specifically for use in sickle cell disease, the patient wishes to end participation, or the patient wishes to enroll in another study for treatment of pulmonary hypertension.

Phase(s): Phase I

Study Type: Interventional

Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00023296

- **L-glutamine Therapy for Sickle Cell Anemia**

  Condition(s): Anemia, Sickle Cell; Thalassemia

  Study Status: This study is currently recruiting patients.

  Sponsor(s): FDA Office of Orphan Products Development

  Purpose - Excerpt: This is a study to determine the efficacy of L-glutamine as therapy for sickle cell anemia and sickle O-thalassemia.

  Phase(s): Phase II; Phase III

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00029887

- **Phase I/II Randomized Study of Hydroxyurea With or Without Clotrimazole in Patients With Sickle Cell Anemia**

  Condition(s): Sickle Cell Anemia

  Study Status: This study is currently recruiting patients.

  Sponsor(s): FDA Office of Orphan Products Development; University of North Carolina

  Purpose - Excerpt: Objectives: I. Compare the efficacy of hydroxyurea with or without clotrimazole in terms of limiting the severity of anemia and the rate of hemolysis in patients with sickle cell anemia.

  Phase(s): Phase I; Phase II

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00004492

- **Phase I/II Study of Nonmyeloablative Allogeneic Bone Marrow Transplantation in Patients With High Risk Hemoglobinopathy**

  Condition(s): Graft Versus Host Disease; Sickle Cell Anemia; Thalassemia

  Study Status: This study is currently recruiting patients.

  Sponsor(s): Fairview University Medical Center

  Purpose - Excerpt: Objectives: I. Demonstrate the absence of grade 3 or 4 regimen related toxicity in patients with high risk hemoglobinopathy treated with busulfan, fludarabine, anti-thymocyte globulin, and radiotherapy followed by allogeneic hematopoietic stem cell transplantation. II. Determine the incidence of chimerism at 100 days, 6 months, and 1 year following this treatment regimen in this patient population. III. Determine the incidence of grade 2-4 and 3-4 acute graft vs host disease (GVHD) at 100 days following this treatment regimen in this patient population. IV. Determine the incidence of chronic GVHD at 6 months and 1 year following this treatment regimen in this patient population. V. Compare the quality of life at 1 year with the pretransplant assessment in these patients treated with this regimen. VI. Determine the survival at 100 days and 1 year in these patients.

  Phase(s): Phase I; Phase II

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00005897

- **Phase II Randomized Trial of Arginine Butyrate Plus Standard Local Therapy in Patients With Refractory Sickle Cell Ulcers**

  Condition(s): Skin Ulcers; Sickle Cell Anemia

  Study Status: This study is currently recruiting patients.

  Sponsor(s): FDA Office of Orphan Products Development; Boston University School of Medicine

  Purpose - Excerpt: Objectives: I. Compare the efficacy of local care alone vs local care plus arginine butyrate in terms of healing rate in patients with refractory sickle cell ulcers. II. Determine the effect of arginine butyrate therapy on tissue factors related to promotion or inhibition of wound healing in these patients. III. Determine whether the regimen used in this study is appropriate for testing in pivotal trials.

  Phase(s): Phase II

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00004412

- **Safety of ICL670 vs. deferoxamine in sickle cell disease patients with iron overload due to blood transfusions**

  Condition(s): Sickle Cell Disease

  Study Status: This study is currently recruiting patients.

  Sponsor(s): Novartis Pharmaceuticals

Purpose - Excerpt: The purpose of this study is to determine if the new orally active iron chelator, ICL670, is as safe as deferoxamine in preventing accumulation of iron in the body while a patient is undergoing repeated blood transfusions.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00067080

- **Secondary Pulmonary Hypertension in Adults with Sickle Cell Anemia**

  Condition(s): Pulmonary Hypertension; Sickle Cell Anemia

  Study Status: This study is currently recruiting patients.

  Sponsor(s): National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

  Purpose - Excerpt: The purpose of this study is to determine how often people with sickle cell anemia develop pulmonary hypertension-a serious disease in which blood pressure in the artery to the lungs is elevated. Men and women 18 years of age and older with sickle cell anemia may be eligible for this study. Participants will undergo an evaluation at Howard University's Comprehensive Sickle Cell Center in Washington, D.C. or at the National Institutes of Health in Bethesda, Maryland. It will include the following: -medical history -physical examination -blood collection (no more than 50 ml., or about 1/3 cup) to confirm the diagnosis of sickle cell anemia, sickle cell trait or beta-thalassemia (Some blood will be stored for future research testing on sickle cell anemia.) -echocardiogram (ultrasound test of the heart) to check the pumping action of the heart and the rate at which blood travels through the tricuspid valve. Following this evaluation, a study nurse will contact participants twice a month for 2 months and then once every 3 months for the next 3 years for a telephone interview. The interview will include questions about general health and recent health-related events, such as hospitalizations or emergency room visits.

  Study Type: Observational

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00011648

- **Stem Cell Transplantation after Reduced-Dose Chemotherapy for Patients with Sickle Cell Disease or Thalassemia**

  Condition(s): Hemoglobinopathies; Anemia, Sickle Cell; Hemoglobin SC Disease; Thalassemia; Thalassemia Major

  Study Status: This study is currently recruiting patients.

  Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

  Purpose - Excerpt: The purpose of this study is to find out if using a lower dose of chemotherapy before stem cell transplantation can cure patients of **sickle cell anemia** or thalassemia while causing fewer severe side effects than conventional high dose chemotherapy with transplantation.

  Phase(s): Phase II

  Study Type: Interventional

  Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00034528

- **Study of Allogeneic Bone Marrow Transplantation Using Matched, Related Donors in Patients With Nonmalignant Hematologic Disorders**

  Condition(s): Neutropenia; Sickle Cell Anemia; Thalassemia Major; Red-Cell Aplasia, Pure

  Study Status: This study is currently recruiting patients.

  Sponsor(s): Fairview University Medical Center

  Purpose - Excerpt: Objectives: I. Determine the efficacy of bone marrow transplantation using matched related donors in patients with nonmalignant hematologic disorders. II. Determine the quality of life, absence of adverse effects (e.g., graft versus host disease and B cell lymphoproliferative disease), and completeness of recovery of their underlying condition in these patients with this treatment regimen.

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00005893

- **Study of Clotrimazole and Hydroxyurea in Patients With Sickle Cell Syndromes**

  Condition(s): Sickle Cell Anemia

  Study Status: This study is currently recruiting patients.

  Sponsor(s): FDA Office of Orphan Products Development; Children's Hospital Boston

  Purpose - Excerpt: Objectives: Determine the effectiveness of the combined use of clotrimazole and hydroxyurea on a specific panel of red cell characteristics in patients with sickle cell syndromes.

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00004404

- **Pediatric Hydroxyurea in Sickle Cell Anemia (BABY HUG)**

  Condition(s): Blood Disease; Anemia, Sickle Cell

  Study Status: This study is not yet open for patient recruitment.

  Sponsor(s): National Heart, Lung, and Blood Institute (NHLBI)

  Purpose - Excerpt: To determine if hydroxyurea therapy is effective in the prevention of chronic end organ damage in pediatric patients with sickle cell anemia.

  Phase(s): Phase III

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00006400

- **Silent Cerebral Infarct Multi-Center Clinical Trial**

  Condition(s): Sickle Cell Anemia; Stroke

  Study Status: This study is not yet open for patient recruitment.

Sponsor(s): National Institute of Neurological Disorders and Stroke (NINDS)

Purpose - Excerpt: The goal of this study is to determine the effectiveness of blood transfusion therapy for prevention of silent cerebral infarct (stroke) in children with **sickle cell anemia.**

Phase(s): Phase III

Study Type: Interventional

Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00072761

Keeping Current on Clinical Trials

The U.S. National Institutes of Health, through the National Library of Medicine, has developed ClinicalTrials.gov to provide current information about clinical research across the broadest number of diseases and conditions.

The site was launched in February 2000 and currently contains approximately 5,700 clinical studies in over 59,000 locations worldwide, with most studies being conducted in the United States. ClinicalTrials.gov receives about 2 million hits per month and hosts approximately 5,400 visitors daily. To access this database, simply go to the Web site at **http://www.clinicaltrials.gov/** and search by "sickle cell anemia" (or synonyms).

While ClinicalTrials.gov is the most comprehensive listing of NIH-supported clinical trials available, not all trials are in the database. The database is updated regularly, so clinical trials are continually being added. The following is a list of specialty databases affiliated with the National Institutes of Health that offer additional information on trials:

- For clinical studies at the Warren Grant Magnuson Clinical Center located in Bethesda, Maryland, visit their Web site: **http://clinicalstudies.info.nih.gov/**
- For clinical studies conducted at the Bayview Campus in Baltimore, Maryland, visit their Web site: **http://www.jhbmc.jhu.edu/studies/index.html**
- For cancer trials, visit the National Cancer Institute: **http://cancertrials.nci.nih.gov/**
- For eye-related trials, visit and search the Web page of the National Eye Institute: **http://www.nei.nih.gov/neitrials/index.htm**
- For heart, lung and blood trials, visit the Web page of the National Heart, Lung and Blood Institute: **http://www.nhlbi.nih.gov/studies/index.htm**
- For trials on aging, visit and search the Web site of the National Institute on Aging: **http://www.grc.nia.nih.gov/studies/index.htm**
- For rare diseases, visit and search the Web site sponsored by the Office of Rare Diseases: **http://ord.aspensys.com/asp/resources/rsch_trials.asp**
- For alcoholism, visit the National Institute on Alcohol Abuse and Alcoholism: **http://www.niaaa.nih.gov/intramural/Web_dicbr_hp/particip.htm**
- For trials on infectious, immune, and allergic diseases, visit the site of the National Institute of Allergy and Infectious Diseases: **http://www.niaid.nih.gov/clintrials/**

- For trials on arthritis, musculoskeletal and skin diseases, visit newly revised site of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health: **http://www.niams.nih.gov/hi/studies/index.htm**
- For hearing-related trials, visit the National Institute on Deafness and Other Communication Disorders: **http://www.nidcd.nih.gov/health/clinical/index.htm**
- For trials on diseases of the digestive system and kidneys, and diabetes, visit the National Institute of Diabetes and Digestive and Kidney Diseases: **http://www.niddk.nih.gov/patient/patient.htm**
- For drug abuse trials, visit and search the Web site sponsored by the National Institute on Drug Abuse: **http://www.nida.nih.gov/CTN/Index.htm**
- For trials on mental disorders, visit and search the Web site of the National Institute of Mental Health: **http://www.nimh.nih.gov/studies/index.cfm**
- For trials on neurological disorders and stroke, visit and search the Web site sponsored by the National Institute of Neurological Disorders and Stroke of the NIH: **http://www.ninds.nih.gov/funding/funding_opportunities.htm#Clinical_Trials**

CHAPTER 6. PATENTS ON SICKLE CELL ANEMIA

Overview

Patents can be physical innovations (e.g. chemicals, pharmaceuticals, medical equipment) or processes (e.g. treatments or diagnostic procedures). The United States Patent and Trademark Office defines a patent as a grant of a property right to the inventor, issued by the Patent and Trademark Office.[9] Patents, therefore, are intellectual property. For the United States, the term of a new patent is 20 years from the date when the patent application was filed. If the inventor wishes to receive economic benefits, it is likely that the invention will become commercially available within 20 years of the initial filing. It is important to understand, therefore, that an inventor's patent does not indicate that a product or service is or will be commercially available. The patent implies only that the inventor has "the right to exclude others from making, using, offering for sale, or selling" the invention in the United States. While this relates to U.S. patents, similar rules govern foreign patents.

In this chapter, we show you how to locate information on patents and their inventors. If you find a patent that is particularly interesting to you, contact the inventor or the assignee for further information. **IMPORTANT NOTE:** When following the search strategy described below, you may discover non-medical patents that use the generic term "sickle cell anemia" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on sickle cell anemia, we have not necessarily excluded non-medical patents in this bibliography.

Patents on Sickle Cell Anemia

By performing a patent search focusing on sickle cell anemia, you can obtain information such as the title of the invention, the names of the inventor(s), the assignee(s) or the company that owns or controls the patent, a short abstract that summarizes the patent, and a few excerpts from the description of the patent. The abstract of a patent tends to be more technical in nature, while the description is often written for the public. Full patent descriptions contain much more information than is presented here (e.g. claims, references, figures, diagrams, etc.). We will tell you how to obtain this information later in the chapter.

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[9]Adapted from the United States Patent and Trademark Office:
http://www.uspto.gov/web/offices/pac/doc/general/whatis.htm.

The following is an example of the type of information that you can expect to obtain from a patent search on sickle cell anemia:

- **Allele specific polymerase chain reaction**

  Inventor(s): Pal; Bijay K. (Arcadia, CA), Ugozzoli; Luis A. (San Rafael, CA), Wallace; R. Bruce (Greenbrae, CA), Wu; Dan Y. (Bellevue, WA)

  Assignee(s): City of Hope (duarte, Ca)

  Patent Number: 5,639,611

  Date filed: November 9, 1994

  Abstract: A rapid, non-radioactive approach to the diagnosis of **sickle cell anemia** is described based on an allele specific polymerase chain reaction (ASPCR) in which the 3'-terminal nucleotide of one of the primers of the primer set forms a match with one allele and a mismatch with the other allele. This method allows the direct detection of the normal or the sickle cell.beta.-globin allele in genomic DNA without the additional steps of probe hybridization, ligation or restriction enzyme cleavage.

  Excerpt(s): This invention entails an allele specific polymerase chain reaction (ASPCR) useful, inter alia, for the direct detection of the normal or the sickle cell.beta.-globin in genomic DNA without the additional steps of probe hybridization, ligation or restriction enzyme cleavage. Sickle cell anemia is the paradigm of a genetic disease caused by a single base-pair mutation, an A.fwdarw.T transversion in the sequence encoding codon 6 of the human.beta.-globin gene. In homozygous **sickle cell anemia,** the substitution of a single amino acid (Glu.fwdarw.Val) in the.beta.-globin subunit of hemoglobin results in a reduced solubility of the deoxy-hemoglobin molecule, and red blood cells assume irregular shapes. The sickled red blood cells become trapped in the microcirculation and cause damage to multiple organs. Kan and Dozy.sup.1 were the first to describe the diagnosis of **sickle cell anemia** in the DNA of affected individuals based on the linkage of the sickle cell allele to an Hpa I restriction fragment length polymorphism. Later, it was shown that the mutation itself affected the cleavage site of both Dde I and Mst II and could be detected directly by restriction enzyme cleavage.sup.2 Conner et al.sup.3 described a more general approach to the direct detection of single nucleotide variation by the use of allele specific oligonucleotide hybridization. In this method, a short synthetic oligonucleotide probe specific for one allele only hybridizes to that allele and not to others under appropriate conditions.

  Web site: http://www.delphion.com/details?pn=US05639611__

- **An improved method of treating sickle cell anemia**

  Inventor(s): Duncan; Alexander (Dunwoody, GA), Hunter; Robert L. (Tucker, GA)

  Assignee(s): Emory University (atlanta, Ga)

  Patent Number: 4,837,014

  Date filed: January 13, 1989

  Abstract: In accordance with the present invention, a method is provided that is effective in treating **sickle cell anemia.** The method comprises a method of treating a person with **sickle cell disease** comprising the step of injecting into the person with **sickle cell disease** a solution with an effective concentration of a surface active copolymer of the following formula:HO(C.sub.2 H.sub.4 O).sub.b (C.sub.3 H.sub.6

O).sub.a (C.sub.2 H.sub.4 O).sub.b Hwherein a is an integer such that the hydrophobe represented by (C.sub.3 H.sub.6 O) has a molecular weight of approximately 950 to 4000 and b is an integer such that the hydrophile portion represented by (C.sub.2 H.sub.4 O) constitutes approximately 50% to 90% by weight of the compound.

Excerpt(s): The present invention relates to a composition and method for lysing fibrin clots, dissolving thrombi, and reestablishing and maintaining perfusion of ischemic tissue. More particularly, the present invention relates to a composition comprising certain ethylene oxide-propylene oxide condensation products, which are surface-active copolymers, in combination with fibrinolytic enzymes. The term "fibrinolytic enzyme" means any enzyme that is capable of cleaving fibrin. Enzymes that are capable of cleaving fibrin include, but are not limited to, streptokinase, urokinase, tissue plasminogen activator (t-PA) produced from cell cultures, tissue plasminogen activator produced by recombinant DNA technology (rt-PA) and tissue plasminogen activator produced by prourokinase (k-PA). The terms "isotonic solution" or "isoosmotic solution" are defined a solutions having the same or similar osmotic pressure as blood. The terms clot, fibrin clot and thrombus are used interchangeably. Each year about 550,000 Americans die from heart attacks. Even more--close to 700,000--have heart attacks and live. While a heart attack victim may survive, part of his or her heart will almost certainly die. The death of heart muscle, called myocardial infarction, is due to coronary artery thrombosis in 70-90% of the cases. When a thrombosis, or blood clot, occludes one of the arteries of the heart, it compromises the flow of blood to the surrounding muscle This deprives the muscle of oxygen and other nutrients. In the past, nothing could be done to reverse this process. The high technology devices in intensive care units mostly supported patients so they could live while a portion of their heart died.

Web site: http://www.delphion.com/details?pn=US04837014__

- **Anti-sickling hemoglobin**

  Inventor(s): McCune; Steven L. (Birmingham, AL), Townes; Tim M. (Birmingham, AL)

  Assignee(s): The Uab Research Foundation (birmingham, Al)

  Patent Number: 5,864,029

  Date filed: June 5, 1995

  Abstract: Disclosed are anti-sickling human hemoglobins for use as **sickle cell anemia** therapeutics.

  Excerpt(s): This invention relates to recombinant anti-sickling hemoglobins suitable for use as therapeutics for the treatment of **sickle cell anemia.** The gene that encodes hemoglobin S (the defect leading to sickle cell anemia) is inherited as an autosomal trait and occurs in the heterozygous condition as the sickle trait in 8-10% of black persons in the Unites States. Two major clinical features characterize sickle cell anemia: (1) chronic hemolysis that is stable and only moderately debilitating, and (2) acute, episodic vaso-occlusive crises that cause organ failure and account for most of the mortality and morbidity associated with the disease. The molecular basis for **sickle cell disease** is an A to T transversion in the 6th codon of the human.beta.-globin gene. This simple transversion changes a polar glutamic acid residue to a non-polar valine (Ingram et al., Nature 178:792, 1956; Ingram et al., Nature 180:326, 1957) in the.beta.-globin polypeptide and, thus, drastically decreases the solubility of this hemoglobin (termed Hb S). When the intracellular concentration of Hb S is high and the partial pressure of oxygen is low in the capillary beds, the non-polar valine, which is on the surface of the hemoglobin

molecule, interacts with two other non-polar residues on the surface of a second hemoglobin molecule, and initiates aggregation (Padlan et al., J. Biol. Chem. 260:8280-8291, 1985; Wishner et al., J. Mol. Biol. 98:179-194, 1975). Once approximately 10 hemoglobin monomers interact, long polymers rapidly accumulate, and complex 14-stranded fibers are formed (Crepeau et al., Nature 274:616-617, 1978; Dykes et al., J. Mol. Biol. 130:451-472, 1979; Eaton et al., Blood 70:1245-1266, 1987; Hofrichter et al., Proc. Natl. Acad. Sci USA 71:4864-4868, 1974). The formation of these fibers reduces the flexibility of red blood cells and leads to the occlusion of small capillaries. Intracellular fiber formation also results in erythrocyte membrane damage and increased red cell lysis (Noguchi et al., Blood 58:1057, 1981; Brittenham et al., Blood 65:183, 1985). The ensuing disease is characterized by a chronic hemolytic anemia with episodes of severe pain, and tissue damage that can result in stroke, kidney failure, heart disease, infection, and other complications (Bunn et al., Hemoglobin: Molecular, Genetic, and Clinical Aspects. (W. B. Saunders, Philadelphia, 1986)).

Web site: http://www.delphion.com/details?pn=US05864029__

- **Assay for nucleic acid sequences, particularly genetic lesions, using interactive labels**

  Inventor(s): Taub; Floyd (Rockville, MD)

  Assignee(s): Digene Diagnostics, Incorporated (md)

  Patent Number: 4,820,630

  Date filed: November 23, 1984

  Abstract: Lesions in genetic sequences, for example, the **sickle cell anemia** mutation in the beta globin gene, are detected by means of interactive labels in a nucleic acid hybridization assay. A signal is generated only if the labels are in physical proximity which is made dependent on whether a predetermined normal or abnormal sequence is present by exposure to appropriate conditions such as restriction enzyme digestion or stringent hybridization.

  Excerpt(s): Embodiments of this invention were disclosed in Disclosure Documents No. 129,717, dated Aug. 2, 1984, recorded Aug. 6, 1984, and 130094, dated Aug. 14, 1984, recorded Aug. 17, 1984, incorporated by reference, which the Patent and Trademark Office is requested to preserve. In the past, genetic diseases were diagnosed based on clinical findings once the disease had developed. Various enzyme and protein tests were subsequently developed to confirm or provide more accurate diagnosis and to allow earlier diagnosis. Unfortunately, for many diseases no such tests are available. Recently, it has become possible to analyze an individual's DNA (which is present in every cell) to determine if certain abnormal genes which will cause genetic diseases are present. These diseases include Huntington chorea, phenylketonuria, thalassemias, and sickel cell anemia. The abnormal genes are found by analyzing restriction site polymorphisms (RSPs) using "Southern blotting" (SB) (Southern, E.M.S., Molecular Biology, 1975, 98:503). This test is time consuming and expensive. However, it is an extremely important method, since it has allowed prenatal diagnosis and thus intervention to prevent birth of severely diseased individuals.

  Web site: http://www.delphion.com/details?pn=US04820630__

- **Blood substitute**

  Inventor(s): Canizaro, deceased; Peter C. (late of Lubbock, TX), Feola; Mario (Lubbock, TX), Simoni; Jan S. (Lubbock, TX)

  Assignee(s): Texas Tech University Health Sciences Center (lubbock, Tx)

  Patent Number: 5,439,882

  Date filed: May 14, 1993

  Abstract: An improved blood substitute comprises purified hemoglobin, preferably bovine, cross-linked intramolecularly with periodate-oxidized ATP (o-ATP) and intermolecularly with periodate-oxidized adenosine (o-adenosine), combined with reduced glutathione (GSH), and optionally enriched with mannitol, non-electrolytes, and/or electrolytes. The blood substitute has prolonged intravascular persistence, can sustain plasma volume, has low oxygen affinity, can work as a physiological oxygen carrier, has vasodilator activity and can reduce the vasoconstriction that follows hemorrhage. A method of treating a human afflicted with acute blood loss and/or a sickling crisis of **sickle cell anemia** comprises intravenously administrating to the human an effective volume of the blood substitute.

  Excerpt(s): This invention relates to a blood substitute and to a method for its preparation. More particularly, it relates to a novel hemoglobin composition which is effective in sustaining life after severe hemorrhage in animals of various species, including humans, that is free of toxicity and blood transmissible diseases. Blood performs many functions, all of which being vital. Severe hemorrhage or loss of blood endangers life for the following two main reasons: 1) the drop in circulating blood volume reduces tissue perfusion and produces ischemia; and 2) the reduction in oxygen transport impairs tissue oxygenation and produces hypoxia. The circulatory system reacts to these changes by producing vasoconstriction, which further aggravates ischemia and hypoxia. Ultimately, alterations of cell metabolism and function develop, which lead to shock and death.

  Web site: http://www.delphion.com/details?pn=US05439882__

- **Composition and method for the treatment of sickle cell anemia**

  Inventor(s): Weinheimer; Alfred J. (Houston, TX)

  Assignee(s): Omex International, Inc. (missouri City, Tx)

  Patent Number: 5,116,545

  Date filed: May 29, 1990

  Abstract: The major component of the carbonate fraction of free acids extractable from alfalfa has shown excellent control of symptoms in patients with **sickle cell disease.** Its structure has been established by proton NMR spectrometry as beign 16-hydroxy-9Z,12Z,14E-octadecatrienoic acid and closely related compounds, such as simple esters, amides, triglycerides, or other derivatives of the carboxylic acid function, and a method for its synthesis from linseed oil or methyl linolenate has been developed. The product from linseed oil, both in the form of the initially formed triglyceride and in the form of its free acid obtained by saponification, is useful for the treatment of **sickle cell disease.**

  Excerpt(s): The present invention relates to 16-hydroxy-9Z,12Z,14E-octadecatrienoic acid and closely related compounds, such as simple esters, amides, triglycerides, or other derivatives of the carboxylic acid function; isolated from the carbonate fraction of free

acids extractable from various plant materials, particularly alfalfa. The invention also relates to compositions, containing the compounds, which are used for retarding red blood cell sickling associated with **sickle cell disease.** Sickle cell disease is an inherited disease stemming from inadequate oxygen transport by an abnormal type of hemoglobin molecule in the red blood cells. It is an inherited disease which can be passed to offspring only if both parents carry the genetic trait. The trait carriers show no sign of the disease, but statistically one in four of their children will be afflicted with the disease. The disease is most prevalent in the black races, but is also known in other races surrounding the Mediterranean Sea and in India. It affects about 0.2% of the U.S. black population but is much more prevalent in central Africa. The most common manifestation of the disease is an extremely painful "crisis," typically lasting several days, and affecting one or another local part of the body. The crisis often occurs following physical stress, and appears to be due to limited oxygen supply to the affected part. This is due to the inferior oxygen-carrying capability of the mutant hemoglobin, as well as to its tendency to aggregate in insoluble gels within the red blood cell, often leading to a form resembling a sickle. The distorted cells no longer freely traverse capillaries, further limiting oxygen supply to the tissues.

Web site: http://www.delphion.com/details?pn=US05116545__

- **Doll for instruction of sickle cell disease clinical observations**

  Inventor(s): Kennedy, Jr.; R. Michael (Moorestown, NJ), Smith-Whitley; Kim (Philadelphia, PA)

  Assignee(s): Children's Hospital of Philadelphia (philadelphia, Pa)

  Patent Number: 6,077,083

  Date filed: March 22, 1999

  Abstract: A medical teaching doll is provided with devices for simulating the differences between normal organs, and organs which are physically altered by sickle cell or other disease. The devices simulate the normal and diseased conditions so that the differences can be clearly seen and/or felt. The doll is used to train parents to recognize the signs or symptoms of **sickle cell disease** so that they may seek medical care for their children before they become more acutely ill. The signs or symptoms which are simulated by the doll include change of color of eye sclera, enlargement of spleen, elevated temperature, labored breathing and/-or coughing, and change of color of skin.

  Excerpt(s): The present invention generally relates to the field of public health, and more specifically to a doll for instruction in the clinical observations of sickle cell and other diseases. Sickle cell disease (SCD) is an inherited hemoglobin disorder. This disorder involves the destruction of red blood cells (hemolysis) and the blockage of small blood vessels (vaso-occlusion). Children with **sickle cell disease** are at risk for serious complications including 1) infections, 2) acute chest syndrome, 3) splenic sequestration, 4) aplastic anemia, 5) painful episodes, 6) stroke, 7) gallstones and gall bladder disease, 8) priapism, 9) increased hemolysis, and 10) dactylitis. Parents of children with **sickle cell disease** need to be aware of these numerous complications, so that they may seek medical care for their children before they become more acutely ill. Studies have evaluated the incidence of splenic sequestration and its morbidity in Jamaican children with **sickle cell disease.** It was found that the incidence of splenic sequestration increased after teaching parents how to check their child's spleen size, and that mortality decreased because the parents brought their children to medical attention sooner.

Web site: http://www.delphion.com/details?pn=US06077083__

- **Hybrid nucleic acid molecules and vectors including.beta.-globin regulatory elements**

  Inventor(s): Ellis; James (Toronto, CA)

  Assignee(s): Hsc Research and Development Limited Partnership (toronto, Ca)

  Patent Number: 6,524,851

  Date filed: October 1, 1999

  Abstract: The invention relates to hybrid nucleic acid molecules for gene therapy in cells of the erythroid lineage, and in particular.alpha.-,.beta.-,.delta.-,.epsilon.,.gamma.-, or.zeta.-globin nucleotide sequences operably linked to.beta.-globin regulatory elements. The hybrid nucleic acid molecules, at single copy, are capable of producing a polypeptide. The hybrid nucleic acid molecules are useful for treatment of hemoglobinopathies such as **sickle cell anemia** or.beta.-thalassemia.The hybrid nucleic acid molecules are useful at single copy for erythroid expression at single copy of RNA and polypeptides in transgenic animals.

  Excerpt(s): This application claims priority from Canadian application no. 2,246,005, filed on Oct. 1, 1998, which is incorporated by reference in its entirety. The invention relates to hybrid nucleic acid molecules and vectors for expression, at single copy, of RNA, polypeptides and for gene therapy in erythroid and other cells. In particular, the invention relates to hybrid nucleic acid molecules and vectors that are useful for treatment of hemoglobinopathies such as **sickle cell anemia** and.beta.- or.alpha.-thalassemia. The invention also relates to hybrid nucleic acid molecules that are useful for erythroid expression at single copy of RNA and polypeptides in transgenic animals.

  Web site: http://www.delphion.com/details?pn=US06524851__

- **Inhibition or erythrocyte sickling by N-L-alpha-aspartyl-L-phenylalanine 1-methyl ester**

  Inventor(s): Edmundson; Allen B. (Oklahoma City, OK), Manion; Carl V. (Oklahoma City, OK)

  Assignee(s): Oklahoma Medical Research Foundation (oklahoma City, Ok)

  Patent Number: 6,384,076

  Date filed: March 22, 2001

  Abstract: It has now been found that N-L-alpha-aspartyl-L-phenylalanine 1-methyl ester (APM) exhibits antisickling properties. In vitro testing verified that APM significantly lowered the frequency of sickling of red blood cells from each of twelve pediatric aged patients being treated for sickle-cell anemia by exchange transfusion. Sickling was also inhibited in an "index" patient after oral administering of APM. These in vitro and in vivo results identify APM as a therapeutic agent for the family of sickle cell molecular diseases.

  Excerpt(s): The present invention relates to the treatment of **sickle cell disease** with N-L-alpha-aspartyl-L-phenylalanine 1-methyl ester. Under low oxygen tension, sickle cell deoxyhemoglobin (HbS) forms multi-stranded fibers (Rodgers, et al. 1987. Proc Natl Acad Sci USA 84:6157-6161; Eaton, W. A. and Hofrichter, J. 1990. Adv Protein Chem 40:63-279) that force a red blood cell (RBC) into a crescent (sickle) shape (Carache, S. and

Davies, S. 1991. Acad Med 66:748-74). In 1949, Pauling et al. demonstrated that HbS was electrophoretically distinct from normal human adult hemoglobin (HbA) and coined the name molecular disease to describe the pathological effects of HbS (Pauling, et al. 1949. Science 110:543-548). Seven years later, Ingram (Ingram, V. M. 1956. Nature 178:792-794) reported that HbS differed from HbA by the substitution of valine for glutamic acid in position 6 of the.beta. chain. This hydrophobic for polar substitution occurs on the surface of the three-dimensional structure of HbS on the first (A).alpha.-helix (Padlan, E. A. and Love, W. E. 1985. J Biol Chem 260:8280-8291). It creates a sticky site which is covered by a complementary (acceptor) crevice between the E and F helices in the.beta. chain of an antiparallel Hb molecule in the fibril. Key contact residues in the acceptor site are phenylalanine 85 and leucine 88 from the F helix. Each.beta. chain thus contains a donor and acceptor site which together interact with two other offset Hb molecules, the key condensation events in producing double stranded helical stacks of indefinite length. As the strands of hemoglobin molecules stack together they, continue to elongate and stretch the normally round, flexible RBC into an inflexible sickle or spiculated shape. Physiologically, the sickled RBCs impair blood flow, enhance hypoxia and accentuate the production of more sickling (Embury, S. H. 1986. Ann Rev Med 37:361-376). The HbS gene is present in about 8-9% of African Americans (Schneider, et al. 1976. Blood 48:629). If homozygous for the gene, a patient shows the severe symptoms of "sickle cell disease" such as anemia, hemolysis, severe muscle pain, thrombotic complications, and even sudden exertional death. A heterozygous individual has "sickle cell trait" with milder symptoms and more infrequent crises. The gene is believed to have been preserved in successive generations because RBCs containing HbS appear to promote survival in endemic malarial regions of Africa, Asia and European countries on the Mediterranean Sea (Allison, A. C. 1956. Scientific American 195:87-94; Friedman, M. J. and Trager, W. 1981. Scientific American 244:154-164).

Web site: http://www.delphion.com/details?pn=US06384076__

- **Method of treating sickle cell anemia**

  Inventor(s): Abraham; Donald J. (Murrysville, PA), Kennedy; Paul E. (Lawrence, KS)

  Assignee(s): University of Pittsburgh (pittsburgh, Pa)

  Patent Number: 4,887,995

  Date filed: January 22, 1985

  Abstract: A method of treating a person for **sickle cell anemia** including administering to the patient's blood a therapeutically effective dosage of ethacrynic acid. The dosage may be administered to blood removed from the patient which blood after addition of the compound is restored to the patient or by other means such as orally.

  Excerpt(s): This invention relates to a method of treating **sickle cell anemia** and, more specifically, it relates to a method of resisting sickling of hemoglobin in a **sickle cell anemia** patient. Sickle cell anemia is a hereditary blood disease which can afflict African, Mediterranean and Mideastern peoples. The anemia results from the physical aggregation of a mutant hemoglobin protein constituent in red blood cells. This aggregation results in a distortion in shape of deoxygenated red blood cells and causes impairment of flow of the blood through the capillaries (sickle cell "crises"). As the principal function of hemoglobin is to transport oxygen from the lungs to body tissues, efficient flow of oxygen throughout the body's tissues is impeded by the anemia due to a lower number of red blood cells. **Sickle cell anemia** also may have an indirect effect on the heart, lungs, kidneys, spleen, hips and brain. **Sickle cell anemia** crises can be

extremely painful, can result in infections such as pneumonia, can result in skin ulceration, can contribute to strokes and seizures in the one afflicted and can also result in the development of chronic bone infections. In general, the result of the differences between cells containing hemoglobin A, the normal hemoglobin, and hemoglobin S, the sickle cell hemoglobin, is that the former cell is generally flexible and bioconcave discoid in shape, while the latter is more rigid and crescent shaped and typically has pointed ends. This rigidity and distortion in shape causes the cells to be lodged in the capillary. Hemoglobin molecules contain two beta polypeptide chains and two alpha polypeptide chains. In the sickle cell hemoglobin, a mutation is present in the beta chains. More specifically, the sixth amino acid of each beta chain is changed from glutamic acid to valine. As a result of this mutation, hemoglobin S upon deoxygenation polymerizes and causes the cell to assume the elongated, sickle-like configuration. As the sickle cells have a much shorter life span than normal red cells, the effect on the body is to deplete the total volume of blood cells thereby creating an anemic condition.

Web site: http://www.delphion.com/details?pn=US04887995__

- **Method of treating sickle cell anemia with danazol**

  Inventor(s): Ahn; Yeon S. (Miami, FL), Harrington; William J. (Miami, FL), Mylvaganam; Ravindra (Miami, FL)

  Assignee(s): University of Miami (coral Gables, Fl)

  Patent Number: 4,835,146

  Date filed: June 8, 1987

  Abstract: Treatment of **sickle cell disease** using danazol.

  Excerpt(s): This invention relates to the use of danazol or an equivalent anabolic steroid in the treatment of hemolytic anemias, particularly **sickle cell disease.** Said earlier applications disclose the use of danazol, a known material, in the treatment of various disorders including hemolytic anemias. The present disclosure is concerned primarily with the treatment of one such form of hemolytic anemia, namely, **sickle cell anemia,** which has become of particular concern in recent years. Sickle cell anemia is a common genetic disorder characterized by anemia, painful crises involving joints, bones, the abdomen and other viscera. It is due to an abnormal hemoglobin that distorts the shape of the affected patient's red blood cells impairing their passage through small blood vessels, leading to minute occlusions (microinfarcts) which not only cause pain and shorten the survival of the red blood cells but also damage vital tissues such as the kidney, heart and brain, leading ultimately to organ failure. At present the only available treatments are blood transfusions and drugs to relieve pain.

  Web site: http://www.delphion.com/details?pn=US04835146__

- **Methods and compositions for the detection of sequences in selected DNA molecules**

  Inventor(s): Lee; Ming-Shen (Houston, TX), LeMaistre; Anne (Humble, TX)

  Assignee(s): Board of Regents, the University of Texas System (austin, Tx)

  Patent Number: 5,137,806

  Date filed: December 11, 1989

Abstract: The present disclosure relates to novel procedures and primers for use in conenction with PCR or in vitro DNA sequence amplification to detect sequence variants, such as sequence modifications or mutations. The invention will have particular applicability in the detection of point or other relatively short mutations where the expected location or configuration of the mutation is known. Primers of the invention incorporate a 3' terminal nucleotide or nucleotides complementary to the sequence variance, and thereby serve to successfuly prime chain elongation only on DNA templates which include the particular variant. Exemplary mutations suitable for detection through practice of the invention include those involved in beta-thalassemia, **sickle cell anemia,** hemoglobin C disease, diabetes, acute intermittent porphyria, lung, breast, and colon cancers and others.

Excerpt(s): The present invention relates to methods and compositions for detecting the presence or absence of a target DNA sequence, such as a mutation, within an identified region of a selected DNA molecule, such as a gene. In particular aspects, the invention relates to the use of novel primer constructs in connection with the polymerase chain reaction (PCR) technique for the detection of genetic mutations in genes, particularly point mutations. The ability to detect specific nucleotide alterations or mutations in DNA sequences such as genes is an invaluable tool for medical science. The ability to identify such alterations provides a means for diagnosis of genetic diseases that involve DNA mutations, including sickle-cell anemia, thalassemia, diabetes, certain oncogenic mutations, and the like. Importantly, the ability to diagnose genetic diseases such as the foregoing would provide numerous advantages, ranging from the ability to prepare for proper care and treatment of affected individuals, such as in the case of prenatal diagnosis, to marital counseling of prospective parents. Unfortunately, the techniques presently available to medical science for such diagnosis have been generally quite limited in one or more aspects. One technique which has been used with some frequency employs the use of the PCR or site-specific DNA amplification technique, in combination with synthetic oligodeoxynucleotides. This technique, exemplified by the procedure set forth in Verlaan-de-Vries, et al.: A dot blot screening procedure for mutated ras oncogenes using synthetic oligonucleotides (Gene 50:313-320, 1986), involves the specific in vitro amplification of genetic regions suspected of containing a particular, known mutation in a specific configuration, followed by hybridization of the amplified DNA under tightly controlled parameters with one or more oligonucleotides which carry complementary mutations. By determining which of the oligonucleotides bind tightly under the specified hybridization conditions, one can attempt to ascertain which, if any, of the mutations are present in the segment of the DNA that is amplified. While this technique has shown some usefulness, it is quite cumbersome in that it requires several steps, including both an amplification step followed by a separate hybridization step. Furthermore, the technique relies upon very tightly controlled hybridization conditions, thus rendering it generally inapplicable to everyday clinical application.

Web site: http://www.delphion.com/details?pn=US05137806__

- **Methods of detecting and treating vaso-occlusive crisis in sickle cell disease**

  Inventor(s): Bageac; Alexandru Cristian (Brookline, MA), Golan; David Eric (Brookline, MA), Thatte; Hemant Sadashiv (Norwood, MA)

  Assignee(s): President and Fellows of Harvard College (cambridge, Ma)

  Patent Number: 5,669,396

  Date filed: January 16, 1996

  Abstract: Methods are described for treating **sickle cell disease,** and in particular, detection and treatment of vaso-occlusive crisis in **sickle cell disease.** Antibodies are employed which bind competitively and suppress adhesion of sickle erythrocytes to autologous lymphocytes.

  Excerpt(s): The present invention relates to methods for treating **sickle cell disease,** and in particular, detection and treatment of vaso-occlusive crisis in **sickle cell disease.** Human hemoglobin is composed, in part, of four polypeptide chains. Two of these chains are identical chains of 141 amino acids (alpha chains) and two of these chains are identical chains of 146 amino acids (beta chains). The gene encoding the beta chain is known to exhibit polymorphism. The normal allele encodes a beta chain having glutamic acid at the sixth position. The mutant allele encodes a beta chain having valine at the sixth position. This difference in amino acids has a profound (most profound when the individual is homozygous for the mutant allele) physiological impact known clinically as **sickle cell anemia** or **sickle cell disease.** In **sickle cell anemia,** the erythrocytes tend to "sickle" at low oxygen tensions, i.e., to assume a crescent, "holly-leaf" or other abnormal shape instead of the biconcave disc conformation of normal erythrocytes. It is believed that the defective hemoglobin polymerizes and thereby distorts the cell shape, allowing secondary membrane abnormalities including calcium (Ca.sup.++) influx, i.e., an influx beyond what the calcium pump can handle, potassium (K.sup.+) efflux, altered transbilayer phospholipid distribution, membrane protein aggregation, cellular dehydration, and autologous antibody deposition, among others. The result is cell damage, cell rigidity, abnormal cell function and ultimately premature cell death.

  Web site: http://www.delphion.com/details?pn=US05669396__

- **Piper guineense, pterocarpus osun, eugenia caryophyllata, and sorghum bicolor extracts for treating sickle cell disease**

  Inventor(s): Gamaniel; K. S. (Abuja, NG), Nasipuri; R. N. (Abuja, NG), Ogunyale; P. O. (Oyo, NG), Okogun; J. I. (Abuja, NG), Olusola; Akin (Abuja, NG), Orisadipe; Abayomi (Abuja, NG), Samuel; Babatunde (Abuja, NG), Wambebe; Charles (Abuja, NG)

  Assignee(s): National Institute for Pharmaceutical Research and Development Federal (abuja, Ng)

  Patent Number: 5,800,819

  Date filed: January 21, 1997

  Abstract: A phytochemical composition for treating **sickle cell disease** is provided. The composition is a cold water extraction product of a mixture containing Piper guineenses seeds, Pterocarpus osum stem, Eugenia caryophyllum fruit, Sorghum bicolor leaves and potash. Also described are mixtures of phytomaterials used for preparing the extraction

product, methods for making the extraction product, and methods for using the extraction product

Excerpt(s): The present invention relates to the field of phytodrugs, and in particular the invention relates to phytodrugs for treatment and management of **sickle cell disease** and methods of preparing and using same. Sickle Cell Disease (SCD) is a genetic disorder which, in particular, shows its clinical manifestations in the Black race. At the present time there is no known safe drug for the management of this disease anywhere in the world. Nigeria, being the most populous Black nation in the world, has the highest incidence of SCD. Conservatively it is estimated that over 2 million Nigerians suffer from SCD while another 25 million Nigerians are carriers. About 100,000 babies are born every year with SCD and it causes approximately 8% of all infant deaths each year. The morbidity and mortality factors associated with **sickle cell disease** are well-known. The acute and chronic trauma of the painful crisis are beyond description. In view of these realities, there is a constant need for drugs which might alleviate the effects of this terrible disease. And the search for such drugs is of the highest priority.

Web site: http://www.delphion.com/details?pn=US05800819__

- **Sickle cell anemia control**

  Inventor(s): Chima; Oji A. (Little Rock, AR)

  Assignee(s): Norris; Jerome J. (rockville, Md)

  Patent Number: 4,904,678

  Date filed: August 25, 1987

  Abstract: Method of providing anti-sickling of red blood cells in **sickle cell anemia** patients without hemolyzing said cells, using thiocyanates alone, or together with Vitamin B.sub.6.

  Excerpt(s): Sickle cell anemia is a blood disorder characterized by anemia arising from low levels of hemoglobin and hematocrit (packed red cell volume). This form of anemia is a hereditary defect resulting from a genetic mutation, wherein a hemoglobin variant (sickle cell) is synthesized instead of the normal adult hemoglobin. In the generic sense, **sickle cell disease** applies to disorders characterized by human red blood cells, which contain an abnormal hemoglobin, that has been designated hemoglobin S. When deprived of oxygen, sickle cell hemoglobin becomes insoluble, and forms hemoglobin crystals. These crystals form rigid rods which distort the normally, nearly spherical red blood cells to the sickle shaped forms. It has been found that sickle cells are more fragile than normal red blood cells, and the abnormal shapes of these cells cause them to be easily hemolyzed (broken) in circulating blood.

  Web site: http://www.delphion.com/details?pn=US04904678__

- **Sickle cell anemia treatment**

  Inventor(s): Goodman; Steven R. (Mobile, AL)

  Assignee(s): South Alabama Medical Science Foundation (mobile, Al)

  Patent Number: 6,087,398

  Date filed: March 1, 1996

Abstract: The present invention provides a method of treating **sickle cell anemia** comprising the step of administering to an individual in need of said treatment a therapeutically acceptable dose of reducing agent. In yet another embodiment of the present invention, there is provided a method of pharmacologically correcting a post-translational modification of the.beta.-actin protein in sickled erythrocytes, comprising the step of contacting said sickled erythrocytes with a pharmacologically effective dose of a reducing agent. In still yet another embodiment of the present invention, there is provided a method of identifying a drug for use in treating **sickle cell anemia.** Any drug which hastens the HDSS Core Skeleton dissociation rate is tested by the in vitro ternary complex dissociation assay to test whether its effect is on HDSS beta-actin. Furthermore, drugs can be tested by the oxygenation-deoxygenation cycling assay for its ability to block ISC formation in vitro. Finally, drugs can be tested for ability to cause the conversion of preformed ISCs back to the biconcave shape.

Excerpt(s): The present invention relates generally to the fields of molecular hematology and protein chemistry. More specifically, the present invention relates to a novel treatment for **sickle cell anemia.** Hemoglobinopathies encompass a number of anemias of genetic origin in which there is decreased production and/or increased destruction (hemolysis) of red blood cells. The blood of normal adult humans contains hemoglobin (designated as HbA) which contains two pairs of polypeptide chains designated alpha and beta. Fetal hemoglobin (HbF), which produces normal red blood cells, is present at birth, but the proportion of HbF decreases during the first months of life and the blood of a normal adult contains only about 2% HbF. There are genetic defects which result in the production by the body of abnormal hemoglobins with a concomitant impaired ability to maintain oxygen concentration. Among these genetically derived anemias are included thalassemia, Cooley's Disease and, most importantly, sickle-cell anemia (HbS disease). Sickle-cell anemia is an inherited chronic hemolytic anemia characterized by sickle-shaped red blood cells present in part of the offspring of parents who are both heterozygotes to the abnormal gene which causes the sickling disease. This disease is recessive, and heterozygotes carrying this gene show no blatant anemia or similar abnormality. Thus, only about 25% of the children of parents who are both heterozygous are expected to be homozygotic to this abnormal gene and will develop **sickle cell anemia** and eventually sickling crisis (aplastic crisis). Few homozygotes live past 40 years of age and many show abnormal body growth patterns. The gene which characterizes sickling trait causes valine to be substituted for glutamic acid in the sixth position of the beta chain, thus producing HbS rather than HbA. Deoxygenated HbS is much less soluble than deoxy HbA and it forms a semisolid gel of rodlike tactoids, thus causing the red blood cells produced from HbS to assume a sickle shape. These abnormally shaped red blood cells form a sort of sludge. In addition, these HbS red blood cells are more fragile than normal red blood cells and hemolyze more easily, thus leading eventually to anemia. The clinical manifestations of an aplastic crisis in sickle-cell homozygotes include arthralgia with fever, jaundice, aseptic necrosis of the femoral head, chronic punched-out ulcers about the ankles plus episodes of severe abdominal pain with vomiting. Thrombosis and/or infarction may also be present. Laboratory findings include a monocytic anemia with an RBC count in the range 2-3 times. Early death, usually before 40, is caused by intercurrent infections (especially tuberculosis), multiple pulmonary emboli or thrombosis of a vessel supplying a vital area. In the past, treatment of sickle-cell anemia was symptomatic only.

Web site: http://www.delphion.com/details?pn=US06087398__

- **Therapeutic uses of green tea polyphenols for sickle cell disease**

  Inventor(s): Ohnishi; Tsuyoshi (502 King of Prussia Rd., Radnor, PA 19087)

  Assignee(s): None Reported

  Patent Number: 6,538,023

  Date filed: September 15, 2000

  Abstract: The method of therapeutic management of **sickle cell anemia** involving oral administration to the patient of an effective dose of green tea polyphenols.

  Excerpt(s): This invention relates to the therapeutic efficacy of green tea polyphenols for patients of **sickle cell anemia** (SCA). SCA is a serious disease generally found in a specific ethnic group, namely, African Americans and inhabitants of the African continent and nearby countries. In America, 1 out of every 500 of African descents suffers, but in Africa, the ratio is ten times higher. Approximate patient numbers are around 100,000 in the United States, but several millions in Africa. When sickle cell crisis occurs, the patients experience severe pain which is caused by the occlusion of blood vessels jammed with red blood cells. Since the average life span of their red blood cells is only about two weeks as opposed to about 120 days for normal subjects, the patients suffer from chronic anemia. Frequently observed symptoms are: acute chest syndromes, splenic infarction; cardiomegaly; neurological disorders such as hemiplegia, convulsions, coma and stupor; pathologic bone abnormalities such as marrow expansion, avascular necrosis, and osteomyelitis; and leg ulceration. In Africa, SCA causes high mortality in infants and children. Their survival rate to adulthood in Africa is less than 50%. Even though the patients' survival to adulthood is not uncommon in the United States, SCA is a disastrous disease. Considering the demographics of SCA, the best hope for the majority of patients would be a low cost self-administered oral therapy. Currently, one such hope for these patients is oral administration of hydroxyurea. This is designed to increase the level of fetal hemoglobin which does not polymerize under deoxygenation. Hydroxyurea therapy has been shown to have beneficial effects, but it is still not free of side effects including bone marrow suppression. If the suppression develops, the patients have to stop the medication until the bone marrow could recover. Since SCA is a genetic disease, any drugs would have to be taken for life-long. There is no guarantee that the prolonged administration of hydroxyurea might cause undesirable side effects. Therefore, a safer method is urgently needed. The inventor found from in vitro experiments that green tea polyphenols could inhibit dense cell formation by inhibiting K-Cl cotransport phenomenon across the sickle red blood cell membrane. This K-Cl cotransport is the major mechanism by which sickle cells are dehydrated in the circulation. It has been shown that the formation of dense cells is the triggering cause for sickle cell crisis (Ballas, S. K. and Smith, E. D. Blood 79:2154-2163, 1992; Fabrey, M. E., Benjamin, L., Lawrence, C. and Nagel, R. L. Blood 64:559-563, 1984).

  Web site: http://www.delphion.com/details?pn=US06538023__

- **Therapeutic uses of specially processed garlic for sickle cell disease**

  Inventor(s): Ohnishi; Tsuyoshi (King of Prussia, PA)

  Assignee(s): Wakunaga of America Co., Ltd. (mission Viejo, Ca)

  Patent Number: 6,254,871

  Date filed: November 12, 1999

Abstract: This invention deals with a therapeutically effective composition and method for use in ameliorating the effects of **sickle cell anemia** and sickle cell crisis. The method preferably involves the oral administration, in preferably four doses daily, of an effective amount of a composition containing S-allyl cysteine and S-allylmercapto cysteine (such as aged garlic extract or AGE) with 1 to 10 grams of Vitamin C and between 200 to 1,200 I.U. of vitamin E.

Excerpt(s): The present invention relates to the therapeutic efficacy of a composition containing components found in specially processed garlic for **sickle cell anemia** patients, particularly, to a method for ameliorating **sickle cell anemia** and more particularly to a method in which the composition or a specially processed garlic is administered on a daily basis for ameliorating anemia and preventing painful crisis in **sickle cell anemia** patients. Sickle cell anemia is a genetic disease seen in both African and African-American populations. The patients have a genetically abnormal hemoglobin (called sickle hemoglobin or HbS), which polymerizes at a low oxygen concentration and forms bundles of hemoglobin polymers, thus stretching and deforming red blood cells into a "sickle" shape. This deformation damages the membrane of patients' red blood cells and makes the average life of the red blood cells in the range of 10 to 20 days as opposed to 120 days for normal individuals. As a result, patients suffer from chronic anemia. These damaged red blood cells have a tendency to adhere to the endothelial cells of the blood vessel, neutrophils and platelets, and thus, obstruct blood flow causing frequent painful seizure called "sickle cell crisis," damaging organs and impairing bone joints. In Africa, one out of fifty persons is estimated to suffer from this disease, and if enough medical assistance is not provided, the average life span of the patients is around 20 years. In the entire African continent, millions of patients are estimated to suffer from this disease. In the United States, about one out of 500 of the African-American population (about 18% of total U.S. population) may suffer from this disease. The total number of sickle cell patients in the United States is estimated to be on the order of 70,000.

Web site: http://www.delphion.com/details?pn=US06254871__

- **Transcription factor, BP1**

  Inventor(s): Berg; Patricia E. (Accokeek, MD)

  Assignee(s): George Washington University (washington, Dc)

  Patent Number: 6,416,956

  Date filed: August 11, 2000

  Abstract: An isolated DNA of SEQ ID NO: 1 is provided that encodes the transcription factor BP1, which is believed to be a repressor of the.beta.-globin gene. A host cell that is transformed with a vector that contains the DNA may be used to produce BP1. Vectors having a controllable promoter operably connected to the BP1 open reading frame may be used to transform.beta.-globin producing cells of patients with **sickle cell anemia,** thereby providing a treatment. Because BP1 is overexpressed in leukemia and breast cancer cells, acute myeloid leukemia, acute lymphocytic leukemia, and breast cancer can be screened for and diagnosed by determining whether BP1 is overexpressed in cell samples of patients who may have these conditions. An antisense DNA or RNA to the DNA encoding BP1 may be used as a treatment for acute myeloid leukemia, acute lymphocytic leukemia, and breast cancer.

Excerpt(s): The present invention relates to a DNA that encodes the transcription factor BP1, a vector containing the DNA and a host cell containing the DNA. The invention also relates to an antisense DNA or RNA to the DNA encoding BP1, methods for treating **sickle cell anemia** by administering an effective amount of BP1, and methods for screening for acute myeloid leukemia, acute lymphocytic leukemia, and breast cancer. Expression of globin genes in the.beta.-globin cluster is restricted to erythropoietic cells, with five different genes expressed during embryonic (.epsilon.), fetal (G.gamma. and A.gamma.) and adult (.delta. and.beta.) development. Transcriptional activation of globin genes occurs not only by binding of transcriptional activator proteins to the promoter of the gene being activated, but also by a regulatory element located 6-18 kb upstream of the.beta.-globin cluster, the Locus Control Region (LCR) (See, for example, Berg, P. E. and A. N. Schechter. 1992. Molecular genetics of disorders of hemoglobin. In T. Friedmann (ed), Molecular Genetic Medicine. Academic Press, San Diego.; Forrester, W. C., C. Thompson, J. T. Elder, and Groudine, M. 1986. A developmentally stable chromatin structure in the human.beta.-globin gene cluster. Proc. Natl. Acad. Sci. USA 83: 1359-1363.; and Tuan, D., W. Soloman, Q. Li, and I. M. London. 1985. The ".beta.-like-globin" gene domain in human erythroid cells. Proc. Natl. Acad. Sci. USA 82: 6384-6388.). Sequential activation of the.beta.-globin cluster genes during ontogeny must be countered by repression of the globin genes inactive during a given developmental stage. Repression is caused by binding of repressor proteins to promoter/upstream DNA and, in the case of the adult.beta.-globin gene, is probably also due to lack of activation by the LCR (see, for example, Crossley, M. and S. H. Orkin. 1993. Regulation of the.beta.-globin locus. Curr. Opinion Gen. Dev. 3: 232-237.). While much is known about transcriptional activators that bind to DNA sequences near the.beta.-globin gene, little is known about the proteins that repress its transcription. As discussed below, BP1 is shown to bind to two silencer DNA sequences upstream of the.beta.-globin gene and therefore, there is strong evidence suggesting that BP1 protein is a repressor of the.beta.-globin gene. The present invention provides for a DNA sequence that encodes BP1, and methods of using information derived from knowledge of the DNA sequence to screen for conditions such as breast cancer, acute myeloid leukemia and acute lymphocytic leukemia. The DNA sequence was found to be closely related to two other human genes, DLX4 and DLX7, described in Quinn, L. M., B. V. Johnson, J. Nicholl, G. R. Sutherland, and B. Kalionis. 1997. Isolation and identification of homeobox genes from human placenta including a novel member of the Distal-less family, DLX4. Gene 187: 55-61 and Nakamura S, Stock DW, Wydner KL, Bollekens JA, Takeshita K, Nagai BM, Chiba , Kitamura T, Freeland TM, Zhao Z, Minowada J, Lawrence JB, Weiss KB, and Ruddle FH. Genomic analysis of a new mammalian Distal-less gene: D1x-7. Genomics 1996; 38: 314-324.

Web site: http://www.delphion.com/details?pn=US06416956__

- **Treatment of sickle cell anemia crises with fructose-1, 6-diphosphate as an analgesic drug**

  Inventor(s): Fox; Anthony W. (Rancho LaCosta, CA), Marangos; Paul J. (Encinitas, CA), Markov; Angel K. (Jackson, MS)

  Assignee(s): Cypros Pharmaceutical Corp. (carlsbad, Ca)

  Patent Number: 6,074,658

  Date filed: October 3, 1997

Abstract: Fructose-1,6-diphosphate (FDP) has been shown, in double-blinded controlled clinical trials on patients with **sickle cell anemia,** to substantially reduce the pain suffered by such patients during the recurrent ischemic crises that are caused by red blood cell sickling. Tests on patients who have been hospitalized for such crises demonstrated that when they received an intravenous injection of FDP, they reported substantially lower pain levels during their hospital stays than control groups that received identical treatment without any FDP. Apparently, FDP has never previously been used or even tested in human clinical trials, to treat **sickle cell anemia.** In addition, FDP has never previously been reported to have any analgesic (pain-reducing) activity.

Excerpt(s): This invention relates to the use of a naturally occurring sugar-phosphate compound called fructose-1,6-diphosphate, for treating the sporadic crises that arise in people suffering from **sickle cell anemia.** Accordingly, **sickle cell anemia** and 1,6-FDP have both been studied extensively. However, there apparently has never been any prior effort to treat **sickle cell anemia,** using 1,6-FDP. This genetic mutation is relatively common in Africa, since a person who carries a single copy of the mutated gene has a relatively high resistance to malaria, without suffering from major adverse health effects. Accordingly, it has been estimated that roughly 30% of all people native to Nigeria (as just one example) carry at least one such gene (Barnhart et al 1976). About 8% of African-Americans also carry at least one such gene, although local populations often contain higher levels. The gene which disposes red blood cells to sickling is often referred to as HbS, where "Hb" refers to hemoglobin, and "S" refers to sickling. By contrast, a normal, healthy, adult hemoglobin is usually referred to as HbA.

Web site: http://www.delphion.com/details?pn=US06074658__

- **Treatment of sickle cell disease**

  Inventor(s): Hider; Robert C. (Clacton, GB2), Huehns; Ernst R. (London, GB2)

  Assignee(s): National Research Development Corporation (london, Gb2)

  Patent Number: 4,866,052

  Date filed: November 2, 1987

  Abstract: Neutral 2:1 ligand:zinc(II) complexes in which at least one ligand is provided by a compound being 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms are of value for use in effecting an enhancement of the oxygen binding ability of a patient's haemoglobin, this being of particular application in the treatment of **sickle cell disease.**

  Excerpt(s): This invention relates to the treatment of **sickle cell disease** and other conditions benefiting from the modification of haemoglobin to enhance its oxygen carrying characteristics. Sickle cell disease comprises a group of disorders resulting from a hereditary defect which causes a modification of the normal AA haemoglobin to haemoglobin of the SS, SC, SD or S.beta.thal form and leads to a polymerisation of the haemoglobin when in the deoxy state to form a linear polymer of a sickle shape. The sickle cells are less readily able to pass through the capilliaries resulting in repeated painful crises for the patient. Various treatments have been developed for **sickle cell disease** involving the oral administration to the patient of one of several drugs having an influence on the behaviour of the haemoglobin molecules, these drugs including cyanates, urea and zinc salts Although each of the drugs can have some beneficial effect,

none of them is really satisfactory and there is still a need for an effective treatment for alleviation of the recurrent pain crises in **sickle cell disease.**

Web site: http://www.delphion.com/details?pn=US04866052__

- **Treatment of sickle cell disease**

  Inventor(s): Lockett; Curtis G. (3063 N. Galvez St., New Orleans, LA 70117)

  Assignee(s): None Reported

  Patent Number: 5,626,884

  Date filed: August 18, 1995

  Abstract: A maintenance regimen with controlled intake of particular vitamin, mineral, and micronutrient formulations, drastically reduces the incidence and severity of **sickle cell disease** crises. The formulations include vitamin A, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, vitamin C, vitamin D, vitamin E, niacinamide, para-aminobenzoic acid (PABA), pantothenic acid, choline bitartrate, inositol, rutin, citrus bioflavonoid complex, betaine hydrochloride, hesperidin complex, folic acid, biotin, calcium, iron, magnesium, zinc, potassium, manganese, iodine, chromium, selenium, and a pharmaceutically acceptable carrier, provided at or just below critical saturation levels, determined for each individual by carefully monitoring tolerance on titration. The daily dose may exceed that necessary as dietary or nutritional supplements, and trigger an increase in the production of viable hemoglobin, and alters the overall blood profile. Platelet concentration is increased up to twice that of seen in normal blood, and the red blood cells produced display increased resistance to sickling. This enhanced biosynthesis is achieved by providing sufficient stores of precursors that stimulate low level manufacture without substantial feedback control by the upper central nervous system.

  Excerpt(s): The present invention relates to the treatment and prophylaxis of hemoglobin disorders. More particularly, the present invention provides a tailored preventative and/or maintenance treatment regimen for an individual suffering from genetic **sickle cell disease.** As described in NIH Publication No. 89-2117, "Management and Therapy of **Sickle Cell Disease,** " 1989 herein incorporated, sickle, cell disease is a generic term for a group of genetic disorders characterized by the predominance of hemoglobin S (Hb S). These disorders include **sickle cell anemia,** the sickle beta thalassemia syndromes, and hemoglobinopathies in which Hb S is in association with another abnormal hemoglobin. The two beta globin genes located on chromosome 11 and the four alpha globin genes located on chromosome 16 determine hemoglobin production. Normal red blood cells are produced in individuals who carry all four alpha globin genes and two normal beta globin genes (.beta.A). Carriers of the **sickle cell trait,** who do not normally physically express the disease, have a normal beta globin gene and a.beta.S globin gene, resulting in the production of both normal hemoglobin A and hemoglobin S, with a predominance of Hb A. Individuals who are homozygous for the sickle beta globin gene (.beta.S) have **sickle cell anemia** (Hb SS). Individuals with sickle beta thalassemia have a.beta.S gene and a gene for beta thalassemia,.beta.thal. Those who have two abnormal beta globin genes,.beta.S and.beta.C, produce hemoglobins Hb S and Hb C, and have Hb SC disease. The absence of two of the alpha globin genes results in alpha thalassemia. Abnormalities in both the beta and alpha genes may be present in the same individual.

  Web site: http://www.delphion.com/details?pn=US05626884__

- **Triaryl methane compounds and analogues thereof useful for the treatment or prevention of sickle cell disease or diseases characterized by abnormal cell proliferation**

  Inventor(s): Bellot, Jr.; Emile M. (Beverly, MA), Brugnara; Carlo (Newton Highlands, MA), Clifford; John J. (Bedford, MA), Froimowitz; Mark (Newton Centre, MA), Gao; Ying-Duo (Neshanic Station, NJ), Haidar; Reem M. (Malden, MA), Halperin; Jose (Brookline, MA), Kelleher; Eugene W. (Somerville, MA), Kher; Falguni M. (Chelmsford, MA), Lombardy; Richard John (Waltham, MA), Moussa; Adel M. (Burlington, MA), Sachdeva; Yesh P. (Concord, MA), Sun; Minghua (Cambridge, MA), Taft; Heather N. (Littleton, MA)

  Assignee(s): Children's Medical Center Corporation (boston, Ma), Ion Pharmaceuticals, Inc. (new York, Ny)

  Patent Number: 6,028,103

  Date filed: March 19, 1997

  Abstract: The present invention provides a class of chemical compounds useful as efficacious drugs in the treatment of **sickle cell disease** and diseases characterized by unwanted or abnormal cell proliferation. The active compounds are substituted triaryl methane compounds or analogues thereof where one or more of the aryl groups is replaced with a heteroaryl, cycloalkyl or heterocycloalkyl group and/or the tertiary carbon atom is replaced with a different atom such as Si, Ge, N or P. The compounds inhibit mammalian cell proliferation, inhibit the Gardos channel of erythrocytes, reduce sickle erythrocyte dehydration and/or delay the occurrence of erythrocyte sickling or deformation.

  Excerpt(s): The present invention relates to aromatic organic compounds which are specific, potent and safe inhibitors of the Ca.sup.2+ -activated potassium channel (Gardos channel) of erythrocytes and/or of mammalian cell proliferation. The compounds can be used to reduce sickle erythrocyte dehydration and/or delay the occurrence of erythrocyte sickling or deformation in situ as a therapeutic approach towards the treatment or prevention of **sickle cell disease.** The compounds can also be used to inhibit mammalian cell proliferation in situ as a therapeutic approach towards the treatment or prevention of diseases characterized by abnormal cell proliferation. Sickle cell disease has been recognized within West Africa for several centuries. **Sickle cell anemia** and the existence of sickle hemoglobin (Hb S) was the first genetic disease to be understood at the molecular level. It is recognized today as the morphological and clinical result of a glycine to valine substitution at the No. 6 position of the beta globin chain (Ingram, 1956, Nature 178:792-794. The origin of the amino acid change and of the disease state is the consequence of a single nucleotide substitution (Marotta et al., 1977, J. Biol. Chem. 252:5040-5053). The major source of morbidity and mortality of patients suffering from **sickle cell disease** is vascular occlusion caused by the sickled cells, which causes repeated episodes of pain in both acute and chronic form and also causes ongoing organ damage with the passage of time. It has long been recognized and accepted that the deformation and distortion of sickle cell erythrocytes upon complete deoxygenation is caused by polymerization and intracellular gelation of sickle hemoglobin, hemoglobin S (Hb S). The phenomenon is well reviewed and discussed by Eaton and Hofrichter, 1987, Blood 70:1245. The intracellular gelatin and polymerization of Hb S can occur at any time during erythrocyte's journey through the vasculature. Thus, erythrocytes in patients with **sickle cell disease** containing no polymerized hemoglobin S may pass through the microcirculation and return to the lungs without sickling, may sickle in the veins or may sickle in the capillaries.

Web site: http://www.delphion.com/details?pn=US06028103__

- **Vectors for expression of globin genes**

  Inventor(s): Atweh; George F. (New York, NY)

  Assignee(s): Mount Sinai School of Medicine of the City University of New York (new York, Ny)

  Patent Number: 6,022,738

  Date filed: February 26, 1997

  Abstract: The present invention relates to vectors comprising an.alpha.-globin locus control region (.alpha.LCR) and a gene encoding an erythroid protein. In articular embodiments, a retroviral vector comprising an.alpha.LCR and a globin gene may be used to treat globin-based genetic disorders, including **sickle cell anemia** and.beta.-thalassemia.

  Excerpt(s): The present invention relates to vectors comprising an.alpha.-globin locus control region (.alpha.LCR) and a gene encoding an erythroid protein. In particular embodiments, a retroviral vector comprising an.alpha.LCR and a globin gene may be used to treat globin-based genetic disorders, including **sickle cell anemia** and.beta.-thalassemia. A variety of blood diseases are caused by mutations involving the structure or expression of erythroid proteins. Mutations involving non-globin erythroid genes are associated with a multitude of disorders, including porphyria, sideroblastic anemia, and glucose-6-phosphate dehydrogenase deficiency. Genetic aberrations in globin gene expression result in several common blood diseases, including **sickle cell anemia** and.beta.-thalassemia. Sickle cell anemia is an autosomal recessive disorder involving a mutation in the.beta.-globin gene that causes hemoglobin to form long polymers under deoxygenated conditions. As a result, the red blood cell is deformed and assumes a "sickle" shape which may compromise the micro-circulation. Patients with this disorder have chronic anemia and typically suffer painful "sickle cell crises" and multiple end-organ damage from obstruction of blood vessels with sickled red blood cells. Medical therapy for **sickle cell anemia** has been largely directed toward managing the complications of vascular insufficiency caused by red cell deformation, although allogeneic bone marrow transplantation, which supplies normal red blood cells, has been shown to be effective (Johnson, et al., N. Eng. J. Med. 311:780-783, 1984).

  Web site: http://www.delphion.com/details?pn=US06022738__

Patent Applications on Sickle Cell Anemia

As of December 2000, U.S. patent applications are open to public viewing.[10] Applications are patent requests which have yet to be granted. (The process to achieve a patent can take several years.) The following patent applications have been filed since December 2000 relating to sickle cell anemia:

[10] This has been a common practice outside the United States prior to December 2000.

- **Method for detecting body condition using nano and microdevices**

  Inventor(s): Bender, Gerald E.; (Cheshire, MA), Donnelly, Denis P.; (Saratoga Springs, NY), Erlach, Julian Van; (Clifton Park, NY), Hirsch, Robert S.; (Troy, NY), Olsen, Arlen L.; (Clifton Park, NY), Peterson, James E.; (Delmar, NY), Scott, Mark D.; (Clifton Park, NY), Smith, Jeffrey M.; (Pittsfield, MA), Smith, Laura B.; (Pittsfield, MA), Stinchcomb, Audra L.; (Latham, NY)

  Correspondence: Arlen L. Olsen; Schmeiser, Olsen & Watts; 3 Lear Jet Lane; Suite 201; Latham; NY; 12110; US

  Patent Application Number: 20020111551

  Date filed: November 30, 2000

  Abstract: A method for detecting body condition using nano and microdevices is disclosed. The microdevice or nanodevice is inserted into a fluid stream within a body, and used in detecting a bodily condition. The bodily condition may be myocardial infarction, stroke, **sickle cell anemia,** phlebitis, or a vascular aneurysm. The micro or nano device may be detected using electron paramagnetic resonance (EPR), electron spin resonance (ESR), and nuclear magnetic resonance (NMR).

  Excerpt(s): The present invention relates to nano and microtechnology. In particular, the present invention relates to a method for detecting a body condition using a microdevice or a nanodevice. Heretofore, various methods and apparatus have been disclosed for using substrates in combination with biological members. U.S. Pat. No. 6,123,819 discloses an array of electrodes built on a single chip used to simultaneously detect, characterize and quantify individual proteins or biological molecules in solutions. U.S. Pat. No. 6,051,380 discloses a microelectronic device designed to carry out and control complex molecular biological processes, including antibody/antigen reactions, nucleic acid hybridizations, DNA amplification, clinical diagnostics and biopolymer synthesis. None of the references, however, adequately describe attaching a substrate to a biological member for controlling and analyzing complex molecular biological processes and bodily conditions.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Method for identifying compounds to treat medical pathologies associated with molecular crystallization**

  Inventor(s): Shell, John W.; (Hillsborough, CA)

  Correspondence: Reed & Associates; 800 Menlo Avenue; Suite 210; Menlo Park; CA; 94025; US

  Patent Application Number: 20020132758

  Date filed: January 17, 2002

  Abstract: Numerous diseases and disorders are caused or exacerbated by the formation of crystalline aggregates of a biomolecule that is normally in solution. Such diseases and disorders include cataracts, **sickle cell anemia,** atherosclerosis, kidney stones, gallstones, gout, and Alzheimer's disease. The present invention provides methods to identify compounds that can inhibit the adverse formation of crystalline aggregates, including fibrils, of a target biomolecule. These methods include the screening of large combinatorial libraries. The identified compounds are tested for their therapeutic utility in treating medical conditions caused or exacerbated by the adverse crystallization of

biomolecules. Molecules that are slight modifications of the target biomolecule are found to be particularly effective in inhibiting the adverse crystallization, including fibril formation, of a target biomolecule.

Excerpt(s): This application claims priority under 35 U.S.C.sctn.1 19(e)(1) to provisional U.S. Patent Application Serial No. 60/262,987, filed Jan. 18, 2001. This invention relates generally to inhibition of molecular crystallization processes associated with one or more medical pathologies, and more particularly relates to a method for screening compounds to identify potentially useful inhibitors of such crystallization processes. The invention additionally relates to a method of determining which, if any, of the identified potentially useful inhibitors are potentially useful as therapeutic agents by virtue of inhibiting a particular crystallization process. The invention also relates to a method for treating ocular cataracts by inhibiting the crystallization of one or more lenticular proteins. Crystalline materials consist of atoms that are regularly ordered in a periodically repeating pattern. At thermodynamic equilibrium, a crystal forms in preference to other possible phases when the total energy of the crystal is less than that of the phase (generally a fluid) from which the crystal grows. Crystals preferentially form because the crystalline phase has lower total energy than that of less-ordered phases, such as amorphous or glassy materials. The Second Law of Thermodynamics, however, requires permissible chemical reactions (including phase changes such as crystallization) to increase the total entropy (disorder) of the universe. Since a crystal is structurally more ordered than the fluid from which is grows, crystallization must proceed by creating a net entropy increase in the environment; this is accomplished by a release of heat (which increases disorder) into the surroundings. The formation of a crystal also requires that more heat be released (entropy increased) by crystallization than by the formation of a glassy or amorphous (non-crystalline) phase.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **METHOD OF TREATING SICKLE CELL DISEASE OR THALASSEMIA**

  Inventor(s): UM, SUZANE LEE; (INDIANAPOLIS, IN), UTTERBACK, BARBARA GAIL; (AVON, IN), YAN, SAU-CHI BETTY; (INDIANAPOLIS, IN)

  Correspondence: Eli Lilly And Company; Lilly Corporate Center; Drop Code 1104; Indianapolis; IN; 46285; US

  Patent Application Number: 20020012662

  Date filed: November 22, 1999

  Abstract: The present invention provides a method of treatment of **sickle cell disease** (SCD) or thalassemia with protein C. The claimed invention provides a needed therapy for potentially serious and debilitating disorders while avoiding complications such as bleeding tendency, toxicity and general side effects of currently available anticoagulant agents.

  Excerpt(s): This application claims priority of U.S. Provisional Application Serial No. 60/109,474 filed Nov. 23, 1998. This invention relates to medical science particularly the treatment of **sickle cell disease** or thalassemia with protein C. Protein C is a vitamin K dependent serine protease and naturally occurring anticoagulant that plays a role in the regulation of hemostasis by inactivating Factors Va and VIIIa in the coagulation cascade. Human protein C circulates as a 2-chain zymogen, but functions at the endothelial and platelet surface following conversion to activated protein C (aPC) by limited proteolysis with thrombin in complex with the cell surface membrane protein, thrombomodulin.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Methods and compositions for the diagnosis and treatment of hematological disorders using 2777**

  Inventor(s): Carroll, Joseph M.; (Cambridge, MA)

  Correspondence: Millennium Pharmaceuticals, INC.; 75 Sidney Street; Cambridge; MA; 02139; US

  Patent Application Number: 20030091571

  Date filed: October 28, 2002

  Abstract: The present invention relates to methods and compositions for the diagnosis and treatment of hematological disorders, including, but not limited to, apalstic anemia, hemophilia, **sickle cell anemia,** thalassisemia, blood loss and other blood disorders, e.g., blood diorders related to bone marrow irradiation or chemotherapy treatment or renal failure. The invention further provides methods for identifying a compound capable of treating a hematological disorder. The invention also provides methods for identifying a compound capable of modulating a hematopoietic cell activity. Yet further, the invention provides a method for modulating a hematopoietic cell activity. In addition, the invention provides a method for treating a subject having a hematological disorder characterized by aberrant 2777 polypeptide activity or aberrant 2777 nucleic acid expression. In another aspect, the invention provides methods for increasing hematopoietic cell proliferation in a subject and methods for modulating hematopoietic cell apoptosis in a subject.

  Excerpt(s): This application claims priority to U.S. provisional application No. 60/335,251, filed Oct. 31, 2001, the entire contents of which are incorporated herein by reference. Hematological disorders are blood associated disorders. Blood is a highly specialized tissue which carries oxygen and nutrients to all parts of the body and waste products back to the lungs, kidneys and liver for disposal. Thus, blood maintains communication between different parts of the body. Blood is also an essential part of the immune system, crucial to fluid and temperature balance, a hydraulic fluid for certain functions and a highway for hormonal messages. All blood cells in adults are produced in the bone marrow. Red cells, white cells and platelets are produced in the marrow of bones, especially the vertebrae, ribs, hips, skull and sternum. These essential blood cells fight infection, carry oxygen and help control bleeding. Specifically, red blood cells are disc-shaped cells containing hemoglobin, which enables these cells to pick up and deliver oxygen to all parts of the body. White blood cells are the body's primary defense against infection. They can move out of the blood stream and reach tissues being invaded. Platelets are small blood cells that control bleeding by forming clusters to plug small holes in blood vessels and assist in the clotting process.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Methods for treatment of sickle cell anemia**

  Inventor(s): Vassilev, Vassil P.; (San Diego, CA), Chen, Long-Shiuh; (San Diego, CA), Lai, Ching-San; (Encinitas, CA)

  Correspondence: Stephen E. Reiter; Foley & Lardner; P.O. Box 80278; San Diego; CA; 92138-0278; US

  Patent Application Number: 20030022923

  Date filed: March 12, 2002

  Abstract: The preparation and use of a protected organic aldehyde is described wherein bioavailability of the orally administered therapeutic aldehyde is improved. The protected aldehyde is prepared by reacting the aldehyde with a protecting group, for example, condensing the aldehyde chemically with a thiazolidine-4-carboxylic acid. The improved bioavailability of such orally administered drugs increases the feasibility of delivering sufficient amounts of vanillin or other therapeutic organic aldehydes in vivo to prevent sickling in **sickle cell anemia.** Combination therapy is also described wherein a protected organic aldehyde is administered to a subject in treatment of **sickle cell anemia** in conjunction with one or more other drugs, such as pain killers, used in treatment of the symptoms of **sickle cell anemia** or **sickle cell disease.**

  Excerpt(s): The present invention generally relates to methods for treating anemia. More specifically, the present invention relates to methods for treating **sickle cell anemia** using protected forms(s) of organic aldehydes. Sickle cell disease is a hemolytic disorder, which affects, in its most severe form, approximately 80,000 patients in the United States (see, for example, D. L. Rucknagel, in R. D. Levere, Ed., **Sickle Cell Anemia** and Other Hemoglobinopathies, Academic Press, New York, 1975, p.1). The disease is caused by a single mutation in the hemoglobin molecule;.beta.6 glutamic acid in normal adult hemoglobin A is changed to valine in sickle hemoglobin S. (see, for example, V. M. Ingram in Nature, 178:792-794 (1956)). Hemoglobin S has a markedly decreased solubility in the deoxygenated state when compared to that of hemoglobin A. Therefore, upon deoxygenation, hemoglobin S molecules within the erythrocyte tend to aggregate and form helical fibers that cause the red cell to assume a variety of irregular shapes, most commonly in the sickled form. After repeated cycles of oxygenation and deoxygenation, the sickle cell in the circulation becomes rigid and no longer can squeeze through the small capillaries in tissues, resulting in delivery of insufficient oxygen and nutrients to the organ, which eventually leads to local tissue necrosis. The prolonged blockage of microvascular circulation and the subsequent induction of tissue necrosis lead to various symptoms of **sickle cell anemia,** including painful crises of vaso-occlusion. Now, most patients with **sickle cell disease** can be expected to survive into adulthood, but still face a lifetime of crises and complications, including chronic hemolytic anemia, vaso-occlusive crises and pain, and the side effects of therapy. Currently, most common therapeutic interventions include blood transfusions, opioid and hydroxyurea therapies (see, for example, S. K. Ballas in Cleveland Clin. J. Med., 66:48-58 (1999). However, all of these therapies are associated with some undesirable side-effects. For example, repeated blood transfusions are known to be associated with the risks of transmission of infectious disease, iron overload, and allergic and febrile reactions. Complications of opioid therapy may include addiction, seizures, dependency, respiratory depression and constipation.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Novel transcription factor, BP1**

  Inventor(s): Berg, Patricia E.; (Accokeek, MD)

  Correspondence: Antonelli, Terry, Stout & Kraus, Llp; 1300 North Seventeenth Street; Suite 1800; Arlington; VA; 22209-9889; US

  Patent Application Number: 20030171273

  Date filed: May 14, 2002

  Abstract: An isolated DNA of SEQ ID NO:1 is provided that encodes the transcription factor BP1, which is believed to be a repressor of the.beta.-globin gene. A host cell that is transformed with a vector that contains the DNA may be used to produce BP1. Vectors having a controllable promoter operably connected to the BPl open reading frame may be used to transform.beta.-globin producing cells of patients with **sickle cell anemia,** thereby providing a treatment. Because BP1 is overexpressed in leukemia and breast cancer cells, acute myeloid leukemia, acute lymphocytic leukemia, and breast cancer can be screened for and diagnosed by determining whether BP1 is overexpressed in cell samples of patients who may have these conditions. An antisense DNA or RNA to the DNA encoding BP1 may be used as a treatment for acute myeloid leukemia, acute lymphocytic leukemia, and breast cancer.

  Excerpt(s): The present application claims the benefit of the filing date of U.S. Provisional Application No. 60/148,940, filed Aug. 13, 1999. The provisional application is incorporated by reference herein. Work described herein was supported by NIH grant R01DK53533. The U.S. Government has certain rights in the invention. The present invention relates to a DNA that encodes the transcription factor BP1, a vector containing the DNA and a host cell containing the DNA. The invention also relates to an antisense DNA or RNA to the DNA encoding BP1, methods for treating **sickle cell anemia** by administering an effective amount of BP1, and methods for screening for acute myeloid leukemia, acute lymphocytic leukemia, and breast cancer.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Oral low dose butyrate compositions**

  Inventor(s): Chaturvedi, Pravin; (Andover, MA), Su, Michael; (Newton, MA), Tung, Roger; (San Diego, CA)

  Correspondence: Vertex Pharmaceuticals Incorporated; 130waverly Street; Cambridge; MA; 02130-4646; US

  Patent Application Number: 20020115716

  Date filed: September 19, 2001

  Excerpt(s): This application claims priority to co-pending International Patent Application PCT/US00/07128, filed Mar. 17, 2000, which claims priority of United States provisional application Ser. No. 60/125,607, which was filed Mar. 19, 1999. The entirety of which is herein incorporated by reference. This invention relates to orally available compositions which deliver an amount of butyrate or a butyrate analogue effective to ameliorate.beta.-hemoglobinopathies, such as.beta.-thalassemia and **sickle cell anemia,** cystic fibrosis, cancer and other diseases which are known to be treatable with butyrate. The invention also relates to methods of treating these diseases with such low dose oral compositions. Recent studies have suggested that butyrate or analogues thereof are useful in treating a wide variety of diseases. For example, butyrate has been

implicated in increasing fetal hemoglobin (HbF) levels, which in turn, can ameliorate the effects of.beta.-hemoglobinopathies, such as **sickle cell anemia** and.beta.-thalassemia [S. Perrine et al., A Short Term Trial of Butyrate to Stimulate Fetal-Globin-Gene Expression in the.beta.-globin Disorders.mu., N. Eng. J. Med., 328, pp. 81-86 (1993); S. P. Perrine et. al., "Isobutyramide, an Orally Bioavailable Butyrate Analogue, Stimulates Fetal Globin Gene Expression In Vitro and In Vivo", British J. Haematology, 88, pp. 555-61 (1994); A. F. Collins et al., "Oral Sodium Phenylbutyrate Therapy in Homozygous.beta. Thalassemia: A Clinical Trial", Blood, 85, pp. 43-49 (1995); see also U.S. Pat. Nos. 4,822,821, Re 36,080, and PCT publication WO097/12855].

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Tetrahydroisoquinoline-3-carboxylic acid alkoxyguanidines as integrin antagonists**

  Inventor(s): Marder, Victor J.; (Los Angeles, CA), U'Prichard, David C.; (Philadelphia, PA), Wang, Aihua; (Jamison, PA)

  Correspondence: Sterne, Kessler, Goldstein & Fox Pllc; 1100 New York Avenue, N.W., Suite 600; Washington; DC; 20005-3934; US

  Patent Application Number: 20020061885

  Date filed: October 3, 2001

  Abstract: The present invention relates to novel tetrahydroisoquinoline-3-carboxylic acid alkoxyguanidine compounds that are antagonists of alpha V (.alpha.v) integrins, for example.alpha.sub.v.beta.sub.3 and.alpha.sub.v.beta.sub.5 integrins, their pharmaceutically acceptable salts, and pharmaceutical compositions thereof. The compounds may be used in the treatment and/or prevention of pathological conditions mediated by.alpha.sub.v.beta.sub.3 and.alpha.sub.v.beta.sub.5 integrins such as tumor growth, metastasis, restenosis, osteoporosis, inflammation, macular degeneration, diabetic retinopathy, rheumatoid arthritis, **sickle cell anemia,** and in treatment and/or prevention of central nervous system (CNS) related disorders such as neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia, surgery, neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, adverse consequences of overstimulation of one or more excitatory amino acids, anxiety, convulsions, chronic pain, psychosis, schizophrenia, anesthesia, and opiate tolerance. The compounds have the general formula: 1where R.sup.1, R.sup.2, R.sup.3, R.sup.4, R.sup.5, R.sup.6, R.sup.7, R.sup.8, R.sup.9, R.sup.10, m and n are defined herein.

  Excerpt(s): This application is a continuation-in-part of U.S. patent application Ser. No. 09/921,759, filed Aug. 6, 2001, which claims priority under 35 U.S.C.sctn. 119(e) to U.S. Provisional Patent Application No. 60/223,478, filed Aug. 7, 2000, now abandoned, both of which are incorporated by reference herein in their entirety. The present invention relates to novel tetrahydroisoquinoline-3-car- boxylic acid alkoxyguanidine compounds that are antagonists of alpha V (.alpha.v) integrins, for example.alpha.sub.v.beta.sub.3 and.alpha.sub.v.beta.sub.5 integrins, their pharmaceutically acceptable salts, and pharmaceutical compositions thereof. Integrins are cell surface glycoprotein receptors which bind extracellular matrix proteins and mediate cell-cell and cell-extracellular matrix interactions (generally referred to as cell adhesion events) (Hynes, R. O., Cell 69:11-25 (1992)). These receptors are composed of noncovalently associated alpha (.alpha.) and beta (.beta.) chains which combine to give a variety of heterodimeric proteins with distinct cellular and adhesive specificities (Albeda, S. M., Lab. Invest. 68:4-14 (1993)). Recent studies have implicated integrins in the regulation of cellular adhesion, migration, invasion, proliferation, apoptosis and gene expression (Albeda, S.

M., Lab. Invest. 68:4-14 (1993); Juliano, R., Cancer Met. Rev. 13:25-30 (1994); Ruoslahti, E. and Reed, J. C., Cell 77:477-478 (1994); and Ruoslahti, E. and Giancotti, F. G., Cancer Cells 1:119-126 (1989)).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

Keeping Current

In order to stay informed about patents and patent applications dealing with sickle cell anemia, you can access the U.S. Patent Office archive via the Internet at the following Web address: **http://www.uspto.gov/patft/index.html**. You will see two broad options: (1) Issued Patent, and (2) Published Applications. To see a list of issued patents, perform the following steps: Under "Issued Patents," click "Quick Search." Then, type "sickle cell anemia" (or synonyms) into the "Term 1" box. After clicking on the search button, scroll down to see the various patents which have been granted to date on sickle cell anemia.

You can also use this procedure to view pending patent applications concerning sickle cell anemia. Simply go back to **http://www.uspto.gov/patft/index.html**. Select "Quick Search" under "Published Applications." Then proceed with the steps listed above.

CHAPTER 7. BOOKS ON SICKLE CELL ANEMIA

Overview

This chapter provides bibliographic book references relating to sickle cell anemia. In addition to online booksellers such as **www.amazon.com** and **www.bn.com**, excellent sources for book titles on sickle cell anemia include the Combined Health Information Database and the National Library of Medicine. Your local medical library also may have these titles available for loan.

Book Summaries: Online Booksellers

Commercial Internet-based booksellers, such as Amazon.com and Barnes&Noble.com, offer summaries which have been supplied by each title's publisher. Some summaries also include customer reviews. Your local bookseller may have access to in-house and commercial databases that index all published books (e.g. Books in Print®). **IMPORTANT NOTE:** Online booksellers typically produce search results for medical and non-medical books. When searching for "sickle cell anemia" at online booksellers' Web sites, you may discover non-medical books that use the generic term "sickle cell anemia" (or a synonym) in their titles. The following is indicative of the results you might find when searching for "sickle cell anemia" (sorted alphabetically by title; follow the hyperlink to view more details at Amazon.com):

- **Advances in the Pathophysiology, Diagnosis, and Treatment of Sickle Cell Disease** by Roland B. Scott (Editor); ISBN: 0471566373; http://www.amazon.com/exec/obidos/ASIN/0471566373/icongroupinterna
- **Advances in the pathophysiology, diagnosis, and treatment of sickle cell disease : proceedings of the tenth annual postgraduate conference on sickle cell disease held in Washington, DC, September 24-26, 1981**; ISBN: 084510098X; http://www.amazon.com/exec/obidos/ASIN/084510098X/icongroupinterna
- **Against All Odds: The Story of My Battle With Sickle Cell Anemia** by Janice Gillespie; ISBN: 0966054903; http://www.amazon.com/exec/obidos/ASIN/0966054903/icongroupinterna

- **Back to Our Roots: Cooking for Control of Sickle Cell Anemia and Cancer Prevention** by Dawud Ujamaa; ISBN: 1884938019; http://www.amazon.com/exec/obidos/ASIN/1884938019/icongroupinterna
- **Comparative Clinical Aspects of Sickle Cell Disease** by Walter Fried (Editor); ISBN: 0444006737; http://www.amazon.com/exec/obidos/ASIN/0444006737/icongroupinterna
- **Development of therapeutic agents for sickle cell disease : proceedings of the International Meeting on Development of Therapeutic Agents for Sickle Cell Disease held in Paris (France), 19-21 July 1978**; ISBN: 0720406714; http://www.amazon.com/exec/obidos/ASIN/0720406714/icongroupinterna
- **Dying in the City of the Blues: Sickle Cell Anemia and the Politics of Race and Health** by Keith Wailoo; ISBN: 0807825840; http://www.amazon.com/exec/obidos/ASIN/0807825840/icongroupinterna
- **Hope and Destiny: A Patient's and Parent's Guide to Sickle Cell Disease and Sickle Cell Trait** by Allan F. Platt, et al; ISBN: 0967525845; http://www.amazon.com/exec/obidos/ASIN/0967525845/icongroupinterna
- **In the Blood: Sickle Cell Anemia and the Politics of Race** by Melbourne Tapper; ISBN: 0812234715; http://www.amazon.com/exec/obidos/ASIN/0812234715/icongroupinterna
- **Let's Talk About Sickle Cell Anemia** by Melanie Apel Gordon; ISBN: 082395417X; http://www.amazon.com/exec/obidos/ASIN/082395417X/icongroupinterna
- **Managing Sickle Cell Disease in Low-Income Families (Health, Society, and Policy)** by Shirley A. Hill; ISBN: 1566391881; http://www.amazon.com/exec/obidos/ASIN/1566391881/icongroupinterna
- **Membrane Abnormalities in Sickle Cell Disease and in Other Red Blood Cell Disorders (CRC Series in Membrane-Linked Diseases)** by S. Tsuyoshi Ohnishi, Tomoko Ohnishi (Editor); ISBN: 0849380928; http://www.amazon.com/exec/obidos/ASIN/0849380928/icongroupinterna
- **New hope for people with sickle cell anemia (SuDoc HE 20.4010/A:SI 1)** by Eleanor Mayfield; ISBN: B00010R340; http://www.amazon.com/exec/obidos/ASIN/B00010R340/icongroupinterna
- **Pathology of Sickle Cell Disease.** by Joseph, Song; ISBN: 039801812X; http://www.amazon.com/exec/obidos/ASIN/039801812X/icongroupinterna
- **Psychosocial Aspects of Sickle Cell Disease: Past, Present, and Future Directions of Research** by Kermit B. Nash (Editor); ISBN: 1560245786; http://www.amazon.com/exec/obidos/ASIN/1560245786/icongroupinterna
- **Sickle Cell Anemia** by Alvin Silverstein, et al; ISBN: 0894907115; http://www.amazon.com/exec/obidos/ASIN/0894907115/icongroupinterna
- **Sickle Cell Anemia** by Anthony Cerami; ISBN: 089388068X; http://www.amazon.com/exec/obidos/ASIN/089388068X/icongroupinterna
- **Sickle Cell Anemia** by Ronald L. Nagel MD, Samuel Charache MD; ISBN: 0865420602; http://www.amazon.com/exec/obidos/ASIN/0865420602/icongroupinterna
- **Sickle Cell Anemia** by David Gerrick; ISBN: 068589679X; http://www.amazon.com/exec/obidos/ASIN/068589679X/icongroupinterna

- **Sickle Cell Anemia (A Venture Book)** by George W. Beshore (Editor); ISBN: 0531125106; http://www.amazon.com/exec/obidos/ASIN/0531125106/icongroupinterna
- **Sickle cell anemia (SuDoc HE 20.3031:Si 1)** by U.S. Dept of Health and Human Services; ISBN: B0001058C4; http://www.amazon.com/exec/obidos/ASIN/B0001058C4/icongroupinterna
- **Sickle cell anemia and other hemoglobinopathies**; ISBN: 0124447503; http://www.amazon.com/exec/obidos/ASIN/0124447503/icongroupinterna
- **Sickle Cell Anemia: Preliminary Survey** by Lenwood G. Davis; ISBN: 0686203976; http://www.amazon.com/exec/obidos/ASIN/0686203976/icongroupinterna
- **Sickle Cell Disease** by Graham R., Md Serjeant, Beryl E. Serjeant; ISBN: 0192630369; http://www.amazon.com/exec/obidos/ASIN/0192630369/icongroupinterna
- **Sickle Cell Disease** by Carol Baldwin; ISBN: 1403402523; http://www.amazon.com/exec/obidos/ASIN/1403402523/icongroupinterna
- **Sickle Cell Disease (Annals of the New York Academy of Sciences, No 565)** by Charles F. Whitten, John F. Bertles (Editor); ISBN: 0897665120; http://www.amazon.com/exec/obidos/ASIN/0897665120/icongroupinterna
- **Sickle Cell Disease (Health Watch)** by Susan Dudley Gold, Lillian McMahon; ISBN: 0766016625; http://www.amazon.com/exec/obidos/ASIN/0766016625/icongroupinterna
- **Sickle Cell Disease (Just the Facts)** by Oliver Gillie; ISBN: 1403446032; http://www.amazon.com/exec/obidos/ASIN/1403446032/icongroupinterna
- **Sickle Cell Disease (Twenty-First Century Medical Library)** by Jacqueline L. Harris; ISBN: 0761314598; http://www.amazon.com/exec/obidos/ASIN/0761314598/icongroupinterna
- **Sickle cell disease : screening, diagnosis, management, and counseling in newborns and infants (SuDoc HE 20.6520:D 63)** by U.S. Dept of Health and Human Services; ISBN: B00010GL48; http://www.amazon.com/exec/obidos/ASIN/B00010GL48/icongroupinterna
- **Sickle Cell Disease: A Handbook for the General Clinician** by A.F. Fleming (Editor); ISBN: 044302037X; http://www.amazon.com/exec/obidos/ASIN/044302037X/icongroupinterna
- **Sickle Cell Disease: Basic Principles and Clinical Practice** by Stephen H. Embury, et al; ISBN: 0781701422; http://www.amazon.com/exec/obidos/ASIN/0781701422/icongroupinterna
- **Sickle Cell Disease: Pathophysiology, Diagnosis, and Management** by Vipul N. Mankad (Author), R. Blaine Moore (Author); ISBN: 027592503X; http://www.amazon.com/exec/obidos/ASIN/027592503X/icongroupinterna
- **Sickle Cell Disease: Psychological and Psychosocial Issues** by Anita Landau Hurtig (Photographer), Carol T. Viera (Editor); ISBN: 0252011864; http://www.amazon.com/exec/obidos/ASIN/0252011864/icongroupinterna
- **Sickle cell disease; transactions. Held on Jan. 20 and 21, 1972**; ISBN: 3794503449; http://www.amazon.com/exec/obidos/ASIN/3794503449/icongroupinterna
- **Sickle disease research : an update : hearing before the Committee on Labor and Human Resources, United States Senate, One Hundred Third Congress, second**

session, on to award a grant to the Louisiana Department of Health and Hospitals to establish and construct the National Center for Sickle Cell Disease Research at Southern University in Baton Rouge, LA, and for related facilities and equipment at such center, July 28, 1994 (SuDoc Y 4.L 11/4:S.HRG.103-694); ISBN: 0160448468; http://www.amazon.com/exec/obidos/ASIN/0160448468/icongroupinterna

- **So That His Death Will Have Not Been in Vain: The Sickle Cell Trait: A Serious Factor to Be Observed by the Military** by Peggy D. Friend; ISBN: 0936026774; http://www.amazon.com/exec/obidos/ASIN/0936026774/icongroupinterna
- **Temperature, hormones, and the kidney in sickle cell disease** by S. Kojo Addae; ISBN: 0876761791; http://www.amazon.com/exec/obidos/ASIN/0876761791/icongroupinterna
- **The 2002 Official Patient's Sourcebook on Sickle Cell Anemia** by Icon Health Publications, et al; ISBN: 0597831572; http://www.amazon.com/exec/obidos/ASIN/0597831572/icongroupinterna
- **The clinical features of sickle cell disease** by Graham R. Serjeant; ISBN: 0444105921; http://www.amazon.com/exec/obidos/ASIN/0444105921/icongroupinterna
- **The Early Life of Jeomie East: Struggling With Sickle Cell Anemia** by Phyllis East; ISBN: 0759668019; http://www.amazon.com/exec/obidos/ASIN/0759668019/icongroupinterna
- **The Handbook on the Psychology of Hemoglobin-S: A Perspicacious View of Sickle Cell Disease** by Samuel Rayford. McElroy; ISBN: 0819111325; http://www.amazon.com/exec/obidos/ASIN/0819111325/icongroupinterna
- **The management of sickle cell disease**; ISBN: B000116V0Q; http://www.amazon.com/exec/obidos/ASIN/B000116V0Q/icongroupinterna
- **The management of sickle cell disease (SuDoc HE 20.3202:2002025224)** by U.S. Dept of Health and Human Services; ISBN: B000116W0K; http://www.amazon.com/exec/obidos/ASIN/B000116W0K/icongroupinterna
- **Understanding Sickle Cell Disease (Understanding Health and Sickness Series)** by Miriam Bloom; ISBN: 0878057455; http://www.amazon.com/exec/obidos/ASIN/0878057455/icongroupinterna

Chapters on Sickle Cell Anemia

In order to find chapters that specifically relate to sickle cell anemia, an excellent source of abstracts is the Combined Health Information Database. You will need to limit your search to book chapters and sickle cell anemia using the "Detailed Search" option. Go to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find book chapters, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Book Chapter." Type "sickle cell anemia" (or synonyms) into the "For these words:" box. The following is a typical result when searching for book chapters on sickle cell anemia:

- **Oral Medicine**

  Source: in Sonis, S.T., ed. Dental Secrets: Questions You Will Be Asked On Rounds, In the Clinic, On Exams, On Boards. Philadelphia, PA: Hanley and Belfus, Inc. 1994. p. 17-32.

Contact: Available from Hanley and Belfus, Inc. Medical Publishers, 210 South 13th Street, Philadelphia, PA 19107. (800) 962-1892 or (215) 546-7293; Fax (215) 790-9330; http://www.hanleyandbelfus.com. PRICE: $36.95 plus shipping and handling. ISBN: 1560530634.

Summary: Presented in a question and answer format, this book chapter on oral medicine is from a mini-textbook that can be used as a review for examinations, rounds, and clinical discussions. Topics covered include disorders of hemostasis, including patient indications for surgery, gingival bleeding, and the use of warfarin; indications for prophylactic antibiotics, including the specific antibiotics and dosages recommended by the American Heart Association; treatment of HIV-positive patients; cardiovascular disease, including the emergency management of a possible cardiovascular event; metabolic disorders, including diabetes mellitus, patients on corticosteroids, and hypothyroidism; allergic reactions, including the symptoms of anaphylaxis; hematology and oncology, including **sickle cell anemia,** leukemia, chemotherapy, and radiation therapy; kidney disease, including patients on dialysis and patients with kidney transplants; pulmonary disease; liver disease; and seizures. This book chapter provides specific management strategies, including the recommended drug administration and dosages. 3 tables. 16 references.

- **Outpatient Management of the Medically Compromised Patient**

  Source: in Lockhart, P.B. Oral Medicine and Hospital Practice. Chicago, IL: Special Care Dentistry. 1997. p. 3.3-3.64.

  Contact: Available from Special Care Dentistry. 211 East Chicago Avenue, Chicago, IL 60611. (312) 440-2660. Fax (312) 440-2824. PRICE: $27.00 (member) or $30.00 (nonmember) plus shipping and handling; institutional prices and bulk orders available. ISBN: 0965719103.

  Summary: This chapter is from a manual designed to help dental residents, students, and practitioners engaged in the care of patients in the hospital setting. This chapter discusses outpatient management of medically compromised patients. The author stresses that a thorough history is necessary to establish the existence and nature of any medical problems to decrease the likelihood of medical emergencies or other problems in management. Topics include history taking; medical history and risk assessment for bacteremias and the need for antibiotics; and considerations for specific medical conditions, including allergy, arthritis, bleeding disorders, cancer, cardiovascular disorders, dementia, diabetes mellitus, drug abuse and alcoholism, fever of unknown origin (FUO), hepatic disease, HIV infection, hydrocephalus, hypertension, Parkinson's disease, pregnancy, prosthetic joints, psychiatric illness, renal and adrenal disorders, respiratory disease, seizures, **sickle cell anemia,** spleen, and thyroid disorders. The chapter includes six tables: common drugs with significant allergic potential; TNM staging for lip and oral cavity tumors; types and durations of insulin therapy; classification of blood pressure for adults 18 years and over; recommendations for follow-up based on initial set of blood pressure measurements for adults; and medications used in asthma. Most information is presented in outline format, for ease of access. 6 tables.

- **Disorders of Hearing in Adults**

  Source: in Wall, L.G., ed. Hearing for the Speech-Language Pathologist and Health Care Professional. Woburn, MA: Butterworth-Heinemann. 1995. p. 71-102.

Contact: Available from Butterworth-Heinemann. 225 Wildwood Avenue, P.O. Box 4500, Woburn, MA 01801-2041. (617) 928-2500; Fax (617) 933-6333. PRICE: $45.00 plus shipping and handling. ISBN: 0750695269.

Summary: This chapter on adult hearing disorders acquaints speech-language pathologists, educators, and health care professionals with hearing disorders and health problems that place adults at risk for hearing loss. Each disorder is described and the suggested management options are discussed; the location of the disorder within the auditory system is defined; and the type of hearing loss, conductive or sensorineural, associated with the disorder is discussed. Disorders covered include outer ear disorders, including atresia, stenosis, cerumen occlusion, ceruminoma, perforation of the tympanic membrane, tympanosclerosis, and otitis externa; middle ear disorders, including otitis media, glomus tumor, otic barotrauma, and otosclerosis; and cochlear and retrocochlear disorders, including vestibular schwannoma (acoustic neuroma), meningiomas, traumatic fractures, and concussion. Other topics covered include the audiologic test results to expect with fractures, concussion, Meniere's disease, multiple sclerosis, noise-induced hearing loss, ototoxicity, presbycusis, sudden hearing loss, and **sickle cell anemia.** 61 references. (AA-M).

- **Diseases and Oral Manifestations of Systemic Disease**

  Source: in Pinkham, J.R., et al., eds. Pediatric Dentistry: Infancy Through Adolescence. 3rd ed. Philadelphia, PA: W.B. Saunders Company. 1999. p. 54-67.

  Contact: Available from W.B. Saunders Company. Book Orders Fulfillment Department, Harcourt Health Sciences, 11830 Westline Industrial Drive, Saint Louis, MO 63146-9988. (800) 545-2522. Website: www.wbsaunders.com. PRICE: $69.00 plus shipping and handling. ISBN: 0721682383.

  Summary: This chapter on diseases and oral manifestations of systemic disease is from a textbook on pediatric dentistry. Topics include herpetic gingivostomatitis, recurrent herpes simplex (herpes labialis), herpes zoster (chicken pox), herpangina, hand, foot and mouth disease, impetigo, scarlet fever, candidiasis, diabetes mellitus, acute lymphoblastic leukemia, **sickle cell anemia,** histiocytoses (hystiocytosis X), hemophilia (hemophilia A; Factor VIII deficiency), and pediatric human immunodeficiency virus (HIV) infection. For each disease, the author reviews the causative agent, evaluation of the patient, diagnosis, and therapy. The chapter includes illustrative case studies for some of the diseases. The chapter is illustrated with numerous black and white photographs of the conditions under consideration. 9 figures. 3 tables. 41 references.

- **Priapism**

  Source: in Lechtenberg, R.; Ohl, D.A. Sexual Dysfunction. Malvern, PA: Lea and Febiger. 1994. p. 128-150.

  Contact: Available from Lea and Febiger. P.O. Box 3024, 200 Chester Field Parkway, Malvern, PA 19355-9725. (215) 251-2230. PRICE: $69.50; plus shipping and handling. ISBN: 0812114965.

  Summary: This chapter, from a book about the neurologic, urologic, and gynecologic aspects of sexual dysfunction, discusses priapism, which is persistent and often painful erection of the penis that develops independently of sexual arousal. Topics include the pathophysiology of priapism; classification; low-flow priapism; the importance of prompt therapy; etiology, including intracavernosal pharmacotherapy of impotence, **sickle cell anemia,** systemic medications, anesthesia, coagulopathies, hemodialysis,

trauma, hyperalimentation, neoplasms and cancer, vascular surgery for impotence, and neurologic conditions; treatment modalities, including nonsurgical therapy, amyl nitrate, anesthesia, aspiration of the corpus cavernosum, fibrinolytic therapy, intracavernosal adrenergic agonists, and surgical therapy; the results of shunting procedures; embolization; management following detumescence therapy; complications of priapism and treatment, including pulmonary embolism, urethrocavernous fistula, and penile gangrene; and the treatment of postpriapism impotence. The chapter includes a strategy for the treatment of priapism. 4 figures. 1 table. 110 references.

- **Anemia**

  Source: in American College of Sports Medicine. ACSM's Exercise Management for Persons with Chronic Diseases and Disabilities. Champaign, IL: Human Kinetics. 1997. p. 125-127.

  Contact: Available from Human Kinetics. 1607 North Market Street, P.O. Box 5076, Champaign, IL 61825-5076. (800) 747-4457 or (217) 351-5076. Fax (217) 351-2674. PRICE: $39.00.

  Summary: This chapter, from a book of sports medicine and exercise management for people with chronic diseases and disabilities, provides information about anemia. The primary symptoms of anemia are easy fatigability with exercise, shortness of breath, and decreased work capacity, so aerobic tests are virtually always abnormal. These symptoms are related primarily to the low oxygen-carrying capacity of anemic blood, but severe iron deficiency may also reduce the activity of muscle enzymes that contain iron and impair the intrinsic ability of skeletal muscle. The author discusses the effects of anemia on the exercise response, the effects of exercise training, management and medications, recommendations for exercise testing, and recommendations for exercise programming. The author notes that the main goal of the exercise program is to improve endurance. Any form of large muscle exercise is acceptable, although intensity of exercise should be moderate. In persons with **sickle cell anemia,** high-intensity exercise leading to dehydration may cause a sickle cell crisis. Persons with either **sickle cell anemia** or trait must maintain liberal fluid intake in order to avoid dehydration. The optimal frequency and duration of training sessions are not known. 2 tables. 5 references. (AA-M).

- **Blood Dyscrasias**

  Source: in Little, J.W.; Falace, D.A. Dental Management of the Medically Compromised Patient. 4th ed. St. Louis, MO: Mosby-Year Book, Inc. 1993. p. 439-459.

  Contact: Available from Mosby-Year Book, Inc. 11830 Westline Industrial Drive, St. Louis, MO 63146-9934. (800) 426-4545 or (314) 872-8370; Fax (800) 535-9935 or (314) 432-1380; E-mail: customer.support@mosby.com; http://www.mosby.com. PRICE: $39.95 plus shipping and handling. ISBN: 0801668379.

  Summary: This chapter, from a handbook on the dental management of medically compromised patients, discusses blood dyscrasias. The authors present the most common disorders of the white and red blood cells that may influence dental treatment. They note that these patients may be susceptible to abnormal bleeding, delayed healing, infection, or mucosal ulceration. Disorders covered are covered in two broad categories. The first is anemia, including during menses and pregnancy, pernicious anemia, glucose-6-phosphate dehydrogenase deficiency, **sickle cell anemia,** and anemia resulting from renal disease. The second category is white blood cell disorders, including leukocytosis and leukopenia, infectious mononucleosis, leukemia and

lymphoma, acute and chronic leukemias, Hodgkin's disease, non-Hodgkin's lymphoma, Burkitt's lymphoma, and multiple myeloma. After a review of each of these conditions, the authors discuss their dental management, including medical considerations, treatment planning modifications, and oral complications. 9 references. 14 tables. 28 references.

- **Disorders of the Blood**

  Source: in Grundy, M.C.; Shaw, L.; and Hamilton, D.V. Illustrated Guide to Dental Care for the Medically Compromised Patient. St. Louis, MO: Mosby-Year Book, Inc. 1993. p. 27-36.

  Contact: Available from Mosby-Year Book, Inc. 11830 Westline Industrial Drive, St. Louis, MO 63146-9934. (800) 426-4545 or (314) 872-8370; Fax (800) 535-9935 or (314) 432-1380; E-mail: customer.support@mosby.com; http://www.mosby.com. PRICE: $24.95 plus shipping and handling. ISBN: 0815140223.

  Summary: This chapter, from an illustrated guide to dental care for medically compromised patients, discusses disorders of the blood. Topics covered include hemophilia; Christmas disease (hemophilia B); Von Willebrand's disease (vascular hemophilia); thrombocytopenia; anemia, including **sickle cell anemia** and thalassemia; and leukemia. For each condition, the authors provide a brief description, the components of medical management, and suggestions for dental care. Illustrations, including photographs, are included. 7 figures.

CHAPTER 8. PERIODICALS AND NEWS ON SICKLE CELL ANEMIA

Overview

In this chapter, we suggest a number of news sources and present various periodicals that cover sickle cell anemia.

News Services and Press Releases

One of the simplest ways of tracking press releases on sickle cell anemia is to search the news wires. In the following sample of sources, we will briefly describe how to access each service. These services only post recent news intended for public viewing.

PR Newswire

To access the PR Newswire archive, simply go to **http://www.prnewswire.com/**. Select your country. Type "sickle cell anemia" (or synonyms) into the search box. You will automatically receive information on relevant news releases posted within the last 30 days. The search results are shown by order of relevance.

Reuters Health

The Reuters' Medical News and Health eLine databases can be very useful in exploring news archives relating to sickle cell anemia. While some of the listed articles are free to view, others are available for purchase for a nominal fee. To access this archive, go to **http://www.reutershealth.com/en/index.html** and search by "sickle cell anemia" (or synonyms). The following was recently listed in this archive for sickle cell anemia:

- **Lung function reduced in children with sickle cell disease**
  Source: Reuters Medical News
  Date: January 15, 2004

- **Decitabine may be option for hydroxyurea-resistant sickle cell disease**
  Source: Reuters Industry Breifing
  Date: December 01, 2003
- **Decitabine boosts HbF levels in sickle cell anemia patients**
  Source: Reuters Industry Breifing
  Date: August 20, 2003
- **Folate supplementation may mask pernicious anemia in sickle cell disease**
  Source: Reuters Medical News
  Date: May 28, 2003
- **Hydroxyurea therapy may increase sickle cell anemia survival**
  Source: Reuters Medical News
  Date: April 02, 2003
- **Gender difference found in sickle cell anemia**
  Source: Reuters Health eLine
  Date: December 23, 2002
- **Ion-channel therapy for sickle cell anemia given US fast-track status**
  Source: Reuters Medical News
  Date: October 07, 2002
- **Icagen sickle cell anemia therapy wins US fast-track status**
  Source: Reuters Industry Breifing
  Date: October 07, 2002
- **Xechem acquires investigational sickle cell anemia drug**
  Source: Reuters Industry Breifing
  Date: August 01, 2002
- **Cancer drug may be safe for sickle cell disease**
  Source: Reuters Health eLine
  Date: May 27, 2002
- **Ongoing decitabine safely maintains HbF in treatment of sickle cell anemia**
  Source: Reuters Industry Breifing
  Date: May 21, 2002
- **NeuroSearch stops sickle cell anemia program**
  Source: Reuters Industry Breifing
  Date: April 25, 2002
- **Hydroxyurea normalizes neutrophils in children with sickle cell anemia**
  Source: Reuters Medical News
  Date: April 12, 2002
- **Zinc may spur growth in children with sickle cell anemia**
  Source: Reuters Medical News
  Date: February 11, 2002
- **Some lab values may predict response to hydroxyurea in pediatric sickle cell anemia**
  Source: Reuters Medical News
  Date: January 29, 2002
- **Transfusion prophylaxis may prevent stroke in sickle cell anemia**
  Source: Reuters Medical News
  Date: December 28, 2001

- **High prevalence of pica observed in children with sickle cell disease**
  Source: Reuters Medical News
  Date: November 21, 2001
- **Aspartame possible therapy for sickle cell anemia**
  Source: Reuters Health eLine
  Date: June 22, 2001
- **SuperGen's decitabine shows promise as treatment for sickle cell anemia**
  Source: Reuters Industry Breifing
  Date: November 02, 2000
- **Long-term hydroxyurea for sickle cell anemia does not cause organ damage**
  Source: Reuters Medical News
  Date: August 31, 2000
- **Novel anion conductance inhibitor treats symptoms of sickle cell anemia**
  Source: Reuters Medical News
  Date: March 13, 2000
- **Day hospital for sickle cell anemia a viable alternative**
  Source: Reuters Medical News
  Date: February 29, 2000
- **Hydroxyurea may cut risk of recurring stroke in children with sickle cell disease**
  Source: Reuters Medical News
  Date: November 09, 1999
- **First successful preimplantation genetic diagnosis reported for sickle cell disease**
  Source: Reuters Medical News
  Date: May 12, 1999
- **Test detects sickle cell disease in embryos**
  Source: Reuters Health eLine
  Date: May 11, 1999
- **Blood transfusions prevent first stroke in children with sickle cell anemia**
  Source: Reuters Medical News
  Date: July 02, 1998
- **Gene therapy may treat sickle cell anemia**
  Source: Reuters Health eLine
  Date: June 04, 1998
- **ACE Inhibitor Could Delay Kidney Damage Caused By Sickle Cell Anemia**
  Source: Reuters Medical News
  Date: May 07, 1998
- **FDA Advisers Urge Approval Of Hydroxyurea For Sickle Cell Anemia**
  Source: Reuters Medical News
  Date: December 19, 1997
- **Mouse Model For Sickle Cell Disease Created**
  Source: Reuters Medical News
  Date: October 31, 1997
- **Marrow, Cord-Blood Transplantation Curative In Patients With Sickle Cell Disease**
  Source: Reuters Medical News
  Date: September 22, 1997

- **Transfusion Therapy Reduces Stroke in Pediatric Sickle Cell Anemia**
  Source: Reuters Medical News
  Date: September 19, 1997
- **Sickle Cell Anemia Patients Respond Variably To Hydroxyurea**
  Source: Reuters Medical News
  Date: February 03, 1997
- **Hydroxyurea Reverses Splenic Dysfunction In Sickle Cell Anemia**
  Source: Reuters Medical News
  Date: October 02, 1996
- **Bone Marrow Transplantation: A Cure For Sickle Cell Anemia**
  Source: Reuters Medical News
  Date: August 08, 1996
- **Hydroxyurea Effective For Patients With Sickle Cell Anemia**
  Source: Reuters Medical News
  Date: May 18, 1995

The NIH

Within MEDLINEplus, the NIH has made an agreement with the New York Times Syndicate, the AP News Service, and Reuters to deliver news that can be browsed by the public. Search news releases at **http://www.nlm.nih.gov/medlineplus/alphanews_a.html**. MEDLINEplus allows you to browse across an alphabetical index. Or you can search by date at the following Web page: **http://www.nlm.nih.gov/medlineplus/newsbydate.html**. Often, news items are indexed by MEDLINEplus within its search engine.

Business Wire

Business Wire is similar to PR Newswire. To access this archive, simply go to **http://www.businesswire.com/**. You can scan the news by industry category or company name.

Market Wire

Market Wire is more focused on technology than the other wires. To browse the latest press releases by topic, such as alternative medicine, biotechnology, fitness, healthcare, legal, nutrition, and pharmaceuticals, access Market Wire's Medical/Health channel at **http://www.marketwire.com/mw/release_index?channel=MedicalHealth**. Or simply go to Market Wire's home page at **http://www.marketwire.com/mw/home**, type "sickle cell anemia" (or synonyms) into the search box, and click on "Search News." As this service is technology oriented, you may wish to use it when searching for press releases covering diagnostic procedures or tests.

Search Engines

Medical news is also available in the news sections of commercial Internet search engines. See the health news page at Yahoo (**http://dir.yahoo.com/Health/News_and_Media/**), or

you can use this Web site's general news search page at **http://news.yahoo.com/**. Type in "sickle cell anemia" (or synonyms). If you know the name of a company that is relevant to sickle cell anemia, you can go to any stock trading Web site (such as **http://www.etrade.com/**) and search for the company name there. News items across various news sources are reported on indicated hyperlinks. Google offers a similar service at **http://news.google.com/**.

BBC

Covering news from a more European perspective, the British Broadcasting Corporation (BBC) allows the public free access to their news archive located at **http://www.bbc.co.uk/**. Search by "sickle cell anemia" (or synonyms).

Newsletter Articles

Use the Combined Health Information Database, and limit your search criteria to "newsletter articles." Again, you will need to use the "Detailed Search" option. Go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. Go to the bottom of the search page where "You may refine your search by." Select the dates and language that you prefer. For the format option, select "Newsletter Article." Type "sickle cell anemia" (or synonyms) into the "For these words:" box. You should check back periodically with this database as it is updated every three months. The following is a typical result when searching for newsletter articles on sickle cell anemia:

- **Keratins: Mechanical Integrators in the Epiderms and Hair and Their Role in Disease**

  Source: Progress in Dermatology. 30(2):1-12; June 1996.

  Contact: Available from Dermatology Foundation, 1560 Sherman Avenue, Evanston, Ill 60201.

  Summary: This newsletter article describes the research that led from the basic science of keratins into the realm of human genetic skin diseases. The author explains that just as genetic defects in globin genes have long been known to give rise to genetic blood disorders such as **sickle cell anemia,** keratin genes have recently been demonstrated to cause a number of different genetic disorders of the skin. These disorders include various forms of epidermolysis bullosa simplex, epidermolytic hyperkeratosis (EH), the EH form of epidermal nevi, epidermolytic and non-epidermolytic forms of palmoplantar keratoderma, and pachyonychia congenita. Each of these diseases is examined in terms of their symptoms and genetic origins. 3 figure, 1 table, 110 references.

Academic Periodicals covering Sickle Cell Anemia

Numerous periodicals are currently indexed within the National Library of Medicine's PubMed database that are known to publish articles relating to sickle cell anemia. In addition to these sources, you can search for articles covering sickle cell anemia that have been published by any of the periodicals listed in previous chapters. To find the latest

studies published, go to **http://www.ncbi.nlm.nih.gov/pubmed**, type the name of the periodical into the search box, and click "Go."

If you want complete details about the historical contents of a journal, you can also visit the following Web site: **http://www.ncbi.nlm.nih.gov/entrez/jrbrowser.cgi**. Here, type in the name of the journal or its abbreviation, and you will receive an index of published articles. At **http://locatorplus.gov/**, you can retrieve more indexing information on medical periodicals (e.g. the name of the publisher). Select the button "Search LOCATORplus." Then type in the name of the journal and select the advanced search option "Journal Title Search."

CHAPTER 9. RESEARCHING MEDICATIONS

Overview

While a number of hard copy or CD-ROM resources are available for researching medications, a more flexible method is to use Internet-based databases. Broadly speaking, there are two sources of information on approved medications: public sources and private sources. We will emphasize free-to-use public sources.

U.S. Pharmacopeia

Because of historical investments by various organizations and the emergence of the Internet, it has become rather simple to learn about the medications recommended for sickle cell anemia. One such source is the United States Pharmacopeia. In 1820, eleven physicians met in Washington, D.C. to establish the first compendium of standard drugs for the United States. They called this compendium the U.S. Pharmacopeia (USP). Today, the USP is a non-profit organization consisting of 800 volunteer scientists, eleven elected officials, and 400 representatives of state associations and colleges of medicine and pharmacy. The USP is located in Rockville, Maryland, and its home page is located at **http://www.usp.org/**. The USP currently provides standards for over 3,700 medications. The resulting USP DI® Advice for the Patient® can be accessed through the National Library of Medicine of the National Institutes of Health. The database is partially derived from lists of federally approved medications in the Food and Drug Administration's (FDA) Drug Approvals database, located at **http://www.fda.gov/cder/da/da.htm**.

While the FDA database is rather large and difficult to navigate, the Phamacopeia is both user-friendly and free to use. It covers more than 9,000 prescription and over-the-counter medications. To access this database, simply type the following hyperlink into your Web browser: **http://www.nlm.nih.gov/medlineplus/druginformation.html**. To view examples of a given medication (brand names, category, description, preparation, proper use, precautions, side effects, etc.), simply follow the hyperlinks indicated within the United States Pharmacopeia (USP).

Below, we have compiled a list of medications associated with sickle cell anemia. If you would like more information on a particular medication, the provided hyperlinks will direct you to ample documentation (e.g. typical dosage, side effects, drug-interaction risks, etc.).

The following drugs have been mentioned in the Pharmacopeia and other sources as being potentially applicable to sickle cell anemia:

Hydroxyurea

- **Systemic - U.S. Brands:** Droxia; Hydrea
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202291.html

Zinc Supplements

- **Systemic - U.S. Brands:** Orazinc; Verazinc; Zinc 15; Zinc-220; Zinca-Pak; Zincate
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202622.html

Commercial Databases

In addition to the medications listed in the USP above, a number of commercial sites are available by subscription to physicians and their institutions. Or, you may be able to access these sources from your local medical library.

Mosby's Drug Consult™

Mosby's Drug Consult™ database (also available on CD-ROM and book format) covers 45,000 drug products including generics and international brands. It provides prescribing information, drug interactions, and patient information. Subscription information is available at the following hyperlink: **http://www.mosbysdrugconsult.com/**.

PDR*health*

The PDR*health* database is a free-to-use, drug information search engine that has been written for the public in layman's terms. It contains FDA-approved drug information adapted from the Physicians' Desk Reference (PDR) database. PDR*health* can be searched by brand name, generic name, or indication. It features multiple drug interactions reports. Search PDR*health* at **http://www.pdrhealth.com/drug_info/index.html**.

Other Web Sites

Drugs.com (**www.drugs.com**) reproduces the information in the Pharmacopeia as well as commercial information. You may also want to consider the Web site of the Medical Letter, Inc. (**http://www.medletter.com/**) which allows users to download articles on various drugs and therapeutics for a nominal fee.

Researching Orphan Drugs

Although the list of orphan drugs is revised on a daily basis, you can quickly research orphan drugs that might be applicable to sickle cell anemia by using the database managed by the National Organization for Rare Disorders, Inc. (NORD), at **http://www.rarediseases.org/**. Scroll down the page, and on the left toolbar, click on

"Orphan Drug Designation Database." On this page (**http://www.rarediseases.org/search/noddsearch.html**), type "sickle cell anemia" (or synonyms) into the search box, and click "Submit Query." When you receive your results, note that not all of the drugs may be relevant, as some may have been withdrawn from orphan status. Write down or print out the name of each drug and the relevant contact information. From there, visit the Pharmacopeia Web site and type the name of each orphan drug into the search box at **http://www.nlm.nih.gov/medlineplus/druginformation.html**. You may need to contact the sponsor or NORD for further information.

NORD conducts "early access programs for investigational new drugs (IND) under the Food and Drug Administration's (FDA's) approval 'Treatment INDs' programs which allow for a limited number of individuals to receive investigational drugs before FDA marketing approval." If the orphan product about which you are seeking information is approved for marketing, information on side effects can be found on the product's label. If the product is not approved, you may need to contact the sponsor.

The following is a list of orphan drugs currently listed in the NORD Orphan Drug Designation Database for sickle cell anemia:

- **Bis)4-flurophenyl)phenylaceta mide**
  http://www.rarediseases.org/nord/search/nodd_full?code=1028
- **L-glutamine (trade name: NONE Assigned)**
  http://www.rarediseases.org/nord/search/nodd_full?code=1176
- **n-(4-bromo-2-(1H-1,2,3,4-terazol-5-y1)pheny1)-N'-(**
  http://www.rarediseases.org/nord/search/nodd_full?code=1276
- **N-(4-bromo-2-(1H-1,2,3,4-tetrazol-5-yI)pheny1)-N'-**
  http://www.rarediseases.org/nord/search/nodd_full?code=1280
- **decutabine**
  http://www.rarediseases.org/nord/search/nodd_full?code=1301
- **Isobutyramide**
  http://www.rarediseases.org/nord/search/nodd_full?code=161
- **OM 401 (trade name: Drepanol)**
  http://www.rarediseases.org/nord/search/nodd_full?code=242
- **Polymeric oxygen**
  http://www.rarediseases.org/nord/search/nodd_full?code=409
- **Clotrimazole**
  http://www.rarediseases.org/nord/search/nodd_full?code=655
- **Arginine Butyrate**
  http://www.rarediseases.org/nord/search/nodd_full?code=674
- **Hydroxyurea (trade name: Droxia)**
  http://www.rarediseases.org/nord/search/nodd_full?code=771
- **Fructose-1,6-diphosphate**
  http://www.rarediseases.org/nord/search/nodd_full?code=920
- **40SD02**
  http://www.rarediseases.org/nord/search/nodd_full?code=959

If you have any questions about a medical treatment, the FDA may have an office near you. Look for their number in the blue pages of the phone book. You can also contact the FDA through its toll-free number, 1-888-INFO-FDA (1-888-463-6332), or on the World Wide Web at **www.fda.gov**.

APPENDICES

APPENDIX A. PHYSICIAN RESOURCES

Overview

In this chapter, we focus on databases and Internet-based guidelines and information resources created or written for a professional audience.

NIH Guidelines

Commonly referred to as "clinical" or "professional" guidelines, the National Institutes of Health publish physician guidelines for the most common diseases. Publications are available at the following by relevant Institute[11]:

- Office of the Director (OD); guidelines consolidated across agencies available at **http://www.nih.gov/health/consumer/conkey.htm**
- National Institute of General Medical Sciences (NIGMS); fact sheets available at **http://www.nigms.nih.gov/news/facts/**
- National Library of Medicine (NLM); extensive encyclopedia (A.D.A.M., Inc.) with guidelines: **http://www.nlm.nih.gov/medlineplus/healthtopics.html**
- National Cancer Institute (NCI); guidelines available at **http://www.cancer.gov/cancerinfo/list.aspx?viewid=5f35036e-5497-4d86-8c2c-714a9f7c8d25**
- National Eye Institute (NEI); guidelines available at **http://www.nei.nih.gov/order/index.htm**
- National Heart, Lung, and Blood Institute (NHLBI); guidelines available at **http://www.nhlbi.nih.gov/guidelines/index.htm**
- National Human Genome Research Institute (NHGRI); research available at **http://www.genome.gov/page.cfm?pageID=10000375**
- National Institute on Aging (NIA); guidelines available at **http://www.nia.nih.gov/health/**

[11] These publications are typically written by one or more of the various NIH Institutes.

- National Institute on Alcohol Abuse and Alcoholism (NIAAA); guidelines available at **http://www.niaaa.nih.gov/publications/publications.htm**
- National Institute of Allergy and Infectious Diseases (NIAID); guidelines available at **http://www.niaid.nih.gov/publications/**
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); fact sheets and guidelines available at **http://www.niams.nih.gov/hi/index.htm**
- National Institute of Child Health and Human Development (NICHD); guidelines available at **http://www.nichd.nih.gov/publications/pubskey.cfm**
- National Institute on Deafness and Other Communication Disorders (NIDCD); fact sheets and guidelines at **http://www.nidcd.nih.gov/health/**
- National Institute of Dental and Craniofacial Research (NIDCR); guidelines available at **http://www.nidr.nih.gov/health/**
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); guidelines available at **http://www.niddk.nih.gov/health/health.htm**
- National Institute on Drug Abuse (NIDA); guidelines available at **http://www.nida.nih.gov/DrugAbuse.html**
- National Institute of Environmental Health Sciences (NIEHS); environmental health information available at **http://www.niehs.nih.gov/external/facts.htm**
- National Institute of Mental Health (NIMH); guidelines available at **http://www.nimh.nih.gov/practitioners/index.cfm**
- National Institute of Neurological Disorders and Stroke (NINDS); neurological disorder information pages available at **http://www.ninds.nih.gov/health_and_medical/disorder_index.htm**
- National Institute of Nursing Research (NINR); publications on selected illnesses at **http://www.nih.gov/ninr/news-info/publications.html**
- National Institute of Biomedical Imaging and Bioengineering; general information at **http://grants.nih.gov/grants/becon/becon_info.htm**
- Center for Information Technology (CIT); referrals to other agencies based on keyword searches available at **http://kb.nih.gov/www_query_main.asp**
- National Center for Complementary and Alternative Medicine (NCCAM); health information available at **http://nccam.nih.gov/health/**
- National Center for Research Resources (NCRR); various information directories available at **http://www.ncrr.nih.gov/publications.asp**
- Office of Rare Diseases; various fact sheets available at **http://rarediseases.info.nih.gov/html/resources/rep_pubs.html**
- Centers for Disease Control and Prevention; various fact sheets on infectious diseases available at **http://www.cdc.gov/publications.htm**

NIH Databases

In addition to the various Institutes of Health that publish professional guidelines, the NIH has designed a number of databases for professionals.[12] Physician-oriented resources provide a wide variety of information related to the biomedical and health sciences, both past and present. The format of these resources varies. Searchable databases, bibliographic citations, full-text articles (when available), archival collections, and images are all available. The following are referenced by the National Library of Medicine:[13]

- **Bioethics:** Access to published literature on the ethical, legal, and public policy issues surrounding healthcare and biomedical research. This information is provided in conjunction with the Kennedy Institute of Ethics located at Georgetown University, Washington, D.C.: **http://www.nlm.nih.gov/databases/databases_bioethics.html**
- **HIV/AIDS Resources:** Describes various links and databases dedicated to HIV/AIDS research: **http://www.nlm.nih.gov/pubs/factsheets/aidsinfs.html**
- **NLM Online Exhibitions:** Describes "Exhibitions in the History of Medicine": **http://www.nlm.nih.gov/exhibition/exhibition.html**. Additional resources for historical scholarship in medicine: **http://www.nlm.nih.gov/hmd/hmd.html**
- **Biotechnology Information:** Access to public databases. The National Center for Biotechnology Information conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information for the better understanding of molecular processes affecting human health and disease: **http://www.ncbi.nlm.nih.gov/**
- **Population Information:** The National Library of Medicine provides access to worldwide coverage of population, family planning, and related health issues, including family planning technology and programs, fertility, and population law and policy: **http://www.nlm.nih.gov/databases/databases_population.html**
- **Cancer Information:** Access to cancer-oriented databases: **http://www.nlm.nih.gov/databases/databases_cancer.html**
- **Profiles in Science:** Offering the archival collections of prominent twentieth-century biomedical scientists to the public through modern digital technology: **http://www.profiles.nlm.nih.gov/**
- **Chemical Information:** Provides links to various chemical databases and references: **http://sis.nlm.nih.gov/Chem/ChemMain.html**
- **Clinical Alerts:** Reports the release of findings from the NIH-funded clinical trials where such release could significantly affect morbidity and mortality: **http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html**
- **Space Life Sciences:** Provides links and information to space-based research (including NASA): **http://www.nlm.nih.gov/databases/databases_space.html**
- **MEDLINE:** Bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the healthcare system, and the pre-clinical sciences: **http://www.nlm.nih.gov/databases/databases_medline.html**

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[12] Remember, for the general public, the National Library of Medicine recommends the databases referenced in MEDLINE*plus* (**http://medlineplus.gov/** or **http://www.nlm.nih.gov/medlineplus/databases.html**).

[13] See **http://www.nlm.nih.gov/databases/databases.html**.

- **Toxicology and Environmental Health Information (TOXNET):** Databases covering toxicology and environmental health: **http://sis.nlm.nih.gov/Tox/ToxMain.html**
- **Visible Human Interface:** Anatomically detailed, three-dimensional representations of normal male and female human bodies: **http://www.nlm.nih.gov/research/visible/visible_human.html**

The NLM Gateway[14]

The NLM (National Library of Medicine) Gateway is a Web-based system that lets users search simultaneously in multiple retrieval systems at the U.S. National Library of Medicine (NLM). It allows users of NLM services to initiate searches from one Web interface, providing one-stop searching for many of NLM's information resources or databases.[15] To use the NLM Gateway, simply go to the search site at **http://gateway.nlm.nih.gov/gw/Cmd**. Type "sickle cell anemia" (or synonyms) into the search box and click "Search." The results will be presented in a tabular form, indicating the number of references in each database category.

Results Summary

Category	Items Found
Journal Articles	12017
Books / Periodicals / Audio Visual	326
Consumer Health	468
Meeting Abstracts	21
Other Collections	43
Total	12875

HSTAT[16]

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.[17] These documents include clinical practice guidelines, quick-reference guides for clinicians, consumer health brochures, evidence reports and technology assessments from the Agency for Healthcare Research and Quality (AHRQ), as well as AHRQ's Put Prevention Into Practice.[18] Simply search by "sickle cell anemia" (or synonyms) at the following Web site: **http://text.nlm.nih.gov**.

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[14] Adapted from NLM: **http://gateway.nlm.nih.gov/gw/Cmd?Overview.x**.

[15] The NLM Gateway is currently being developed by the Lister Hill National Center for Biomedical Communications (LHNCBC) at the National Library of Medicine (NLM) of the National Institutes of Health (NIH).

[16] Adapted from HSTAT: **http://www.nlm.nih.gov/pubs/factsheets/hstat.html**.

[17] The HSTAT URL is **http://hstat.nlm.nih.gov/**.

[18] Other important documents in HSTAT include: the National Institutes of Health (NIH) Consensus Conference Reports and Technology Assessment Reports; the HIV/AIDS Treatment Information Service (ATIS) resource documents; the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (SAMHSA/CSAT) Treatment Improvement Protocols (TIP) and Center for Substance Abuse Prevention (SAMHSA/CSAP) Prevention Enhancement Protocols System (PEPS); the Public Health Service (PHS) Preventive Services Task Force's *Guide to Clinical Preventive Services*; the independent, nonfederal Task Force on Community Services' *Guide to Community Preventive Services*; and the Health Technology Advisory Committee (HTAC) of the Minnesota Health Care Commission (MHCC) health technology evaluations.

Coffee Break: Tutorials for Biologists[19]

Coffee Break is a general healthcare site that takes a scientific view of the news and covers recent breakthroughs in biology that may one day assist physicians in developing treatments. Here you will find a collection of short reports on recent biological discoveries. Each report incorporates interactive tutorials that demonstrate how bioinformatics tools are used as a part of the research process. Currently, all Coffee Breaks are written by NCBI staff.[20] Each report is about 400 words and is usually based on a discovery reported in one or more articles from recently published, peer-reviewed literature.[21] This site has new articles every few weeks, so it can be considered an online magazine of sorts. It is intended for general background information. You can access the Coffee Break Web site at the following hyperlink: **http://www.ncbi.nlm.nih.gov/Coffeebreak/**.

Other Commercial Databases

In addition to resources maintained by official agencies, other databases exist that are commercial ventures addressing medical professionals. Here are some examples that may interest you:

- **CliniWeb International:** Index and table of contents to selected clinical information on the Internet; see **http://www.ohsu.edu/cliniweb/**.
- **Medical World Search:** Searches full text from thousands of selected medical sites on the Internet; see **http://www.mwsearch.com/**.

The Genome Project and Sickle Cell Anemia

In the following section, we will discuss databases and references which relate to the Genome Project and sickle cell anemia.

Online Mendelian Inheritance in Man (OMIM)

The Online Mendelian Inheritance in Man (OMIM) database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere. OMIM was developed for the World Wide Web by the National Center for Biotechnology Information (NCBI).[22] The database contains textual information, pictures, and reference information. It also contains copious links to NCBI's Entrez database of MEDLINE articles and sequence information.

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[19] Adapted from **http://www.ncbi.nlm.nih.gov/Coffeebreak/Archive/FAQ.html**.

[20] The figure that accompanies each article is frequently supplied by an expert external to NCBI, in which case the source of the figure is cited. The result is an interactive tutorial that tells a biological story.

[21] After a brief introduction that sets the work described into a broader context, the report focuses on how a molecular understanding can provide explanations of observed biology and lead to therapies for diseases. Each vignette is accompanied by a figure and hypertext links that lead to a series of pages that interactively show how NCBI tools and resources are used in the research process.

[22] Adapted from **http://www.ncbi.nlm.nih.gov/**. Established in 1988 as a national resource for molecular biology information, NCBI creates public databases, conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information--all for the better understanding of molecular processes affecting human health and disease.

To search the database, go to **http://www.ncbi.nlm.nih.gov/Omim/searchomim.html**. Type "sickle cell anemia" (or synonyms) into the search box, and click "Submit Search." If too many results appear, you can narrow the search by adding the word "clinical." Each report will have additional links to related research and databases. In particular, the option "Database Links" will search across technical databases that offer an abundance of information. The following is an example of the results you can obtain from the OMIM for sickle cell anemia:

- **Sickle Cell Anemia**
  Web site: http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?603903

Genes and Disease (NCBI - Map)

The Genes and Disease database is produced by the National Center for Biotechnology Information of the National Library of Medicine at the National Institutes of Health. This Web site categorizes each disorder by system of the body. Go to **http://www.ncbi.nlm.nih.gov/disease/**, and browse the system pages to have a full view of important conditions linked to human genes. Since this site is regularly updated, you may wish to revisit it from time to time. The following systems and associated disorders are addressed:

- **Cancer:** Uncontrolled cell division.
  Examples: Breast and ovarian cancer, Burkitt lymphoma, chronic myeloid leukemia, colon cancer, lung cancer, malignant melanoma, multiple endocrine neoplasia, neurofibromatosis, p53 tumor suppressor, pancreatic cancer, prostate cancer, Ras oncogene, RB: retinoblastoma, von Hippel-Lindau syndrome.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Cancer.html**

- **Immune System:** Fights invaders.
  Examples: Asthma, autoimmune polyglandular syndrome, Crohn's disease, DiGeorge syndrome, familial Mediterranean fever, immunodeficiency with Hyper-IgM, severe combined immunodeficiency.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Immune.html**

- **Metabolism:** Food and energy.
  Examples: Adreno-leukodystrophy, atherosclerosis, Best disease, Gaucher disease, glucose galactose malabsorption, gyrate atrophy, juvenile-onset diabetes, obesity, paroxysmal nocturnal hemoglobinuria, phenylketonuria, Refsum disease, Tangier disease, Tay-Sachs disease.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Metabolism.html**

- **Muscle and Bone:** Movement and growth.
  Examples: Duchenne muscular dystrophy, Ellis-van Creveld syndrome, Marfan syndrome, myotonic dystrophy, spinal muscular atrophy.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Muscle.html**

- **Nervous System:** Mind and body.
  Examples: Alzheimer disease, amyotrophic lateral sclerosis, Angelman syndrome, Charcot-Marie-Tooth disease, epilepsy, essential tremor, fragile X syndrome, Friedreich's ataxia, Huntington disease, Niemann-Pick disease, Parkinson disease, Prader-Willi syndrome, Rett syndrome, spinocerebellar atrophy, Williams syndrome.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Brain.html**

- **Signals:** Cellular messages.
  Examples: Ataxia telangiectasia, Cockayne syndrome, glaucoma, male-patterned baldness, SRY: sex determination, tuberous sclerosis, Waardenburg syndrome, Werner syndrome.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Signals.html**
- **Transporters:** Pumps and channels.
  Examples: Cystic fibrosis, deafness, diastrophic dysplasia, Hemophilia A, long-QT syndrome, Menkes syndrome, Pendred syndrome, polycystic kidney disease, sickle cell anemia, Wilson's disease, Zellweger syndrome.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Transporters.html**

Entrez

Entrez is a search and retrieval system that integrates several linked databases at the National Center for Biotechnology Information (NCBI). These databases include nucleotide sequences, protein sequences, macromolecular structures, whole genomes, and MEDLINE through PubMed. Entrez provides access to the following databases:

- **3D Domains:** Domains from Entrez Structure,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=geo**
- **Books:** Online books,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=books**
- **Genome:** Complete genome assemblies,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Genome**
- **NCBI's Protein Sequence Information Survey Results:**
  Web site: **http://www.ncbi.nlm.nih.gov/About/proteinsurvey/**
- **Nucleotide Sequence Database (Genbank):**
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Nucleotide**
- **OMIM:** Online Mendelian Inheritance in Man,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM**
- **PopSet:** Population study data sets,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Popset**
- **ProbeSet:** Gene Expression Omnibus (GEO),
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=geo**
- **Protein Sequence Database:**
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein**
- **PubMed:** Biomedical literature (PubMed),
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed**
- **Structure:** Three-dimensional macromolecular structures,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Structure**
- **Taxonomy:** Organisms in GenBank,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Taxonomy**

To access the Entrez system at the National Center for Biotechnology Information, go to **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=genome**, and then

select the database that you would like to search. The databases available are listed in the drop box next to "Search." Enter "sickle cell anemia" (or synonyms) into the search box and click "Go."

Jablonski's Multiple Congenital Anomaly/Mental Retardation (MCA/MR) Syndromes Database[23]

This online resource has been developed to facilitate the identification and differentiation of syndromic entities. Special attention is given to the type of information that is usually limited or completely omitted in existing reference sources due to space limitations of the printed form.

At **http://www.nlm.nih.gov/mesh/jablonski/syndrome_toc/toc_a.html**, you can search across syndromes using an alphabetical index**.** Search by keywords at **http://www.nlm.nih.gov/mesh/jablonski/syndrome_db.html**.

The Genome Database[24]

Established at Johns Hopkins University in Baltimore, Maryland in 1990, the Genome Database (GDB) is the official central repository for genomic mapping data resulting from the Human Genome Initiative. In the spring of 1999, the Bioinformatics Supercomputing Centre (BiSC) at the Hospital for Sick Children in Toronto, Ontario assumed the management of GDB. The Human Genome Initiative is a worldwide research effort focusing on structural analysis of human DNA to determine the location and sequence of the estimated 100,000 human genes. In support of this project, GDB stores and curates data generated by researchers worldwide who are engaged in the mapping effort of the Human Genome Project (HGP). GDB's mission is to provide scientists with an encyclopedia of the human genome which is continually revised and updated to reflect the current state of scientific knowledge. Although GDB has historically focused on gene mapping, its focus will broaden as the Genome Project moves from mapping to sequence, and finally, to functional analysis.

To access the GDB, simply go to the following hyperlink: **http://www.gdb.org/**. Search "All Biological Data" by "Keyword." Type "sickle cell anemia" (or synonyms) into the search box, and review the results. If more than one word is used in the search box, then separate each one with the word "and" or "or" (using "or" might be useful when using synonyms).

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[23] Adapted from the National Library of Medicine: **http://www.nlm.nih.gov/mesh/jablonski/about_syndrome.html**.

[24] Adapted from the Genome Database: **http://gdbwww.gdb.org/gdb/aboutGDB.html - mission**.

APPENDIX B. PATIENT RESOURCES

Overview

Official agencies, as well as federally funded institutions supported by national grants, frequently publish a variety of guidelines written with the patient in mind. These are typically called "Fact Sheets" or "Guidelines." They can take the form of a brochure, information kit, pamphlet, or flyer. Often they are only a few pages in length. Since new guidelines on sickle cell anemia can appear at any moment and be published by a number of sources, the best approach to finding guidelines is to systematically scan the Internet-based services that post them.

Patient Guideline Sources

The remainder of this chapter directs you to sources which either publish or can help you find additional guidelines on topics related to sickle cell anemia. Due to space limitations, these sources are listed in a concise manner. Do not hesitate to consult the following sources by either using the Internet hyperlink provided, or, in cases where the contact information is provided, contacting the publisher or author directly.

The National Institutes of Health

The NIH gateway to patients is located at **http://health.nih.gov/**. From this site, you can search across various sources and institutes, a number of which are summarized below.

Topic Pages: MEDLINEplus

The National Library of Medicine has created a vast and patient-oriented healthcare information portal called MEDLINEplus. Within this Internet-based system are "health topic pages" which list links to available materials relevant to sickle cell anemia. To access this system, log on to **http://www.nlm.nih.gov/medlineplus/healthtopics.html**. From there you can either search using the alphabetical index or browse by broad topic areas. Recently, MEDLINEplus listed the following when searched for "sickle cell anemia":

- Guides on sickle cell anemia

  Sickle Cell Anemia
  http://www.nlm.nih.gov/medlineplus/sicklecellanemia.html

- Other guides

  Anemia
  http://www.nlm.nih.gov/medlineplus/anemia.html

  Blood and Blood Disorders
  http://www.nlm.nih.gov/medlineplus/bloodandblooddisorders.html

  Blood Transfusion and Donation
  http://www.nlm.nih.gov/medlineplus/bloodtransfusionanddonation.html

  Bone Marrow Diseases
  http://www.nlm.nih.gov/medlineplus/bonemarrowdiseases.html

  Bone Marrow Transplantation
  http://www.nlm.nih.gov/medlineplus/bonemarrowtransplantation.html

  Genetic Disorders
  http://www.nlm.nih.gov/medlineplus/geneticdisorders.html

  Genetic Testing/Counseling
  http://www.nlm.nih.gov/medlineplus/genetictestingcounseling.html

  Kidney Diseases
  http://www.nlm.nih.gov/medlineplus/kidneydiseases.html

  Laboratory Tests
  http://www.nlm.nih.gov/medlineplus/laboratorytests.html

  Stem Cells and Stem Cell Transplantation
  http://www.nlm.nih.gov/medlineplus/stemcellsandstemcelltransplantation.html

Within the health topic page dedicated to sickle cell anemia, the following was listed:

- General/Overviews

  Genetic Disease Profile: Sickle Cell Anemia
  Source: Dept. of Energy, Human Genome Project
  http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/sca.shtml

  Sickle Cell Anemia
  Source: Mayo Foundation for Medical Education and Research
  http://www.mayoclinic.com/invoke.cfm?id=DS00324

  Sickle Cell Anemia
  Source: Nemours Foundation
  http://kidshealth.org/parent/medical/heart/sickle_cell_anemia.html

- Treatment

  Blood and Marrow Stem Cell Transplantation
  Source: Leukemia & Lymphoma Society
  http://www.leukemia-lymphoma.org/all_mat_toc.adp?item_id=2443

  Bone Marrow and Cord Blood Stem Cell Transplant
  Source: Georgia Comprehensive Sickle Cell Center at Grady Health System
  http://www.SCInfo.org/bonemarr.htm

  Hydroxyurea Therapy Improves Survival in Most Severely Affected Sickle Cell Patients
  Source: National Heart, Lung, and Blood Institute
  http://www.nih.gov/news/pr/apr2003/nhlbi-01.htm

- Specific Conditions/Aspects

  Sickle Cell Disease: Practical Tips for Preventing a Sickle Cell Crisis
  Source: American Academy of Family Physicians
  http://familydoctor.org/550.xml

- Children

  Do You Know About Sickle Cell Anemia?
  Source: Nemours Foundation
  http://kidshealth.org/kid/health_problems/blood/sickle_cell.html

  Truth About Transfusions
  Source: Nemours Foundation
  http://kidshealth.org/kid/feel_better/things/transfusions.html

- From the National Institutes of Health

  Facts About Sickle Cell Anemia
  Source: National Heart, Lung, and Blood Institute
  http://www.nhlbi.nih.gov/health/public/blood/sickle/sca_fact.pdf

- Latest News

  High Blood Pressure in the Lungs a Major Risk for Death in Adults with Sickle Cell Disease
  Source: 02/25/2004, National Institutes of Health, Clinical Center
  http://www.nih.gov/news/pr/feb2004/cc-25.htm

  New Testing Urged for Sickle-Cell Patients
  Source: 02/26/2004, United Press International
  http://www.nlm.nih.gov//www.nlm.nih.gov/medlineplus/news/fullstory_16278.html

- Law and Policy

  Sickle Cell Disease: Americans With Disabilities Act
  Source: Georgia Comprehensive Sickle Cell Center at Grady Health System
  http://www.SCInfo.org/adainfo.htm

- Organizations

  National Heart, Lung, and Blood Institute
  http://www.nhlbi.nih.gov/

  Save Babies Through Screening
  http://www.savebabies.org/

  Sickle Cell Information Center
  Source: Georgia Comprehensive Sickle Cell Center at Grady Health System
  http://www.SCInfo.org/

- Prevention/Screening

  Genetic Counseling
  Source: Nemours Foundation
  http://kidshealth.org/parent/system/medical/genetic_counseling.html

  Newborn Screening Tests
  Source: March of Dimes Birth Defects Foundation
  http://www.marchofdimes.com/pnhec/298_834.asp

  Sickle Cell Test
  Source: American Association for Clinical Chemistry
  http://www.labtestsonline.org/understanding/analytes/sickle/test.html

- Research

  Exploring Important Medicinal Uses for Watermelon Rinds
  Source: Dept. of Agriculture
  http://www.ars.usda.gov/is/pr/2003/030221.htm

  Exposure to Tobacco Smoke Harms Children with Sickle Cell Disease
  Source: Nemours Foundation
  http://kidshealth.org/research/tobacco_sickle_cell.html

  Hydroxyurea in Pediatric Patients with Sickle Cell Disease
  Source: National Heart, Lung, and Blood Institute
  http://www.nhlbi.nih.gov/health/public/blood/sickle/hydrox.htm

  Scientists Use Gene Therapy to Correct Sickle Cell Disease in Mice
  Source: National Heart, Lung, and Blood Institute
  http://www.nih.gov/news/pr/dec2001/nhlbi-13.htm

  Sickle Cell Research for Treatment and Cure
  Source: National Heart, Lung, and Blood Institute
  http://www.nhlbi.nih.gov/resources/docs/scd30/scd30.pdf

- Teenagers

  Blood Transfusions
  Source: Nemours Foundation
  http://kidshealth.org/teen/your_body/medical_care/transfusions.html

  Story on Sickle Cell Anemia
  Source: Nemours Foundation
  http://kidshealth.org/teen/diseases_conditions/genetic/sickle_cell_anemia.html

You may also choose to use the search utility provided by MEDLINEplus at the following Web address: **http://www.nlm.nih.gov/medlineplus/**. Simply type a keyword into the search box and click "Search." This utility is similar to the NIH search utility, with the exception that it only includes materials that are linked within the MEDLINEplus system (mostly patient-oriented information). It also has the disadvantage of generating unstructured results. We recommend, therefore, that you use this method only if you have a very targeted search.

The Combined Health Information Database (CHID)

CHID Online is a reference tool that maintains a database directory of thousands of journal articles and patient education guidelines on sickle cell anemia. CHID offers summaries that describe the guidelines available, including contact information and pricing. CHID's general Web site is **http://chid.nih.gov/**. To search this database, go to **http://chid.nih.gov/detail/detail.html**. In particular, you can use the advanced search options to look up pamphlets, reports, brochures, and information kits. The following was recently posted in this archive:

- **Oral Health and Sickle Cell Disease**

  Source: Columbus, OH: Ohio Department of Health. 1992 2 p.

  Contact: Available from Special Populations Program Coordinator. Ohio Department of Health, Bureau of Dental Health, 246 N. High Street, Columbus, OH 43266-0588. (614) 466-4180. PRICE: Single copy free (reproduction permitted).

  Summary: This brief patient education brochure is designed to help patients with sickle cell anemia understand and manage the oral health complications of the disease. Topics covered include the manifestations of oral manifestations of sickle cell; dental care and the use of prophylactic antibiotics; and mouth care, including toothbrushing and flossing. The brochure concludes with a map of Ohio and the addresses and phone numbers of the 11 sickle cell healthcare centers located in the state.

- **Facts about sickle cell anemia and sickle cell trait**

  Source: Norfolk, VA: Society for the Aid of Sickle Cell Anemia. n.d. 2 pp.

  Contact: Available from Lyman Beecher Brooks Medical Center, Society for the Aid of Sickle Cell Anemia, 930 Majestic Avenue, Suite 150, Norfolk, VA 23504. Telephone: (804) 624-9225.

  Summary: This pamphlet provides general information on sickle cell disorders. It includes a form for readers to fill out for more information on sickle cell disorders from the Society for the Aid of Sickle Cell Anemia, which serves southeastern Virginia.

The National Guideline Clearinghouse™

The National Guideline Clearinghouse™ offers hundreds of evidence-based clinical practice guidelines published in the United States and other countries. You can search this site located at **http://www.guideline.gov/** by using the keyword "sickle cell anemia" (or synonyms). The following was recently posted:

- **Guideline for the management of acute and chronic pain in sickle cell disease**

  Source: American Pain Society - Professional Association; 1999 August; 96 pages

  http://www.guideline.gov/summary/summary.aspx?doc_id=2621&nbr=1847&string=sickle+AND+cell+AND+anemia

Healthfinder™

Healthfinder™ is sponsored by the U.S. Department of Health and Human Services and offers links to hundreds of other sites that contain healthcare information. This Web site is located at **http://www.healthfinder.gov**. Again, keyword searches can be used to find guidelines. The following was recently found in this database:

- **Facts About Sickle Cell Anemia**

  Source: National Heart, Lung, and Blood Institute, National Institutes of Health

  http://www.healthfinder.gov/scripts/recordpass.asp?RecordType=0&RecordID=1214

- **FAQ - About Sickle Cell Anemia**

  Summary: This site contains online answers to questions from patients and the general public regarding this blood disorder. Also available, are links to additional information about this disease.

  Source: Sickle Cell Information Center

  http://www.healthfinder.gov/scripts/recordpass.asp?RecordType=0&RecordID=2892

- **Sickle Cell Disease**

  Source: March of Dimes Birth Defects Foundation

  http://www.healthfinder.gov/scripts/recordpass.asp?RecordType=0&RecordID=3270

- **Sickle Cell Disease Glossary**

  Summary: This is a glossary of sickle cell disease terms.

  Source: Sickle Cell Disease Association of America

  http://www.healthfinder.gov/scripts/recordpass.asp?RecordType=0&RecordID=7733

The NIH Search Utility

The NIH search utility allows you to search for documents on over 100 selected Web sites that comprise the NIH-WEB-SPACE. Each of these servers is "crawled" and indexed on an ongoing basis. Your search will produce a list of various documents, all of which will relate in some way to sickle cell anemia. The drawbacks of this approach are that the information is not organized by theme and that the references are often a mix of information for professionals and patients. Nevertheless, a large number of the listed Web sites provide useful background information. We can only recommend this route, therefore, for relatively rare or specific disorders, or when using highly targeted searches. To use the NIH search utility, visit the following Web page: **http://search.nih.gov/index.html**.

Additional Web Sources

A number of Web sites are available to the public that often link to government sites. These can also point you in the direction of essential information. The following is a representative sample:

- AOL: **http://search.aol.com/cat.adp?id=168&layer=&from=subcats**
- Family Village: **http://www.familyvillage.wisc.edu/specific.htm**
- Google: **http://directory.google.com/Top/Health/Conditions_and_Diseases/**
- Med Help International: **http://www.medhelp.org/HealthTopics/A.html**
- Open Directory Project: **http://dmoz.org/Health/Conditions_and_Diseases/**
- Yahoo.com: **http://dir.yahoo.com/Health/Diseases_and_Conditions/**
- WebMD®Health: **http://my.webmd.com/health_topics**

Associations and Sickle Cell Anemia

The following is a list of associations that provide information on and resources relating to sickle cell anemia:

- **American Sickle Cell Anemia Association**

  Telephone: (216) 229-8600

  Fax: (216) 229-4500

  Email: irabragg@ascaa.org

  Web Site: http://www.ascaa.org

  Background: The American **Sickle Cell Anemia** Association (ASCAA) is a regional not-for-profit organization that is committed to providing services to the community at risk for sickling diseases. Serving the greater Cleveland area, the Association provides medical and social support to people affected by **Sickle Cell Anemia** and their families. Established in 1971, the Association provides educational materials including informational brochures and operates support groups to help people cope with this disorder.

  Relevant area(s) of interest: Sickle Cell Disease

- **Center for Sickle Cell Disease**

  Telephone: (202) 806-7930

  Fax: (202) 806-4517

  Email: None.

  Web Site: None

  Background: The Center for **Sickle Cell Disease** is a clinical and service facility dedicated to treating individuals with **Sickle Cell Disease.** The research arm of the facility is located in Washington, D.C. and is dedicated to innovative medical studies into the causes, treatments, and cure of **Sickle Cell Disease** and other Sickling Diseases.

Educational materials are available to affected individuals, and the Center makes referrals to other physicians who are familiar with the treatment of these disorders.

Relevant area(s) of interest: Sickle Cell Disease

- **Sickle Cell Disease Association of America, Inc**

  Telephone: (310) 216-6363 Toll-free: (800) 421-8453

  Fax: (310) 215-3722

  Email: scdaa@sicklecelldiseases.org

  Web Site: www.sicklecelldisease.org

  Background: The **Sickle Cell Disease** Association of America (SCDAA) is a voluntary service organization dedicated to educating the public and providing support to people affected by **Sickle Cell Disease.** The Association was founded in 1971 as the umbrella organization for community-based groups providing support and services to persons affected by sickle cell conditions. The Association seeks to educate the public about **sickle cell disease** and the **sickle cell trait** and develop educational materials on these conditions for extensive circulation. It also educates legislators on issues regarding **sickle cell disease** and other genetic disorders and fosters ongoing medical research to improve the well-being of those affected by **sickle cell disease.** In addition, the Association supports research, advocates on behalf of all individuals affected by sickle cell diseases, and provides appropriate referrals to medical professionals. The Association is the only national community-based voluntary health agency working full-time to resolve issues surrounding sickle cell conditions. The **Sickle Cell Disease** Association provides an extensive supply of resources. These include guidebooks, brochures, pamphlets, audio and visual tapes, fact sheets, and a periodic newsletter entitled 'Sickle Cell News.'

  Relevant area(s) of interest: Sickle Cell Disease, Sickle Cell Trait

Finding Associations

There are several Internet directories that provide lists of medical associations with information on or resources relating to sickle cell anemia. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with sickle cell anemia.

The National Health Information Center (NHIC)

The National Health Information Center (NHIC) offers a free referral service to help people find organizations that provide information about sickle cell anemia. For more information, see the NHIC's Web site at **http://www.health.gov/NHIC/** or contact an information specialist by calling 1-800-336-4797.

Directory of Health Organizations

The Directory of Health Organizations, provided by the National Library of Medicine Specialized Information Services, is a comprehensive source of information on associations.

The Directory of Health Organizations database can be accessed via the Internet at **http://www.sis.nlm.nih.gov/Dir/DirMain.html**. It is composed of two parts: DIRLINE and Health Hotlines.

The DIRLINE database comprises some 10,000 records of organizations, research centers, and government institutes and associations that primarily focus on health and biomedicine. To access DIRLINE directly, go to the following Web site: **http://dirline.nlm.nih.gov/**. Simply type in "sickle cell anemia" (or a synonym), and you will receive information on all relevant organizations listed in the database.

Health Hotlines directs you to toll-free numbers to over 300 organizations. You can access this database directly at **http://www.sis.nlm.nih.gov/hotlines/**. On this page, you are given the option to search by keyword or by browsing the subject list. When you have received your search results, click on the name of the organization for its description and contact information.

The Combined Health Information Database

Another comprehensive source of information on healthcare associations is the Combined Health Information Database. Using the "Detailed Search" option, you will need to limit your search to "Organizations" and "sickle cell anemia". Type the following hyperlink into your Web browser: **http://chid.nih.gov/detail/detail.html**. To find associations, use the drop boxes at the bottom of the search page where "You may refine your search by." For publication date, select "All Years." Then, select your preferred language and the format option "Organization Resource Sheet." Type "sickle cell anemia" (or synonyms) into the "For these words:" box. You should check back periodically with this database since it is updated every three months.

The National Organization for Rare Disorders, Inc.

The National Organization for Rare Disorders, Inc. has prepared a Web site that provides, at no charge, lists of associations organized by health topic. You can access this database at the following Web site: **http://www.rarediseases.org/search/orgsearch.html**. Type "sickle cell anemia" (or a synonym) into the search box, and click "Submit Query."

APPENDIX C. FINDING MEDICAL LIBRARIES

Overview

In this Appendix, we show you how to quickly find a medical library in your area.

Preparation

Your local public library and medical libraries have interlibrary loan programs with the National Library of Medicine (NLM), one of the largest medical collections in the world. According to the NLM, most of the literature in the general and historical collections of the National Library of Medicine is available on interlibrary loan to any library. If you would like to access NLM medical literature, then visit a library in your area that can request the publications for you.[25]

Finding a Local Medical Library

The quickest method to locate medical libraries is to use the Internet-based directory published by the National Network of Libraries of Medicine (NN/LM). This network includes 4626 members and affiliates that provide many services to librarians, health professionals, and the public. To find a library in your area, simply visit **http://nnlm.gov/members/adv.html** or call 1-800-338-7657.

Medical Libraries in the U.S. and Canada

In addition to the NN/LM, the National Library of Medicine (NLM) lists a number of libraries with reference facilities that are open to the public. The following is the NLM's list and includes hyperlinks to each library's Web site. These Web pages can provide information on hours of operation and other restrictions. The list below is a small sample of

[25] Adapted from the NLM: **http://www.nlm.nih.gov/psd/cas/interlibrary.html**.

libraries recommended by the National Library of Medicine (sorted alphabetically by name of the U.S. state or Canadian province where the library is located)[26]:

- **Alabama:** Health InfoNet of Jefferson County (Jefferson County Library Cooperative, Lister Hill Library of the Health Sciences), **http://www.uab.edu/infonet/**
- **Alabama:** Richard M. Scrushy Library (American Sports Medicine Institute)
- **Arizona:** Samaritan Regional Medical Center: The Learning Center (Samaritan Health System, Phoenix, Arizona), **http://www.samaritan.edu/library/bannerlibs.htm**
- **California:** Kris Kelly Health Information Center (St. Joseph Health System, Humboldt), **http://www.humboldt1.com/~kkhic/index.html**
- **California:** Community Health Library of Los Gatos, **http://www.healthlib.org/orgresources.html**
- **California:** Consumer Health Program and Services (CHIPS) (County of Los Angeles Public Library, Los Angeles County Harbor-UCLA Medical Center Library) - Carson, CA, **http://www.colapublib.org/services/chips.html**
- **California:** Gateway Health Library (Sutter Gould Medical Foundation)
- **California:** Health Library (Stanford University Medical Center), **http://www-med.stanford.edu/healthlibrary/**
- **California:** Patient Education Resource Center - Health Information and Resources (University of California, San Francisco), **http://sfghdean.ucsf.edu/barnett/PERC/default.asp**
- **California:** Redwood Health Library (Petaluma Health Care District), **http://www.phcd.org/rdwdlib.html**
- **California:** Los Gatos PlaneTree Health Library, **http://planetreesanjose.org/**
- **California:** Sutter Resource Library (Sutter Hospitals Foundation, Sacramento), **http://suttermedicalcenter.org/library/**
- **California:** Health Sciences Libraries (University of California, Davis), **http://www.lib.ucdavis.edu/healthsci/**
- **California:** ValleyCare Health Library & Ryan Comer Cancer Resource Center (ValleyCare Health System, Pleasanton), **http://gaelnet.stmarys-ca.edu/other.libs/gbal/east/vchl.html**
- **California:** Washington Community Health Resource Library (Fremont), **http://www.healthlibrary.org/**
- **Colorado:** William V. Gervasini Memorial Library (Exempla Healthcare), **http://www.saintjosephdenver.org/yourhealth/libraries/**
- **Connecticut:** Hartford Hospital Health Science Libraries (Hartford Hospital), **http://www.harthosp.org/library/**
- **Connecticut:** Healthnet: Connecticut Consumer Health Information Center (University of Connecticut Health Center, Lyman Maynard Stowe Library), **http://library.uchc.edu/departm/hnet/**

[26] Abstracted from **http://www.nlm.nih.gov/medlineplus/libraries.html**.

- **Connecticut:** Waterbury Hospital Health Center Library (Waterbury Hospital, Waterbury), **http://www.waterburyhospital.com/library/consumer.shtml**
- **Delaware:** Consumer Health Library (Christiana Care Health System, Eugene du Pont Preventive Medicine & Rehabilitation Institute, Wilmington), **http://www.christianacare.org/health_guide/health_guide_pmri_health_info.cfm**
- **Delaware:** Lewis B. Flinn Library (Delaware Academy of Medicine, Wilmington), **http://www.delamed.org/chls.html**
- **Georgia:** Family Resource Library (Medical College of Georgia, Augusta), **http://cmc.mcg.edu/kids_families/fam_resources/fam_res_lib/frl.htm**
- **Georgia:** Health Resource Center (Medical Center of Central Georgia, Macon), **http://www.mccg.org/hrc/hrchome.asp**
- **Hawaii:** Hawaii Medical Library: Consumer Health Information Service (Hawaii Medical Library, Honolulu), **http://hml.org/CHIS/**
- **Idaho:** DeArmond Consumer Health Library (Kootenai Medical Center, Coeur d'Alene), **http://www.nicon.org/DeArmond/index.htm**
- **Illinois:** Health Learning Center of Northwestern Memorial Hospital (Chicago), **http://www.nmh.org/health_info/hlc.html**
- **Illinois:** Medical Library (OSF Saint Francis Medical Center, Peoria), **http://www.osfsaintfrancis.org/general/library/**
- **Kentucky:** Medical Library - Services for Patients, Families, Students & the Public (Central Baptist Hospital, Lexington), **http://www.centralbap.com/education/community/library.cfm**
- **Kentucky:** University of Kentucky - Health Information Library (Chandler Medical Center, Lexington), **http://www.mc.uky.edu/PatientEd/**
- **Louisiana:** Alton Ochsner Medical Foundation Library (Alton Ochsner Medical Foundation, New Orleans), **http://www.ochsner.org/library/**
- **Louisiana:** Louisiana State University Health Sciences Center Medical Library-Shreveport, **http://lib-sh.lsuhsc.edu/**
- **Maine:** Franklin Memorial Hospital Medical Library (Franklin Memorial Hospital, Farmington), **http://www.fchn.org/fmh/lib.htm**
- **Maine:** Gerrish-True Health Sciences Library (Central Maine Medical Center, Lewiston), **http://www.cmmc.org/library/library.html**
- **Maine:** Hadley Parrot Health Science Library (Eastern Maine Healthcare, Bangor), **http://www.emh.org/hll/hpl/guide.htm**
- **Maine:** Maine Medical Center Library (Maine Medical Center, Portland), **http://www.mmc.org/library/**
- **Maine:** Parkview Hospital (Brunswick), **http://www.parkviewhospital.org/**
- **Maine:** Southern Maine Medical Center Health Sciences Library (Southern Maine Medical Center, Biddeford), **http://www.smmc.org/services/service.php3?choice=10**
- **Maine:** Stephens Memorial Hospital's Health Information Library (Western Maine Health, Norway), **http://www.wmhcc.org/Library/**

- **Manitoba, Canada:** Consumer & Patient Health Information Service (University of Manitoba Libraries), **http://www.umanitoba.ca/libraries/units/health/reference/chis.html**
- **Manitoba, Canada:** J.W. Crane Memorial Library (Deer Lodge Centre, Winnipeg), **http://www.deerlodge.mb.ca/crane_library/about.asp**
- **Maryland:** Health Information Center at the Wheaton Regional Library (Montgomery County, Dept. of Public Libraries, Wheaton Regional Library), **http://www.mont.lib.md.us/healthinfo/hic.asp**
- **Massachusetts:** Baystate Medical Center Library (Baystate Health System), **http://www.baystatehealth.com/1024/**
- **Massachusetts:** Boston University Medical Center Alumni Medical Library (Boston University Medical Center), **http://med-libwww.bu.edu/library/lib.html**
- **Massachusetts:** Lowell General Hospital Health Sciences Library (Lowell General Hospital, Lowell), **http://www.lowellgeneral.org/library/HomePageLinks/WWW.htm**
- **Massachusetts:** Paul E. Woodard Health Sciences Library (New England Baptist Hospital, Boston), **http://www.nebh.org/health_lib.asp**
- **Massachusetts:** St. Luke's Hospital Health Sciences Library (St. Luke's Hospital, Southcoast Health System, New Bedford), **http://www.southcoast.org/library/**
- **Massachusetts:** Treadwell Library Consumer Health Reference Center (Massachusetts General Hospital), **http://www.mgh.harvard.edu/library/chrcindex.html**
- **Massachusetts:** UMass HealthNet (University of Massachusetts Medical School, Worchester), **http://healthnet.umassmed.edu/**
- **Michigan:** Botsford General Hospital Library - Consumer Health (Botsford General Hospital, Library & Internet Services), **http://www.botsfordlibrary.org/consumer.htm**
- **Michigan:** Helen DeRoy Medical Library (Providence Hospital and Medical Centers), **http://www.providence-hospital.org/library/**
- **Michigan:** Marquette General Hospital - Consumer Health Library (Marquette General Hospital, Health Information Center), **http://www.mgh.org/center.html**
- **Michigan:** Patient Education Resouce Center - University of Michigan Cancer Center (University of Michigan Comprehensive Cancer Center, Ann Arbor), **http://www.cancer.med.umich.edu/learn/leares.htm**
- **Michigan:** Sladen Library & Center for Health Information Resources - Consumer Health Information (Detroit), **http://www.henryford.com/body.cfm?id=39330**
- **Montana:** Center for Health Information (St. Patrick Hospital and Health Sciences Center, Missoula)
- **National:** Consumer Health Library Directory (Medical Library Association, Consumer and Patient Health Information Section), **http://caphis.mlanet.org/directory/index.html**
- **National:** National Network of Libraries of Medicine (National Library of Medicine) - provides library services for health professionals in the United States who do not have access to a medical library, **http://nnlm.gov/**
- **National:** NN/LM List of Libraries Serving the Public (National Network of Libraries of Medicine), **http://nnlm.gov/members/**

- **Nevada:** Health Science Library, West Charleston Library (Las Vegas-Clark County Library District, Las Vegas), **http://www.lvccld.org/special_collections/medical/index.htm**
- **New Hampshire:** Dartmouth Biomedical Libraries (Dartmouth College Library, Hanover), **http://www.dartmouth.edu/~biomed/resources.htmld/conshealth.htmld/**
- **New Jersey:** Consumer Health Library (Rahway Hospital, Rahway), **http://www.rahwayhospital.com/library.htm**
- **New Jersey:** Dr. Walter Phillips Health Sciences Library (Englewood Hospital and Medical Center, Englewood), **http://www.englewoodhospital.com/links/index.htm**
- **New Jersey:** Meland Foundation (Englewood Hospital and Medical Center, Englewood), **http://www.geocities.com/ResearchTriangle/9360/**
- **New York:** Choices in Health Information (New York Public Library) - NLM Consumer Pilot Project participant, **http://www.nypl.org/branch/health/links.html**
- **New York:** Health Information Center (Upstate Medical University, State University of New York, Syracuse), **http://www.upstate.edu/library/hic/**
- **New York:** Health Sciences Library (Long Island Jewish Medical Center, New Hyde Park), **http://www.lij.edu/library/library.html**
- **New York:** ViaHealth Medical Library (Rochester General Hospital), **http://www.nyam.org/library/**
- **Ohio:** Consumer Health Library (Akron General Medical Center, Medical & Consumer Health Library), **http://www.akrongeneral.org/hwlibrary.htm**
- **Oklahoma:** The Health Information Center at Saint Francis Hospital (Saint Francis Health System, Tulsa), **http://www.sfh-tulsa.com/services/healthinfo.asp**
- **Oregon:** Planetree Health Resource Center (Mid-Columbia Medical Center, The Dalles), **http://www.mcmc.net/phrc/**
- **Pennsylvania:** Community Health Information Library (Milton S. Hershey Medical Center, Hershey), **http://www.hmc.psu.edu/commhealth/**
- **Pennsylvania:** Community Health Resource Library (Geisinger Medical Center, Danville), **http://www.geisinger.edu/education/commlib.shtml**
- **Pennsylvania:** HealthInfo Library (Moses Taylor Hospital, Scranton), **http://www.mth.org/healthwellness.html**
- **Pennsylvania:** Hopwood Library (University of Pittsburgh, Health Sciences Library System, Pittsburgh), **http://www.hsls.pitt.edu/guides/chi/hopwood/index_html**
- **Pennsylvania:** Koop Community Health Information Center (College of Physicians of Philadelphia), **http://www.collphyphil.org/kooppg1.shtml**
- **Pennsylvania:** Learning Resources Center - Medical Library (Susquehanna Health System, Williamsport), **http://www.shscares.org/services/lrc/index.asp**
- **Pennsylvania:** Medical Library (UPMC Health System, Pittsburgh), **http://www.upmc.edu/passavant/library.htm**
- **Quebec, Canada:** Medical Library (Montreal General Hospital), **http://www.mghlib.mcgill.ca/**

- **South Dakota:** Rapid City Regional Hospital Medical Library (Rapid City Regional Hospital), **http://www.rcrh.org/Services/Library/Default.asp**
- **Texas:** Houston HealthWays (Houston Academy of Medicine-Texas Medical Center Library), **http://hhw.library.tmc.edu/**
- **Washington:** Community Health Library (Kittitas Valley Community Hospital), **http://www.kvch.com/**
- **Washington:** Southwest Washington Medical Center Library (Southwest Washington Medical Center, Vancouver), **http://www.swmedicalcenter.com/body.cfm?id=72**

ONLINE GLOSSARIES

The Internet provides access to a number of free-to-use medical dictionaries. The National Library of Medicine has compiled the following list of online dictionaries:

- ADAM Medical Encyclopedia (A.D.A.M., Inc.), comprehensive medical reference: **http://www.nlm.nih.gov/medlineplus/encyclopedia.html**
- MedicineNet.com Medical Dictionary (MedicineNet, Inc.): **http://www.medterms.com/Script/Main/hp.asp**
- Merriam-Webster Medical Dictionary (Inteli-Health, Inc.): **http://www.intelihealth.com/IH/**
- Multilingual Glossary of Technical and Popular Medical Terms in Eight European Languages (European Commission) - Danish, Dutch, English, French, German, Italian, Portuguese, and Spanish: **http://allserv.rug.ac.be/~rvdstich/eugloss/welcome.html**
- On-line Medical Dictionary (CancerWEB): **http://cancerweb.ncl.ac.uk/omd/**
- Rare Diseases Terms (Office of Rare Diseases): **http://ord.aspensys.com/asp/diseases/diseases.asp**
- Technology Glossary (National Library of Medicine) - Health Care Technology: **http://www.nlm.nih.gov/nichsr/ta101/ta10108.htm**

Beyond these, MEDLINEplus contains a very patient-friendly encyclopedia covering every aspect of medicine (licensed from A.D.A.M., Inc.). The ADAM Medical Encyclopedia can be accessed at **http://www.nlm.nih.gov/medlineplus/encyclopedia.html**. ADAM is also available on commercial Web sites such as drkoop.com (**http://www.drkoop.com/**) and Web MD (**http://my.webmd.com/adam/asset/adam_disease_articles/a_to_z/a**). The NIH suggests the following Web sites in the ADAM Medical Encyclopedia when searching for information on sickle cell anemia:

- **Basic Guidelines for Sickle Cell Anemia**

  Sickle cell anemia
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000527.htm

  Sickle cell anemia - resources
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002200.htm

- **Signs & Symptoms for Sickle Cell Anemia**

  Abdominal pain
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003120.htm

  Blood in the urine
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003138.htm

  Bone pain
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003180.htm

Breathlessness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003075.htm

Chest pain
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003079.htm

Cough
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003072.htm

Delayed growth
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003021.htm

Fatigue
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003088.htm

Fever
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003090.htm

Hematuria
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003138.htm

Jaundice
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003243.htm

Joint pain
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003261.htm

Paleness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003244.htm

Priapism
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003166.htm

Rapid heart rate
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003077.htm

Stress
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003211.htm

Thirst, excessive
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003085.htm

Urination, excessive volume
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003146.htm

Vomiting
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003117.htm

Weakness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003174.htm

- **Diagnostics and Tests for Sickle Cell Anemia**

  Bilirubin
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003479.htm

  CBC
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003642.htm

  Creatinine
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003475.htm

  ESR
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003638.htm

  Hemoglobin
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003645.htm

  Hemoglobin electrophoresis
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003639.htm

  Hemoglobin S screening test
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003639.htm

  Hemoglobin; serum
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003677.htm

  MRI
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003335.htm

  Peripheral smear
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003665.htm

  Sickle cell test
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003666.htm

  Sickle cell trait
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003666.htm

  Ulcers
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003228.htm

  Urinary casts
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003586.htm

  White blood cell count
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003643.htm

  X-ray
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003337.htm

- **Nutrition for Sickle Cell Anemia**

  Folic acid
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002408.htm

- **Surgery and Procedures for Sickle Cell Anemia**

  Bone marrow transplant
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003009.htm

  Exchange transfusion
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002923.htm

  Gallbladder removal
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002930.htm

  Kidney transplant
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003005.htm

  Splenectomy
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002944.htm

- **Background Topics for Sickle Cell Anemia**

  Acute
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002215.htm

  Analgesics
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002123.htm

  Aplastic
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002233.htm

  Chronic
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002312.htm

  Electrolytes
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002350.htm

  Incidence
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002387.htm

  Intravenous
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002383.htm

  Necrosis
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002266.htm

  Physical activity
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/001941.htm

Prenatal diagnosis
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002053.htm

Sickle cell anemia - support group
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002200.htm

Online Dictionary Directories

The following are additional online directories compiled by the National Library of Medicine, including a number of specialized medical dictionaries:

- Medical Dictionaries: Medical & Biological (World Health Organization): **http://www.who.int/hlt/virtuallibrary/English/diction.htm#Medical**
- MEL-Michigan Electronic Library List of Online Health and Medical Dictionaries (Michigan Electronic Library): **http://mel.lib.mi.us/health/health-dictionaries.html**
- Patient Education: Glossaries (DMOZ Open Directory Project): **http://dmoz.org/Health/Education/Patient_Education/Glossaries/**
- Web of Online Dictionaries (Bucknell University): **http://www.yourdictionary.com/diction5.html#medicine**

SICKLE CELL ANEMIA DICTIONARY

The definitions below are derived from official public sources, including the National Institutes of Health [NIH] and the European Union [EU].

Abdomen: That portion of the body that lies between the thorax and the pelvis. [NIH]

Abdominal: Having to do with the abdomen, which is the part of the body between the chest and the hips that contains the pancreas, stomach, intestines, liver, gallbladder, and other organs. [NIH]

Abdominal Pain: Sensation of discomfort, distress, or agony in the abdominal region. [NIH]

Aberrant: Wandering or deviating from the usual or normal course. [EU]

Ablation: The removal of an organ by surgery. [NIH]

Abscess: A localized, circumscribed collection of pus. [NIH]

Absenteeism: Chronic absence from work or other duty. [NIH]

Acceptor: A substance which, while normally not oxidized by oxygen or reduced by hydrogen, can be oxidized or reduced in presence of a substance which is itself undergoing oxidation or reduction. [NIH]

Acetylcholine: A neurotransmitter. Acetylcholine in vertebrates is the major transmitter at neuromuscular junctions, autonomic ganglia, parasympathetic effector junctions, a subset of sympathetic effector junctions, and at many sites in the central nervous system. It is generally not used as an administered drug because it is broken down very rapidly by cholinesterases, but it is useful in some ophthalmological applications. [NIH]

Acidosis: A pathologic condition resulting from accumulation of acid or depletion of the alkaline reserve (bicarbonate content) in the blood and body tissues, and characterized by an increase in hydrogen ion concentration. [EU]

Acoustic: Having to do with sound or hearing. [NIH]

Acrylonitrile: A highly poisonous compound used widely in the manufacture of plastics, adhesives and synthetic rubber. [NIH]

Actin: Essential component of the cell skeleton. [NIH]

Acute lymphoblastic leukemia: ALL. A quickly progressing disease in which too many immature white blood cells called lymphoblasts are found in the blood and bone marrow. Also called acute lymphocytic leukemia. [NIH]

Acute lymphocytic leukemia: ALL. A quickly progressing disease in which too many immature white blood cells called lymphoblasts are found in the blood and bone marrow. Also called acute lymphoblastic leukemia. [NIH]

Acute myelogenous leukemia: AML. A quickly progressing disease in which too many immature blood-forming cells are found in the blood and bone marrow. Also called acute myeloid leukemia or acute nonlymphocytic leukemia. [NIH]

Acute myeloid leukemia: AML. A quickly progressing disease in which too many immature blood-forming cells are found in the blood and bone marrow. Also called acute myelogenous leukemia or acute nonlymphocytic leukemia. [NIH]

Acute nonlymphocytic leukemia: A quickly progressing disease in which too many immature blood-forming cells are found in the blood and bone marrow. Also called acute myeloid leukemia or acute myelogenous leukemia. [NIH]

Acute renal: A condition in which the kidneys suddenly stop working. In most cases, kidneys can recover from almost complete loss of function. [NIH]

Adaptability: Ability to develop some form of tolerance to conditions extremely different from those under which a living organism evolved. [NIH]

Adenine: A purine base and a fundamental unit of adenine nucleotides. [NIH]

Adenosine: A nucleoside that is composed of adenine and d-ribose. Adenosine or adenosine derivatives play many important biological roles in addition to being components of DNA and RNA. Adenosine itself is a neurotransmitter. [NIH]

Adjuvant: A substance which aids another, such as an auxiliary remedy; in immunology, nonspecific stimulator (e.g., BCG vaccine) of the immune response. [EU]

Adolescence: The period of life beginning with the appearance of secondary sex characteristics and terminating with the cessation of somatic growth. The years usually referred to as adolescence lie between 13 and 18 years of age. [NIH]

Adrenal Glands: Paired glands situated in the retroperitoneal tissues at the superior pole of each kidney. [NIH]

Adrenal Medulla: The inner part of the adrenal gland; it synthesizes, stores and releases catecholamines. [NIH]

Adrenergic: Activated by, characteristic of, or secreting epinephrine or substances with similar activity; the term is applied to those nerve fibres that liberate norepinephrine at a synapse when a nerve impulse passes, i.e., the sympathetic fibres. [EU]

Adrenergic Agonists: Drugs that bind to and activate adrenergic receptors. [NIH]

Adverse Effect: An unwanted side effect of treatment. [NIH]

Aerobic: In biochemistry, reactions that need oxygen to happen or happen when oxygen is present. [NIH]

Aerosol: A solution of a drug which can be atomized into a fine mist for inhalation therapy. [EU]

Affinity: 1. Inherent likeness or relationship. 2. A special attraction for a specific element, organ, or structure. 3. Chemical affinity; the force that binds atoms in molecules; the tendency of substances to combine by chemical reaction. 4. The strength of noncovalent chemical binding between two substances as measured by the dissociation constant of the complex. 5. In immunology, a thermodynamic expression of the strength of interaction between a single antigen-binding site and a single antigenic determinant (and thus of the stereochemical compatibility between them), most accurately applied to interactions among simple, uniform antigenic determinants such as haptens. Expressed as the association constant (K litres mole -1), which, owing to the heterogeneity of affinities in a population of antibody molecules of a given specificity, actually represents an average value (mean intrinsic association constant). 6. The reciprocal of the dissociation constant. [EU]

Age Groups: Persons classified by age from birth (infant, newborn) to octogenarians and older (aged, 80 and over). [NIH]

Aged, 80 and Over: A person 80 years of age and older. [NIH]

Agonist: In anatomy, a prime mover. In pharmacology, a drug that has affinity for and stimulates physiologic activity at cell receptors normally stimulated by naturally occurring substances. [EU]

Albumin: 1. Any protein that is soluble in water and moderately concentrated salt solutions and is coagulable by heat. 2. Serum albumin; the major plasma protein (approximately 60 per cent of the total), which is responsible for much of the plasma colloidal osmotic pressure

and serves as a transport protein carrying large organic anions, such as fatty acids, bilirubin, and many drugs, and also carrying certain hormones, such as cortisol and thyroxine, when their specific binding globulins are saturated. Albumin is synthesized in the liver. Low serum levels occur in protein malnutrition, active inflammation and serious hepatic and renal disease. [EU]

Aldehydes: Organic compounds containing a carbonyl group in the form -CHO. [NIH]

Alfalfa: A deep-rooted European leguminous plant (Medicago sativa) widely grown for hay and forage. [NIH]

Algorithms: A procedure consisting of a sequence of algebraic formulas and/or logical steps to calculate or determine a given task. [NIH]

Alimentary: Pertaining to food or nutritive material, or to the organs of digestion. [EU]

Alkaline: Having the reactions of an alkali. [EU]

Alkaline Phosphatase: An enzyme that catalyzes the conversion of an orthophosphoric monoester and water to an alcohol and orthophosphate. EC 3.1.3.1. [NIH]

Alkylating Agents: Highly reactive chemicals that introduce alkyl radicals into biologically active molecules and thereby prevent their proper functioning. Many are used as antineoplastic agents, but most are very toxic, with carcinogenic, mutagenic, teratogenic, and immunosuppressant actions. They have also been used as components in poison gases. [NIH]

Alleles: Mutually exclusive forms of the same gene, occupying the same locus on homologous chromosomes, and governing the same biochemical and developmental process. [NIH]

Allogeneic: Taken from different individuals of the same species. [NIH]

Allogeneic bone marrow transplantation: A procedure in which a person receives stem cells, the cells from which all blood cells develop, from a compatible, though not genetically identical, donor. [NIH]

Alopecia: Absence of hair from areas where it is normally present. [NIH]

Alpha Particles: Positively charged particles composed of two protons and two neutrons, i.e., helium nuclei, emitted during disintegration of very heavy isotopes; a beam of alpha particles or an alpha ray has very strong ionizing power, but weak penetrability. [NIH]

Alpha-helix: One of the secondary element of protein. [NIH]

Alpha-Thalassemia: A disorder characterized by reduced synthesis of the alpha chains of hemoglobin. The severity of this condition can vary from mild anemia to death, depending on the number of genes deleted. [NIH]

Alternative medicine: Practices not generally recognized by the medical community as standard or conventional medical approaches and used instead of standard treatments. Alternative medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Amber: A yellowish fossil resin, the gum of several species of coniferous trees, found in the alluvial deposits of northeastern Germany. It is used in molecular biology in the analysis of organic matter fossilized in amber. [NIH]

Ameliorated: A changeable condition which prevents the consequence of a failure or accident from becoming as bad as it otherwise would. [NIH]

Ameliorating: A changeable condition which prevents the consequence of a failure or accident from becoming as bad as it otherwise would. [NIH]

Amino Acid Sequence: The order of amino acids as they occur in a polypeptide chain. This is referred to as the primary structure of proteins. It is of fundamental importance in determining protein conformation. [NIH]

Amino Acid Substitution: The naturally occurring or experimentally induced replacement of one or more amino acids in a protein with another. If a functionally equivalent amino acid is substituted, the protein may retain wild-type activity. Substitution may also diminish or eliminate protein function. Experimentally induced substitution is often used to study enzyme activities and binding site properties. [NIH]

Amino Acids: Organic compounds that generally contain an amino (-NH2) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form proteins. [NIH]

Amino Acids: Organic compounds that generally contain an amino (-NH2) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form proteins. [NIH]

Ammonia: A colorless alkaline gas. It is formed in the body during decomposition of organic materials during a large number of metabolically important reactions. [NIH]

Amplification: The production of additional copies of a chromosomal DNA sequence, found as either intrachromosomal or extrachromosomal DNA. [NIH]

Ampulla: A sac-like enlargement of a canal or duct. [NIH]

Amyloidosis: A group of diseases in which protein is deposited in specific organs (localized amyloidosis) or throughout the body (systemic amyloidosis). Amyloidosis may be either primary (with no known cause) or secondary (caused by another disease, including some types of cancer). Generally, primary amyloidosis affects the nerves, skin, tongue, joints, heart, and liver; secondary amyloidosis often affects the spleen, kidneys, liver, and adrenal glands. [NIH]

Anabolic: Relating to, characterized by, or promoting anabolism. [EU]

Anaerobic: 1. Lacking molecular oxygen. 2. Growing, living, or occurring in the absence of molecular oxygen; pertaining to an anaerobe. [EU]

Anaesthesia: Loss of feeling or sensation. Although the term is used for loss of tactile sensibility, or of any of the other senses, it is applied especially to loss of the sensation of pain, as it is induced to permit performance of surgery or other painful procedures. [EU]

Anal: Having to do with the anus, which is the posterior opening of the large bowel. [NIH]

Analgesic: An agent that alleviates pain without causing loss of consciousness. [EU]

Analogous: Resembling or similar in some respects, as in function or appearance, but not in origin or development;. [EU]

Analytes: A component of a test sample the presence of which has to be demonstrated. The term "analyte" includes where appropriate formed from the analyte during the analyses. [NIH]

Anaphylatoxins: The family of peptides C3a, C4a, C5a, and C5a des-arginine produced in the serum during complement activation. They produce smooth muscle contraction, mast cell histamine release, affect platelet aggregation, and act as mediators of the local inflammatory process. The order of anaphylatoxin activity from strongest to weakest is C5a, C3a, C4a, and C5a des-arginine. The latter is the so-called "classical" anaphylatoxin but shows no spasmogenic activity though it contains some chemotactic ability. [NIH]

Anaphylaxis: An acute hypersensitivity reaction due to exposure to a previously encountered antigen. The reaction may include rapidly progressing urticaria, respiratory distress, vascular collapse, systemic shock, and death. [NIH]

Anaplasia: Loss of structural differentiation and useful function of neoplastic cells. [NIH]

Anatomical: Pertaining to anatomy, or to the structure of the organism. [EU]

Androgenic: Producing masculine characteristics. [EU]

Anemia: A reduction in the number of circulating erythrocytes or in the quantity of hemoglobin. [NIH]

Anemia, Sickle Cell: A disease characterized by chronic hemolytic anemia, episodic painful crises, and pathologic involvement of many organs. It is the clinical expression of homozygosity for hemoglobin S. [NIH]

Anemic: Hypoxia due to reduction of the oxygen-carrying capacity of the blood as a result of a decrease in the total hemoglobin or an alteration of the hemoglobin constituents. [NIH]

Anesthesia: A state characterized by loss of feeling or sensation. This depression of nerve function is usually the result of pharmacologic action and is induced to allow performance of surgery or other painful procedures. [NIH]

Anesthetics: Agents that are capable of inducing a total or partial loss of sensation, especially tactile sensation and pain. They may act to induce general anesthesia, in which an unconscious state is achieved, or may act locally to induce numbness or lack of sensation at a targeted site. [NIH]

Aneurysm: A sac formed by the dilatation of the wall of an artery, a vein, or the heart. [NIH]

Angina: Chest pain that originates in the heart. [NIH]

Angiogenesis: Blood vessel formation. Tumor angiogenesis is the growth of blood vessels from surrounding tissue to a solid tumor. This is caused by the release of chemicals by the tumor. [NIH]

Animal model: An animal with a disease either the same as or like a disease in humans. Animal models are used to study the development and progression of diseases and to test new treatments before they are given to humans. Animals with transplanted human cancers or other tissues are called xenograft models. [NIH]

Annealing: The spontaneous alignment of two single DNA strands to form a double helix. [NIH]

Anorexia: Lack or loss of appetite for food. Appetite is psychologic, dependent on memory and associations. Anorexia can be brought about by unattractive food, surroundings, or company. [NIH]

Antibiotic: A drug used to treat infections caused by bacteria and other microorganisms. [NIH]

Antibodies: Immunoglobulin molecules having a specific amino acid sequence by virtue of which they interact only with the antigen that induced their synthesis in cells of the lymphoid series (especially plasma cells), or with an antigen closely related to it. [NIH]

Antibody: A type of protein made by certain white blood cells in response to a foreign substance (antigen). Each antibody can bind to only a specific antigen. The purpose of this binding is to help destroy the antigen. Antibodies can work in several ways, depending on the nature of the antigen. Some antibodies destroy antigens directly. Others make it easier for white blood cells to destroy the antigen. [NIH]

Antibody therapy: Treatment with an antibody, a substance that can directly kill specific tumor cells or stimulate the immune system to kill tumor cells. [NIH]

Anticoagulant: A drug that helps prevent blood clots from forming. Also called a blood thinner. [NIH]

Antiemetic: An agent that prevents or alleviates nausea and vomiting. Also antinauseant.

[EU]

Antigen: Any substance which is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibody or specifically sensitized T-lymphocytes, or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (q.v.) combines with antibody or a specific receptor on a lymphocyte. Abbreviated Ag. [EU]

Antigen-Antibody Complex: The complex formed by the binding of antigen and antibody molecules. The deposition of large antigen-antibody complexes leading to tissue damage causes immune complex diseases. [NIH]

Anti-infective: An agent that so acts. [EU]

Anti-inflammatory: Having to do with reducing inflammation. [NIH]

Anti-Inflammatory Agents: Substances that reduce or suppress inflammation. [NIH]

Antimicrobial: Killing microorganisms, or suppressing their multiplication or growth. [EU]

Antimycotic: Suppressing the growth of fungi. [EU]

Antineoplastic: Inhibiting or preventing the development of neoplasms, checking the maturation and proliferation of malignant cells. [EU]

Antioxidant: A substance that prevents damage caused by free radicals. Free radicals are highly reactive chemicals that often contain oxygen. They are produced when molecules are split to give products that have unpaired electrons. This process is called oxidation. [NIH]

Antiplasmin: A member of the serpin superfamily found in human plasma that inhibits the lysis of fibrin clots which are induced by plasminogen activator. It is a glycoprotein, molecular weight approximately 70,000 that migrates in the alpha 2 region in immunoelectrophoresis. It is the principal plasmin inactivator in blood, rapidly forming a very stable complex with plasmin. [NIH]

Antipsychotic: Effective in the treatment of psychosis. Antipsychotic drugs (called also neuroleptic drugs and major tranquilizers) are a chemically diverse (including phenothiazines, thioxanthenes, butyrophenones, dibenzoxazepines, dibenzodiazepines, and diphenylbutylpiperidines) but pharmacologically similar class of drugs used to treat schizophrenic, paranoid, schizoaffective, and other psychotic disorders; acute delirium and dementia, and manic episodes (during induction of lithium therapy); to control the movement disorders associated with Huntington's chorea, Gilles de la Tourette's syndrome, and ballismus; and to treat intractable hiccups and severe nausea and vomiting. Antipsychotic agents bind to dopamine, histamine, muscarinic cholinergic, a-adrenergic, and serotonin receptors. Blockade of dopaminergic transmission in various areas is thought to be responsible for their major effects : antipsychotic action by blockade in the mesolimbic and mesocortical areas; extrapyramidal side effects (dystonia, akathisia, parkinsonism, and tardive dyskinesia) by blockade in the basal ganglia; and antiemetic effects by blockade in the chemoreceptor trigger zone of the medulla. Sedation and autonomic side effects (orthostatic hypotension, blurred vision, dry mouth, nasal congestion and constipation) are caused by blockade of histamine, cholinergic, and adrenergic receptors. [EU]

Antisickling Agents: Agents used to prevent or reverse the pathological events leading to sickling of erythrocytes in sickle cell conditions. [NIH]

Anuria: Inability to form or excrete urine. [NIH]

Anus: The opening of the rectum to the outside of the body. [NIH]

Anxiety: Persistent feeling of dread, apprehension, and impending disaster. [NIH]

Aphakia: Absence of crystalline lens totally or partially from field of vision, from any cause except after cataract extraction. Aphakia is mainly congenital or as result of lens dislocation and subluxation. [NIH]

Aplastic anemia: A condition in which the bone marrow is unable to produce blood cells. [NIH]

Apolipoproteins: The protein components of lipoproteins which remain after the lipids to which the proteins are bound have been removed. They play an important role in lipid transport and metabolism. [NIH]

Apoptosis: One of the two mechanisms by which cell death occurs (the other being the pathological process of necrosis). Apoptosis is the mechanism responsible for the physiological deletion of cells and appears to be intrinsically programmed. It is characterized by distinctive morphologic changes in the nucleus and cytoplasm, chromatin cleavage at regularly spaced sites, and the endonucleolytic cleavage of genomic DNA (DNA fragmentation) at internucleosomal sites. This mode of cell death serves as a balance to mitosis in regulating the size of animal tissues and in mediating pathologic processes associated with tumor growth. [NIH]

Applicability: A list of the commodities to which the candidate method can be applied as presented or with minor modifications. [NIH]

Aquaporins: Membrane proteins which facilitate the passage of water. They are members of the family of membrane channel proteins which includes the lens major intrinsic protein and bacterial glycerol transporters. [NIH]

Aqueous: Having to do with water. [NIH]

Arginine: An essential amino acid that is physiologically active in the L-form. [NIH]

Arginine butyrate: A substance that is being studied as a treatment for cancer. [NIH]

Aromatic: Having a spicy odour. [EU]

Arterial: Pertaining to an artery or to the arteries. [EU]

Arteries: The vessels carrying blood away from the heart. [NIH]

Arterioles: The smallest divisions of the arteries located between the muscular arteries and the capillaries. [NIH]

Arteriosus: Circle composed of anastomosing arteries derived from two long posterior ciliary and seven anterior ciliary arteries, located in the ciliary body about the root of the iris. [NIH]

Arteriovenous: Both arterial and venous; pertaining to or affecting an artery and a vein. [EU]

Arthralgia: Pain in the joint. [NIH]

Articular: Of or pertaining to a joint. [EU]

Ascorbic Acid: A six carbon compound related to glucose. It is found naturally in citrus fruits and many vegetables. Ascorbic acid is an essential nutrient in human diets, and necessary to maintain connective tissue and bone. Its biologically active form, vitamin C, functions as a reducing agent and coenzyme in several metabolic pathways. Vitamin C is considered an antioxidant. [NIH]

Aseptic: Free from infection or septic material; sterile. [EU]

Asphyxia: A pathological condition caused by lack of oxygen, manifested in impending or actual cessation of life. [NIH]

Aspiration: The act of inhaling. [NIH]

Aspirin: A drug that reduces pain, fever, inflammation, and blood clotting. Aspirin belongs

to the family of drugs called nonsteroidal anti-inflammatory agents. It is also being studied in cancer prevention. [NIH]

Assay: Determination of the amount of a particular constituent of a mixture, or of the biological or pharmacological potency of a drug. [EU]

Asymptomatic: Having no signs or symptoms of disease. [NIH]

Ataxia: Impairment of the ability to perform smoothly coordinated voluntary movements. This condition may affect the limbs, trunk, eyes, pharnyx, larnyx, and other structures. Ataxia may result from impaired sensory or motor function. Sensory ataxia may result from posterior column injury or peripheral nerve diseases. Motor ataxia may be associated with cerebellar diseases; cerebral cortex diseases; thalamic diseases; basal ganglia diseases; injury to the red nucleus; and other conditions. [NIH]

Atmospheric Pressure: The pressure at any point in an atmosphere due solely to the weight of the atmospheric gases above the point concerned. [NIH]

Atresia: Lack of a normal opening from the esophagus, intestines, or anus. [NIH]

Atrial: Pertaining to an atrium. [EU]

Atrial Fibrillation: Disorder of cardiac rhythm characterized by rapid, irregular atrial impulses and ineffective atrial contractions. [NIH]

Atrium: A chamber; used in anatomical nomenclature to designate a chamber affording entrance to another structure or organ. Usually used alone to designate an atrium of the heart. [EU]

Atrophy: Decrease in the size of a cell, tissue, organ, or multiple organs, associated with a variety of pathological conditions such as abnormal cellular changes, ischemia, malnutrition, or hormonal changes. [NIH]

Atypical: Irregular; not conformable to the type; in microbiology, applied specifically to strains of unusual type. [EU]

Auditory: Pertaining to the sense of hearing. [EU]

Autoimmune disease: A condition in which the body recognizes its own tissues as foreign and directs an immune response against them. [NIH]

Autologous: Taken from an individual's own tissues, cells, or DNA. [NIH]

Autologous bone marrow transplantation: A procedure in which bone marrow is removed from a person, stored, and then given back to the person after intensive treatment. [NIH]

Autologous lymphocytes: A person's white blood cells. Lymphocytes have a number of roles in the immune system, including the production of antibodies and other substances that fight infection and disease. [NIH]

Autonomic: Self-controlling; functionally independent. [EU]

Bacteremia: The presence of viable bacteria circulating in the blood. Fever, chills, tachycardia, and tachypnea are common acute manifestations of bacteremia. The majority of cases are seen in already hospitalized patients, most of whom have underlying diseases or procedures which render their bloodstreams susceptible to invasion. [NIH]

Bacteria: Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccal, rodlike or bacillary, and spiral or spirochetal. [NIH]

Bacterial Infections: Infections by bacteria, general or unspecified. [NIH]

Bacteriophage: A virus whose host is a bacterial cell; A virus that exclusively infects bacteria. It generally has a protein coat surrounding the genome (DNA or RNA). One of the

coliphages most extensively studied is the lambda phage, which is also one of the most important. [NIH]

Bacterium: Microscopic organism which may have a spherical, rod-like, or spiral unicellular or non-cellular body. Bacteria usually reproduce through asexual processes. [NIH]

Barotrauma: Injury following pressure changes; includes injury to the eustachian tube, ear drum, lung and stomach. [NIH]

Basal Ganglia: Large subcortical nuclear masses derived from the telencephalon and located in the basal regions of the cerebral hemispheres. [NIH]

Basal Ganglia Diseases: Diseases of the basal ganglia including the putamen; globus pallidus; claustrum; amygdala; and caudate nucleus. Dyskinesias (most notably involuntary movements and alterations of the rate of movement) represent the primary clinical manifestations of these disorders. Common etiologies include cerebrovascular disease; neurodegenerative diseases; and craniocerebral trauma. [NIH]

Base: In chemistry, the nonacid part of a salt; a substance that combines with acids to form salts; a substance that dissociates to give hydroxide ions in aqueous solutions; a substance whose molecule or ion can combine with a proton (hydrogen ion); a substance capable of donating a pair of electrons (to an acid) for the formation of a coordinate covalent bond. [EU]

Basement Membrane: Ubiquitous supportive tissue adjacent to epithelium and around smooth and striated muscle cells. This tissue contains intrinsic macromolecular components such as collagen, laminin, and sulfated proteoglycans. As seen by light microscopy one of its subdivisions is the basal (basement) lamina. [NIH]

Basophils: Granular leukocytes characterized by a relatively pale-staining, lobate nucleus and cytoplasm containing coarse dark-staining granules of variable size and stainable by basic dyes. [NIH]

Benign: Not cancerous; does not invade nearby tissue or spread to other parts of the body. [NIH]

Beta-Thalassemia: A disorder characterized by reduced synthesis of the beta chains of hemoglobin. There is retardation of hemoglobin A synthesis in the heterozygous form (thalassemia minor), which is asymptomatic, while in the homozygous form (thalassemia major, Cooley's anemia, Mediterranean anemia, erythroblastic anemia), which can result in severe complications and even death, hemoglobin A synthesis is absent. [NIH]

Bilateral: Affecting both the right and left side of body. [NIH]

Bile: An emulsifying agent produced in the liver and secreted into the duodenum. Its composition includes bile acids and salts, cholesterol, and electrolytes. It aids digestion of fats in the duodenum. [NIH]

Bile Ducts: Tubes that carry bile from the liver to the gallbladder for storage and to the small intestine for use in digestion. [NIH]

Bile Pigments: Pigments that give a characteristic color to bile including: bilirubin, biliverdine, and bilicyanin. [NIH]

Biliary: Having to do with the liver, bile ducts, and/or gallbladder. [NIH]

Bilirubin: A bile pigment that is a degradation product of heme. [NIH]

Binding Sites: The reactive parts of a macromolecule that directly participate in its specific combination with another molecule. [NIH]

Bioavailability: The degree to which a drug or other substance becomes available to the target tissue after administration. [EU]

Biochemical: Relating to biochemistry; characterized by, produced by, or involving

chemical reactions in living organisms. [EU]

Biological therapy: Treatment to stimulate or restore the ability of the immune system to fight infection and disease. Also used to lessen side effects that may be caused by some cancer treatments. Also known as immunotherapy, biotherapy, or biological response modifier (BRM) therapy. [NIH]

Biological Transport: The movement of materials (including biochemical substances and drugs) across cell membranes and epithelial layers, usually by passive diffusion. [NIH]

Biophysics: The science of physical phenomena and processes in living organisms. [NIH]

Biosynthesis: The building up of a chemical compound in the physiologic processes of a living organism. [EU]

Biotechnology: Body of knowledge related to the use of organisms, cells or cell-derived constituents for the purpose of developing products which are technically, scientifically and clinically useful. Alteration of biologic function at the molecular level (i.e., genetic engineering) is a central focus; laboratory methods used include transfection and cloning technologies, sequence and structure analysis algorithms, computer databases, and gene and protein structure function analysis and prediction. [NIH]

Biotin: Hexahydro-2-oxo-1H-thieno(3,4-d)imidazole-4-pentanoic acid. Growth factor present in minute amounts in every living cell. It occurs mainly bound to proteins or polypeptides and is abundant in liver, kidney, pancreas, yeast, and milk.The biotin content of cancerous tissue is higher than that of normal tissue. [NIH]

Bladder: The organ that stores urine. [NIH]

Blastocyst: The mammalian embryo in the post-morula stage in which a fluid-filled cavity, enclosed primarily by trophoblast, contains an inner cell mass which becomes the embryonic disc. [NIH]

Bleeding Time: Duration of blood flow after skin puncture. This test is used as a measure of capillary and platelet function. [NIH]

Blood Cell Count: A count of the number of leukocytes and erythrocytes per unit volume in a sample of venous blood. A complete blood count (CBC) also includes measurement of the hemoglobin, hematocrit, and erythrocyte indices. [NIH]

Blood Coagulation: The process of the interaction of blood coagulation factors that results in an insoluble fibrin clot. [NIH]

Blood Glucose: Glucose in blood. [NIH]

Blood Platelets: Non-nucleated disk-shaped cells formed in the megakaryocyte and found in the blood of all mammals. They are mainly involved in blood coagulation. [NIH]

Blood pressure: The pressure of blood against the walls of a blood vessel or heart chamber. Unless there is reference to another location, such as the pulmonary artery or one of the heart chambers, it refers to the pressure in the systemic arteries, as measured, for example, in the forearm. [NIH]

Blood Substitutes: Substances that can carry oxygen to and carbon dioxide away from the tissues when introduced into the blood stream. They are used to replace hemoglobin in severe hemorrhage and also to perfuse isolated organs. The best known are perfluorocarbon emulsions and various hemoglobin solutions. [NIH]

Blood transfusion: The administration of blood or blood products into a blood vessel. [NIH]

Blood vessel: A tube in the body through which blood circulates. Blood vessels include a network of arteries, arterioles, capillaries, venules, and veins. [NIH]

Blood Viscosity: The internal resistance of the blood to shear forces. The in vitro measure of

whole blood viscosity is of limited clinical utility because it bears little relationship to the actual viscosity within the circulation, but an increase in the viscosity of circulating blood can contribute to morbidity in patients suffering from disorders such as sickle cell anemia and polycythemia. [NIH]

Blood Volume: Volume of circulating blood. It is the sum of the plasma volume and erythrocyte volume. [NIH]

Blot: To transfer DNA, RNA, or proteins to an immobilizing matrix such as nitrocellulose. [NIH]

Body Burden: The total amount of a chemical, metal or radioactive substance present at any time after absorption in the body of man or animal. [NIH]

Body Composition: The relative amounts of various components in the body, such as percent body fat. [NIH]

Body Fluids: Liquid components of living organisms. [NIH]

Bone Conduction: Sound transmission through the bones of the skull to the inner ear. [NIH]

Bone Marrow: The soft tissue filling the cavities of bones. Bone marrow exists in two types, yellow and red. Yellow marrow is found in the large cavities of large bones and consists mostly of fat cells and a few primitive blood cells. Red marrow is a hematopoietic tissue and is the site of production of erythrocytes and granular leukocytes. Bone marrow is made up of a framework of connective tissue containing branching fibers with the frame being filled with marrow cells. [NIH]

Bone Marrow Cells: Cells contained in the bone marrow including fat cells, stromal cells, megakaryocytes, and the immediate precursors of most blood cells. [NIH]

Bone Marrow Transplantation: The transference of bone marrow from one human or animal to another. [NIH]

Bone scan: A technique to create images of bones on a computer screen or on film. A small amount of radioactive material is injected into a blood vessel and travels through the bloodstream; it collects in the bones and is detected by a scanner. [NIH]

Bowel: The long tube-shaped organ in the abdomen that completes the process of digestion. There is both a small and a large bowel. Also called the intestine. [NIH]

Bowel Movement: Body wastes passed through the rectum and anus. [NIH]

Brachytherapy: A collective term for interstitial, intracavity, and surface radiotherapy. It uses small sealed or partly-sealed sources that may be placed on or near the body surface or within a natural body cavity or implanted directly into the tissues. [NIH]

Bradykinin: A nonapeptide messenger that is enzymatically produced from kallidin in the blood where it is a potent but short-lived agent of arteriolar dilation and increased capillary permeability. Bradykinin is also released from mast cells during asthma attacks, from gut walls as a gastrointestinal vasodilator, from damaged tissues as a pain signal, and may be a neurotransmitter. [NIH]

Brain Neoplasms: Neoplasms of the intracranial components of the central nervous system, including the cerebral hemispheres, basal ganglia, hypothalamus, thalamus, brain stem, and cerebellum. Brain neoplasms are subdivided into primary (originating from brain tissue) and secondary (i.e., metastatic) forms. Primary neoplasms are subdivided into benign and malignant forms. In general, brain tumors may also be classified by age of onset, histologic type, or presenting location in the brain. [NIH]

Branch: Most commonly used for branches of nerves, but applied also to other structures. [NIH]

Breakdown: A physical, metal, or nervous collapse. [NIH]

Breeding: The science or art of changing the constitution of a population of plants or animals through sexual reproduction. [NIH]

Bronchi: The larger air passages of the lungs arising from the terminal bifurcation of the trachea. [NIH]

Buccal: Pertaining to or directed toward the cheek. In dental anatomy, used to refer to the buccal surface of a tooth. [EU]

Buffers: A chemical system that functions to control the levels of specific ions in solution. When the level of hydrogen ion in solution is controlled the system is called a pH buffer. [NIH]

Busulfan: An anticancer drug that belongs to the family of drugs called alkylating agents. [NIH]

Butyrates: Salts and esters of butyric acid [NIH]

Butyric Acid: A four carbon acid, CH3CH2CH2COOH, with an unpleasant odor that occurs in butter and animal fat as the glycerol ester. [NIH]

Bypass: A surgical procedure in which the doctor creates a new pathway for the flow of body fluids. [NIH]

Calcium: A basic element found in nearly all organized tissues. It is a member of the alkaline earth family of metals with the atomic symbol Ca, atomic number 20, and atomic weight 40. Calcium is the most abundant mineral in the body and combines with phosphorus to form calcium phosphate in the bones and teeth. It is essential for the normal functioning of nerves and muscles and plays a role in blood coagulation (as factor IV) and in many enzymatic processes. [NIH]

Calculi: An abnormal concretion occurring mostly in the urinary and biliary tracts, usually composed of mineral salts. Also called stones. [NIH]

Candidiasis: Infection with a fungus of the genus Candida. It is usually a superficial infection of the moist cutaneous areas of the body, and is generally caused by C. albicans; it most commonly involves the skin (dermatocandidiasis), oral mucous membranes (thrush, def. 1), respiratory tract (bronchocandidiasis), and vagina (vaginitis). Rarely there is a systemic infection or endocarditis. Called also moniliasis, candidosis, oidiomycosis, and formerly blastodendriosis. [EU]

Candidosis: An infection caused by an opportunistic yeasts that tends to proliferate and become pathologic when the environment is favorable and the host resistance is weakened. [NIH]

Capillary: Any one of the minute vessels that connect the arterioles and venules, forming a network in nearly all parts of the body. Their walls act as semipermeable membranes for the interchange of various substances, including fluids, between the blood and tissue fluid; called also vas capillare. [EU]

Capillary Fragility: The lack of resistance, or susceptibility, of capillaries to damage or disruption under conditions of increased stress. [NIH]

Capsules: Hard or soft soluble containers used for the oral administration of medicine. [NIH]

Captopril: A potent and specific inhibitor of peptidyl-dipeptidase A. It blocks the conversion of angiotensin I to angiotensin II, a vasoconstrictor and important regulator of arterial blood pressure. Captopril acts to suppress the renin-angiotensin system and inhibits pressure responses to exogenous angiotensin. [NIH]

Carbohydrates: The largest class of organic compounds, including starches, glycogens, cellulose, gums, and simple sugars. Carbohydrates are composed of carbon, hydrogen, and oxygen in a ratio of Cn(H2O)n. [NIH]

Carbon Dioxide: A colorless, odorless gas that can be formed by the body and is necessary for the respiration cycle of plants and animals. [NIH]

Carcinogenic: Producing carcinoma. [EU]

Carcinogens: Substances that increase the risk of neoplasms in humans or animals. Both genotoxic chemicals, which affect DNA directly, and nongenotoxic chemicals, which induce neoplasms by other mechanism, are included. [NIH]

Carcinoma: Cancer that begins in the skin or in tissues that line or cover internal organs. [NIH]

Cardiac: Having to do with the heart. [NIH]

Cardiac catheterization: A procedure in which a thin, hollow tube is inserted into a blood vessel. The tube is then advanced through the vessel into the heart, enabling a physician to study the heart and its pumping activity. [NIH]

Cardiac Output: The volume of blood passing through the heart per unit of time. It is usually expressed as liters (volume) per minute so as not to be confused with stroke volume (volume per beat). [NIH]

Cardiomegaly: Hypertrophy or enlargement of the heart. [NIH]

Cardiopulmonary: Having to do with the heart and lungs. [NIH]

Cardiopulmonary Bypass: Diversion of the flow of blood from the entrance of the right atrium directly to the aorta (or femoral artery) via an oxygenator thus bypassing both the heart and lungs. [NIH]

Cardiovascular: Having to do with the heart and blood vessels. [NIH]

Cardiovascular disease: Any abnormal condition characterized by dysfunction of the heart and blood vessels. CVD includes atherosclerosis (especially coronary heart disease, which can lead to heart attacks), cerebrovascular disease (e.g., stroke), and hypertension (high blood pressure). [NIH]

Carotene: The general name for a group of pigments found in green, yellow, and leafy vegetables, and yellow fruits. The pigments are fat-soluble, unsaturated aliphatic hydrocarbons functioning as provitamins and are converted to vitamin A through enzymatic processes in the intestinal wall. [NIH]

Carotenoids: Substance found in yellow and orange fruits and vegetables and in dark green, leafy vegetables. May reduce the risk of developing cancer. [NIH]

Carpal Tunnel Syndrome: A median nerve injury inside the carpal tunnel that results in symptoms of pain, numbness, tingling, clumsiness, and a lack of sweating, which can be caused by work with certain hand and wrist postures. [NIH]

Carrier Proteins: Transport proteins that carry specific substances in the blood or across cell membranes. [NIH]

Case report: A detailed report of the diagnosis, treatment, and follow-up of an individual patient. Case reports also contain some demographic information about the patient (for example, age, gender, ethnic origin). [NIH]

Case series: A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. [NIH]

Catabolism: Any destructive metabolic process by which organisms convert substances into excreted compounds. [EU]

Cataract: An opacity, partial or complete, of one or both eyes, on or in the lens or capsule, especially an opacity impairing vision or causing blindness. The many kinds of cataract are classified by their morphology (size, shape, location) or etiology (cause and time of occurrence). [EU]

Catecholamine: A group of chemical substances manufactured by the adrenal medulla and secreted during physiological stress. [NIH]

Catheterization: Use or insertion of a tubular device into a duct, blood vessel, hollow organ, or body cavity for injecting or withdrawing fluids for diagnostic or therapeutic purposes. It differs from intubation in that the tube here is used to restore or maintain patency in obstructions. [NIH]

Cathode: An electrode, usually an incandescent filament of tungsten, which emits electrons in an X-ray tube. [NIH]

Cations: Postively charged atoms, radicals or groups of atoms which travel to the cathode or negative pole during electrolysis. [NIH]

Causal: Pertaining to a cause; directed against a cause. [EU]

Ceftriaxone: Broad-spectrum cephalosporin antibiotic with a very long half-life and high penetrability to usually inaccessible infections, including those involving the meninges, eyes, inner ears, and urinary tract. [NIH]

Cell: The individual unit that makes up all of the tissues of the body. All living things are made up of one or more cells. [NIH]

Cell Adhesion: Adherence of cells to surfaces or to other cells. [NIH]

Cell Count: A count of the number of cells of a specific kind, usually measured per unit volume of sample. [NIH]

Cell Cycle: The complex series of phenomena, occurring between the end of one cell division and the end of the next, by which cellular material is divided between daughter cells. [NIH]

Cell Death: The termination of the cell's ability to carry out vital functions such as metabolism, growth, reproduction, responsiveness, and adaptability. [NIH]

Cell Division: The fission of a cell. [NIH]

Cell Lineage: The developmental history of cells as traced from the first division of the original cell or cells in the embryo. [NIH]

Cell membrane: Cell membrane = plasma membrane. The structure enveloping a cell, enclosing the cytoplasm, and forming a selective permeability barrier; it consists of lipids, proteins, and some carbohydrates, the lipids thought to form a bilayer in which integral proteins are embedded to varying degrees. [EU]

Cell proliferation: An increase in the number of cells as a result of cell growth and cell division. [NIH]

Cell Survival: The span of viability of a cell characterized by the capacity to perform certain functions such as metabolism, growth, reproduction, some form of responsiveness, and adaptability. [NIH]

Cell Transplantation: Transference of cells within an individual, between individuals of the same species, or between individuals of different species. [NIH]

Central Nervous System: The main information-processing organs of the nervous system, consisting of the brain, spinal cord, and meninges. [NIH]

Central Nervous System Infections: Pathogenic infections of the brain, spinal cord, and meninges. DNA virus infections; RNA virus infections; bacterial infections; mycoplasma

infections; Spirochaetales infections; fungal infections; protozoan infections; helminthiasis; and prion diseases may involve the central nervous system as a primary or secondary process. [NIH]

Centrifugation: A method of separating organelles or large molecules that relies upon differential sedimentation through a preformed density gradient under the influence of a gravitational field generated in a centrifuge. [NIH]

Cerebellar: Pertaining to the cerebellum. [EU]

Cerebral: Of or pertaining of the cerebrum or the brain. [EU]

Cerebral Angiography: Radiography of the vascular system of the brain after injection of a contrast medium. [NIH]

Cerebral Infarction: The formation of an area of necrosis in the cerebrum caused by an insufficiency of arterial or venous blood flow. Infarcts of the cerebrum are generally classified by hemisphere (i.e., left vs. right), lobe (e.g., frontal lobe infarction), arterial distribution (e.g., infarction, anterior cerebral artery), and etiology (e.g., embolic infarction). [NIH]

Cerebrospinal: Pertaining to the brain and spinal cord. [EU]

Cerebrospinal fluid: CSF. The fluid flowing around the brain and spinal cord. Cerebrospinal fluid is produced in the ventricles in the brain. [NIH]

Cerebrovascular: Pertaining to the blood vessels of the cerebrum, or brain. [EU]

Cerebrum: The largest part of the brain. It is divided into two hemispheres, or halves, called the cerebral hemispheres. The cerebrum controls muscle functions of the body and also controls speech, emotions, reading, writing, and learning. [NIH]

Cerumen: The yellow or brown waxy secretions produced by vestigial apocrine sweat glands in the external ear canal. [NIH]

Cervical: Relating to the neck, or to the neck of any organ or structure. Cervical lymph nodes are located in the neck; cervical cancer refers to cancer of the uterine cervix, which is the lower, narrow end (the "neck") of the uterus. [NIH]

Chelation: Combination with a metal in complexes in which the metal is part of a ring. [EU]

Chelation Therapy: Therapy of heavy metal poisoning using agents which sequester the metal from organs or tissues and bind it firmly within the ring structure of a new compound which can be eliminated from the body. [NIH]

Chemokines: Class of pro-inflammatory cytokines that have the ability to attract and activate leukocytes. They can be divided into at least three structural branches: C (chemokines, C), CC (chemokines, CC), and CXC (chemokines, CXC), according to variations in a shared cysteine motif. [NIH]

Chemokines, C: Group of chemokines without adjacent cysteines that are chemoattractants for lymphocytes only. [NIH]

Chemotactic Factors: Chemical substances that attract or repel cells or organisms. The concept denotes especially those factors released as a result of tissue injury, invasion, or immunologic activity, that attract leukocytes, macrophages, or other cells to the site of infection or insult. [NIH]

Chemotherapy: Treatment with anticancer drugs. [NIH]

Chest Pain: Pressure, burning, or numbness in the chest. [NIH]

Chest wall: The ribs and muscles, bones, and joints that make up the area of the body between the neck and the abdomen. [NIH]

Chimeras: Organism that contains a mixture of genetically different cells. [NIH]

Chlorpromazine: The prototypical phenothiazine antipsychotic drug. Like the other drugs in this class chlorpromazine's antipsychotic actions are thought to be due to long-term adaptation by the brain to blocking dopamine receptors. Chlorpromazine has several other actions and therapeutic uses, including as an antiemetic and in the treatment of intractable hiccup. [NIH]

Cholelithiasis: Presence or formation of gallstones. [NIH]

Cholestasis: Impairment of biliary flow at any level from the hepatocyte to Vater's ampulla. [NIH]

Cholesterol: The principal sterol of all higher animals, distributed in body tissues, especially the brain and spinal cord, and in animal fats and oils. [NIH]

Cholesterol Esters: Fatty acid esters of cholesterol which constitute about two-thirds of the cholesterol in the plasma. The accumulation of cholesterol esters in the arterial intima is a characteristic feature of atherosclerosis. [NIH]

Choline: A basic constituent of lecithin that is found in many plants and animal organs. It is important as a precursor of acetylcholine, as a methyl donor in various metabolic processes, and in lipid metabolism. [NIH]

Chorea: Involuntary, forcible, rapid, jerky movements that may be subtle or become confluent, markedly altering normal patterns of movement. Hypotonia and pendular reflexes are often associated. Conditions which feature recurrent or persistent episodes of chorea as a primary manifestation of disease are referred to as choreatic disorders. Chorea is also a frequent manifestation of basal ganglia diseases. [NIH]

Choreatic Disorders: Acquired and hereditary conditions which feature chorea as a primary manifestation of the disease process. [NIH]

Choroid: The thin, highly vascular membrane covering most of the posterior of the eye between the retina and sclera. [NIH]

Chromatin: The material of chromosomes. It is a complex of DNA, histones, and nonhistone proteins (chromosomal proteins, non-histone) found within the nucleus of a cell. [NIH]

Chromium: A trace element that plays a role in glucose metabolism. It has the atomic symbol Cr, atomic number 24, and atomic weight 52. According to the Fourth Annual Report on Carcinogens (NTP85-002,1985), chromium and some of its compounds have been listed as known carcinogens. [NIH]

Chromosomal: Pertaining to chromosomes. [EU]

Chromosome: Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes. [NIH]

Chromosome Banding: Staining of bands, or chromosome segments, allowing the precise identification of individual chromosomes or parts of chromosomes. Applications include the determination of chromosome rearrangements in malformation syndromes and cancer, the chemistry of chromosome segments, chromosome changes during evolution, and, in conjunction with cell hybridization studies, chromosome mapping. [NIH]

Chronic: A disease or condition that persists or progresses over a long period of time. [NIH]

Chronic Disease: Disease or ailment of long duration. [NIH]

Chronic leukemia: A slowly progressing cancer of the blood-forming tissues. [NIH]

Chronic renal: Slow and progressive loss of kidney function over several years, often resulting in end-stage renal disease. People with end-stage renal disease need dialysis or transplantation to replace the work of the kidneys. [NIH]

Chylomicrons: A class of lipoproteins that carry dietary cholesterol and triglycerides from the small intestines to the tissues. [NIH]

Circulatory system: The system that contains the heart and the blood vessels and moves blood throughout the body. This system helps tissues get enough oxygen and nutrients, and it helps them get rid of waste products. The lymph system, which connects with the blood system, is often considered part of the circulatory system. [NIH]

CIS: Cancer Information Service. The CIS is the National Cancer Institute's link to the public, interpreting and explaining research findings in a clear and understandable manner, and providing personalized responses to specific questions about cancer. Access the CIS by calling 1-800-4-CANCER, or by using the Web site at http://cis.nci.nih.gov. [NIH]

Citrus: Any tree or shrub of the Rue family or the fruit of these plants. [NIH]

Clinical Medicine: The study and practice of medicine by direct examination of the patient. [NIH]

Clinical Protocols: Precise and detailed plans for the study of a medical or biomedical problem and/or plans for a regimen of therapy. [NIH]

Clinical study: A research study in which patients receive treatment in a clinic or other medical facility. Reports of clinical studies can contain results for single patients (case reports) or many patients (case series or clinical trials). [NIH]

Clinical trial: A research study that tests how well new medical treatments or other interventions work in people. Each study is designed to test new methods of screening, prevention, diagnosis, or treatment of a disease. [NIH]

Clone: The term "clone" has acquired a new meaning. It is applied specifically to the bits of inserted foreign DNA in the hybrid molecules of the population. Each inserted segment originally resided in the DNA of a complex genome amid millions of other DNA segment. [NIH]

Cloning: The production of a number of genetically identical individuals; in genetic engineering, a process for the efficient replication of a great number of identical DNA molecules. [NIH]

Clot Retraction: Retraction of a clot resulting from contraction of platelet pseudopods attached to fibrin strands that is dependent on the contractile protein thrombosthenin. Used as a measure of platelet function. [NIH]

Clotrimazole: An imidazole derivative with a broad spectrum of antimycotic activity. It inhibits biosynthesis of the sterol ergostol, an important component of fungal cell membranes. Its action leads to increased membrane permeability and apparent disruption of enzyme systems bound to the membrane. [NIH]

Coagulation: 1. The process of clot formation. 2. In colloid chemistry, the solidification of a sol into a gelatinous mass; an alteration of a disperse phase or of a dissolved solid which causes the separation of the system into a liquid phase and an insoluble mass called the clot or curd. Coagulation is usually irreversible. 3. In surgery, the disruption of tissue by physical means to form an amorphous residuum, as in electrocoagulation and photocoagulation. [EU]

Cobalt: A trace element that is a component of vitamin B12. It has the atomic symbol Co, atomic number 27, and atomic weight 58.93. It is used in nuclear weapons, alloys, and pigments. Deficiency in animals leads to anemia; its excess in humans can lead to erythrocytosis. [NIH]

Cochlea: The part of the internal ear that is concerned with hearing. It forms the anterior part of the labyrinth, is conical, and is placed almost horizontally anterior to the vestibule. [NIH]

Cochlear: Of or pertaining to the cochlea. [EU]

Codon: A set of three nucleotides in a protein coding sequence that specifies individual amino acids or a termination signal (codon, terminator). Most codons are universal, but some organisms do not produce the transfer RNAs (RNA, transfer) complementary to all codons. These codons are referred to as unassigned codons (codons, nonsense). [NIH]

Coenzyme: An organic nonprotein molecule, frequently a phosphorylated derivative of a water-soluble vitamin, that binds with the protein molecule (apoenzyme) to form the active enzyme (holoenzyme). [EU]

Cofactor: A substance, microorganism or environmental factor that activates or enhances the action of another entity such as a disease-causing agent. [NIH]

Collagen: A polypeptide substance comprising about one third of the total protein in mammalian organisms. It is the main constituent of skin, connective tissue, and the organic substance of bones and teeth. Different forms of collagen are produced in the body but all consist of three alpha-polypeptide chains arranged in a triple helix. Collagen is differentiated from other fibrous proteins, such as elastin, by the content of proline, hydroxyproline, and hydroxylysine; by the absence of tryptophan; and particularly by the high content of polar groups which are responsible for its swelling properties. [NIH]

Collapse: 1. A state of extreme prostration and depression, with failure of circulation. 2. Abnormal falling in of the walls of any part of organ. [EU]

Colloidal: Of the nature of a colloid. [EU]

Combination Therapy: Association of 3 drugs to treat AIDS (AZT + DDC or DDI + protease inhibitor). [NIH]

Combinatorial: A cut-and-paste process that churns out thousands of potentially valuable compounds at once. [NIH]

Complement: A term originally used to refer to the heat-labile factor in serum that causes immune cytolysis, the lysis of antibody-coated cells, and now referring to the entire functionally related system comprising at least 20 distinct serum proteins that is the effector not only of immune cytolysis but also of other biologic functions. Complement activation occurs by two different sequences, the classic and alternative pathways. The proteins of the classic pathway are termed 'components of complement' and are designated by the symbols C1 through C9. C1 is a calcium-dependent complex of three distinct proteins C1q, C1r and C1s. The proteins of the alternative pathway (collectively referred to as the properdin system) and complement regulatory proteins are known by semisystematic or trivial names. Fragments resulting from proteolytic cleavage of complement proteins are designated with lower-case letter suffixes, e.g., C3a. Inactivated fragments may be designated with the suffix 'i', e.g. C3bi. Activated components or complexes with biological activity are designated by a bar over the symbol e.g. C1 or C4b,2a. The classic pathway is activated by the binding of C1 to classic pathway activators, primarily antigen-antibody complexes containing IgM, IgG1, IgG3; C1q binds to a single IgM molecule or two adjacent IgG molecules. The alternative pathway can be activated by IgA immune complexes and also by nonimmunologic materials including bacterial endotoxins, microbial polysaccharides, and cell walls. Activation of the classic pathway triggers an enzymatic cascade involving C1, C4, C2 and C3; activation of the alternative pathway triggers a cascade involving C3 and factors B, D and P. Both result in the cleavage of C5 and the formation of the membrane attack complex. Complement activation also results in the formation of many biologically active complement fragments that act as anaphylatoxins, opsonins, or chemotactic factors. [EU]

Complementary and alternative medicine: CAM. Forms of treatment that are used in addition to (complementary) or instead of (alternative) standard treatments. These practices

are not considered standard medical approaches. CAM includes dietary supplements, megadose vitamins, herbal preparations, special teas, massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Complementary medicine: Practices not generally recognized by the medical community as standard or conventional medical approaches and used to enhance or complement the standard treatments. Complementary medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Complementation: The production of a wild-type phenotype when two different mutations are combined in a diploid or a heterokaryon and tested in trans-configuration. [NIH]

Computational Biology: A field of biology concerned with the development of techniques for the collection and manipulation of biological data, and the use of such data to make biological discoveries or predictions. This field encompasses all computational methods and theories applicable to molecular biology and areas of computer-based techniques for solving biological problems including manipulation of models and datasets. [NIH]

Computed tomography: CT scan. A series of detailed pictures of areas inside the body, taken from different angles; the pictures are created by a computer linked to an x-ray machine. Also called computerized tomography and computerized axial tomography (CAT) scan. [NIH]

Computerized axial tomography: A series of detailed pictures of areas inside the body, taken from different angles; the pictures are created by a computer linked to an x-ray machine. Also called CAT scan, computed tomography (CT scan), or computerized tomography. [NIH]

Computerized tomography: A series of detailed pictures of areas inside the body, taken from different angles; the pictures are created by a computer linked to an x-ray machine. Also called computerized axial tomography (CAT) scan and computed tomography (CT scan). [NIH]

Conception: The onset of pregnancy, marked by implantation of the blastocyst; the formation of a viable zygote. [EU]

Concomitant: Accompanying; accessory; joined with another. [EU]

Conduction: The transfer of sound waves, heat, nervous impulses, or electricity. [EU]

Cones: One type of specialized light-sensitive cells (photoreceptors) in the retina that provide sharp central vision and color vision. [NIH]

Confidence Intervals: A range of values for a variable of interest, e.g., a rate, constructed so that this range has a specified probability of including the true value of the variable. [NIH]

Congenita: Displacement, subluxation, or malposition of the crystalline lens. [NIH]

Conjugation: 1. The act of joining together or the state of being conjugated. 2. A sexual process seen in bacteria, ciliate protozoa, and certain fungi in which nuclear material is exchanged during the temporary fusion of two cells (conjugants). In bacterial genetics a form of sexual reproduction in which a donor bacterium (male) contributes some, or all, of its DNA (in the form of a replicated set) to a recipient (female) which then incorporates differing genetic information into its own chromosome by recombination and passes the recombined set on to its progeny by replication. In ciliate protozoa, two conjugants of separate mating types exchange micronuclear material and then separate, each now being a fertilized cell. In certain fungi, the process involves fusion of two gametes, resulting in union of their nuclei and formation of a zygote. 3. In chemistry, the joining together of two compounds to produce another compound, such as the combination of a toxic product with

some substance in the body to form a detoxified product, which is then eliminated. [EU]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Consciousness: Sense of awareness of self and of the environment. [NIH]

Consensus Sequence: A theoretical representative nucleotide or amino acid sequence in which each nucleotide or amino acid is the one which occurs most frequently at that site in the different sequences which occur in nature. The phrase also refers to an actual sequence which approximates the theoretical consensus. A known conserved sequence set is represented by a consensus sequence. Commonly observed supersecondary protein structures (amino acid motifs) are often formed by conserved sequences. [NIH]

Conserved Sequence: A sequence of amino acids in a polypeptide or of nucleotides in DNA or RNA that is similar across multiple species. A known set of conserved sequences is represented by a consensus sequence. Amino acid motifs are often composed of conserved sequences. [NIH]

Consolidation: The healing process of a bone fracture. [NIH]

Constipation: Infrequent or difficult evacuation of feces. [NIH]

Constriction: The act of constricting. [NIH]

Constriction, Pathologic: The condition of an anatomical structure's being constricted beyond normal dimensions. [NIH]

Consumption: Pulmonary tuberculosis. [NIH]

Contamination: The soiling or pollution by inferior material, as by the introduction of organisms into a wound, or sewage into a stream. [EU]

Contraindications: Any factor or sign that it is unwise to pursue a certain kind of action or treatment, e. g. giving a general anesthetic to a person with pneumonia. [NIH]

Contrast Media: Substances used in radiography that allow visualization of certain tissues. [NIH]

Control group: In a clinical trial, the group that does not receive the new treatment being studied. This group is compared to the group that receives the new treatment, to see if the new treatment works. [NIH]

Controlled clinical trial: A clinical study that includes a comparison (control) group. The comparison group receives a placebo, another treatment, or no treatment at all. [NIH]

Conus: A large, circular, white patch around the optic disk due to the exposing of the sclera as a result of degenerative change or congenital abnormality in the choroid and retina. [NIH]

Convulsions: A general term referring to sudden and often violent motor activity of cerebral or brainstem origin. Convulsions may also occur in the absence of an electrical cerebral discharge (e.g., in response to hypotension). [NIH]

Coordination: Muscular or motor regulation or the harmonious cooperation of muscles or groups of muscles, in a complex action or series of actions. [NIH]

Cornea: The transparent part of the eye that covers the iris and the pupil and allows light to enter the inside. [NIH]

Coronary: Encircling in the manner of a crown; a term applied to vessels; nerves, ligaments, etc. The term usually denotes the arteries that supply the heart muscle and, by extension, a pathologic involvement of them. [EU]

Coronary heart disease: A type of heart disease caused by narrowing of the coronary arteries that feed the heart, which needs a constant supply of oxygen and nutrients carried by the blood in the coronary arteries. When the coronary arteries become narrowed or clogged by fat and cholesterol deposits and cannot supply enough blood to the heart, CHD results. [NIH]

Coronary Thrombosis: Presence of a thrombus in a coronary artery, often causing a myocardial infarction. [NIH]

Corpus: The body of the uterus. [NIH]

Corpuscle: A small mass or body; a sensory nerve end bulb; a cell, especially that of the blood or the lymph. [NIH]

Cortex: The outer layer of an organ or other body structure, as distinguished from the internal substance. [EU]

Cortical: Pertaining to or of the nature of a cortex or bark. [EU]

Cortices: The outer layer of an organ; used especially of the cerebrum and cerebellum. [NIH]

Corticosteroids: Hormones that have antitumor activity in lymphomas and lymphoid leukemias; in addition, corticosteroids (steroids) may be used for hormone replacement and for the management of some of the complications of cancer and its treatment. [NIH]

Coxsackieviruses: A heterogeneous group of the genus enterovirus found in association with various diseases in man and other animals. Two groups (A and B) have been identified with a number of serotypes in each. The name is derived from a village in New York State where the virus was first identified. [NIH]

Craniocerebral Trauma: Traumatic injuries involving the cranium and intracranial structures (i.e., brain; cranial nerves; meninges; and other structures). Injuries may be classified by whether or not the skull is penetrated (i.e., penetrating vs. nonpenetrating) or whether there is an associated hemorrhage. [NIH]

Crossing-over: The exchange of corresponding segments between chromatids of homologous chromosomes during meiosia, forming a chiasma. [NIH]

Cryofixation: Fixation of a tissue by localized cooling at very low temperature. [NIH]

Cryopreservation: Preservation of cells, tissues, organs, or embryos by freezing. In histological preparations, cryopreservation or cryofixation is used to maintain the existing form, structure, and chemical composition of all the constituent elements of the specimens. [NIH]

Crystallization: The formation of crystals; conversion to a crystalline form. [EU]

Curative: Tending to overcome disease and promote recovery. [EU]

Cutaneous: Having to do with the skin. [NIH]

Cyanates: Organic salts of cyanic acid containing the -OCN radical. [NIH]

Cyanosis: A bluish or purplish discoloration of the skin and mucous membranes due to an increase in the amount of deoxygenated hemoglobin in the blood or a structural defect in the hemoglobin molecule. [NIH]

Cyclic: Pertaining to or occurring in a cycle or cycles; the term is applied to chemical compounds that contain a ring of atoms in the nucleus. [EU]

Cyclophosphamide: Precursor of an alkylating nitrogen mustard antineoplastic and immunosuppressive agent that must be activated in the liver to form the active aldophosphamide. It is used in the treatment of lymphomas, leukemias, etc. Its side effect, alopecia, has been made use of in defleecing sheep. Cyclophosphamide may also cause sterility, birth defects, mutations, and cancer. [NIH]

Cyclosporine: A drug used to help reduce the risk of rejection of organ and bone marrow transplants by the body. It is also used in clinical trials to make cancer cells more sensitive to anticancer drugs. [NIH]

Cystathionine beta-Synthase: A multifunctional pyridoxal phosphate enzyme. In the second stage of cysteine biosynthesis it catalyzes the reaction of homocysteine with serine to form cystathionine with the elimination of water. Deficiency of this enzyme leads to hyperhomocysteinemia and homocystinuria. EC 4.2.1.22. [NIH]

Cysteine: A thiol-containing non-essential amino acid that is oxidized to form cystine. [NIH]

Cystine: A covalently linked dimeric nonessential amino acid formed by the oxidation of cysteine. Two molecules of cysteine are joined together by a disulfide bridge to form cystine. [NIH]

Cytokine: Small but highly potent protein that modulates the activity of many cell types, including T and B cells. [NIH]

Cytomegalovirus: A genus of the family Herpesviridae, subfamily Betaherpesvirinae, infecting the salivary glands, liver, spleen, lungs, eyes, and other organs, in which they produce characteristically enlarged cells with intranuclear inclusions. Infection with Cytomegalovirus is also seen as an opportunistic infection in AIDS. [NIH]

Cytoplasm: The protoplasm of a cell exclusive of that of the nucleus; it consists of a continuous aqueous solution (cytosol) and the organelles and inclusions suspended in it (phaneroplasm), and is the site of most of the chemical activities of the cell. [EU]

Cytoskeleton: The network of filaments, tubules, and interconnecting filamentous bridges which give shape, structure, and organization to the cytoplasm. [NIH]

Cytotoxic: Cell-killing. [NIH]

Cytotoxicity: Quality of being capable of producing a specific toxic action upon cells of special organs. [NIH]

Danazol: A synthetic steroid with antigonadotropic and anti-estrogenic activities that acts as an anterior pituitary suppressant by inhibiting the pituitary output of gonadotropins. It possesses some androgenic properties. Danazol has been used in the treatment of endometriosis and some benign breast disorders. [NIH]

Databases, Bibliographic: Extensive collections, reputedly complete, of references and citations to books, articles, publications, etc., generally on a single subject or specialized subject area. Databases can operate through automated files, libraries, or computer disks. The concept should be differentiated from factual databases which is used for collections of data and facts apart from bibliographic references to them. [NIH]

De novo: In cancer, the first occurrence of cancer in the body. [NIH]

Deamination: The removal of an amino group (NH2) from a chemical compound. [NIH]

Decidua: The epithelial lining of the endometrium that is formed before the fertilized ovum reaches the uterus. The fertilized ovum embeds in the decidua. If the ovum is not fertilized, the decidua is shed during menstruation. [NIH]

Decision Making: The process of making a selective intellectual judgment when presented with several complex alternatives consisting of several variables, and usually defining a course of action or an idea. [NIH]

Decitabine: An anticancer drug that belongs to the family of drugs called antimetabolites. [NIH]

Decompression: Decompression external to the body, most often the slow lessening of external pressure on the whole body (especially in caisson workers, deep sea divers, and persons who ascend to great heights) to prevent decompression sickness. It includes also

sudden accidental decompression, but not surgical (local) decompression or decompression applied through body openings. [NIH]

Decompression Sickness: A condition occurring as a result of exposure to a rapid fall in ambient pressure. Gases, nitrogen in particular, come out of solution and form bubbles in body fluid and blood. These gas bubbles accumulate in joint spaces and the peripheral circulation impairing tissue oxygenation causing disorientation, severe pain, and potentially death. [NIH]

Defense Mechanisms: Unconscious process used by an individual or a group of individuals in order to cope with impulses, feelings or ideas which are not acceptable at their conscious level; various types include reaction formation, projection and self reversal. [NIH]

Deferoxamine: Natural product isolated from Streptomyces pilosus. It forms iron complexes and is used as a chelating agent, particularly in the form of its mesylate. [NIH]

Degenerative: Undergoing degeneration : tending to degenerate; having the character of or involving degeneration; causing or tending to cause degeneration. [EU]

Dehydration: The condition that results from excessive loss of body water. [NIH]

Deletion: A genetic rearrangement through loss of segments of DNA (chromosomes), bringing sequences, which are normally separated, into close proximity. [NIH]

Delusions: A false belief regarding the self or persons or objects outside the self that persists despite the facts, and is not considered tenable by one's associates. [NIH]

Dementia: An acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behavior, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive, and initially spares the level of consciousness. [NIH]

Denaturation: Rupture of the hydrogen bonds by heating a DNA solution and then cooling it rapidly causes the two complementary strands to separate. [NIH]

Dendrites: Extensions of the nerve cell body. They are short and branched and receive stimuli from other neurons. [NIH]

Density: The logarithm to the base 10 of the opacity of an exposed and processed film. [NIH]

Dental Care: The total of dental diagnostic, preventive, and restorative services provided to meet the needs of a patient (from Illustrated Dictionary of Dentistry, 1982). [NIH]

Dental Caries: Localized destruction of the tooth surface initiated by decalcification of the enamel followed by enzymatic lysis of organic structures and leading to cavity formation. If left unchecked, the cavity may penetrate the enamel and dentin and reach the pulp. The three most prominent theories used to explain the etiology of the disase are that acids produced by bacteria lead to decalcification; that micro-organisms destroy the enamel protein; or that keratolytic micro-organisms produce chelates that lead to decalcification. [NIH]

Deoxycytidine: A drug that protects healthy tissues from the toxic effects of anticancer drugs. [NIH]

Deprivation: Loss or absence of parts, organs, powers, or things that are needed. [EU]

Dermal: Pertaining to or coming from the skin. [NIH]

Deuterium: Deuterium. The stable isotope of hydrogen. It has one neutron and one proton in the nucleus. [NIH]

Diabetes Mellitus: A heterogeneous group of disorders that share glucose intolerance in common. [NIH]

Diabetic Retinopathy: Retinopathy associated with diabetes mellitus, which may be of the background type, progressively characterized by microaneurysms, interretinal punctuate macular edema, or of the proliferative type, characterized by neovascularization of the retina and optic disk, which may project into the vitreous, proliferation of fibrous tissue, vitreous hemorrhage, and retinal detachment. [NIH]

Diagnostic procedure: A method used to identify a disease. [NIH]

Dialyzer: A part of the hemodialysis machine. (See hemodialysis under dialysis.) The dialyzer has two sections separated by a membrane. One section holds dialysate. The other holds the patient's blood. [NIH]

Diarrhea: Passage of excessively liquid or excessively frequent stools. [NIH]

Diarrhoea: Abnormal frequency and liquidity of faecal discharges. [EU]

Diastole: Period of relaxation of the heart, especially the ventricles. [NIH]

Diastolic: Of or pertaining to the diastole. [EU]

Diffusion: The tendency of a gas or solute to pass from a point of higher pressure or concentration to a point of lower pressure or concentration and to distribute itself throughout the available space; a major mechanism of biological transport. [NIH]

Digestion: The process of breakdown of food for metabolism and use by the body. [NIH]

Digestive system: The organs that take in food and turn it into products that the body can use to stay healthy. Waste products the body cannot use leave the body through bowel movements. The digestive system includes the salivary glands, mouth, esophagus, stomach, liver, pancreas, gallbladder, small and large intestines, and rectum. [NIH]

Dihydrotestosterone: Anabolic agent. [NIH]

Dihydroxy: AMPA/Kainate antagonist. [NIH]

Dilatation: The act of dilating. [NIH]

Dilatation, Pathologic: The condition of an anatomical structure's being dilated beyond normal dimensions. [NIH]

Dilation: A process by which the pupil is temporarily enlarged with special eye drops (mydriatic); allows the eye care specialist to better view the inside of the eye. [NIH]

Dilution: A diluted or attenuated medicine; in homeopathy, the diffusion of a given quantity of a medicinal agent in ten or one hundred times the same quantity of water. [NIH]

Dimerization: The process by which two molecules of the same chemical composition form a condensation product or polymer. [NIH]

Diploid: Having two sets of chromosomes. [NIH]

Dipyridamole: A drug that prevents blood cell clumping and enhances the effectiveness of fluorouracil and other chemotherapeutic agents. [NIH]

Direct: 1. Straight; in a straight line. 2. Performed immediately and without the intervention of subsidiary means. [EU]

Discoid: Shaped like a disk. [EU]

Disease Progression: The worsening of a disease over time. This concept is most often used for chronic and incurable diseases where the stage of the disease is an important determinant of therapy and prognosis. [NIH]

Disparity: Failure of the two retinal images of an object to fall on corresponding retinal points. [NIH]

Disposition: A tendency either physical or mental toward certain diseases. [EU]

Dissociation: 1. The act of separating or state of being separated. 2. The separation of a molecule into two or more fragments (atoms, molecules, ions, or free radicals) produced by the absorption of light or thermal energy or by solvation. 3. In psychology, a defense mechanism in which a group of mental processes are segregated from the rest of a person's mental activity in order to avoid emotional distress, as in the dissociative disorders (q.v.), or in which an idea or object is segregated from its emotional significance; in the first sense it is roughly equivalent to splitting, in the second, to isolation. 4. A defect of mental integration in which one or more groups of mental processes become separated off from normal consciousness and, thus separated, function as a unitary whole. [EU]

Dissociative Disorders: Sudden temporary alterations in the normally integrative functions of consciousness. [NIH]

Distal: Remote; farther from any point of reference; opposed to proximal. In dentistry, used to designate a position on the dental arch farther from the median line of the jaw. [EU]

Diuretic: A drug that increases the production of urine. [NIH]

Dopamine: An endogenous catecholamine and prominent neurotransmitter in several systems of the brain. In the synthesis of catecholamines from tyrosine, it is the immediate precursor to norepinephrine and epinephrine. Dopamine is a major transmitter in the extrapyramidal system of the brain, and important in regulating movement. A family of dopaminergic receptor subtypes mediate its action. Dopamine is used pharmacologically for its direct (beta adrenergic agonist) and indirect (adrenergic releasing) sympathomimetic effects including its actions as an inotropic agent and as a renal vasodilator. [NIH]

Dose-limiting: Describes side effects of a drug or other treatment that are serious enough to prevent an increase in dose or level of that treatment. [NIH]

Double-blinded: A clinical trial in which neither the medical staff nor the person knows which of several possible therapies the person is receiving. [NIH]

Drive: A state of internal activity of an organism that is a necessary condition before a given stimulus will elicit a class of responses; e.g., a certain level of hunger (drive) must be present before food will elicit an eating response. [NIH]

Drug Design: The molecular designing of drugs for specific purposes (such as DNA-binding, enzyme inhibition, anti-cancer efficacy, etc.) based on knowledge of molecular properties such as activity of functional groups, molecular geometry, and electronic structure, and also on information cataloged on analogous molecules. Drug design is generally computer-assisted molecular modeling and does not include pharmacokinetics, dosage analysis, or drug administration analysis. [NIH]

Drug Interactions: The action of a drug that may affect the activity, metabolism, or toxicity of another drug. [NIH]

Drug Resistance: Diminished or failed response of an organism, disease or tissue to the intended effectiveness of a chemical or drug. It should be differentiated from drug tolerance which is the progressive diminution of the susceptibility of a human or animal to the effects of a drug, as a result of continued administration. [NIH]

Drug Tolerance: Progressive diminution of the susceptibility of a human or animal to the effects of a drug, resulting from its continued administration. It should be differentiated from drug resistance wherein an organism, disease, or tissue fails to respond to the intended effectiveness of a chemical or drug. It should also be differentiated from maximum tolerated dose and no-observed-adverse-effect level. [NIH]

Duct: A tube through which body fluids pass. [NIH]

Duke: A lamp which produces ultraviolet radiations for certain ophthalmologic therapy. [NIH]

Duodenum: The first part of the small intestine. [NIH]

Dysplasia: Cells that look abnormal under a microscope but are not cancer. [NIH]

Dystrophic: Pertaining to toxic habitats low in nutrients. [NIH]

Dystrophy: Any disorder arising from defective or faulty nutrition, especially the muscular dystrophies. [EU]

Echocardiography: Ultrasonic recording of the size, motion, and composition of the heart and surrounding tissues. The standard approach is transthoracic. [NIH]

Ectopic: Pertaining to or characterized by ectopia. [EU]

Edema: Excessive amount of watery fluid accumulated in the intercellular spaces, most commonly present in subcutaneous tissue. [NIH]

Effector: It is often an enzyme that converts an inactive precursor molecule into an active second messenger. [NIH]

Efficacy: The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions. Ideally, the determination of efficacy is based on the results of a randomized control trial. [NIH]

Elastin: The protein that gives flexibility to tissues. [NIH]

Electrocardiogram: Measurement of electrical activity during heartbeats. [NIH]

Electrocoagulation: Electrosurgical procedures used to treat hemorrhage (e.g., bleeding ulcers) and to ablate tumors, mucosal lesions, and refractory arrhythmias. [NIH]

Electrolysis: Destruction by passage of a galvanic electric current, as in disintegration of a chemical compound in solution. [NIH]

Electrolyte: A substance that dissociates into ions when fused or in solution, and thus becomes capable of conducting electricity; an ionic solute. [EU]

Electrons: Stable elementary particles having the smallest known negative charge, present in all elements; also called negatrons. Positively charged electrons are called positrons. The numbers, energies and arrangement of electrons around atomic nuclei determine the chemical identities of elements. Beams of electrons are called cathode rays or beta rays, the latter being a high-energy biproduct of nuclear decay. [NIH]

Electrophoresis: An electrochemical process in which macromolecules or colloidal particles with a net electric charge migrate in a solution under the influence of an electric current. [NIH]

Elementary Particles: Individual components of atoms, usually subatomic; subnuclear particles are usually detected only when the atomic nucleus decays and then only transiently, as most of them are unstable, often yielding pure energy without substance, i.e., radiation. [NIH]

Emboli: Bit of foreign matter which enters the blood stream at one point and is carried until it is lodged or impacted in an artery and obstructs it. It may be a blood clot, an air bubble, fat or other tissue, or clumps of bacteria. [NIH]

Embolism: Blocking of a blood vessel by a blood clot or foreign matter that has been transported from a distant site by the blood stream. [NIH]

Embolization: The blocking of an artery by a clot or foreign material. Embolization can be done as treatment to block the flow of blood to a tumor. [NIH]

Embolus: Bit of foreign matter which enters the blood stream at one point and is carried until it is lodged or impacted in an artery and obstructs it. It may be a blood clot, an air bubble, fat or other tissue, or clumps of bacteria. [NIH]

Embryo: The prenatal stage of mammalian development characterized by rapid morphological changes and the differentiation of basic structures. [NIH]

Emulsions: Colloids of two immiscible liquids where either phase may be either fatty or aqueous; lipid-in-water emulsions are usually liquid, like milk or lotion and water-in-lipid emulsions tend to be creams. [NIH]

Enamel: A very hard whitish substance which covers the dentine of the anatomical crown of a tooth. [NIH]

Endemic: Present or usually prevalent in a population or geographical area at all times; said of a disease or agent. Called also endemial. [EU]

Endocarditis: Exudative and proliferative inflammatory alterations of the endocardium, characterized by the presence of vegetations on the surface of the endocardium or in the endocardium itself, and most commonly involving a heart valve, but sometimes affecting the inner lining of the cardiac chambers or the endocardium elsewhere. It may occur as a primary disorder or as a complication of or in association with another disease. [EU]

Endometriosis: A condition in which tissue more or less perfectly resembling the uterine mucous membrane (the endometrium) and containing typical endometrial granular and stromal elements occurs aberrantly in various locations in the pelvic cavity. [NIH]

Endothelial cell: The main type of cell found in the inside lining of blood vessels, lymph vessels, and the heart. [NIH]

Endothelium: A layer of epithelium that lines the heart, blood vessels (endothelium, vascular), lymph vessels (endothelium, lymphatic), and the serous cavities of the body. [NIH]

Endothelium, Lymphatic: Unbroken cellular lining (intima) of the lymph vessels (e.g., the high endothelial lymphatic venules). It is more permeable than vascular endothelium, lacking selective absorption and functioning mainly to remove plasma proteins that have filtered through the capillaries into the tissue spaces. [NIH]

Endothelium, Vascular: Single pavement layer of cells which line the luminal surface of the entire vascular system and regulate the transport of macromolecules and blood components from interstitium to lumen; this function has been most intensively studied in the blood capillaries. [NIH]

Endothelium-derived: Small molecule that diffuses to the adjacent muscle layer and relaxes it. [NIH]

Endotoxin: Toxin from cell walls of bacteria. [NIH]

End-stage renal: Total chronic kidney failure. When the kidneys fail, the body retains fluid and harmful wastes build up. A person with ESRD needs treatment to replace the work of the failed kidneys. [NIH]

Enhancer: Transcriptional element in the virus genome. [NIH]

Enucleation: Removal of the nucleus from an eucaryiotic cell. [NIH]

Environmental Exposure: The exposure to potentially harmful chemical, physical, or biological agents in the environment or to environmental factors that may include ionizing radiation, pathogenic organisms, or toxic chemicals. [NIH]

Environmental Health: The science of controlling or modifying those conditions, influences, or forces surrounding man which relate to promoting, establishing, and maintaining health. [NIH]

Enzymatic: Phase where enzyme cuts the precursor protein. [NIH]

Enzyme: A protein that speeds up chemical reactions in the body. [NIH]

Enzyme Induction: An increase in the rate of synthesis of an enzyme due to the presence of

an inducer which acts to derepress the gene responsible for enzyme synthesis. [NIH]

Enzyme Inhibitors: Compounds or agents that combine with an enzyme in such a manner as to prevent the normal substrate-enzyme combination and the catalytic reaction. [NIH]

Enzyme Repression: The interference in synthesis of an enzyme due to the elevated level of an effector substance, usually a metabolite, whose presence would cause depression of the gene responsible for enzyme synthesis. [NIH]

Eosinophils: Granular leukocytes with a nucleus that usually has two lobes connected by a slender thread of chromatin, and cytoplasm containing coarse, round granules that are uniform in size and stainable by eosin. [NIH]

Epidemic: Occurring suddenly in numbers clearly in excess of normal expectancy; said especially of infectious diseases but applied also to any disease, injury, or other health-related event occurring in such outbreaks. [EU]

Epidemiological: Relating to, or involving epidemiology. [EU]

Epidermal: Pertaining to or resembling epidermis. Called also epidermic or epidermoid. [EU]

Epidermis: Nonvascular layer of the skin. It is made up, from within outward, of five layers: 1) basal layer (stratum basale epidermidis); 2) spinous layer (stratum spinosum epidermidis); 3) granular layer (stratum granulosum epidermidis); 4) clear layer (stratum lucidum epidermidis); and 5) horny layer (stratum corneum epidermidis). [NIH]

Epidermolysis Bullosa: Group of genetically determined disorders characterized by the blistering of skin and mucosae. There are four major forms: acquired, simple, junctional, and dystrophic. Each of the latter three has several varieties. [NIH]

Epidermolysis Bullosa Simplex: Form of epidermolysis bullosa characterized by autosomal dominant inheritance and by serous bullae that heal without scarring. [NIH]

Epigastric: Having to do with the upper middle area of the abdomen. [NIH]

Epinephrine: The active sympathomimetic hormone from the adrenal medulla in most species. It stimulates both the alpha- and beta- adrenergic systems, causes systemic vasoconstriction and gastrointestinal relaxation, stimulates the heart, and dilates bronchi and cerebral vessels. It is used in asthma and cardiac failure and to delay absorption of local anesthetics. [NIH]

Epiphyseal: Pertaining to or of the nature of an epiphysis. [EU]

Epiphyses: The head of a long bone that is separated from the shaft by the epiphyseal plate until bone growth stops. At that time, the plate disappears and the head and shaft are united. [NIH]

Epithelial: Refers to the cells that line the internal and external surfaces of the body. [NIH]

Epithelial Cells: Cells that line the inner and outer surfaces of the body. [NIH]

Epithelium: One or more layers of epithelial cells, supported by the basal lamina, which covers the inner or outer surfaces of the body. [NIH]

Epitope: A molecule or portion of a molecule capable of binding to the combining site of an antibody. For every given antigenic determinant, the body can construct a variety of antibody-combining sites, some of which fit almost perfectly, and others which barely fit. [NIH]

Erectile: The inability to get or maintain an erection for satisfactory sexual intercourse. Also called impotence. [NIH]

Erection: The condition of being made rigid and elevated; as erectile tissue when filled with blood. [EU]

ERV: The expiratory reserve volume is the largest volume of gas that can be expired from the end-expiratory level. [NIH]

Erythroblasts: Immature, nucleated erythrocytes occupying the stage of erythropoiesis that follows formation of erythroid progenitor cells and precedes formation of reticulocytes. Popularly called normoblasts. [NIH]

Erythrocyte Deformability: Ability of erythrocytes to change shape as they pass through narrow spaces, such as the microvasculature. [NIH]

Erythrocyte Indices: Quantification of size and cell hemoglobin content or concentration of the erythrocyte, usually derived from erythrocyte count, blood hemoglobin concentration, and hematocrit. Includes the mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC). Use also for cell diameter and thickness. [NIH]

Erythrocyte Membrane: The semipermeable outer portion of the red corpuscle. It is known as a 'ghost' after hemolysis. [NIH]

Erythrocyte Volume: Volume of circulating erythrocytes. It is usually measured by radioisotope dilution technique. [NIH]

Erythrocytes: Red blood cells. Mature erythrocytes are non-nucleated, biconcave disks containing hemoglobin whose function is to transport oxygen. [NIH]

Erythroid Progenitor Cells: Committed, erythroid stem cells derived from myeloid stem cells. The progenitor cells develop in two phases: erythroid burst-forming units (BFU-E) followed by erythroid colony-forming units (CFU-E). BFU-E differentiate into CFU-E on stimulation by erythropoietin, and then further differentiate into erythroblasts when stimulated by other factors. [NIH]

Erythropoiesis: The production of erythrocytes. [EU]

Erythropoietin: Glycoprotein hormone, secreted chiefly by the kidney in the adult and the liver in the fetus, that acts on erythroid stem cells of the bone marrow to stimulate proliferation and differentiation. [NIH]

Esophagus: The muscular tube through which food passes from the throat to the stomach. [NIH]

Essential Tremor: A rhythmic, involuntary, purposeless, oscillating movement resulting from the alternate contraction and relaxation of opposing groups of muscles. [NIH]

Ethacrynic Acid: A compound that inhibits symport of sodium, potassium, and chloride primarily in the ascending limb of Henle, but also in the proximal and distal tubules. This pharmacological action results in excretion of these ions, increased urinary output, and reduction in extracelluar fluid. This compound has been classified as a loop or high ceiling diuretic. [NIH]

Euchromatin: Chromosome regions that are loosely packaged and more accessible to RNA polymerases than heterochromatin. These regions also stain differentially in chromosome banding preparations. [NIH]

Eukaryotic Cells: Cells of the higher organisms, containing a true nucleus bounded by a nuclear membrane. [NIH]

Eustachian tube: The middle ear cavity is in communication with the back of the nose through the Eustachian tube, which is normally closed, but opens on swallowing, in order to maintain equal air pressure. [NIH]

Evacuation: An emptying, as of the bowels. [EU]

Evoke: The electric response recorded from the cerebral cortex after stimulation of a peripheral sense organ. [NIH]

Excitatory: When cortical neurons are excited, their output increases and each new input they receive while they are still excited raises their output markedly. [NIH]

Excitatory Amino Acids: Endogenous amino acids released by neurons as excitatory neurotransmitters. Glutamic acid is the most common excitatory neurotransmitter in the brain. Aspartic acid has been regarded as an excitatory transmitter for many years, but the extent of its role as a transmitter is unclear. [NIH]

Excrete: To get rid of waste from the body. [NIH]

Exercise Test: Controlled physical activity, more strenuous than at rest, which is performed in order to allow assessment of physiological functions, particularly cardiovascular and pulmonary, but also aerobic capacity. Maximal (most intense) exercise is usually required but submaximal exercise is also used. The intensity of exercise is often graded, using criteria such as rate of work done, oxygen consumption, and heart rate. Physiological data obtained from an exercise test may be used for diagnosis, prognosis, and evaluation of disease severity, and to evaluate therapy. Data may also be used in prescribing exercise by determining a person's exercise capacity. [NIH]

Exercise Tolerance: The exercise capacity of an individual as measured by endurance (maximal exercise duration and/or maximal attained work load) during an exercise test. [NIH]

Exhaustion: The feeling of weariness of mind and body. [NIH]

Exocrine: Secreting outwardly, via a duct. [EU]

Exogenous: Developed or originating outside the organism, as exogenous disease. [EU]

Exon: The part of the DNA that encodes the information for the actual amino acid sequence of the protein. In many eucaryotic genes, the coding sequences consist of a series of exons alternating with intron sequences. [NIH]

Expiratory: The volume of air which leaves the breathing organs in each expiration. [NIH]

Expiratory Reserve Volume: The extra volume of air that can be expired with maximum effort beyond the level reached at the end of a normal, quiet expiration. Common abbreviation is ERV. [NIH]

External-beam radiation: Radiation therapy that uses a machine to aim high-energy rays at the cancer. Also called external radiation. [NIH]

Extracellular: Outside a cell or cells. [EU]

Extracellular Matrix: A meshwork-like substance found within the extracellular space and in association with the basement membrane of the cell surface. It promotes cellular proliferation and provides a supporting structure to which cells or cell lysates in culture dishes adhere. [NIH]

Extracellular Matrix Proteins: Macromolecular organic compounds that contain carbon, hydrogen, oxygen, nitrogen, and usually, sulfur. These macromolecules (proteins) form an intricate meshwork in which cells are embedded to construct tissues. Variations in the relative types of macromolecules and their organization determine the type of extracellular matrix, each adapted to the functional requirements of the tissue. The two main classes of macromolecules that form the extracellular matrix are: glycosaminoglycans, usually linked to proteins (proteoglycans), and fibrous proteins (e.g., collagen, elastin, fibronectins and laminin). [NIH]

Extracellular Space: Interstitial space between cells, occupied by fluid as well as amorphous and fibrous substances. [NIH]

Extraction: The process or act of pulling or drawing out. [EU]

Extremity: A limb; an arm or leg (membrum); sometimes applied specifically to a hand or foot. [EU]

Family Planning: Programs or services designed to assist the family in controlling reproduction by either improving or diminishing fertility. [NIH]

Fat: Total lipids including phospholipids. [NIH]

Fatty acids: A major component of fats that are used by the body for energy and tissue development. [NIH]

Febrile: Pertaining to or characterized by fever. [EU]

Feces: The excrement discharged from the intestines, consisting of bacteria, cells exfoliated from the intestines, secretions, chiefly of the liver, and a small amount of food residue. [EU]

Femoral: Pertaining to the femur, or to the thigh. [EU]

Femur: The longest and largest bone of the skeleton, it is situated between the hip and the knee. [NIH]

Fermentation: An enzyme-induced chemical change in organic compounds that takes place in the absence of oxygen. The change usually results in the production of ethanol or lactic acid, and the production of energy. [NIH]

Ferritin: An iron-containing protein complex that is formed by a combination of ferric iron with the protein apoferritin. [NIH]

Fetal Development: Morphologic and physiologic growth and development of the mammalian embryo or fetus. [NIH]

Fetal Hemoglobin: The major component of hemoglobin in the fetus. This hemoglobin has two alpha and two gamma polypeptide subunits in comparison to normal adult hemoglobin, which has two alpha and two beta polypeptide subunits. Fetal hemoglobin concentrations can be elevated (usually above 0.5%) in children and adults affected by leukemia and several types of anemia. [NIH]

Fetus: The developing offspring from 7 to 8 weeks after conception until birth. [NIH]

Fever of Unknown Origin: Fever in which the etiology cannot be ascertained. [NIH]

Fibril: Most bacterial viruses have a hollow tail with specialized fibrils at its tip. The tail fibers attach to the cell wall of the host. [NIH]

Fibrin: A protein derived from fibrinogen in the presence of thrombin, which forms part of the blood clot. [NIH]

Fibrinogen: Plasma glycoprotein clotted by thrombin, composed of a dimer of three non-identical pairs of polypeptide chains (alpha, beta, gamma) held together by disulfide bonds. Fibrinogen clotting is a sol-gel change involving complex molecular arrangements: whereas fibrinogen is cleaved by thrombin to form polypeptides A and B, the proteolytic action of other enzymes yields different fibrinogen degradation products. [NIH]

Fibrinolysis: The natural enzymatic dissolution of fibrin. [NIH]

Fibrinolytic: Pertaining to, characterized by, or causing the dissolution of fibrin by enzymatic action [EU]

Fibronectin: An adhesive glycoprotein. One form circulates in plasma, acting as an opsonin; another is a cell-surface protein which mediates cellular adhesive interactions. [NIH]

Fibrosis: Any pathological condition where fibrous connective tissue invades any organ, usually as a consequence of inflammation or other injury. [NIH]

Fistula: Abnormal communication most commonly seen between two internal organs, or between an internal organ and the surface of the body. [NIH]

Flatus: Gas passed through the rectum. [NIH]

Fludarabine: An anticancer drug that belongs to the family of drugs called antimetabolites. [NIH]

Fluorescence: The property of emitting radiation while being irradiated. The radiation emitted is usually of longer wavelength than that incident or absorbed, e.g., a substance can be irradiated with invisible radiation and emit visible light. X-ray fluorescence is used in diagnosis. [NIH]

Fluorouracil: A pyrimidine analog that acts as an antineoplastic antimetabolite and also has immunosuppressant. It interferes with DNA synthesis by blocking the thymidylate synthetase conversion of deoxyuridylic acid to thymidylic acid. [NIH]

Folate: A B-complex vitamin that is being studied as a cancer prevention agent. Also called folic acid. [NIH]

Fold: A plication or doubling of various parts of the body. [NIH]

Folic Acid: N-(4-(((2-Amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl)amino)benzoyl)-L-glutamic acid. A member of the vitamin B family that stimulates the hematopoietic system. It is present in the liver and kidney and is found in mushrooms, spinach, yeast, green leaves, and grasses. Folic acid is used in the treatment and prevention of folate deficiencies and megaloblastic anemia. [NIH]

Forearm: The part between the elbow and the wrist. [NIH]

Fructose: A type of sugar found in many fruits and vegetables and in honey. Fructose is used to sweeten some diet foods. It is considered a nutritive sweetener because it has calories. [NIH]

Fungus: A general term used to denote a group of eukaryotic protists, including mushrooms, yeasts, rusts, moulds, smuts, etc., which are characterized by the absence of chlorophyll and by the presence of a rigid cell wall composed of chitin, mannans, and sometimes cellulose. They are usually of simple morphological form or show some reversible cellular specialization, such as the formation of pseudoparenchymatous tissue in the fruiting body of a mushroom. The dimorphic fungi grow, according to environmental conditions, as moulds or yeasts. [EU]

Gallbladder: The pear-shaped organ that sits below the liver. Bile is concentrated and stored in the gallbladder. [NIH]

Gallstones: The solid masses or stones made of cholesterol or bilirubin that form in the gallbladder or bile ducts. [NIH]

Gamma Rays: Very powerful and penetrating, high-energy electromagnetic radiation of shorter wavelength than that of x-rays. They are emitted by a decaying nucleus, usually between 0.01 and 10 MeV. They are also called nuclear x-rays. [NIH]

Ganglia: Clusters of multipolar neurons surrounded by a capsule of loosely organized connective tissue located outside the central nervous system. [NIH]

Gangrene: Death and putrefaction of tissue usually due to a loss of blood supply. [NIH]

Gas: Air that comes from normal breakdown of food. The gases are passed out of the body through the rectum (flatus) or the mouth (burp). [NIH]

Gas exchange: Primary function of the lungs; transfer of oxygen from inhaled air into the blood and of carbon dioxide from the blood into the lungs. [NIH]

Gastrin: A hormone released after eating. Gastrin causes the stomach to produce more acid. [NIH]

Gastritis: Inflammation of the stomach. [EU]

Gastroenteritis: An acute inflammation of the lining of the stomach and intestines, characterized by anorexia, nausea, diarrhoea, abdominal pain, and weakness, which has various causes, including food poisoning due to infection with such organisms as Escherichia coli, Staphylococcus aureus, and Salmonella species; consumption of irritating food or drink; or psychological factors such as anger, stress, and fear. Called also enterogastritis. [EU]

Gastrointestinal: Refers to the stomach and intestines. [NIH]

Gelatin: A product formed from skin, white connective tissue, or bone collagen. It is used as a protein food adjuvant, plasma substitute, hemostatic, suspending agent in pharmaceutical preparations, and in the manufacturing of capsules and suppositories. [NIH]

Gels: Colloids with a solid continuous phase and liquid as the dispersed phase; gels may be unstable when, due to temperature or other cause, the solid phase liquifies; the resulting colloid is called a sol. [NIH]

Gene: The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein. [NIH]

Gene Expression: The phenotypic manifestation of a gene or genes by the processes of gene action. [NIH]

Gene Silencing: Interruption or suppression of the expression of a gene at transcriptional or translational levels. [NIH]

Genetic Code: The specifications for how information, stored in nucleic acid sequence (base sequence), is translated into protein sequence (amino acid sequence). The start, stop, and order of amino acids of a protein is specified by consecutive triplets of nucleotides called codons (codon). [NIH]

Genetic Counseling: Advising families of the risks involved pertaining to birth defects, in order that they may make an informed decision on current or future pregnancies. [NIH]

Genetic Engineering: Directed modification of the gene complement of a living organism by such techniques as altering the DNA, substituting genetic material by means of a virus, transplanting whole nuclei, transplanting cell hybrids, etc. [NIH]

Genetic testing: Analyzing DNA to look for a genetic alteration that may indicate an increased risk for developing a specific disease or disorder. [NIH]

Genetics: The biological science that deals with the phenomena and mechanisms of heredity. [NIH]

Genital: Pertaining to the genitalia. [EU]

Genitourinary: Pertaining to the genital and urinary organs; urogenital; urinosexual. [EU]

Genomics: The systematic study of the complete DNA sequences (genome) of organisms. [NIH]

Genotype: The genetic constitution of the individual; the characterization of the genes. [NIH]

Germ Cells: The reproductive cells in multicellular organisms. [NIH]

Gestation: The period of development of the young in viviparous animals, from the time of fertilization of the ovum until birth. [EU]

Gland: An organ that produces and releases one or more substances for use in the body. Some glands produce fluids that affect tissues or organs. Others produce hormones or participate in blood production. [NIH]

Globins: The protein constituents of hemoglobin.The term is used for proteins attached to iron-porphyrin molecules such as hemoglobin and myoglobin proteins. [NIH]

Glomerular: Pertaining to or of the nature of a glomerulus, especially a renal glomerulus. [EU]

Glomerular Filtration Rate: The volume of water filtered out of plasma through glomerular capillary walls into Bowman's capsules per unit of time. It is considered to be equivalent to inulin clearance. [NIH]

Glomeruli: Plural of glomerulus. [NIH]

Glomerulosclerosis: Scarring of the glomeruli. It may result from diabetes mellitus (diabetic glomerulosclerosis) or from deposits in parts of the glomerulus (focal segmental glomerulosclerosis). The most common signs of glomerulosclerosis are proteinuria and kidney failure. [NIH]

Glomerulus: A tiny set of looping blood vessels in the nephron where blood is filtered in the kidney. [NIH]

Glucose: D-Glucose. A primary source of energy for living organisms. It is naturally occurring and is found in fruits and other parts of plants in its free state. It is used therapeutically in fluid and nutrient replacement. [NIH]

Glucose Intolerance: A pathological state in which the fasting plasma glucose level is less than 140 mg per deciliter and the 30-, 60-, or 90-minute plasma glucose concentration following a glucose tolerance test exceeds 200 mg per deciliter. This condition is seen frequently in diabetes mellitus but also occurs with other diseases. [NIH]

Glucuronosyltransferase: A family of enzymes accepting a wide range of substrates, including phenols, alcohols, amines, and fatty acids. They function as drug-metabolizing enzymes that catalyze the conjugation of UDPglucuronic acid to a variety of endogenous and exogenous compounds. EC 2.4.1.17. [NIH]

Glutamate: Excitatory neurotransmitter of the brain. [NIH]

Glutamic Acid: A non-essential amino acid naturally occurring in the L-form. Glutamic acid (glutamate) is the most common excitatory neurotransmitter in the central nervous system. [NIH]

Glutamine: A non-essential amino acid present abundantly throught the body and is involved in many metabolic processes. It is synthesized from glutamic acid and ammonia. It is the principal carrier of nitrogen in the body and is an important energy source for many cells. [NIH]

Glutathione Peroxidase: An enzyme catalyzing the oxidation of 2 moles of glutathione in the presence of hydrogen peroxide to yield oxidized glutathione and water. EC 1.11.1.9. [NIH]

Glycerol: A trihydroxy sugar alcohol that is an intermediate in carbohydrate and lipid metabolism. It is used as a solvent, emollient, pharmaceutical agent, and sweetening agent. [NIH]

Glycerophospholipids: Derivatives of phosphatidic acid in which the hydrophobic regions are composed of two fatty acids and a polar alcohol is joined to the C-3 position of glycerol through a phosphodiester bond. They are named according to their polar head groups, such as phosphatidylcholine and phosphatidylethanolamine. [NIH]

Glycine: A non-essential amino acid. It is found primarily in gelatin and silk fibroin and used therapeutically as a nutrient. It is also a fast inhibitory neurotransmitter. [NIH]

Glycols: A generic grouping for dihydric alcohols with the hydroxy groups (-OH) located on different carbon atoms. They are viscous liquids with high boiling points for their molecular weights. [NIH]

Glycoprotein: A protein that has sugar molecules attached to it. [NIH]

Glycosaminoglycans: Heteropolysaccharides which contain an N-acetylated hexosamine in a characteristic repeating disaccharide unit. The repeating structure of each disaccharide involves alternate 1,4- and 1,3-linkages consisting of either N-acetylglucosamine or N-acetylgalactosamine. [NIH]

Gonad: A sex organ, such as an ovary or a testicle, which produces the gametes in most multicellular animals. [NIH]

Gonadal: Pertaining to a gonad. [EU]

Gout: Hereditary metabolic disorder characterized by recurrent acute arthritis, hyperuricemia and deposition of sodium urate in and around the joints, sometimes with formation of uric acid calculi. [NIH]

Governing Board: The group in which legal authority is vested for the control of health-related institutions and organizations. [NIH]

Grade: The grade of a tumor depends on how abnormal the cancer cells look under a microscope and how quickly the tumor is likely to grow and spread. Grading systems are different for each type of cancer. [NIH]

Graft: Healthy skin, bone, or other tissue taken from one part of the body and used to replace diseased or injured tissue removed from another part of the body. [NIH]

Graft vs Host Disease: The clinical entity characterized by anorexia, diarrhea, loss of hair, leukopenia, thrombocytopenia, growth retardation, and eventual death brought about by the graft vs host reaction. [NIH]

Graft vs Host Reaction: An immunological attack mounted by a graft against the host because of tissue incompatibility when immunologically competent cells are transplanted to an immunologically incompetent host; the resulting clinical picture is that of graft vs host disease. [NIH]

Grafting: The operation of transfer of tissue from one site to another. [NIH]

Graft-versus-host disease: GVHD. A reaction of donated bone marrow or peripheral stem cells against a person's tissue. [NIH]

Gram-negative: Losing the stain or decolorized by alcohol in Gram's method of staining, a primary characteristic of bacteria having a cell wall composed of a thin layer of peptidoglycan covered by an outer membrane of lipoprotein and lipopolysaccharide. [EU]

Granulocytes: Leukocytes with abundant granules in the cytoplasm. They are divided into three groups: neutrophils, eosinophils, and basophils. [NIH]

Grasses: A large family, Gramineae, of narrow-leaved herbaceous monocots. Many grasses produce highly allergenic pollens and are hosts to cattle parasites and toxic fungi. [NIH]

Growth: The progressive development of a living being or part of an organism from its earliest stage to maturity. [NIH]

Growth factors: Substances made by the body that function to regulate cell division and cell survival. Some growth factors are also produced in the laboratory and used in biological therapy. [NIH]

Guanylate Cyclase: An enzyme that catalyzes the conversion of GTP to 3',5'-cyclic GMP and pyrophosphate. It also acts on ITP and dGTP. (From Enzyme Nomenclature, 1992) EC 4.6.1.2. [NIH]

Half-Life: The time it takes for a substance (drug, radioactive nuclide, or other) to lose half of its pharmacologic, physiologic, or radiologic activity. [NIH]

Hand, Foot and Mouth Disease: A mild, highly infectious viral disease of children, characterized by vesicular lesions in the mouth and on the hands and feet. It is caused by

coxsackieviruses A. [NIH]

Haplotypes: The genetic constitution of individuals with respect to one member of a pair of allelic genes, or sets of genes that are closely linked and tend to be inherited together such as those of the major histocompatibility complex. [NIH]

Haptens: Small antigenic determinants capable of eliciting an immune response only when coupled to a carrier. Haptens bind to antibodies but by themselves cannot elicit an antibody response. [NIH]

Headache: Pain in the cranial region that may occur as an isolated and benign symptom or as a manifestation of a wide variety of conditions including subarachnoid hemorrhage; craniocerebral trauma; central nervous system infections; intracranial hypertension; and other disorders. In general, recurrent headaches that are not associated with a primary disease process are referred to as headache disorders (e.g., migraine). [NIH]

Health Services: Services for the diagnosis and treatment of disease and the maintenance of health. [NIH]

Hearing Disorders: Conditions that impair the transmission or perception of auditory impulses and information from the level of the ear to the temporal cortices, including the sensorineural pathways. [NIH]

Hearing Loss, Conductive: Hearing loss due to interference with the acoustic transmission of sound to the cochlea. The interference is in the outer or middle ear. [NIH]

Heart attack: A seizure of weak or abnormal functioning of the heart. [NIH]

Heart Catheterization: Procedure which includes placement of catheter, recording of intracardiac and intravascular pressure, obtaining blood samples for chemical analysis, and cardiac output measurement, etc. Specific angiographic injection techniques are also involved. [NIH]

Hematocrit: Measurement of the volume of packed red cells in a blood specimen by centrifugation. The procedure is performed using a tube with graduated markings or with automated blood cell counters. It is used as an indicator of erythrocyte status in disease. For example, anemia shows a low hematocrit, polycythemia, high values. [NIH]

Hematologist: A doctor who specializes in treating diseases of the blood. [NIH]

Hematology: A subspecialty of internal medicine concerned with morphology, physiology, and pathology of the blood and blood-forming tissues. [NIH]

Hematopoiesis: The development and formation of various types of blood cells. [NIH]

Hematopoietic growth factors: A group of proteins that cause blood cells to grow and mature. [NIH]

Hematopoietic Stem Cell Transplantation: The transference of stem cells from one animal or human to another (allogeneic), or within the same individual (autologous). The source for the stem cells may be the bone marrow or peripheral blood. Stem cell transplantation has been used as an alternative to autologous bone marrow transplantation in the treatment of a variety of neoplasms. [NIH]

Hematopoietic Stem Cells: Progenitor cells from which all blood cells derive. [NIH]

Heme: The color-furnishing portion of hemoglobin. It is found free in tissues and as the prosthetic group in many hemeproteins. [NIH]

Hemiparesis: The weakness or paralysis affecting one side of the body. [NIH]

Hemiplegia: Severe or complete loss of motor function on one side of the body. This condition is usually caused by BRAIN DISEASES that are localized to the cerebral hemisphere opposite to the side of weakness. Less frequently, BRAIN STEM lesions; cervical

spinal cord diseases; peripheral nervous system diseases; and other conditions may manifest as hemiplegia. The term hemiparesis (see paresis) refers to mild to moderate weakness involving one side of the body. [NIH]

Hemochromatosis: A disease that occurs when the body absorbs too much iron. The body stores the excess iron in the liver, pancreas, and other organs. May cause cirrhosis of the liver. Also called iron overload disease. [NIH]

Hemodialysis: The use of a machine to clean wastes from the blood after the kidneys have failed. The blood travels through tubes to a dialyzer, which removes wastes and extra fluid. The cleaned blood then flows through another set of tubes back into the body. [NIH]

Hemodilution: Reduction of blood viscosity usually by the addition of cell free solutions. Used clinically l) in states of impaired microcirculation, 2) for replacement of intraoperative blood loss without homologous blood transfusion, and 3) in cardiopulmonary bypass and hypothermia. [NIH]

Hemodynamics: The movements of the blood and the forces involved in systemic or regional blood circulation. [NIH]

Hemoglobin: One of the fractions of glycosylated hemoglobin A1c. Glycosylated hemoglobin is formed when linkages of glucose and related monosaccharides bind to hemoglobin A and its concentration represents the average blood glucose level over the previous several weeks. HbA1c levels are used as a measure of long-term control of plasma glucose (normal, 4 to 6 percent). In controlled diabetes mellitus, the concentration of glycosylated hemoglobin A is within the normal range, but in uncontrolled cases the level may be 3 to 4 times the normal conentration. Generally, complications are substantially lower among patients with Hb levels of 7 percent or less than in patients with HbA1c levels of 9 percent or more. [NIH]

Hemoglobin A: Normal adult human hemoglobin. The globin moiety consists of two alpha and two beta chains. [NIH]

Hemoglobin C: A commonly occurring abnormal hemoglobin in which lysine replaces a glutamic acid residue at the sixth position of the beta chains. It results in reduced plasticity of erythrocytes. [NIH]

Hemoglobin E: An abnormal hemoglobin that results from the substitution of lysine for glutamic acid at position 26 of the beta chain. It is most frequently observed in southeast Asian populations. [NIH]

Hemoglobin H: An abnormal hemoglobin composed of four beta chains. It is caused by the reduced synthesis of the alpha chain. This abnormality results in alpha-thalassemia. [NIH]

Hemoglobin M: A group of abnormal hemoglobins in which amino acid substitutions take place in either the alpha or beta chains but near the heme iron. This results in facilitated oxidation of the hemoglobin to yield excess methemoglobin which leads to cyanosis. [NIH]

Hemoglobinopathies: A group of inherited disorders characterized by structural alterations within the hemoglobin molecule. [NIH]

Hemoglobinuria: The presence of free hemoglobin in the urine. [NIH]

Hemolysis: The destruction of erythrocytes by many different causal agents such as antibodies, bacteria, chemicals, temperature, and changes in tonicity. [NIH]

Hemolytic: A disease that affects the blood and blood vessels. It destroys red blood cells, cells that cause the blood to clot, and the lining of blood vessels. HUS is often caused by the Escherichia coli bacterium in contaminated food. People with HUS may develop acute renal failure. [NIH]

Hemorrhage: Bleeding or escape of blood from a vessel. [NIH]

Hemosiderin: Molecule which can bind large numbers of iron atoms. [NIH]

Hemosiderosis: Conditions in which there is a generalized increase in the iron stores of body tissues, particularly of liver and the reticuloendothelial system, without demonstrable tissue damage. The name refers to the presence of stainable iron in the tissue in the form of hemosiderin. [NIH]

Hemostasis: The process which spontaneously arrests the flow of blood from vessels carrying blood under pressure. It is accomplished by contraction of the vessels, adhesion and aggregation of formed blood elements, and the process of blood or plasma coagulation. [NIH]

Hepatic: Refers to the liver. [NIH]

Hepatic Vein Thrombosis: Occlusion of the hepatic veins caused by thrombi or fibrous obliteration of the veins. [NIH]

Hepatic Veins: Veins which drain the liver. [NIH]

Hepatitis: Inflammation of the liver and liver disease involving degenerative or necrotic alterations of hepatocytes. [NIH]

Hepatocyte: A liver cell. [NIH]

Hepatomegaly: Enlargement of the liver. [NIH]

Hereditary: Of, relating to, or denoting factors that can be transmitted genetically from one generation to another. [NIH]

Heredity: 1. The genetic transmission of a particular quality or trait from parent to offspring. 2. The genetic constitution of an individual. [EU]

Heritability: The proportion of observed variation in a particular trait that can be attributed to inherited genetic factors in contrast to environmental ones. [NIH]

Herpes: Any inflammatory skin disease caused by a herpesvirus and characterized by the formation of clusters of small vesicles. When used alone, the term may refer to herpes simplex or to herpes zoster. [EU]

Herpes Zoster: Acute vesicular inflammation. [NIH]

Hesperidin: Predominant flavonoid in lemons and sweet oranges. [NIH]

Heterochromatin: The portion of chromosome material that remains condensed and is transcriptionally inactive during interphase. [NIH]

Heterodimer: Zippered pair of nonidentical proteins. [NIH]

Heterogeneity: The property of one or more samples or populations which implies that they are not identical in respect of some or all of their parameters, e. g. heterogeneity of variance. [NIH]

Heterozygotes: Having unlike alleles at one or more corresponding loci on homologous chromosomes. [NIH]

Histology: The study of tissues and cells under a microscope. [NIH]

Histone Deacetylase: Hydrolyzes N-acetyl groups on histones. [NIH]

Homeobox: Distinctive sequence of DNA bases. [NIH]

Homologous: Corresponding in structure, position, origin, etc., as (a) the feathers of a bird and the scales of a fish, (b) antigen and its specific antibody, (c) allelic chromosomes. [EU]

Homozygotes: An individual having a homozygous gene pair. [NIH]

Hormonal: Pertaining to or of the nature of a hormone. [EU]

Hormone: A substance in the body that regulates certain organs. Hormones such as gastrin

help in breaking down food. Some hormones come from cells in the stomach and small intestine. [NIH]

Host: Any animal that receives a transplanted graft. [NIH]

Humoral: Of, relating to, proceeding from, or involving a bodily humour - now often used of endocrine factors as opposed to neural or somatic. [EU]

Hybrid: Cross fertilization between two varieties or, more usually, two species of vines, see also crossing. [NIH]

Hybridization: The genetic process of crossbreeding to produce a hybrid. Hybrid nucleic acids can be formed by nucleic acid hybridization of DNA and RNA molecules. Protein hybridization allows for hybrid proteins to be formed from polypeptide chains. [NIH]

Hydration: Combining with water. [NIH]

Hydrocephalus: Excessive accumulation of cerebrospinal fluid within the cranium which may be associated with dilation of cerebral ventricles, intracranial hypertension; headache; lethargy; urinary incontinence; and ataxia (and in infants macrocephaly). This condition may be caused by obstruction of cerebrospinal fluid pathways due to neurologic abnormalities, intracranial hemorrhages; central nervous system infections; brain neoplasms; craniocerebral trauma; and other conditions. Impaired resorption of cerebrospinal fluid from the arachnoid villi results in a communicating form of hydrocephalus. Hydrocephalus ex-vacuo refers to ventricular dilation that occurs as a result of brain substance loss from cerebral infarction and other conditions. [NIH]

Hydrogen: The first chemical element in the periodic table. It has the atomic symbol H, atomic number 1, and atomic weight 1. It exists, under normal conditions, as a colorless, odorless, tasteless, diatomic gas. Hydrogen ions are protons. Besides the common H1 isotope, hydrogen exists as the stable isotope deuterium and the unstable, radioactive isotope tritium. [NIH]

Hydrogen Bonding: A low-energy attractive force between hydrogen and another element. It plays a major role in determining the properties of water, proteins, and other compounds. [NIH]

Hydrogen Peroxide: A strong oxidizing agent used in aqueous solution as a ripening agent, bleach, and topical anti-infective. It is relatively unstable and solutions deteriorate over time unless stabilized by the addition of acetanilide or similar organic materials. [NIH]

Hydrolysis: The process of cleaving a chemical compound by the addition of a molecule of water. [NIH]

Hydrophobic: Not readily absorbing water, or being adversely affected by water, as a hydrophobic colloid. [EU]

Hydroxides: Inorganic compounds that contain the OH- group. [NIH]

Hydroxyl Radical: The univalent radical OH that is present in hydroxides, alcohols, phenols, glycols. [NIH]

Hydroxyurea: An antineoplastic agent that inhibits DNA synthesis through the inhibition of ribonucleoside diphosphate reductase. [NIH]

Hyperbaric: Characterized by greater than normal pressure or weight; applied to gases under greater than atmospheric pressure, as hyperbaric oxygen, or to a solution of greater specific gravity than another taken as a standard of reference. [EU]

Hyperbaric oxygen: Oxygen that is at an atmospheric pressure higher than the pressure at sea level. Breathing hyperbaric oxygen to enhance the effectiveness of radiation therapy is being studied. [NIH]

Hyperbilirubinemia: Pathologic process consisting of an abnormal increase in the amount of bilirubin in the circulating blood, which may result in jaundice. [NIH]

Hyperhomocysteinemia: An inborn error of methionone metabolism which produces an excess of homocysteine in the blood. It is often caused by a deficiency of cystathionine beta-synthase and is a risk factor for coronary vascular disease. [NIH]

Hyperkeratosis: 1. Hypertrophy of the corneous layer of the skin. 2a. Any of various conditions marked by hyperkeratosis. 2b. A disease of cattle marked by thickening and wringling of the hide and formation of papillary outgrowths on the buccal mucous membranes, often accompanied by watery discharge from eyes and nose, diarrhoea, loss of condition, and abortion of pregnant animals, and now believed to result from ingestion of the chlorinated naphthalene of various lubricating oils. [EU]

Hyperplasia: An increase in the number of cells in a tissue or organ, not due to tumor formation. It differs from hypertrophy, which is an increase in bulk without an increase in the number of cells. [NIH]

Hypersensitivity: Altered reactivity to an antigen, which can result in pathologic reactions upon subsequent exposure to that particular antigen. [NIH]

Hypertension: Persistently high arterial blood pressure. Currently accepted threshold levels are 140 mm Hg systolic and 90 mm Hg diastolic pressure. [NIH]

Hypertrophy: General increase in bulk of a part or organ, not due to tumor formation, nor to an increase in the number of cells. [NIH]

Hyperuricemia: A buildup of uric acid (a byproduct of metabolism) in the blood; a side effect of some anticancer drugs. [NIH]

Hypoglycemia: Abnormally low blood sugar [NIH]

Hypoplasia: Incomplete development or underdevelopment of an organ or tissue. [EU]

Hypotension: Abnormally low blood pressure. [NIH]

Hypothermia: Lower than normal body temperature, especially in warm-blooded animals; in man usually accidental or unintentional. [NIH]

Hypothyroidism: Deficiency of thyroid activity. In adults, it is most common in women and is characterized by decrease in basal metabolic rate, tiredness and lethargy, sensitivity to cold, and menstrual disturbances. If untreated, it progresses to full-blown myxoedema. In infants, severe hypothyroidism leads to cretinism. In juveniles, the manifestations are intermediate, with less severe mental and developmental retardation and only mild symptoms of the adult form. When due to pituitary deficiency of thyrotropin secretion it is called secondary hypothyroidism. [EU]

Hypoxia: Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood. [EU]

Id: The part of the personality structure which harbors the unconscious instinctive desires and strivings of the individual. [NIH]

Imaging procedures: Methods of producing pictures of areas inside the body. [NIH]

Imidazole: C3H4N2. The ring is present in polybenzimidazoles. [NIH]

Immune response: The activity of the immune system against foreign substances (antigens). [NIH]

Immune Sera: Serum that contains antibodies. It is obtained from an animal that has been immunized either by antigen injection or infection with microorganisms containing the antigen. [NIH]

Immune system: The organs, cells, and molecules responsible for the recognition and

disposal of foreign ("non-self") material which enters the body. [NIH]

Immunodeficiency: The decreased ability of the body to fight infection and disease. [NIH]

Immunoelectrophoresis: A technique that combines protein electrophoresis and double immunodiffusion. In this procedure proteins are first separated by gel electrophoresis (usually agarose), then made visible by immunodiffusion of specific antibodies. A distinct elliptical precipitin arc results for each protein detectable by the antisera. [NIH]

Immunofluorescence: A technique for identifying molecules present on the surfaces of cells or in tissues using a highly fluorescent substance coupled to a specific antibody. [NIH]

Immunoglobulin: A protein that acts as an antibody. [NIH]

Immunologic: The ability of the antibody-forming system to recall a previous experience with an antigen and to respond to a second exposure with the prompt production of large amounts of antibody. [NIH]

Immunology: The study of the body's immune system. [NIH]

Immunosuppressive: Describes the ability to lower immune system responses. [NIH]

Immunosuppressive Agents: Agents that suppress immune function by one of several mechanisms of action. Classical cytotoxic immunosuppressants act by inhibiting DNA synthesis. Others may act through activation of suppressor T-cell populations or by inhibiting the activation of helper cells. While immunosuppression has been brought about in the past primarily to prevent rejection of transplanted organs, new applications involving mediation of the effects of interleukins and other cytokines are emerging. [NIH]

Immunosuppressive therapy: Therapy used to decrease the body's immune response, such as drugs given to prevent transplant rejection. [NIH]

Impairment: In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [NIH]

Impetigo: A common superficial bacterial infection caused by staphylococcus aureus or group A beta-hemolytic streptococci. Characteristics include pustular lesions that rupture and discharge a thin, amber-colored fluid that dries and forms a crust. This condition is commonly located on the face, especially about the mouth and nose. [NIH]

Implant radiation: A procedure in which radioactive material sealed in needles, seeds, wires, or catheters is placed directly into or near the tumor. Also called [NIH]

Impotence: The inability to perform sexual intercourse. [NIH]

In situ: In the natural or normal place; confined to the site of origin without invasion of neighbouring tissues. [EU]

In Situ Hybridization: A technique that localizes specific nucleic acid sequences within intact chromosomes, eukaryotic cells, or bacterial cells through the use of specific nucleic acid-labeled probes. [NIH]

In vitro: In the laboratory (outside the body). The opposite of in vivo (in the body). [NIH]

In vivo: In the body. The opposite of in vitro (outside the body or in the laboratory). [NIH]

Incontinence: Inability to control the flow of urine from the bladder (urinary incontinence) or the escape of stool from the rectum (fecal incontinence). [NIH]

Incubation: The development of an infectious disease from the entrance of the pathogen to the appearance of clinical symptoms. [EU]

Incubation period: The period of time likely to elapse between exposure to the agent of the disease and the onset of clinical symptoms. [NIH]

Indicative: That indicates; that points out more or less exactly; that reveals fairly clearly. [EU]

Induction: The act or process of inducing or causing to occur, especially the production of a specific morphogenetic effect in the developing embryo through the influence of evocators or organizers, or the production of anaesthesia or unconsciousness by use of appropriate agents. [EU]

Infant, Newborn: An infant during the first month after birth. [NIH]

Infarction: A pathological process consisting of a sudden insufficient blood supply to an area, which results in necrosis of that area. It is usually caused by a thrombus, an embolus, or a vascular torsion. [NIH]

Infection: 1. Invasion and multiplication of microorganisms in body tissues, which may be clinically unapparent or result in local cellular injury due to competitive metabolism, toxins, intracellular replication, or antigen-antibody response. The infection may remain localized, subclinical, and temporary if the body's defensive mechanisms are effective. A local infection may persist and spread by extension to become an acute, subacute, or chronic clinical infection or disease state. A local infection may also become systemic when the microorganisms gain access to the lymphatic or vascular system. 2. An infectious disease. [EU]

Infectious Mononucleosis: A common, acute infection usually caused by the Epstein-Barr virus (Human herpesvirus 4). There is an increase in mononuclear white blood cells and other atypical lymphocytes, generalized lymphadenopathy, splenomegaly, and occasionally hepatomegaly with hepatitis. [NIH]

Inflammation: A pathological process characterized by injury or destruction of tissues caused by a variety of cytologic and chemical reactions. It is usually manifested by typical signs of pain, heat, redness, swelling, and loss of function. [NIH]

Infusion: A method of putting fluids, including drugs, into the bloodstream. Also called intravenous infusion. [NIH]

Ingestion: Taking into the body by mouth [NIH]

Inhalation: The drawing of air or other substances into the lungs. [EU]

Initiation: Mutation induced by a chemical reactive substance causing cell changes; being a step in a carcinogenic process. [NIH]

Inner ear: The labyrinth, comprising the vestibule, cochlea, and semicircular canals. [NIH]

Inositol: An isomer of glucose that has traditionally been considered to be a B vitamin although it has an uncertain status as a vitamin and a deficiency syndrome has not been identified in man. (From Martindale, The Extra Pharmacopoeia, 30th ed, p1379) Inositol phospholipids are important in signal transduction. [NIH]

Insight: The capacity to understand one's own motives, to be aware of one's own psychodynamics, to appreciate the meaning of symbolic behavior. [NIH]

Insulator: Material covering the metal conductor of the lead. It is usually polyurethane or silicone. [NIH]

Insulin: A protein hormone secreted by beta cells of the pancreas. Insulin plays a major role in the regulation of glucose metabolism, generally promoting the cellular utilization of glucose. It is also an important regulator of protein and lipid metabolism. Insulin is used as a drug to control insulin-dependent diabetes mellitus. [NIH]

Insulin-dependent diabetes mellitus: A disease characterized by high levels of blood glucose resulting from defects in insulin secretion, insulin action, or both. Autoimmune, genetic, and environmental factors are involved in the development of type I diabetes. [NIH]

Insulin-like: Muscular growth factor. [NIH]

Integrins: A family of transmembrane glycoproteins consisting of noncovalent heterodimers. They interact with a wide variety of ligands including extracellular matrix glycoproteins, complement, and other cells, while their intracellular domains interact with the cytoskeleton. The integrins consist of at least three identified families: the cytoadhesin receptors, the leukocyte adhesion receptors, and the very-late-antigen receptors. Each family contains a common beta-subunit combined with one or more distinct alpha-subunits. These receptors participate in cell-matrix and cell-cell adhesion in many physiologically important processes, including embryological development, hemostasis, thrombosis, wound healing, immune and nonimmune defense mechanisms, and oncogenic transformation. [NIH]

Intensive Care: Advanced and highly specialized care provided to medical or surgical patients whose conditions are life-threatening and require comprehensive care and constant monitoring. It is usually administered in specially equipped units of a health care facility. [NIH]

Intensive Care Units: Hospital units providing continuous surveillance and care to acutely ill patients. [NIH]

Intermittent: Occurring at separated intervals; having periods of cessation of activity. [EU]

Internal Medicine: A medical specialty concerned with the diagnosis and treatment of diseases of the internal organ systems of adults. [NIH]

Internal radiation: A procedure in which radioactive material sealed in needles, seeds, wires, or catheters is placed directly into or near the tumor. Also called brachytherapy, implant radiation, or interstitial radiation therapy. [NIH]

Interphase: The interval between two successive cell divisions during which the chromosomes are not individually distinguishable and DNA replication occurs. [NIH]

Interstitial: Pertaining to or situated between parts or in the interspaces of a tissue. [EU]

Intestinal: Having to do with the intestines. [NIH]

Intestines: The section of the alimentary canal from the stomach to the anus. It includes the large intestine and small intestine. [NIH]

Intracellular: Inside a cell. [NIH]

Intracellular Membranes: Membranes of subcellular structures. [NIH]

Intracranial Hemorrhages: Bleeding within the intracranial cavity, including hemorrhages in the brain and within the cranial epidural, subdural, and subarachnoid spaces. [NIH]

Intracranial Hypertension: Increased pressure within the cranial vault. This may result from several conditions, including hydrocephalus; brain edema; intracranial masses; severe systemic hypertension; pseudotumor cerebri; and other disorders. [NIH]

Intrahepatic: Within the liver. [NIH]

Intramuscular: IM. Within or into muscle. [NIH]

Intraperitoneal: IP. Within the peritoneal cavity (the area that contains the abdominal organs). [NIH]

Intravascular: Within a vessel or vessels. [EU]

Intravenous: IV. Into a vein. [NIH]

Intrinsic: Situated entirely within or pertaining exclusively to a part. [EU]

Intubation: Introduction of a tube into a hollow organ to restore or maintain patency if obstructed. It is differentiated from catheterization in that the insertion of a catheter is usually performed for the introducing or withdrawing of fluids from the body. [NIH]

Invasive: 1. Having the quality of invasiveness. 2. Involving puncture or incision of the skin

or insertion of an instrument or foreign material into the body; said of diagnostic techniques. [EU]

Involuntary: Reaction occurring without intention or volition. [NIH]

Iodine: A nonmetallic element of the halogen group that is represented by the atomic symbol I, atomic number 53, and atomic weight of 126.90. It is a nutritionally essential element, especially important in thyroid hormone synthesis. In solution, it has anti-infective properties and is used topically. [NIH]

Ion Channels: Gated, ion-selective glycoproteins that traverse membranes. The stimulus for channel gating can be a membrane potential, drug, transmitter, cytoplasmic messenger, or a mechanical deformation. Ion channels which are integral parts of ionotropic neurotransmitter receptors are not included. [NIH]

Ion Transport: The movement of ions across energy-transducing cell membranes. Transport can be active or passive. Passive ion transport (facilitated diffusion) derives its energy from the concentration gradient of the ion itself and allows the transport of a single solute in one direction (uniport). Active ion transport is usually coupled to an energy-yielding chemical or photochemical reaction such as ATP hydrolysis. This form of primary active transport is called an ion pump. Secondary active transport utilizes the voltage and ion gradients produced by the primary transport to drive the cotransport of other ions or molecules. These may be transported in the same (symport) or opposite (antiport) direction. [NIH]

Ionizing: Radiation comprising charged particles, e. g. electrons, protons, alpha-particles, etc., having sufficient kinetic energy to produce ionization by collision. [NIH]

Ions: An atom or group of atoms that have a positive or negative electric charge due to a gain (negative charge) or loss (positive charge) of one or more electrons. Atoms with a positive charge are known as cations; those with a negative charge are anions. [NIH]

Irradiation: The use of high-energy radiation from x-rays, neutrons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy) or from materials called radioisotopes. Radioisotopes produce radiation and can be placed in or near the tumor or in the area near cancer cells. This type of radiation treatment is called internal radiation therapy, implant radiation, interstitial radiation, or brachytherapy. Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. Irradiation is also called radiation therapy, radiotherapy, and x-ray therapy. [NIH]

Irrigation: The washing of a body cavity or surface by flowing solution which is inserted and then removed. Any drug in the irrigation solution may be absorbed. [NIH]

Ischemia: Deficiency of blood in a part, due to functional constriction or actual obstruction of a blood vessel. [EU]

Isotonic: A biological term denoting a solution in which body cells can be bathed without a net flow of water across the semipermeable cell membrane. Also, denoting a solution having the same tonicity as some other solution with which it is compared, such as physiologic salt solution and the blood serum. [EU]

Jaundice: A clinical manifestation of hyperbilirubinemia, consisting of deposition of bile pigments in the skin, resulting in a yellowish staining of the skin and mucous membranes. [NIH]

Joint: The point of contact between elements of an animal skeleton with the parts that surround and support it. [NIH]

Kb: A measure of the length of DNA fragments, 1 Kb = 1000 base pairs. The largest DNA fragments are up to 50 kilobases long. [NIH]

Keratin: A class of fibrous proteins or scleroproteins important both as structural proteins

and as keys to the study of protein conformation. The family represents the principal constituent of epidermis, hair, nails, horny tissues, and the organic matrix of tooth enamel. Two major conformational groups have been characterized, alpha-keratin, whose peptide backbone forms an alpha-helix, and beta-keratin, whose backbone forms a zigzag or pleated sheet structure. [NIH]

Keratolytic: An agent that promotes keratolysis. [EU]

Kidney Disease: Any one of several chronic conditions that are caused by damage to the cells of the kidney. People who have had diabetes for a long time may have kidney damage. Also called nephropathy. [NIH]

Kidney Failure: The inability of a kidney to excrete metabolites at normal plasma levels under conditions of normal loading, or the inability to retain electrolytes under conditions of normal intake. In the acute form (kidney failure, acute), it is marked by uremia and usually by oliguria or anuria, with hyperkalemia and pulmonary edema. The chronic form (kidney failure, chronic) is irreversible and requires hemodialysis. [NIH]

Kidney Failure, Acute: A clinical syndrome characterized by a sudden decrease in glomerular filtration rate, often to values of less than 1 to 2 ml per minute. It is usually associated with oliguria (urine volumes of less than 400 ml per day) and is always associated with biochemical consequences of the reduction in glomerular filtration rate such as a rise in blood urea nitrogen (BUN) and serum creatinine concentrations. [NIH]

Kidney Failure, Chronic: An irreversible and usually progressive reduction in renal function in which both kidneys have been damaged by a variety of diseases to the extent that they are unable to adequately remove the metabolic products from the blood and regulate the body's electrolyte composition and acid-base balance. Chronic kidney failure requires hemodialysis or surgery, usually kidney transplantation. [NIH]

Kidney stone: A stone that develops from crystals that form in urine and build up on the inner surfaces of the kidney, in the renal pelvis, or in the ureters. [NIH]

Kinetics: The study of rate dynamics in chemical or physical systems. [NIH]

Labile: 1. Gliding; moving from point to point over the surface; unstable; fluctuating. 2. Chemically unstable. [EU]

Labyrinth: The internal ear; the essential part of the organ of hearing. It consists of an osseous and a membranous portion. [NIH]

Laminin: Large, noncollagenous glycoprotein with antigenic properties. It is localized in the basement membrane lamina lucida and functions to bind epithelial cells to the basement membrane. Evidence suggests that the protein plays a role in tumor invasion. [NIH]

Large Intestine: The part of the intestine that goes from the cecum to the rectum. The large intestine absorbs water from stool and changes it from a liquid to a solid form. The large intestine is 5 feet long and includes the appendix, cecum, colon, and rectum. Also called colon. [NIH]

Latent: Phoria which occurs at one distance or another and which usually has no troublesome effect. [NIH]

Lectin: A complex molecule that has both protein and sugars. Lectins are able to bind to the outside of a cell and cause biochemical changes in it. Lectins are made by both animals and plants. [NIH]

Leg Ulcer: Ulceration of the skin and underlying structures of the lower extremity. About 90% of the cases are due to venous insufficiency (varicose ulcer), 5% to arterial disease, and the remaining 5% to other causes. [NIH]

Lens: The transparent, double convex (outward curve on both sides) structure suspended

between the aqueous and vitreous; helps to focus light on the retina. [NIH]

Lenticular: 1. Pertaining to or shaped like a lens. 2. Pertaining to the crystalline lens. 3. Pertaining to the lenticular nucleus. [EU]

Lentivirus: A genus of the family Retroviridae consisting of non-oncogenic retroviruses that produce multi-organ diseases characterized by long incubation periods and persistent infection. Lentiviruses are unique in that they contain open reading frames (ORFs) between the pol and env genes and in the 3' env region. Five serogroups are recognized, reflecting the mammalian hosts with which they are associated. HIV-1 is the type species. [NIH]

Lesion: An area of abnormal tissue change. [NIH]

Lethal: Deadly, fatal. [EU]

Lethargy: Abnormal drowsiness or stupor; a condition of indifference. [EU]

Leucine: An essential branched-chain amino acid important for hemoglobin formation. [NIH]

Leukemia: Cancer of blood-forming tissue. [NIH]

Leukocytes: White blood cells. These include granular leukocytes (basophils, eosinophils, and neutrophils) as well as non-granular leukocytes (lymphocytes and monocytes). [NIH]

Leukocytosis: A transient increase in the number of leukocytes in a body fluid. [NIH]

Leukopenia: A condition in which the number of leukocytes (white blood cells) in the blood is reduced. [NIH]

Library Services: Services offered to the library user. They include reference and circulation. [NIH]

Life Expectancy: A figure representing the number of years, based on known statistics, to which any person of a given age may reasonably expect to live. [NIH]

Ligament: A band of fibrous tissue that connects bones or cartilages, serving to support and strengthen joints. [EU]

Ligands: A RNA simulation method developed by the MIT. [NIH]

Ligation: Application of a ligature to tie a vessel or strangulate a part. [NIH]

Linkage: The tendency of two or more genes in the same chromosome to remain together from one generation to the next more frequently than expected according to the law of independent assortment. [NIH]

Lip: Either of the two fleshy, full-blooded margins of the mouth. [NIH]

Lipid: Fat. [NIH]

Lipid Peroxidation: Peroxidase catalyzed oxidation of lipids using hydrogen peroxide as an electron acceptor. [NIH]

Lipopolysaccharide: Substance consisting of polysaccaride and lipid. [NIH]

Lipoprotein: Any of the lipid-protein complexes in which lipids are transported in the blood; lipoprotein particles consist of a spherical hydrophobic core of triglycerides or cholesterol esters surrounded by an amphipathic monolayer of phospholipids, cholesterol, and apolipoproteins; the four principal classes are high-density, low-density, and very-low-density lipoproteins and chylomicrons. [EU]

Liposomes: Artificial, single or multilaminar vesicles (made from lecithins or other lipids) that are used for the delivery of a variety of biological molecules or molecular complexes to cells, for example, drug delivery and gene transfer. They are also used to study membranes and membrane proteins. [NIH]

Liver: A large, glandular organ located in the upper abdomen. The liver cleanses the blood

and aids in digestion by secreting bile. [NIH]

Liver scan: An image of the liver created on a computer screen or on film. A radioactive substance is injected into a blood vessel and travels through the bloodstream. It collects in the liver, especially in abnormal areas, and can be detected by the scanner. [NIH]

Localized: Cancer which has not metastasized yet. [NIH]

Locus Control Region: A regulatory region first identified in the human beta-globin locus but subsequently found in other loci. The region is believed to regulate transcription by opening and remodeling chromatin structure. It may also have enhancer activity. [NIH]

Longitudinal study: Also referred to as a "cohort study" or "prospective study"; the analytic method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of this type of study is to observe large numbers of subjects over an extended time, with comparisons of incidence rates in groups that differ in exposure levels. [NIH]

Loop: A wire usually of platinum bent at one end into a small loop (usually 4 mm inside diameter) and used in transferring microorganisms. [NIH]

Low-density lipoprotein: Lipoprotein that contains most of the cholesterol in the blood. LDL carries cholesterol to the tissues of the body, including the arteries. A high level of LDL increases the risk of heart disease. LDL typically contains 60 to 70 percent of the total serum cholesterol and both are directly correlated with CHD risk. [NIH]

Lucida: An instrument, invented by Wollaton, consisting essentially of a prism or a mirror through which an object can be viewed so as to appear on a plane surface seen in direct view and on which the outline of the object may be traced. [NIH]

Lumbar: Pertaining to the loins, the part of the back between the thorax and the pelvis. [EU]

Lupus: A form of cutaneous tuberculosis. It is seen predominantly in women and typically involves the nasal, buccal, and conjunctival mucosa. [NIH]

Lymph: The almost colorless fluid that travels through the lymphatic system and carries cells that help fight infection and disease. [NIH]

Lymphadenopathy: Disease or swelling of the lymph nodes. [NIH]

Lymphatic: The tissues and organs, including the bone marrow, spleen, thymus, and lymph nodes, that produce and store cells that fight infection and disease. [NIH]

Lymphatic system: The tissues and organs that produce, store, and carry white blood cells that fight infection and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes and a network of thin tubes that carry lymph and white blood cells. These tubes branch, like blood vessels, into all the tissues of the body. [NIH]

Lymphoblastic: One of the most aggressive types of non-Hodgkin lymphoma. [NIH]

Lymphoblasts: Interferon produced predominantly by leucocyte cells. [NIH]

Lymphocyte: A white blood cell. Lymphocytes have a number of roles in the immune system, including the production of antibodies and other substances that fight infection and diseases. [NIH]

Lymphocyte Subsets: A classification of lymphocytes based on structurally or functionally different populations of cells. [NIH]

Lymphocytic: Referring to lymphocytes, a type of white blood cell. [NIH]

Lymphoid: Referring to lymphocytes, a type of white blood cell. Also refers to tissue in which lymphocytes develop. [NIH]

Lymphoma: A general term for various neoplastic diseases of the lymphoid tissue. [NIH]

Lymphoproliferative: Disorders characterized by proliferation of lymphoid tissue, general or unspecified. [NIH]

Lysine: An essential amino acid. It is often added to animal feed. [NIH]

Macrophage: A type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells. [NIH]

Macula: A stain, spot, or thickening. Often used alone to refer to the macula retinae. [EU]

Macula Lutea: An oval area in the retina, 3 to 5 mm in diameter, usually located temporal to the superior pole of the eye and slightly below the level of the optic disk. [NIH]

Macular Degeneration: Degenerative changes in the macula lutea of the retina. [NIH]

Magnetic Resonance Angiography: Non-invasive method of vascular imaging and determination of internal anatomy without injection of contrast media or radiation exposure. The technique is used especially in cerebral angiography as well as for studies of other vascular structures. [NIH]

Magnetic Resonance Imaging: Non-invasive method of demonstrating internal anatomy based on the principle that atomic nuclei in a strong magnetic field absorb pulses of radiofrequency energy and emit them as radiowaves which can be reconstructed into computerized images. The concept includes proton spin tomographic techniques. [NIH]

Major Histocompatibility Complex: The genetic region which contains the loci of genes which determine the structure of the serologically defined (SD) and lymphocyte-defined (LD) transplantation antigens, genes which control the structure of the immune response-associated (Ia) antigens, the immune response (Ir) genes which control the ability of an animal to respond immunologically to antigenic stimuli, and genes which determine the structure and/or level of the first four components of complement. [NIH]

Malabsorption: Impaired intestinal absorption of nutrients. [EU]

Malaria: A protozoan disease caused in humans by four species of the genus Plasmodium (P. falciparum (malaria, falciparum), P. vivax (malaria, vivax), P. ovale, and P. malariae) and transmitted by the bite of an infected female mosquito of the genus Anopheles. Malaria is endemic in parts of Asia, Africa, Central and South America, Oceania, and certain Caribbean islands. It is characterized by extreme exhaustion associated with paroxysms of high fever, sweating, shaking chills, and anemia. Malaria in animals is caused by other species of plasmodia. [NIH]

Malaria, Falciparum: Malaria caused by Plasmodium falciparum. This is the severest form of malaria and is associated with the highest levels of parasites in the blood. This disease is characterized by irregularly recurring febrile paroxysms that in extreme cases occur with acute cerebral, renal, or gastrointestinal manifestations. [NIH]

Malaria, Vivax: Malaria caused by Plasmodium vivax. This form of malaria is less severe than malaria, falciparum, but there is a higher probability for relapses to occur. Febrile paroxysms often occur every other day. [NIH]

Malignant: Cancerous; a growth with a tendency to invade and destroy nearby tissue and spread to other parts of the body. [NIH]

Malignant tumor: A tumor capable of metastasizing. [NIH]

Malnutrition: A condition caused by not eating enough food or not eating a balanced diet. [NIH]

Manic: Affected with mania. [EU]

Manic-depressive psychosis: One of a group of psychotic reactions, fundamentally marked

by severe mood swings and a tendency to remission and recurrence. [NIH]

Manifest: Being the part or aspect of a phenomenon that is directly observable : concretely expressed in behaviour. [EU]

Mannitol: A diuretic and renal diagnostic aid related to sorbitol. It has little significant energy value as it is largely eliminated from the body before any metabolism can take place. It can be used to treat oliguria associated with kidney failure or other manifestations of inadequate renal function and has been used for determination of glomerular filtration rate. Mannitol is also commonly used as a research tool in cell biological studies, usually to control osmolarity. [NIH]

Meatus: A canal running from the internal auditory foramen through the petrous portion of the temporal bone. It gives passage to the facial and auditory nerves together with the auditory branch of the basilar artery and the internal auditory veins. [NIH]

Median Nerve: A major nerve of the upper extremity. In humans, the fibers of the median nerve originate in the lower cervical and upper thoracic spinal cord (usually C6 to T1), travel via the brachial plexus, and supply sensory and motor innervation to parts of the forearm and hand. [NIH]

Mediate: Indirect; accomplished by the aid of an intervening medium. [EU]

Mediator: An object or substance by which something is mediated, such as (1) a structure of the nervous system that transmits impulses eliciting a specific response; (2) a chemical substance (transmitter substance) that induces activity in an excitable tissue, such as nerve or muscle; or (3) a substance released from cells as the result of the interaction of antigen with antibody or by the action of antigen with a sensitized lymphocyte. [EU]

Medical Assistance: Financing of medical care provided to public assistance recipients. [NIH]

Medical Staff: Professional medical personnel who provide care to patients in an organized facility, institution or agency. [NIH]

MEDLINE: An online database of MEDLARS, the computerized bibliographic Medical Literature Analysis and Retrieval System of the National Library of Medicine. [NIH]

Medullary: Pertaining to the marrow or to any medulla; resembling marrow. [EU]

Megakaryocytes: Very large bone marrow cells which release mature blood platelets. [NIH]

Megaloblastic: A large abnormal red blood cell appearing in the blood in pernicious anaemia. [EU]

Melanin: The substance that gives the skin its color. [NIH]

Melanocytes: Epidermal dendritic pigment cells which control long-term morphological color changes by alteration in their number or in the amount of pigment they produce and store in the pigment containing organelles called melanosomes. Melanophores are larger cells which do not exist in mammals. [NIH]

Melanoma: A form of skin cancer that arises in melanocytes, the cells that produce pigment. Melanoma usually begins in a mole. [NIH]

Membrane: A very thin layer of tissue that covers a surface. [NIH]

Membrane Proteins: Proteins which are found in membranes including cellular and intracellular membranes. They consist of two types, peripheral and integral proteins. They include most membrane-associated enzymes, antigenic proteins, transport proteins, and drug, hormone, and lectin receptors. [NIH]

Memory: Complex mental function having four distinct phases: (1) memorizing or learning, (2) retention, (3) recall, and (4) recognition. Clinically, it is usually subdivided into immediate, recent, and remote memory. [NIH]

Meninges: The three membranes that cover and protect the brain and spinal cord. [NIH]

Mental Disorders: Psychiatric illness or diseases manifested by breakdowns in the adaptational process expressed primarily as abnormalities of thought, feeling, and behavior producing either distress or impairment of function. [NIH]

Mental Health: The state wherein the person is well adjusted. [NIH]

Mental Processes: Conceptual functions or thinking in all its forms. [NIH]

Metabolic disorder: A condition in which normal metabolic processes are disrupted, usually because of a missing enzyme. [NIH]

Metastasis: The spread of cancer from one part of the body to another. Tumors formed from cells that have spread are called "secondary tumors" and contain cells that are like those in the original (primary) tumor. The plural is metastases. [NIH]

Methionine: A sulfur containing essential amino acid that is important in many body functions. It is a chelating agent for heavy metals. [NIH]

MI: Myocardial infarction. Gross necrosis of the myocardium as a result of interruption of the blood supply to the area; it is almost always caused by atherosclerosis of the coronary arteries, upon which coronary thrombosis is usually superimposed. [NIH]

Mice Minute Virus: The type species of parvovirus prevalent in mouse colonies and found as a contaminant of many transplanted tumors or leukemias. [NIH]

Microbe: An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

Microbiology: The study of microorganisms such as fungi, bacteria, algae, archaea, and viruses. [NIH]

Microcirculation: The vascular network lying between the arterioles and venules; includes capillaries, metarterioles and arteriovenous anastomoses. Also, the flow of blood through this network. [NIH]

Microorganism: An organism that can be seen only through a microscope. Microorganisms include bacteria, protozoa, algae, and fungi. Although viruses are not considered living organisms, they are sometimes classified as microorganisms. [NIH]

Micro-organism: An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

Microscopy: The application of microscope magnification to the study of materials that cannot be properly seen by the unaided eye. [NIH]

Microsomal: Of or pertaining to microsomes : vesicular fragments of endoplasmic reticulum formed after disruption and centrifugation of cells. [EU]

Migration: The systematic movement of genes between populations of the same species, geographic race, or variety. [NIH]

Mitochondrial Swelling: Increase in volume of mitochondria due to an influx of fluid; it occurs in hypotonic solutions due to osmotic pressure and in isotonic solutions as a result of altered permeability of the membranes of respiring mitochondria. [NIH]

Mitosis: A method of indirect cell division by means of which the two daughter nuclei normally receive identical complements of the number of chromosomes of the somatic cells of the species. [NIH]

Mobility: Capability of movement, of being moved, or of flowing freely. [EU]

Modeling: A treatment procedure whereby the therapist presents the target behavior which the learner is to imitate and make part of his repertoire. [NIH]

Modification: A change in an organism, or in a process in an organism, that is acquired from its own activity or environment. [NIH]

Molecular: Of, pertaining to, or composed of molecules : a very small mass of matter. [EU]

Molecular Structure: The location of the atoms, groups or ions relative to one another in a molecule, as well as the number, type and location of covalent bonds. [NIH]

Molecule: A chemical made up of two or more atoms. The atoms in a molecule can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms. [NIH]

Monitor: An apparatus which automatically records such physiological signs as respiration, pulse, and blood pressure in an anesthetized patient or one undergoing surgical or other procedures. [NIH]

Monoclonal: An antibody produced by culturing a single type of cell. It therefore consists of a single species of immunoglobulin molecules. [NIH]

Monoclonal antibodies: Laboratory-produced substances that can locate and bind to cancer cells wherever they are in the body. Many monoclonal antibodies are used in cancer detection or therapy; each one recognizes a different protein on certain cancer cells. Monoclonal antibodies can be used alone, or they can be used to deliver drugs, toxins, or radioactive material directly to a tumor. [NIH]

Monocyte: A type of white blood cell. [NIH]

Monogenic: A human disease caused by a mutation in a single gene. [NIH]

Mononuclear: A cell with one nucleus. [NIH]

Morphine: The principal alkaloid in opium and the prototype opiate analgesic and narcotic. Morphine has widespread effects in the central nervous system and on smooth muscle. [NIH]

Morphological: Relating to the configuration or the structure of live organs. [NIH]

Morphology: The science of the form and structure of organisms (plants, animals, and other forms of life). [NIH]

Motor Activity: The physical activity of an organism as a behavioral phenomenon. [NIH]

Mucosa: A mucous membrane, or tunica mucosa. [EU]

Mucosal Ulceration: Skin ulceration in workers who work with lime and lime solutions. [NIH]

Multicenter study: A clinical trial that is carried out at more than one medical institution. [NIH]

Multiple Myeloma: A malignant tumor of plasma cells usually arising in the bone marrow; characterized by diffuse involvement of the skeletal system, hyperglobulinemia, Bence-Jones proteinuria, and anemia. [NIH]

Multiple sclerosis: A disorder of the central nervous system marked by weakness, numbness, a loss of muscle coordination, and problems with vision, speech, and bladder control. Multiple sclerosis is thought to be an autoimmune disease in which the body's immune system destroys myelin. Myelin is a substance that contains both protein and fat (lipid) and serves as a nerve insulator and helps in the transmission of nerve signals. [NIH]

Muscle Fibers: Large single cells, either cylindrical or prismatic in shape, that form the basic unit of muscle tissue. They consist of a soft contractile substance enclosed in a tubular sheath. [NIH]

Muscle Relaxation: That phase of a muscle twitch during which a muscle returns to a resting position. [NIH]

Muscular Atrophy: Derangement in size and number of muscle fibers occurring with aging, reduction in blood supply, or following immobilization, prolonged weightlessness, malnutrition, and particularly in denervation. [NIH]

Muscular Dystrophies: A general term for a group of inherited disorders which are characterized by progressive degeneration of skeletal muscles. [NIH]

Musculoskeletal System: Themuscles, bones, and cartilage of the body. [NIH]

Mutagenesis: Process of generating genetic mutations. It may occur spontaneously or be induced by mutagens. [NIH]

Mutagens: Chemical agents that increase the rate of genetic mutation by interfering with the function of nucleic acids. A clastogen is a specific mutagen that causes breaks in chromosomes. [NIH]

Mycophenolate mofetil: A drug that is being studied for its effectiveness in preventing graft-versus-host disease and autoimmune disorders. [NIH]

Myelin: The fatty substance that covers and protects nerves. [NIH]

Myocardial infarction: Gross necrosis of the myocardium as a result of interruption of the blood supply to the area; it is almost always caused by atherosclerosis of the coronary arteries, upon which coronary thrombosis is usually superimposed. [NIH]

Myocardium: The muscle tissue of the heart composed of striated, involuntary muscle known as cardiac muscle. [NIH]

Myoglobin: A conjugated protein which is the oxygen-transporting pigment of muscle. It is made up of one globin polypeptide chain and one heme group. [NIH]

Myopia: That error of refraction in which rays of light entering the eye parallel to the optic axis are brought to a focus in front of the retina, as a result of the eyeball being too long from front to back (axial m.) or of an increased strength in refractive power of the media of the eye (index m.). Called also nearsightedness, because the near point is less distant than it is in emmetropia with an equal amplitude of accommodation. [EU]

Myotonic Dystrophy: A condition presenting muscle weakness and wasting which may be progressive. [NIH]

Nalbuphine: A narcotic used as a pain medication. It appears to be an agonist at kappa opioid receptors and an antagonist or partial agonist at mu opioid receptors. [NIH]

Narcosis: A general and nonspecific reversible depression of neuronal excitability, produced by a number of physical and chemical aspects, usually resulting in stupor. [NIH]

Narcotic: 1. Pertaining to or producing narcosis. 2. An agent that produces insensibility or stupor, applied especially to the opioids, i.e. to any natural or synthetic drug that has morphine-like actions. [EU]

NCI: National Cancer Institute. NCI, part of the National Institutes of Health of the United States Department of Health and Human Services, is the federal government's principal agency for cancer research. NCI conducts, coordinates, and funds cancer research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer. Access the NCI Web site at http://cancer.gov. [NIH]

Necrosis: A pathological process caused by the progressive degradative action of enzymes that is generally associated with severe cellular trauma. It is characterized by mitochondrial swelling, nuclear flocculation, uncontrolled cell lysis, and ultimately cell death. [NIH]

Need: A state of tension or dissatisfaction felt by an individual that impels him to action toward a goal he believes will satisfy the impulse. [NIH]

Neonatal: Pertaining to the first four weeks after birth. [EU]

Neonatal period: The first 4 weeks after birth. [NIH]

Neoplasia: Abnormal and uncontrolled cell growth. [NIH]

Neoplasm: A new growth of benign or malignant tissue. [NIH]

Neoplastic: Pertaining to or like a neoplasm (= any new and abnormal growth); pertaining to neoplasia (= the formation of a neoplasm). [EU]

Nephropathy: Disease of the kidneys. [EU]

Nerve: A cordlike structure of nervous tissue that connects parts of the nervous system with other tissues of the body and conveys nervous impulses to, or away from, these tissues. [NIH]

Nervous System: The entire nerve apparatus composed of the brain, spinal cord, nerves and ganglia. [NIH]

Neural: 1. Pertaining to a nerve or to the nerves. 2. Situated in the region of the spinal axis, as the neutral arch. [EU]

Neurodegenerative Diseases: Hereditary and sporadic conditions which are characterized by progressive nervous system dysfunction. These disorders are often associated with atrophy of the affected central or peripheral nervous system structures. [NIH]

Neurologic: Having to do with nerves or the nervous system. [NIH]

Neuroma: A tumor that arises in nerve cells. [NIH]

Neuromuscular: Pertaining to muscles and nerves. [EU]

Neuromuscular Junction: The synapse between a neuron and a muscle. [NIH]

Neuronal: Pertaining to a neuron or neurons (= conducting cells of the nervous system). [EU]

Neurons: The basic cellular units of nervous tissue. Each neuron consists of a body, an axon, and dendrites. Their purpose is to receive, conduct, and transmit impulses in the nervous system. [NIH]

Neuropathy: A problem in any part of the nervous system except the brain and spinal cord. Neuropathies can be caused by infection, toxic substances, or disease. [NIH]

Neurotransmitters: Endogenous signaling molecules that alter the behavior of neurons or effector cells. Neurotransmitter is used here in its most general sense, including not only messengers that act directly to regulate ion channels, but also those that act through second messenger systems, and those that act at a distance from their site of release. Included are neuromodulators, neuroregulators, neuromediators, and neurohumors, whether or not acting at synapses. [NIH]

Neutrons: Electrically neutral elementary particles found in all atomic nuclei except light hydrogen; the mass is equal to that of the proton and electron combined and they are unstable when isolated from the nucleus, undergoing beta decay. Slow, thermal, epithermal, and fast neutrons refer to the energy levels with which the neutrons are ejected from heavier nuclei during their decay. [NIH]

Neutrophil: A type of white blood cell. [NIH]

Niacinamide: An important compound functioning as a component of the coenzyme NAD. Its primary significance is in the prevention and/or cure of blacktongue and pellagra. Most animals cannot manufacture this compound in amounts sufficient to prevent nutritional deficiency and it therefore must be supplemented through dietary intake. [NIH]

Nitric Oxide: A free radical gas produced endogenously by a variety of mammalian cells. It is synthesized from arginine by a complex reaction, catalyzed by nitric oxide synthase. Nitric oxide is endothelium-derived relaxing factor. It is released by the vascular endothelium and mediates the relaxation induced by some vasodilators such as

acetylcholine and bradykinin. It also inhibits platelet aggregation, induces disaggregation of aggregated platelets, and inhibits platelet adhesion to the vascular endothelium. Nitric oxide activates cytosolic guanylate cyclase and thus elevates intracellular levels of cyclic GMP. [NIH]

Nitrogen: An element with the atomic symbol N, atomic number 7, and atomic weight 14. Nitrogen exists as a diatomic gas and makes up about 78% of the earth's atmosphere by volume. It is a constituent of proteins and nucleic acids and found in all living cells. [NIH]

Nitroprusside: (OC-6-22)-Pentakis(cyano-C)nitrosoferrate(2-). A powerful vasodilator used in emergencies to lower blood pressure or to improve cardiac function. It is also an indicator for free sulfhydryl groups in proteins. [NIH]

Nitrous Oxide: Nitrogen oxide (N2O). A colorless, odorless gas that is used as an anesthetic and analgesic. High concentrations cause a narcotic effect and may replace oxygen, causing death by asphyxia. It is also used as a food aerosol in the preparation of whipping cream. [NIH]

Nonmalignant: Not cancerous. [NIH]

Nonmalignant hematologic disorders: Disorders of the blood, some of which lead to leukemia. [NIH]

Norepinephrine: Precursor of epinephrine that is secreted by the adrenal medulla and is a widespread central and autonomic neurotransmitter. Norepinephrine is the principal transmitter of most postganglionic sympathetic fibers and of the diffuse projection system in the brain arising from the locus ceruleus. It is also found in plants and is used pharmacologically as a sympathomimetic. [NIH]

Normotensive: 1. Characterized by normal tone, tension, or pressure, as by normal blood pressure. 2. A person with normal blood pressure. [EU]

Nuclear: A test of the structure, blood flow, and function of the kidneys. The doctor injects a mildly radioactive solution into an arm vein and uses x-rays to monitor its progress through the kidneys. [NIH]

Nuclei: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Nucleic acid: Either of two types of macromolecule (DNA or RNA) formed by polymerization of nucleotides. Nucleic acids are found in all living cells and contain the information (genetic code) for the transfer of genetic information from one generation to the next. [NIH]

Nucleic Acid Hybridization: The process whereby two single-stranded polynucleotides form a double-stranded molecule, with hydrogen bonding between the complementary bases in the two strains. [NIH]

Nucleus: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Nursing Care: Care given to patients by nursing service personnel. [NIH]

Ocular: 1. Of, pertaining to, or affecting the eye. 2. Eyepiece. [EU]

Odour: A volatile emanation that is perceived by the sense of smell. [EU]

Oligonucleotide Probes: Synthetic or natural oligonucleotides used in hybridization studies in order to identify and study specific nucleic acid fragments, e.g., DNA segments near or within a specific gene locus or gene. The probe hybridizes with a specific mRNA, if present. Conventional techniques used for testing for the hybridization product include dot blot assays, Southern blot assays, and DNA:RNA hybrid-specific antibody tests. Conventional labels for the probe include the radioisotope labels 32P and 125I and the chemical label

biotin. [NIH]

Oliguria: Clinical manifestation of the urinary system consisting of a decrease in the amount of urine secreted. [NIH]

Oncogene: A gene that normally directs cell growth. If altered, an oncogene can promote or allow the uncontrolled growth of cancer. Alterations can be inherited or caused by an environmental exposure to carcinogens. [NIH]

Oncogenic: Chemical, viral, radioactive or other agent that causes cancer; carcinogenic. [NIH]

Oncologist: A doctor who specializes in treating cancer. Some oncologists specialize in a particular type of cancer treatment. For example, a radiation oncologist specializes in treating cancer with radiation. [NIH]

Oncology: The study of cancer. [NIH]

Oocytes: Female germ cells in stages between the prophase of the first maturation division and the completion of the second maturation division. [NIH]

Opacity: Degree of density (area most dense taken for reading). [NIH]

Open Reading Frames: Reading frames where successive nucleotide triplets can be read as codons specifying amino acids and where the sequence of these triplets is not interrupted by stop codons. [NIH]

Operon: The genetic unit consisting of a feedback system under the control of an operator gene, in which a structural gene transcribes its message in the form of mRNA upon blockade of a repressor produced by a regulator gene. Included here is the attenuator site of bacterial operons where transcription termination is regulated. [NIH]

Ophthalmologic: Pertaining to ophthalmology (= the branch of medicine dealing with the eye). [EU]

Ophthalmoscope: A lighted instrument used to examine the inside of the eye, including the retina and the optic nerve. [NIH]

Opsin: A protein formed, together with retinene, by the chemical breakdown of meta-rhodopsin. [NIH]

Optic Disk: The portion of the optic nerve seen in the fundus with the ophthalmoscope. It is formed by the meeting of all the retinal ganglion cell axons as they enter the optic nerve. [NIH]

Optic Nerve: The 2nd cranial nerve. The optic nerve conveys visual information from the retina to the brain. The nerve carries the axons of the retinal ganglion cells which sort at the optic chiasm and continue via the optic tracts to the brain. The largest projection is to the lateral geniculate nuclei; other important targets include the superior colliculi and the suprachiasmatic nuclei. Though known as the second cranial nerve, it is considered part of the central nervous system. [NIH]

Oral Health: The optimal state of the mouth and normal functioning of the organs of the mouth without evidence of disease. [NIH]

Oral Manifestations: Disorders of the mouth attendant upon non-oral disease or injury. [NIH]

Oral Surgical Procedures: Procedures used to treat disease, injuries, and defects of the oral and maxillofacial region. [NIH]

Orbit: One of the two cavities in the skull which contains an eyeball. Each eye is located in a bony socket or orbit. [NIH]

Orbital: Pertaining to the orbit (= the bony cavity that contains the eyeball). [EU]

Organ Culture: The growth in aseptic culture of plant organs such as roots or shoots,

beginning with organ primordia or segments and maintaining the characteristics of the organ. [NIH]

Organelles: Specific particles of membrane-bound organized living substances present in eukaryotic cells, such as the mitochondria; the golgi apparatus; endoplasmic reticulum; lysomomes; plastids; and vacuoles. [NIH]

Orthopaedic: Pertaining to the correction of deformities of the musculoskeletal system; pertaining to orthopaedics. [EU]

Osmolarity: The concentration of osmotically active particles expressed in terms of osmoles of solute per litre of solution. [EU]

Osmosis: Tendency of fluids (e.g., water) to move from the less concentrated to the more concentrated side of a semipermeable membrane. [NIH]

Osmotic: Pertaining to or of the nature of osmosis (= the passage of pure solvent from a solution of lesser to one of greater solute concentration when the two solutions are separated by a membrane which selectively prevents the passage of solute molecules, but is permeable to the solvent). [EU]

Ossicles: The hammer, anvil and stirrup, the small bones of the middle ear, which transmit the vibrations from the tympanic membrane to the oval window. [NIH]

Osteogenic sarcoma: A malignant tumor of the bone. Also called osteosarcoma. [NIH]

Osteomyelitis: Inflammation of bone caused by a pyogenic organism. It may remain localized or may spread through the bone to involve the marrow, cortex, cancellous tissue, and periosteum. [EU]

Osteoporosis: Reduction of bone mass without alteration in the composition of bone, leading to fractures. Primary osteoporosis can be of two major types: postmenopausal osteoporosis and age-related (or senile) osteoporosis. [NIH]

Osteosarcoma: A cancer of the bone that affects primarily children and adolescents. Also called osteogenic sarcoma. [NIH]

Otitis: Inflammation of the ear, which may be marked by pain, fever, abnormalities of hearing, hearing loss, tinnitus, and vertigo. [EU]

Otitis Media: Inflammation of the middle ear. [NIH]

Otosclerosis: The formation of spongy bone in the labyrinth capsule. The ossicles can become fixed and unable to transmit sound vibrations, thereby causing deafness. [NIH]

Outer ear: The pinna and external meatus of the ear. [NIH]

Outpatient: A patient who is not an inmate of a hospital but receives diagnosis or treatment in a clinic or dispensary connected with the hospital. [NIH]

Oxidants: Oxidizing agents or electron-accepting molecules in chemical reactions in which electrons are transferred from one molecule to another (oxidation-reduction). In vivo, it appears that phagocyte-generated oxidants function as tumor promoters or cocarcinogens rather than as complete carcinogens perhaps because of the high levels of endogenous antioxidant defenses. It is also thought that oxidative damage in joints may trigger the autoimmune response that characterizes the persistence of the rheumatoid disease process. [NIH]

Oxidation: The act of oxidizing or state of being oxidized. Chemically it consists in the increase of positive charges on an atom or the loss of negative charges. Most biological oxidations are accomplished by the removal of a pair of hydrogen atoms (dehydrogenation) from a molecule. Such oxidations must be accompanied by reduction of an acceptor molecule. Univalent o. indicates loss of one electron; divalent o., the loss of two electrons. [EU]

Oxidation-Reduction: A chemical reaction in which an electron is transferred from one molecule to another. The electron-donating molecule is the reducing agent or reductant; the electron-accepting molecule is the oxidizing agent or oxidant. Reducing and oxidizing agents function as conjugate reductant-oxidant pairs or redox pairs (Lehninger, Principles of Biochemistry, 1982, p471). [NIH]

Oxidative Stress: A disturbance in the prooxidant-antioxidant balance in favor of the former, leading to potential damage. Indicators of oxidative stress include damaged DNA bases, protein oxidation products, and lipid peroxidation products (Sies, Oxidative Stress, 1991, pxv-xvi). [NIH]

Oximetry: The determination of oxygen-hemoglobin saturation of blood either by withdrawing a sample and passing it through a classical photoelectric oximeter or by electrodes attached to some translucent part of the body like finger, earlobe, or skin fold. It includes non-invasive oxygen monitoring by pulse oximetry. [NIH]

Oxygen Consumption: The oxygen consumption is determined by calculating the difference between the amount of oxygen inhaled and exhaled. [NIH]

Oxygenation: The process of supplying, treating, or mixing with oxygen. No:1245 - oxygenation the process of supplying, treating, or mixing with oxygen. [EU]

Oxypurinol: A xanthine oxidase inhibitor. [NIH]

Palliative: 1. Affording relief, but not cure. 2. An alleviating medicine. [EU]

Pallor: A clinical manifestation consisting of an unnatural paleness of the skin. [NIH]

Pancreas: A mixed exocrine and endocrine gland situated transversely across the posterior abdominal wall in the epigastric and hypochondriac regions. The endocrine portion is comprised of the Islets of Langerhans, while the exocrine portion is a compound acinar gland that secretes digestive enzymes. [NIH]

Pancreatic: Having to do with the pancreas. [NIH]

Pancreatic cancer: Cancer of the pancreas, a salivary gland of the abdomen. [NIH]

Papilla: A small nipple-shaped elevation. [NIH]

Papillary: Pertaining to or resembling papilla, or nipple. [EU]

Parenteral: Not through the alimentary canal but rather by injection through some other route, as subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, etc. [EU]

Paresis: A general term referring to a mild to moderate degree of muscular weakness, occasionally used as a synonym for paralysis (severe or complete loss of motor function). In the older literature, paresis often referred specifically to paretic neurosyphilis. "General paresis" and "general paralysis" may still carry that connotation. Bilateral lower extremity paresis is referred to as paraparesis. [NIH]

Paroxysmal: Recurring in paroxysms (= spasms or seizures). [EU]

Particle: A tiny mass of material. [EU]

Parvovirus: A genus of the family Parvoviridae, subfamily Parvovirinae, infecting a variety of vertebrates including humans. Parvoviruses are responsible for a number of important diseases but also can be non-pathogenic in certain hosts. The type species is mice minute virus. [NIH]

Pathogen: Any disease-producing microorganism. [EU]

Pathogenesis: The cellular events and reactions that occur in the development of disease. [NIH]

Pathologic: 1. Indicative of or caused by a morbid condition. 2. Pertaining to pathology (= branch of medicine that treats the essential nature of the disease, especially the structural and functional changes in tissues and organs of the body caused by the disease). [EU]

Pathologic Processes: The abnormal mechanisms and forms involved in the dysfunctions of tissues and organs. [NIH]

Pathologies: The study of abnormality, especially the study of diseases. [NIH]

Pathophysiology: Altered functions in an individual or an organ due to disease. [NIH]

Patient Care Management: Generating, planning, organizing, and administering medical and nursing care and services for patients. [NIH]

Patient Education: The teaching or training of patients concerning their own health needs. [NIH]

Patient Selection: Criteria and standards used for the determination of the appropriateness of the inclusion of patients with specific conditions in proposed treatment plans and the criteria used for the inclusion of subjects in various clinical trials and other research protocols. [NIH]

Pediatric Dentistry: The practice of dentistry concerned with the dental problems of children, proper maintenance, and treatment. The dental care may include the services provided by dental specialists. [NIH]

Pelvic: Pertaining to the pelvis. [EU]

Penicillin: An antibiotic drug used to treat infection. [NIH]

Penis: The external reproductive organ of males. It is composed of a mass of erectile tissue enclosed in three cylindrical fibrous compartments. Two of the three compartments, the corpus cavernosa, are placed side-by-side along the upper part of the organ. The third compartment below, the corpus spongiosum, houses the urethra. [NIH]

Pentoxifylline: A methylxanthine derivative that inhibits phosphodiesterase and affects blood rheology. It improves blood flow by increasing erythrocyte and leukocyte flexibility. It also inhibits platelet aggregation. Pentoxifylline modulates immunologic activity by stimulating cytokine production. [NIH]

Peptide: Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [NIH]

Perception: The ability quickly and accurately to recognize similarities and differences among presented objects, whether these be pairs of words, pairs of number series, or multiple sets of these or other symbols such as geometric figures. [NIH]

Perforation: 1. The act of boring or piercing through a part. 2. A hole made through a part or substance. [EU]

Performance status: A measure of how well a patient is able to perform ordinary tasks and carry out daily activities. [NIH]

Perfusion: Bathing an organ or tissue with a fluid. In regional perfusion, a specific area of the body (usually an arm or a leg) receives high doses of anticancer drugs through a blood vessel. Such a procedure is performed to treat cancer that has not spread. [NIH]

Perinatal: Pertaining to or occurring in the period shortly before and after birth; variously defined as beginning with completion of the twentieth to twenty-eighth week of gestation and ending 7 to 28 days after birth. [EU]

Perioperative: Around the time of surgery; usually lasts from the time of going into the hospital or doctor's office for surgery until the time the patient goes home. [NIH]

Peripheral blood: Blood circulating throughout the body. [NIH]

Peripheral Nervous System: The nervous system outside of the brain and spinal cord. The peripheral nervous system has autonomic and somatic divisions. The autonomic nervous system includes the enteric, parasympathetic, and sympathetic subdivisions. The somatic nervous system includes the cranial and spinal nerves and their ganglia and the peripheral sensory receptors. [NIH]

Peripheral Nervous System Diseases: Diseases of the peripheral nerves external to the brain and spinal cord, which includes diseases of the nerve roots, ganglia, plexi, autonomic nerves, sensory nerves, and motor nerves. [NIH]

Peripheral stem cells: Immature cells found circulating in the bloodstream. New blood cells develop from peripheral stem cells. [NIH]

Peripheral Vascular Disease: Disease in the large blood vessels of the arms, legs, and feet. People who have had diabetes for a long time may get this because major blood vessels in their arms, legs, and feet are blocked and these limbs do not receive enough blood. The signs of PVD are aching pains in the arms, legs, and feet (especially when walking) and foot sores that heal slowly. Although people with diabetes cannot always avoid PVD, doctors say they have a better chance of avoiding it if they take good care of their feet, do not smoke, and keep both their blood pressure and diabetes under good control. [NIH]

Peritoneal: Having to do with the peritoneum (the tissue that lines the abdominal wall and covers most of the organs in the abdomen). [NIH]

Peritoneal Cavity: The space enclosed by the peritoneum. It is divided into two portions, the greater sac and the lesser sac or omental bursa, which lies behind the stomach. The two sacs are connected by the foramen of Winslow, or epiploic foramen. [NIH]

Pernicious: Tending to a fatal issue. [EU]

Pernicious anemia: A type of anemia (low red blood cell count) caused by the body's inability to absorb vitamin B12. [NIH]

Peroxidase: A hemeprotein from leukocytes. Deficiency of this enzyme leads to a hereditary disorder coupled with disseminated moniliasis. It catalyzes the conversion of a donor and peroxide to an oxidized donor and water. EC 1.11.1.7. [NIH]

Peroxide: Chemical compound which contains an atom group with two oxygen atoms tied to each other. [NIH]

Phagocyte: An immune system cell that can surround and kill microorganisms and remove dead cells. Phagocytes include macrophages. [NIH]

Pharmaceutical Preparations: Drugs intended for human or veterinary use, presented in their finished dosage form. Included here are materials used in the preparation and/or formulation of the finished dosage form. [NIH]

Pharmacokinetic: The mathematical analysis of the time courses of absorption, distribution, and elimination of drugs. [NIH]

Pharmacologic: Pertaining to pharmacology or to the properties and reactions of drugs. [EU]

Pharmacotherapy: A regimen of using appetite suppressant medications to manage obesity by decreasing appetite or increasing the feeling of satiety. These medications decrease appetite by increasing serotonin or catecholamine—two brain chemicals that affect mood and appetite. [NIH]

Pharyngitis: Inflammation of the throat. [NIH]

Phenotype: The outward appearance of the individual. It is the product of interactions between genes and between the genotype and the environment. This includes the killer phenotype, characteristic of yeasts. [NIH]

Phenyl: Ingredient used in cold and flu remedies. [NIH]

Phenylalanine: An aromatic amino acid that is essential in the animal diet. It is a precursor of melanin, dopamine, noradrenalin, and thyroxine. [NIH]

Phenylbutyrate: An anticancer drug that belongs to the family of drugs called differentiating agents. [NIH]

Phlebitis: Inflammation of a vein. [NIH]

Phosphodiesterase: Effector enzyme that regulates the levels of a second messenger, the cyclic GMP. [NIH]

Phospholipids: Lipids containing one or more phosphate groups, particularly those derived from either glycerol (phosphoglycerides; glycerophospholipids) or sphingosine (sphingolipids). They are polar lipids that are of great importance for the structure and function of cell membranes and are the most abundant of membrane lipids, although not stored in large amounts in the system. [NIH]

Phosphorus: A non-metallic element that is found in the blood, muscles, nevers, bones, and teeth, and is a component of adenosine triphosphate (ATP; the primary energy source for the body's cells.) [NIH]

Phosphorylation: The introduction of a phosphoryl group into a compound through the formation of an ester bond between the compound and a phosphorus moiety. [NIH]

Photocoagulation: Using a special strong beam of light (laser) to seal off bleeding blood vessels such as in the eye. The laser can also burn away blood vessels that should not have grown in the eye. This is the main treatment for diabetic retinopathy. [NIH]

Photoreceptors: Cells specialized to detect and transduce light. [NIH]

Phylogeny: The relationships of groups of organisms as reflected by their evolutionary history. [NIH]

Physical Examination: Systematic and thorough inspection of the patient for physical signs of disease or abnormality. [NIH]

Physical Fitness: A state of well-being in which performance is optimal, often as a result of physical conditioning which may be prescribed for disease therapy. [NIH]

Physiologic: Having to do with the functions of the body. When used in the phrase "physiologic age," it refers to an age assigned by general health, as opposed to calendar age. [NIH]

Physiology: The science that deals with the life processes and functions of organismus, their cells, tissues, and organs. [NIH]

Pigment: A substance that gives color to tissue. Pigments are responsible for the color of skin, eyes, and hair. [NIH]

Pilot study: The initial study examining a new method or treatment. [NIH]

Placenta: A highly vascular fetal organ through which the fetus absorbs oxygen and other nutrients and excretes carbon dioxide and other wastes. It begins to form about the eighth day of gestation when the blastocyst adheres to the decidua. [NIH]

Plants: Multicellular, eukaryotic life forms of the kingdom Plantae. They are characterized by a mainly photosynthetic mode of nutrition; essentially unlimited growth at localized regions of cell divisions (meristems); cellulose within cells providing rigidity; the absence of organs of locomotion; absense of nervous and sensory systems; and an alteration of haploid and diploid generations. [NIH]

Plasma: The clear, yellowish, fluid part of the blood that carries the blood cells. The proteins that form blood clots are in plasma. [NIH]

Plasma cells: A type of white blood cell that produces antibodies. [NIH]

Plasma protein: One of the hundreds of different proteins present in blood plasma, including carrier proteins (such albumin, transferrin, and haptoglobin), fibrinogen and other coagulation factors, complement components, immunoglobulins, enzyme inhibitors, precursors of substances such as angiotension and bradykinin, and many other types of proteins. [EU]

Plasma Volume: Volume of plasma in the circulation. It is usually measured by indicator dilution techniques. [NIH]

Plasmin: A product of the lysis of plasminogen (profibrinolysin) by plasminogen activators. It is composed of two polypeptide chains, light (B) and heavy (A), with a molecular weight of 75,000. It is the major proteolytic enzyme involved in blood clot retraction or the lysis of fibrin and quickly inactivated by antiplasmins. EC 3.4.21.7. [NIH]

Plasminogen: Precursor of fibrinolysin (plasmin). It is a single-chain beta-globulin of molecular weight 80-90,000 found mostly in association with fibrinogen in plasma; plasminogen activators change it to fibrinolysin. It is used in wound debriding and has been investigated as a thrombolytic agent. [NIH]

Plasminogen Activators: A heterogeneous group of proteolytic enzymes that convert plasminogen to plasmin. They are concentrated in the lysosomes of most cells and in the vascular endothelium, particularly in the vessels of the microcirculation. EC 3.4.21.-. [NIH]

Plasticity: In an individual or a population, the capacity for adaptation: a) through gene changes (genetic plasticity) or b) through internal physiological modifications in response to changes of environment (physiological plasticity). [NIH]

Platelet Aggregation: The attachment of platelets to one another. This clumping together can be induced by a number of agents (e.g., thrombin, collagen) and is part of the mechanism leading to the formation of a thrombus. [NIH]

Platelets: A type of blood cell that helps prevent bleeding by causing blood clots to form. Also called thrombocytes. [NIH]

Platinum: Platinum. A heavy, soft, whitish metal, resembling tin, atomic number 78, atomic weight 195.09, symbol Pt. (From Dorland, 28th ed) It is used in manufacturing equipment for laboratory and industrial use. It occurs as a black powder (platinum black) and as a spongy substance (spongy platinum) and may have been known in Pliny's time as "alutiae". [NIH]

Pleated: Particular three-dimensional pattern of amyloidoses. [NIH]

Plumbism: Disease caused by the gradual accumulation of a significant body burden of lead. [NIH]

Point Mutation: A mutation caused by the substitution of one nucleotide for another. This results in the DNA molecule having a change in a single base pair. [NIH]

Poisoning: A condition or physical state produced by the ingestion, injection or inhalation of, or exposure to a deleterious agent. [NIH]

Polycystic: An inherited disorder characterized by many grape-like clusters of fluid-filled cysts that make both kidneys larger over time. These cysts take over and destroy working kidney tissue. PKD may cause chronic renal failure and end-stage renal disease. [NIH]

Polyethylene: A vinyl polymer made from ethylene. It can be branched or linear. Branched or low-density polyethylene is tough and pliable but not to the same degree as linear polyethylene. Linear or high-density polyethylene has a greater hardness and tensile strength. Polyethylene is used in a variety of products, including implants and prostheses. [NIH]

Polymerase: An enzyme which catalyses the synthesis of DNA using a single DNA strand as a template. The polymerase copies the template in the 5'-3'direction provided that sufficient quantities of free nucleotides, dATP and dTTP are present. [NIH]

Polymerase Chain Reaction: In vitro method for producing large amounts of specific DNA or RNA fragments of defined length and sequence from small amounts of short oligonucleotide flanking sequences (primers). The essential steps include thermal denaturation of the double-stranded target molecules, annealing of the primers to their complementary sequences, and extension of the annealed primers by enzymatic synthesis with DNA polymerase. The reaction is efficient, specific, and extremely sensitive. Uses for the reaction include disease diagnosis, detection of difficult-to-isolate pathogens, mutation analysis, genetic testing, DNA sequencing, and analyzing evolutionary relationships. [NIH]

Polymers: Compounds formed by the joining of smaller, usually repeating, units linked by covalent bonds. These compounds often form large macromolecules (e.g., polypeptides, proteins, plastics). [NIH]

Polymorphism: The occurrence together of two or more distinct forms in the same population. [NIH]

Polypeptide: A peptide which on hydrolysis yields more than two amino acids; called tripeptides, tetrapeptides, etc. according to the number of amino acids contained. [EU]

Polysaccharide: A type of carbohydrate. It contains sugar molecules that are linked together chemically. [NIH]

Polyunsaturated fat: An unsaturated fat found in greatest amounts in foods derived from plants, including safflower, sunflower, corn, and soybean oils. [NIH]

Porphyria: A group of disorders characterized by the excessive production of porphyrins or their precursors that arises from abnormalities in the regulation of the porphyrin-heme pathway. The porphyrias are usually divided into three broad groups, erythropoietic, hepatic, and erythrohepatic, according to the major sites of abnormal porphyrin synthesis. [NIH]

Porphyrins: A group of compounds containing the porphin structure, four pyrrole rings connected by methine bridges in a cyclic configuration to which a variety of side chains are attached. The nature of the side chain is indicated by a prefix, as uroporphyrin, hematoporphyrin, etc. The porphyrins, in combination with iron, form the heme component in biologically significant compounds such as hemoglobin and myoglobin. [NIH]

Posterior: Situated in back of, or in the back part of, or affecting the back or dorsal surface of the body. In lower animals, it refers to the caudal end of the body. [EU]

Postmenopausal: Refers to the time after menopause. Menopause is the time in a woman's life when menstrual periods stop permanently; also called "change of life." [NIH]

Postnatal: Occurring after birth, with reference to the newborn. [EU]

Post-translational: The cleavage of signal sequence that directs the passage of the protein through a cell or organelle membrane. [NIH]

Potassium: An element that is in the alkali group of metals. It has an atomic symbol K, atomic number 19, and atomic weight 39.10. It is the chief cation in the intracellular fluid of muscle and other cells. Potassium ion is a strong electrolyte and it plays a significant role in the regulation of fluid volume and maintenance of the water-electrolyte balance. [NIH]

Practice Guidelines: Directions or principles presenting current or future rules of policy for the health care practitioner to assist him in patient care decisions regarding diagnosis, therapy, or related clinical circumstances. The guidelines may be developed by government agencies at any level, institutions, professional societies, governing boards, or by the

convening of expert panels. The guidelines form a basis for the evaluation of all aspects of health care and delivery. [NIH]

Preclinical: Before a disease becomes clinically recognizable. [EU]

Precursor: Something that precedes. In biological processes, a substance from which another, usually more active or mature substance is formed. In clinical medicine, a sign or symptom that heralds another. [EU]

Prenatal: Existing or occurring before birth, with reference to the fetus. [EU]

Prenatal Diagnosis: Determination of the nature of a pathological condition or disease in the postimplantation embryo, fetus, or pregnant female before birth. [NIH]

Presbycusis: Progressive bilateral loss of hearing that occurs in the aged. Syn: senile deafness. [NIH]

Prevalence: The total number of cases of a given disease in a specified population at a designated time. It is differentiated from incidence, which refers to the number of new cases in the population at a given time. [NIH]

Priapism: Persistent abnormal erection of the penis, usually without sexual desire, and accompanied by pain and tenderness. It is seen in diseases and injuries of the spinal cord, and may be caused by vesical calculus and certain injuries to the penis. [EU]

Primary endpoint: The main result that is measured at the end of a study to see if a given treatment worked (e.g., the number of deaths or the difference in survival between the treatment group and the control group). What the primary endpoint will be is decided before the study begins. [NIH]

Probe: An instrument used in exploring cavities, or in the detection and dilatation of strictures, or in demonstrating the potency of channels; an elongated instrument for exploring or sounding body cavities. [NIH]

Progeny: The offspring produced in any generation. [NIH]

Progesterone: Pregn-4-ene-3,20-dione. The principal progestational hormone of the body, secreted by the corpus luteum, adrenal cortex, and placenta. Its chief function is to prepare the uterus for the reception and development of the fertilized ovum. It acts as an antiovulatory agent when administered on days 5-25 of the menstrual cycle. [NIH]

Progression: Increase in the size of a tumor or spread of cancer in the body. [NIH]

Progressive: Advancing; going forward; going from bad to worse; increasing in scope or severity. [EU]

Promazine: A phenothiazine with actions similar to chlorpromazine but with less antipsychotic activity. It is primarily used in short-term treatment of disturbed behavior and as an antiemetic. [NIH]

Promoter: A chemical substance that increases the activity of a carcinogenic process. [NIH]

Prophase: The first phase of cell division, in which the chromosomes become visible, the nucleus starts to lose its identity, the spindle appears, and the centrioles migrate toward opposite poles. [NIH]

Prophylaxis: An attempt to prevent disease. [NIH]

Prospective study: An epidemiologic study in which a group of individuals (a cohort), all free of a particular disease and varying in their exposure to a possible risk factor, is followed over a specific amount of time to determine the incidence rates of the disease in the exposed and unexposed groups. [NIH]

Prostate: A gland in males that surrounds the neck of the bladder and the urethra. It secretes a substance that liquifies coagulated semen. It is situated in the pelvic cavity behind the

lower part of the pubic symphysis, above the deep layer of the triangular ligament, and rests upon the rectum. [NIH]

Protease: Proteinase (= any enzyme that catalyses the splitting of interior peptide bonds in a protein). [EU]

Protein C: A vitamin-K dependent zymogen present in the blood, which, upon activation by thrombin and thrombomodulin exerts anticoagulant properties by inactivating factors Va and VIIIa at the rate-limiting steps of thrombin formation. [NIH]

Protein S: The vitamin K-dependent cofactor of activated protein C. Together with protein C, it inhibits the action of factors VIIIa and Va. A deficiency in protein S can lead to recurrent venous and arterial thrombosis. [NIH]

Proteins: Polymers of amino acids linked by peptide bonds. The specific sequence of amino acids determines the shape and function of the protein. [NIH]

Proteinuria: The presence of protein in the urine, indicating that the kidneys are not working properly. [NIH]

Proteoglycans: Glycoproteins which have a very high polysaccharide content. [NIH]

Proteolytic: 1. Pertaining to, characterized by, or promoting proteolysis. 2. An enzyme that promotes proteolysis (= the splitting of proteins by hydrolysis of the peptide bonds with formation of smaller polypeptides). [EU]

Prothrombin: A plasma protein that is the inactive precursor of thrombin. It is converted to thrombin by a prothrombin activator complex consisting of factor Xa, factor V, phospholipid, and calcium ions. Deficiency of prothrombin leads to hypoprothrombinemia. [NIH]

Protocol: The detailed plan for a clinical trial that states the trial's rationale, purpose, drug or vaccine dosages, length of study, routes of administration, who may participate, and other aspects of trial design. [NIH]

Protons: Stable elementary particles having the smallest known positive charge, found in the nuclei of all elements. The proton mass is less than that of a neutron. A proton is the nucleus of the light hydrogen atom, i.e., the hydrogen ion. [NIH]

Proximal: Nearest; closer to any point of reference; opposed to distal. [EU]

Psychiatric: Pertaining to or within the purview of psychiatry. [EU]

Psychiatry: The medical science that deals with the origin, diagnosis, prevention, and treatment of mental disorders. [NIH]

Psychic: Pertaining to the psyche or to the mind; mental. [EU]

Psychology: The science dealing with the study of mental processes and behavior in man and animals. [NIH]

Psychosis: A mental disorder characterized by gross impairment in reality testing as evidenced by delusions, hallucinations, markedly incoherent speech, or disorganized and agitated behaviour without apparent awareness on the part of the patient of the incomprehensibility of his behaviour; the term is also used in a more general sense to refer to mental disorders in which mental functioning is sufficiently impaired as to interfere grossly with the patient's capacity to meet the ordinary demands of life. Historically, the term has been applied to many conditions, e.g. manic-depressive psychosis, that were first described in psychotic patients, although many patients with the disorder are not judged psychotic. [EU]

Public Assistance: Financial assistance to impoverished persons for the essentials of living through federal, state or local government programs. [NIH]

Public Health: Branch of medicine concerned with the prevention and control of disease and disability, and the promotion of physical and mental health of the population on the international, national, state, or municipal level. [NIH]

Public Policy: A course or method of action selected, usually by a government, from among alternatives to guide and determine present and future decisions. [NIH]

Publishing: "The business or profession of the commercial production and issuance of literature" (Webster's 3d). It includes the publisher, publication processes, editing and editors. Production may be by conventional printing methods or by electronic publishing. [NIH]

Pulmonary: Relating to the lungs. [NIH]

Pulmonary Artery: The short wide vessel arising from the conus arteriosus of the right ventricle and conveying unaerated blood to the lungs. [NIH]

Pulmonary Edema: An accumulation of an excessive amount of watery fluid in the lungs, may be caused by acute exposure to dangerous concentrations of irritant gasses. [NIH]

Pulmonary Embolism: Embolism in the pulmonary artery or one of its branches. [NIH]

Pulmonary hypertension: Abnormally high blood pressure in the arteries of the lungs. [NIH]

Pulmonary Ventilation: The total volume of gas per minute inspired or expired measured in liters per minute. [NIH]

Pulse: The rhythmical expansion and contraction of an artery produced by waves of pressure caused by the ejection of blood from the left ventricle of the heart as it contracts. [NIH]

Purifying: Respiratory equipment whose function is to remove contaminants from otherwise wholesome air. [NIH]

Purines: A series of heterocyclic compounds that are variously substituted in nature and are known also as purine bases. They include adenine and guanine, constituents of nucleic acids, as well as many alkaloids such as caffeine and theophylline. Uric acid is the metabolic end product of purine metabolism. [NIH]

Pustular: Pertaining to or of the nature of a pustule; consisting of pustules (= a visible collection of pus within or beneath the epidermis). [EU]

Putrefaction: The process of decomposition of animal and vegetable matter by living organisms. [NIH]

Pyogenic: Producing pus; pyopoietic (= liquid inflammation product made up of cells and a thin fluid called liquor puris). [EU]

Pyridoxal: 3-Hydroxy-5-(hydroxymethyl)-2-methyl-4- pyridinecarboxaldehyde. [NIH]

Quality of Life: A generic concept reflecting concern with the modification and enhancement of life attributes, e.g., physical, political, moral and social environment. [NIH]

Quiescent: Marked by a state of inactivity or repose. [EU]

Race: A population within a species which exhibits general similarities within itself, but is both discontinuous and distinct from other populations of that species, though not sufficiently so as to achieve the status of a taxon. [NIH]

Radiation: Emission or propagation of electromagnetic energy (waves/rays), or the waves/rays themselves; a stream of electromagnetic particles (electrons, neutrons, protons, alpha particles) or a mixture of these. The most common source is the sun. [NIH]

Radiation oncologist: A doctor who specializes in using radiation to treat cancer. [NIH]

Radiation therapy: The use of high-energy radiation from x-rays, gamma rays, neutrons,

and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body in the area near cancer cells (internal radiation therapy, implant radiation, or brachytherapy). Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. Also called radiotherapy. [NIH]

Radioactive: Giving off radiation. [NIH]

Radioimmunotherapy: Radiotherapy where cytotoxic radionuclides are linked to antibodies in order to deliver toxins directly to tumor targets. Therapy with targeted radiation rather than antibody-targeted toxins (immunotoxins) has the advantage that adjacent tumor cells, which lack the appropriate antigenic determinants, can be destroyed by radiation cross-fire. Radioimmunotherapy is sometimes called targeted radiotherapy, but this latter term can also refer to radionuclides linked to non-immune molecules (radiotherapy). [NIH]

Radioisotope: An unstable element that releases radiation as it breaks down. Radioisotopes can be used in imaging tests or as a treatment for cancer. [NIH]

Radiolabeled: Any compound that has been joined with a radioactive substance. [NIH]

Radiotherapy: The use of ionizing radiation to treat malignant neoplasms and other benign conditions. The most common forms of ionizing radiation used as therapy are x-rays, gamma rays, and electrons. A special form of radiotherapy, targeted radiotherapy, links a cytotoxic radionuclide to a molecule that targets the tumor. When this molecule is an antibody or other immunologic molecule, the technique is called radioimmunotherapy. [NIH]

Randomized: Describes an experiment or clinical trial in which animal or human subjects are assigned by chance to separate groups that compare different treatments. [NIH]

Reabsorption: 1. The act or process of absorbing again, as the selective absorption by the kidneys of substances (glucose, proteins, sodium, etc.) already secreted into the renal tubules, and their return to the circulating blood. 2. Resorption. [EU]

Reactivation: The restoration of activity to something that has been inactivated. [EU]

Reagent: A substance employed to produce a chemical reaction so as to detect, measure, produce, etc., other substances. [EU]

Reality Testing: The individual's objective evaluation of the external world and the ability to differentiate adequately between it and the internal world; considered to be a primary ego function. [NIH]

Receptor: A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell. [NIH]

Recessive gene: A gene that is phenotypically expressed only when homozygous. [NIH]

Recombinant: A cell or an individual with a new combination of genes not found together in either parent; usually applied to linked genes. [EU]

Recombination: The formation of new combinations of genes as a result of segregation in crosses between genetically different parents; also the rearrangement of linked genes due to crossing-over. [NIH]

Reconstitution: 1. A type of regeneration in which a new organ forms by the rearrangement of tissues rather than from new formation at an injured surface. 2. The restoration to original form of a substance previously altered for preservation and storage, as the restoration to a liquid state of blood serum or plasma that has been dried and stored. [EU]

Rectum: The last 8 to 10 inches of the large intestine. [NIH]

Recurrence: The return of a sign, symptom, or disease after a remission. [NIH]

Red blood cells: RBCs. Cells that carry oxygen to all parts of the body. Also called erythrocytes. [NIH]

Red Nucleus: A pinkish-yellow portion of the midbrain situated in the rostral mesencephalic tegmentum. It receives a large projection from the contralateral half of the cerebellum via the superior cerebellar peduncle and a projection from the ipsilateral motor cortex. [NIH]

Reductase: Enzyme converting testosterone to dihydrotestosterone. [NIH]

Refer: To send or direct for treatment, aid, information, de decision. [NIH]

Refractory: Not readily yielding to treatment. [EU]

Regeneration: The natural renewal of a structure, as of a lost tissue or part. [EU]

Regimen: A treatment plan that specifies the dosage, the schedule, and the duration of treatment. [NIH]

Remission: A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although there still may be cancer in the body. [NIH]

Renal failure: Progressive renal insufficiency and uremia, due to irreversible and progressive renal glomerular tubular or interstitial disease. [NIH]

Renal pelvis: The area at the center of the kidney. Urine collects here and is funneled into the ureter, the tube that connects the kidney to the bladder. [NIH]

Renin: An enzyme which is secreted by the kidney and is formed from prorenin in plasma and kidney. The enzyme cleaves the Leu-Leu bond in angiotensinogen to generate angiotensin I. EC 3.4.23.15. (Formerly EC 3.4.99.19). [NIH]

Renin-Angiotensin System: A system consisting of renin, angiotensin-converting enzyme, and angiotensin II. Renin, an enzyme produced in the kidney, acts on angiotensinogen, an alpha-2 globulin produced by the liver, forming angiotensin I. The converting enzyme contained in the lung acts on angiotensin I in the plasma converting it to angiotensin II, the most powerful directly pressor substance known. It causes contraction of the arteriolar smooth muscle and has other indirect actions mediated through the adrenal cortex. [NIH]

Repopulation: The replacement of functional cells, usually by proliferation, following or during irradiation. [NIH]

Repressor: Any of the specific allosteric protein molecules, products of regulator genes, which bind to the operator of operons and prevent RNA polymerase from proceeding into the operon to transcribe messenger RNA. [NIH]

Repressor Proteins: Proteins which are normally bound to the operator locus of an operon, thereby preventing transcription of the structural genes. In enzyme induction, the substrate of the inducible enzyme binds to the repressor protein, causing its release from the operator and freeing the structural genes for transcription. In enzyme repression, the end product of the enzyme sequence binds to the free repressor protein, the resulting complex then binds to the operator and prevents transcription of the structural genes. [NIH]

Research Design: A plan for collecting and utilizing data so that desired information can be obtained with sufficient precision or so that an hypothesis can be tested properly. [NIH]

Resorption: The loss of substance through physiologic or pathologic means, such as loss of dentin and cementum of a tooth, or of the alveolar process of the mandible or maxilla. [EU]

Respiration: The act of breathing with the lungs, consisting of inspiration, or the taking into the lungs of the ambient air, and of expiration, or the expelling of the modified air which

contains more carbon dioxide than the air taken in (Blakiston's Gould Medical Dictionary, 4th ed.). This does not include tissue respiration (= oxygen consumption) or cell respiration (= cell respiration). [NIH]

Respiratory distress syndrome: A lung disease that occurs primarily in premature infants; the newborn must struggle for each breath and blueing of its skin reflects the baby's inability to get enough oxygen. [NIH]

Resting metabolic rate: RMR accounts for 65 to 75 percent of daily energy expenditure and represents the minimum energy needed to maintain all physiological cell functions in the resting state. The principal determinant of RMR is lean body mass (LBM). Obese subjects have a higher RMR in absolute terms than lean individuals, an equivalent RMR when corrected for LBM and per unit surface area, and a lower RMR when expressed per kilogram of body weight. Obese persons require more energy for any given activity because of a larger mass, but they tend to be more sedentary than lean subjects. [NIH]

Restoration: Broad term applied to any inlay, crown, bridge or complete denture which restores or replaces loss of teeth or oral tissues. [NIH]

Reticulocytes: Immature erythrocytes. In humans, these are erythroid cells that have just undergone extrusion of their cell nucleus. They still contain some organelles that gradually decrease in number as the cells mature. ribosomes are last to disappear. Certain staining techniques cause components of the ribosomes to precipitate into characteristic "reticulum" (not the same as the endoplasmic reticulum), hence the name reticulocytes. [NIH]

Retina: The ten-layered nervous tissue membrane of the eye. It is continuous with the optic nerve and receives images of external objects and transmits visual impulses to the brain. Its outer surface is in contact with the choroid and the inner surface with the vitreous body. The outer-most layer is pigmented, whereas the inner nine layers are transparent. [NIH]

Retinal: 1. Pertaining to the retina. 2. The aldehyde of retinol, derived by the oxidative enzymatic splitting of absorbed dietary carotene, and having vitamin A activity. In the retina, retinal combines with opsins to form visual pigments. One isomer, 11-cis retinal combines with opsin in the rods (scotopsin) to form rhodopsin, or visual purple. Another, all-trans retinal (trans-r.); visual yellow; xanthopsin) results from the bleaching of rhodopsin by light, in which the 11-cis form is converted to the all-trans form. Retinal also combines with opsins in the cones (photopsins) to form the three pigments responsible for colour vision. Called also retinal, and retinene1. [EU]

Retinal Detachment: Separation of the inner layers of the retina (neural retina) from the pigment epithelium. Retinal detachment occurs more commonly in men than in women, in eyes with degenerative myopia, in aging and in aphakia. It may occur after an uncomplicated cataract extraction, but it is seen more often if vitreous humor has been lost during surgery. (Dorland, 27th ed; Newell, Ophthalmology: Principles and Concepts, 7th ed, p310-12). [NIH]

Retinal pigment epithelium: The pigment cell layer that nourishes the retinal cells; located just outside the retina and attached to the choroid. [NIH]

Retinoblastoma: An eye cancer that most often occurs in children younger than 5 years. It occurs in hereditary and nonhereditary (sporadic) forms. [NIH]

Retinol: Vitamin A. It is essential for proper vision and healthy skin and mucous membranes. Retinol is being studied for cancer prevention; it belongs to the family of drugs called retinoids. [NIH]

Retinopathy: 1. Retinitis (= inflammation of the retina). 2. Retinosis (= degenerative, noninflammatory condition of the retina). [EU]

Retrocochlear: Hearing loss in which the air conduction threshold and the bone conduction

threshold have risen almost equally with no gap between them. In such cases the defect is usually either in the cochlea of the inner ear or in the central pathways. [NIH]

Retroviral vector: RNA from a virus that is used to insert genetic material into cells. [NIH]

Rheology: The study of the deformation and flow of matter, usually liquids or fluids, and of the plastic flow of solids. The concept covers consistency, dilatancy, liquefaction, resistance to flow, shearing, thixotrophy, and viscosity. [NIH]

Rheumatism: A group of disorders marked by inflammation or pain in the connective tissue structures of the body. These structures include bone, cartilage, and fat. [NIH]

Rheumatoid: Resembling rheumatism. [EU]

Rheumatoid arthritis: A form of arthritis, the cause of which is unknown, although infection, hypersensitivity, hormone imbalance and psychologic stress have been suggested as possible causes. [NIH]

Riboflavin: Nutritional factor found in milk, eggs, malted barley, liver, kidney, heart, and leafy vegetables. The richest natural source is yeast. It occurs in the free form only in the retina of the eye, in whey, and in urine; its principal forms in tissues and cells are as FMN and FAD. [NIH]

Ribonucleoside Diphosphate Reductase: An enzyme of the oxidoreductase class that catalyzes the formation of 2'-deoxyribonucleotides from the corresponding ribonucleotides using NADPH as the ultimate electron donor. The deoxyribonucleoside diphosphates are used in DNA synthesis. (From Dorland, 27th ed) EC 1.17.4.1. [NIH]

Ribose: A pentose active in biological systems usually in its D-form. [NIH]

Rigidity: Stiffness or inflexibility, chiefly that which is abnormal or morbid; rigor. [EU]

Risk factor: A habit, trait, condition, or genetic alteration that increases a person's chance of developing a disease. [NIH]

Rod: A reception for vision, located in the retina. [NIH]

Rubber: A high-molecular-weight polymeric elastomer derived from the milk juice (latex) of Hevea brasiliensis and other trees. It is a substance that can be stretched at room temperature to atleast twice its original length and after releasing the stress, retractrapidly, and recover its original dimensions fully. Synthetic rubber is made from many different chemicals, including styrene, acrylonitrile, ethylene, propylene, and isoprene. [NIH]

Rutin: 3-((6-O-(6-Deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranosyl)oxy)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one. Found in many plants, including buckwheat, tobacco, forsythia, hydrangea, pansies, etc. It has been used therapeutically to decrease capillary fragility. [NIH]

Saline: A solution of salt and water. [NIH]

Salivary: The duct that convey saliva to the mouth. [NIH]

Salivary glands: Glands in the mouth that produce saliva. [NIH]

Salmonella: A genus of gram-negative, facultatively anaerobic, rod-shaped bacteria that utilizes citrate as a sole carbon source. It is pathogenic for humans, causing enteric fevers, gastroenteritis, and bacteremia. Food poisoning is the most common clinical manifestation. Organisms within this genus are separated on the basis of antigenic characteristics, sugar fermentation patterns, and bacteriophage susceptibility. [NIH]

Saponification: The hydrolysis of an ester into an alcohol and acid. [NIH]

Saponins: Sapogenin glycosides. A type of glycoside widely distributed in plants. Each consists of a sapogenin as the aglycon moiety, and a sugar. The sapogenin may be a steroid or a triterpene and the sugar may be glucose, galactose, a pentose, or a methylpentose.

Sapogenins are poisonous towards the lower forms of life and are powerful hemolytics when injected into the blood stream able to dissolve red blood cells at even extreme dilutions. [NIH]

Scans: Pictures of structures inside the body. Scans often used in diagnosing, staging, and monitoring disease include liver scans, bone scans, and computed tomography (CT) or computerized axial tomography (CAT) scans and magnetic resonance imaging (MRI) scans. In liver scanning and bone scanning, radioactive substances that are injected into the bloodstream collect in these organs. A scanner that detects the radiation is used to create pictures. In CT scanning, an x-ray machine linked to a computer is used to produce detailed pictures of organs inside the body. MRI scans use a large magnet connected to a computer to create pictures of areas inside the body. [NIH]

Scarlet Fever: Infection with group A streptococci that is characterized by tonsillitis and pharyngitis. An erythematous rash is commonly present. [NIH]

Schizophrenia: A mental disorder characterized by a special type of disintegration of the personality. [NIH]

Schwannoma: A tumor of the peripheral nervous system that begins in the nerve sheath (protective covering). It is almost always benign, but rare malignant schwannomas have been reported. [NIH]

Sclera: The tough white outer coat of the eyeball, covering approximately the posterior five-sixths of its surface, and continuous anteriorly with the cornea and posteriorly with the external sheath of the optic nerve. [EU]

Scleroproteins: Simple proteins characterized by their insolubility and fibrous structure. Within the body, they perform a supportive or protective function. [NIH]

Sclerosis: A pathological process consisting of hardening or fibrosis of an anatomical structure, often a vessel or a nerve. [NIH]

Screening: Checking for disease when there are no symptoms. [NIH]

Secondary tumor: Cancer that has spread from the organ in which it first appeared to another organ. For example, breast cancer cells may spread (metastasize) to the lungs and cause the growth of a new tumor. When this happens, the disease is called metastatic breast cancer, and the tumor in the lungs is called a secondary tumor. Also called secondary cancer. [NIH]

Secretion: 1. The process of elaborating a specific product as a result of the activity of a gland; this activity may range from separating a specific substance of the blood to the elaboration of a new chemical substance. 2. Any substance produced by secretion. [EU]

Secretory: Secreting; relating to or influencing secretion or the secretions. [NIH]

Sedentary: 1. Sitting habitually; of inactive habits. 2. Pertaining to a sitting posture. [EU]

Segmental: Describing or pertaining to a structure which is repeated in similar form in successive segments of an organism, or which is undergoing segmentation. [NIH]

Segregation: The separation in meiotic cell division of homologous chromosome pairs and their contained allelomorphic gene pairs. [NIH]

Seizures: Clinical or subclinical disturbances of cortical function due to a sudden, abnormal, excessive, and disorganized discharge of brain cells. Clinical manifestations include abnormal motor, sensory and psychic phenomena. Recurrent seizures are usually referred to as epilepsy or "seizure disorder." [NIH]

Selenium: An element with the atomic symbol Se, atomic number 34, and atomic weight 78.96. It is an essential micronutrient for mammals and other animals but is toxic in large

amounts. Selenium protects intracellular structures against oxidative damage. It is an essential component of glutathione peroxidase. [NIH]

Semen: The thick, yellowish-white, viscid fluid secretion of male reproductive organs discharged upon ejaculation. In addition to reproductive organ secretions, it contains spermatozoa and their nutrient plasma. [NIH]

Senile: Relating or belonging to old age; characteristic of old age; resulting from infirmity of old age. [NIH]

Septic: Produced by or due to decomposition by microorganisms; putrefactive. [EU]

Sequela: Any lesion or affection following or caused by an attack of disease. [EU]

Sequencing: The determination of the order of nucleotides in a DNA or RNA chain. [NIH]

Sequester: A portion of dead bone which has become detached from the healthy bone tissue, as occurs in necrosis. [NIH]

Serine: A non-essential amino acid occurring in natural form as the L-isomer. It is synthesized from glycine or threonine. It is involved in the biosynthesis of purines, pyrimidines, and other amino acids. [NIH]

Serotonin: A biochemical messenger and regulator, synthesized from the essential amino acid L-tryptophan. In humans it is found primarily in the central nervous system, gastrointestinal tract, and blood platelets. Serotonin mediates several important physiological functions including neurotransmission, gastrointestinal motility, hemostasis, and cardiovascular integrity. Multiple receptor families (receptors, serotonin) explain the broad physiological actions and distribution of this biochemical mediator. [NIH]

Serous: Having to do with serum, the clear liquid part of blood. [NIH]

Serum: The clear liquid part of the blood that remains after blood cells and clotting proteins have been removed. [NIH]

Sex Characteristics: Those characteristics that distinguish one sex from the other. The primary sex characteristics are the ovaries and testes and their related hormones. Secondary sex characteristics are those which are masculine or feminine but not directly related to reproduction. [NIH]

Sex Determination: The biological characteristics which distinguish human beings as female or male. [NIH]

Shock: The general bodily disturbance following a severe injury; an emotional or moral upset occasioned by some disturbing or unexpected experience; disruption of the circulation, which can upset all body functions: sometimes referred to as circulatory shock. [NIH]

Shunt: A surgically created diversion of fluid (e.g., blood or cerebrospinal fluid) from one area of the body to another area of the body. [NIH]

Sickle Cell Trait: The condition of being heterozygous for hemoglobin S. [NIH]

Side effect: A consequence other than the one(s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other than the one sought to be benefited by its administration. [EU]

Signal Transduction: The intercellular or intracellular transfer of information (biological activation/inhibition) through a signal pathway. In each signal transduction system, an activation/inhibition signal from a biologically active molecule (hormone, neurotransmitter) is mediated via the coupling of a receptor/enzyme to a second messenger system or to an ion channel. Signal transduction plays an important role in activating cellular functions, cell differentiation, and cell proliferation. Examples of signal transduction systems are the

GABA-postsynaptic receptor-calcium ion channel system, the receptor-mediated T-cell activation pathway, and the receptor-mediated activation of phospholipases. Those coupled to membrane depolarization or intracellular release of calcium include the receptor-mediated activation of cytotoxic functions in granulocytes and the synaptic potentiation of protein kinase activation. Some signal transduction pathways may be part of larger signal transduction pathways; for example, protein kinase activation is part of the platelet activation signal pathway. [NIH]

Skeletal: Having to do with the skeleton (boney part of the body). [NIH]

Skeleton: The framework that supports the soft tissues of vertebrate animals and protects many of their internal organs. The skeletons of vertebrates are made of bone and/or cartilage. [NIH]

Skull: The skeleton of the head including the bones of the face and the bones enclosing the brain. [NIH]

Sludge: A clump of agglutinated red blood cells. [NIH]

Small intestine: The part of the digestive tract that is located between the stomach and the large intestine. [NIH]

Social Environment: The aggregate of social and cultural institutions, forms, patterns, and processes that influence the life of an individual or community. [NIH]

Social Support: Support systems that provide assistance and encouragement to individuals with physical or emotional disabilities in order that they may better cope. Informal social support is usually provided by friends, relatives, or peers, while formal assistance is provided by churches, groups, etc. [NIH]

Social Work: The use of community resources, individual case work, or group work to promote the adaptive capacities of individuals in relation to their social and economic environments. It includes social service agencies. [NIH]

Sodium: An element that is a member of the alkali group of metals. It has the atomic symbol Na, atomic number 11, and atomic weight 23. With a valence of 1, it has a strong affinity for oxygen and other nonmetallic elements. Sodium provides the chief cation of the extracellular body fluids. Its salts are the most widely used in medicine. (From Dorland, 27th ed) Physiologically the sodium ion plays a major role in blood pressure regulation, maintenance of fluid volume, and electrolyte balance. [NIH]

Soft tissue: Refers to muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body. [NIH]

Solid tumor: Cancer of body tissues other than blood, bone marrow, or the lymphatic system. [NIH]

Solvent: 1. Dissolving; effecting a solution. 2. A liquid that dissolves or that is capable of dissolving; the component of a solution that is present in greater amount. [EU]

Somatic: 1. Pertaining to or characteristic of the soma or body. 2. Pertaining to the body wall in contrast to the viscera. [EU]

Sorbitol: A polyhydric alcohol with about half the sweetness of sucrose. Sorbitol occurs naturally and is also produced synthetically from glucose. It was formerly used as a diuretic and may still be used as a laxative and in irrigating solutions for some surgical procedures. It is also used in many manufacturing processes, as a pharmaceutical aid, and in several research applications. [NIH]

Sound wave: An alteration of properties of an elastic medium, such as pressure, particle displacement, or density, that propagates through the medium, or a superposition of such alterations. [NIH]

Soybean Oil: Oil from soybean or soybean plant. [NIH]

Specialist: In medicine, one who concentrates on 1 special branch of medical science. [NIH]

Species: A taxonomic category subordinate to a genus (or subgenus) and superior to a subspecies or variety, composed of individuals possessing common characters distinguishing them from other categories of individuals of the same taxonomic level. In taxonomic nomenclature, species are designated by the genus name followed by a Latin or Latinized adjective or noun. [EU]

Specificity: Degree of selectivity shown by an antibody with respect to the number and types of antigens with which the antibody combines, as well as with respect to the rates and the extents of these reactions. [NIH]

Spectrin: A high molecular weight (220-250 kDa) water-soluble protein which can be extracted from erythrocyte ghosts in low ionic strength buffers. The protein contains no lipids or carbohydrates, is the predominant species of peripheral erythrocyte membrane proteins, and exists as a fibrous coating on the inner, cytoplasmic surface of the membrane. [NIH]

Spectrum: A charted band of wavelengths of electromagnetic vibrations obtained by refraction and diffraction. By extension, a measurable range of activity, such as the range of bacteria affected by an antibiotic (antibacterial s.) or the complete range of manifestations of a disease. [EU]

Sperm: The fecundating fluid of the male. [NIH]

Spherocytes: Small, abnormal spherical red blood cells with more than the normal amount of hemoglobin. [NIH]

Spherocytosis: A condition in which there are abnormally thick, almost spherical, red blood cells or spherocytes in the blood. [NIH]

Spinal cord: The main trunk or bundle of nerves running down the spine through holes in the spinal bone (the vertebrae) from the brain to the level of the lower back. [NIH]

Spinal Cord Diseases: Pathologic conditions which feature spinal cord damage or dysfunction, including disorders involving the meninges and perimeningeal spaces surrounding the spinal cord. Traumatic injuries, vascular diseases, infections, and inflammatory/autoimmune processes may affect the spinal cord. [NIH]

Spleen: An organ that is part of the lymphatic system. The spleen produces lymphocytes, filters the blood, stores blood cells, and destroys old blood cells. It is located on the left side of the abdomen near the stomach. [NIH]

Splenomegaly: Enlargement of the spleen. [NIH]

Sporadic: Neither endemic nor epidemic; occurring occasionally in a random or isolated manner. [EU]

Sports Medicine: The field of medicine concerned with physical fitness and the diagnosis and treatment of injuries sustained in sports activities. [NIH]

Stabilization: The creation of a stable state. [EU]

Staging: Performing exams and tests to learn the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. [NIH]

Standardize: To compare with or conform to a standard; to establish standards. [EU]

Staphylococcus: A genus of gram-positive, facultatively anaerobic, coccoid bacteria. Its organisms occur singly, in pairs, and in tetrads and characteristically divide in more than one plane to form irregular clusters. Natural populations of Staphylococcus are membranes

of warm-blooded animals. Some species are opportunistic pathogens of humans and animals. [NIH]

Staphylococcus aureus: Potentially pathogenic bacteria found in nasal membranes, skin, hair follicles, and perineum of warm-blooded animals. They may cause a wide range of infections and intoxications. [NIH]

Stasis: A word termination indicating the maintenance of (or maintaining) a constant level; preventing increase or multiplication. [EU]

Statistically significant: Describes a mathematical measure of difference between groups. The difference is said to be statistically significant if it is greater than what might be expected to happen by chance alone. [NIH]

Steady state: Dynamic equilibrium. [EU]

Stem cell transplantation: A method of replacing immature blood-forming cells that were destroyed by cancer treatment. The stem cells are given to the person after treatment to help the bone marrow recover and continue producing healthy blood cells. [NIH]

Stem Cells: Relatively undifferentiated cells of the same lineage (family type) that retain the ability to divide and cycle throughout postnatal life to provide cells that can become specialized and take the place of those that die or are lost. [NIH]

Sterile: Unable to produce children. [NIH]

Sterility: 1. The inability to produce offspring, i.e., the inability to conceive (female s.) or to induce conception (male s.). 2. The state of being aseptic, or free from microorganisms. [EU]

Sternum: Breast bone. [NIH]

Steroid: A group name for lipids that contain a hydrogenated cyclopentanoperhydrophenanthrene ring system. Some of the substances included in this group are progesterone, adrenocortical hormones, the gonadal hormones, cardiac aglycones, bile acids, sterols (such as cholesterol), toad poisons, saponins, and some of the carcinogenic hydrocarbons. [EU]

Stimulant: 1. Producing stimulation; especially producing stimulation by causing tension on muscle fibre through the nervous tissue. 2. An agent or remedy that produces stimulation. [EU]

Stimulus: That which can elicit or evoke action (response) in a muscle, nerve, gland or other excitable issue, or cause an augmenting action upon any function or metabolic process. [NIH]

Stomach: An organ of digestion situated in the left upper quadrant of the abdomen between the termination of the esophagus and the beginning of the duodenum. [NIH]

Strand: DNA normally exists in the bacterial nucleus in a helix, in which two strands are coiled together. [NIH]

Streptococcal: Caused by infection due to any species of streptococcus. [NIH]

Streptococci: A genus of spherical Gram-positive bacteria occurring in chains or pairs. They are widely distributed in nature, being important pathogens but often found as normal commensals in the mouth, skin, and intestine of humans and other animals. [NIH]

Streptococcus: A genus of gram-positive, coccoid bacteria whose organisms occur in pairs or chains. No endospores are produced. Many species exist as commensals or parasites on man or animals with some being highly pathogenic. A few species are saprophytes and occur in the natural environment. [NIH]

Streptokinase: Streptococcal fibrinolysin . An enzyme produced by hemolytic streptococci. It hydrolyzes amide linkages and serves as an activator of plasminogen. It is used in thrombolytic therapy and is used also in mixtures with streptodornase (streptodornase and

streptokinase). EC 3.4.-. [NIH]

Stress: Forcibly exerted influence; pressure. Any condition or situation that causes strain or tension. Stress may be either physical or psychologic, or both. [NIH]

Stroke: Sudden loss of function of part of the brain because of loss of blood flow. Stroke may be caused by a clot (thrombosis) or rupture (hemorrhage) of a blood vessel to the brain. [NIH]

Stroma: The middle, thickest layer of tissue in the cornea. [NIH]

Stromal: Large, veil-like cell in the bone marrow. [NIH]

Stromal Cells: Connective tissue cells of an organ found in the loose connective tissue. These are most often associated with the uterine mucosa and the ovary as well as the hematopoietic system and elsewhere. [NIH]

Stupor: Partial or nearly complete unconsciousness, manifested by the subject's responding only to vigorous stimulation. Also, in psychiatry, a disorder marked by reduced responsiveness. [EU]

Styrene: A colorless, toxic liquid with a strong aromatic odor. It is used to make rubbers, polymers and copolymers, and polystyrene plastics. [NIH]

Subacute: Somewhat acute; between acute and chronic. [EU]

Subclinical: Without clinical manifestations; said of the early stage(s) of an infection or other disease or abnormality before symptoms and signs become apparent or detectable by clinical examination or laboratory tests, or of a very mild form of an infection or other disease or abnormality. [EU]

Subcutaneous: Beneath the skin. [NIH]

Subspecies: A category intermediate in rank between species and variety, based on a smaller number of correlated characters than are used to differentiate species and generally conditioned by geographical and/or ecological occurrence. [NIH]

Substance P: An eleven-amino acid neurotransmitter that appears in both the central and peripheral nervous systems. It is involved in transmission of pain, causes rapid contractions of the gastrointestinal smooth muscle, and modulates inflammatory and immune responses. [NIH]

Substrate: A substance upon which an enzyme acts. [EU]

Sulfur: An element that is a member of the chalcogen family. It has an atomic symbol S, atomic number 16, and atomic weight 32.066. It is found in the amino acids cysteine and methionine. [NIH]

Superoxide: Derivative of molecular oxygen that can damage cells. [NIH]

Supplementation: Adding nutrients to the diet. [NIH]

Support group: A group of people with similar disease who meet to discuss how better to cope with their cancer and treatment. [NIH]

Suppositories: A small cone-shaped medicament having cocoa butter or gelatin at its basis and usually intended for the treatment of local conditions in the rectum. [NIH]

Suppression: A conscious exclusion of disapproved desire contrary with repression, in which the process of exclusion is not conscious. [NIH]

Suppressive: Tending to suppress : effecting suppression; specifically : serving to suppress activity, function, symptoms. [EU]

Survival Rate: The proportion of survivors in a group, e.g., of patients, studied and followed over a period, or the proportion of persons in a specified group alive at the beginning of a time interval who survive to the end of the interval. It is often studied using

life table methods. [NIH]

Sweat: The fluid excreted by the sweat glands. It consists of water containing sodium chloride, phosphate, urea, ammonia, and other waste products. [NIH]

Sweat Glands: Sweat-producing structures that are embedded in the dermis. Each gland consists of a single tube, a coiled body, and a superficial duct. [NIH]

Sympathomimetic: 1. Mimicking the effects of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. 2. An agent that produces effects similar to those of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. Called also adrenergic. [EU]

Symphysis: A secondary cartilaginous joint. [NIH]

Symptomatic: Having to do with symptoms, which are signs of a condition or disease. [NIH]

Synergistic: Acting together; enhancing the effect of another force or agent. [EU]

Systemic: Affecting the entire body. [NIH]

Systemic disease: Disease that affects the whole body. [NIH]

Systolic: Indicating the maximum arterial pressure during contraction of the left ventricle of the heart. [EU]

Tachycardia: Excessive rapidity in the action of the heart, usually with a heart rate above 100 beats per minute. [NIH]

Tachypnea: Rapid breathing. [NIH]

Tacrolimus: A macrolide isolated from the culture broth of a strain of Streptomyces tsukubaensis that has strong immunosuppressive activity in vivo and prevents the activation of T-lymphocytes in response to antigenic or mitogenic stimulation in vitro. [NIH]

Telangiectasia: The permanent enlargement of blood vessels, causing redness in the skin or mucous membranes. [NIH]

Temporal: One of the two irregular bones forming part of the lateral surfaces and base of the skull, and containing the organs of hearing. [NIH]

Terminator: A DNA sequence sited at the end of a transcriptional unit that signals the end of transcription. [NIH]

Testosterone: A hormone that promotes the development and maintenance of male sex characteristics. [NIH]

Thalamic: Cell that reaches the lateral nucleus of amygdala. [NIH]

Thalamic Diseases: Disorders of the centrally located thalamus, which integrates a wide range of cortical and subcortical information. Manifestations include sensory loss, movement disorders; ataxia, pain syndromes, visual disorders, a variety of neuropsychological conditions, and coma. Relatively common etiologies include cerebrovascular disorders; craniocerebral trauma; brain neoplasms; brain hypoxia; intracranial hemorrhages; and infectious processes. [NIH]

Thalassemia: A group of hereditary hemolytic anemias in which there is decreased synthesis of one or more hemoglobin polypeptide chains. There are several genetic types with clinical pictures ranging from barely detectable hematologic abnormality to severe and fatal anemia. [NIH]

Therapeutics: The branch of medicine which is concerned with the treatment of diseases, palliative or curative. [NIH]

Thermal: Pertaining to or characterized by heat. [EU]

Thigh: A leg; in anatomy, any elongated process or part of a structure more or less

comparable to a leg. [NIH]

Thiocyanates: Organic derivatives of thiocyanic acid which contain the general formula R-SCN. [NIH]

Thorax: A part of the trunk between the neck and the abdomen; the chest. [NIH]

Threonine: An essential amino acid occurring naturally in the L-form, which is the active form. It is found in eggs, milk, gelatin, and other proteins. [NIH]

Threshold: For a specified sensory modality (e. g. light, sound, vibration), the lowest level (absolute threshold) or smallest difference (difference threshold, difference limen) or intensity of the stimulus discernible in prescribed conditions of stimulation. [NIH]

Thrombasthenia: A congenital bleeding disorder with prolonged bleeding time, absence of aggregation of platelets in response to most agents, especially ADP, and impaired or absent clot retraction. Platelet membranes are deficient in or have a defect in the glycoprotein IIb-IIIa complex (platelet glycoprotein GPIIB-IIIA complex). [NIH]

Thrombin: An enzyme formed from prothrombin that converts fibrinogen to fibrin. (Dorland, 27th ed) EC 3.4.21.5. [NIH]

Thrombocytes: Blood cells that help prevent bleeding by causing blood clots to form. Also called platelets. [NIH]

Thrombocytopenia: A decrease in the number of blood platelets. [NIH]

Thromboembolism: Obstruction of a vessel by a blood clot that has been transported from a distant site by the blood stream. [NIH]

Thrombolytic: 1. Dissolving or splitting up a thrombus. 2. A thrombolytic agent. [EU]

Thrombolytic Therapy: Use of infusions of fibrinolytic agents to destroy or dissolve thrombi in blood vessels or bypass grafts. [NIH]

Thrombomodulin: A cell surface glycoprotein of endothelial cells that binds thrombin and serves as a cofactor in the activation of protein C and its regulation of blood coagulation. [NIH]

Thrombophilia: A disorder of hemostasis in which there is a tendency for the occurrence of thrombosis. [NIH]

Thrombosis: The formation or presence of a blood clot inside a blood vessel. [NIH]

Thrombus: An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causing vascular obstruction at the point of its formation. Some authorities thus differentiate thrombus formation from simple coagulation or clot formation. [EU]

Thyroid: A gland located near the windpipe (trachea) that produces thyroid hormone, which helps regulate growth and metabolism. [NIH]

Thyrotropin: A peptide hormone secreted by the anterior pituitary. It promotes the growth of the thyroid gland and stimulates the synthesis of thyroid hormones and the release of thyroxine by the thyroid gland. [NIH]

Thyroxine: An amino acid of the thyroid gland which exerts a stimulating effect on thyroid metabolism. [NIH]

Tic: An involuntary compulsive, repetitive, stereotyped movement, resembling a purposeful movement because it is coordinated and involves muscles in their normal synergistic relationships; tics usually involve the face and shoulders. [EU]

Tin: A trace element that is required in bone formation. It has the atomic symbol Sn, atomic number 50, and atomic weight 118.71. [NIH]

Tinnitus: Sounds that are perceived in the absence of any external noise source which may take the form of buzzing, ringing, clicking, pulsations, and other noises. Objective tinnitus refers to noises generated from within the ear or adjacent structures that can be heard by other individuals. The term subjective tinnitus is used when the sound is audible only to the affected individual. Tinnitus may occur as a manifestation of cochlear diseases; vestibulocochlear nerve diseases; intracranial hypertension; craniocerebral trauma; and other conditions. [NIH]

Tissue: A group or layer of cells that are alike in type and work together to perform a specific function. [NIH]

Tissue Culture: Maintaining or growing of tissue, organ primordia, or the whole or part of an organ in vitro so as to preserve its architecture and/or function (Dorland, 28th ed). Tissue culture includes both organ culture and cell culture. [NIH]

Tissue Plasminogen Activator: A proteolytic enzyme in the serine protease family found in many tissues which converts plasminogen to plasmin. It has fibrin-binding activity and is immunologically different from urinary plasminogen activator. The primary sequence, composed of 527 amino acids, is identical in both the naturally occurring and synthetic proteases. EC 3.4.21.68. [NIH]

Tolerance: 1. The ability to endure unusually large doses of a drug or toxin. 2. Acquired drug tolerance; a decreasing response to repeated constant doses of a drug or the need for increasing doses to maintain a constant response. [EU]

Tomography: Imaging methods that result in sharp images of objects located on a chosen plane and blurred images located above or below the plane. [NIH]

Tonicity: The normal state of muscular tension. [NIH]

Tonsillitis: Inflammation of the tonsils, especially the palatine tonsils. It is often caused by a bacterium. Tonsillitis may be acute, chronic, or recurrent. [NIH]

Torsion: A twisting or rotation of a bodily part or member on its axis. [NIH]

Toxic: Having to do with poison or something harmful to the body. Toxic substances usually cause unwanted side effects. [NIH]

Toxicity: The quality of being poisonous, especially the degree of virulence of a toxic microbe or of a poison. [EU]

Toxicology: The science concerned with the detection, chemical composition, and pharmacologic action of toxic substances or poisons and the treatment and prevention of toxic manifestations. [NIH]

Toxins: Specific, characterizable, poisonous chemicals, often proteins, with specific biological properties, including immunogenicity, produced by microbes, higher plants, or animals. [NIH]

Trace element: Substance or element essential to plant or animal life, but present in extremely small amounts. [NIH]

Tracer: A substance (such as a radioisotope) used in imaging procedures. [NIH]

Trachea: The cartilaginous and membranous tube descending from the larynx and branching into the right and left main bronchi. [NIH]

Transcription Factors: Endogenous substances, usually proteins, which are effective in the initiation, stimulation, or termination of the genetic transcription process. [NIH]

Transduction: The transfer of genes from one cell to another by means of a viral (in the case of bacteria, a bacteriophage) vector or a vector which is similar to a virus particle (pseudovirion). [NIH]

Transfection: The uptake of naked or purified DNA into cells, usually eukaryotic. It is analogous to bacterial transformation. [NIH]

Transfusion: The infusion of components of blood or whole blood into the bloodstream. The blood may be donated from another person, or it may have been taken from the person earlier and stored until needed. [NIH]

Transgenes: Genes that are introduced into an organism using gene transfer techniques. [NIH]

Translational: The cleavage of signal sequence that directs the passage of the protein through a cell or organelle membrane. [NIH]

Transmitter: A chemical substance which effects the passage of nerve impulses from one cell to the other at the synapse. [NIH]

Transplantation: Transference of a tissue or organ, alive or dead, within an individual, between individuals of the same species, or between individuals of different species. [NIH]

Transplantation Conditioning: Preparative treatment of transplant recipient with various conditioning regimens including radiation, immune sera, chemotherapy, and/or immunosuppressive agents, prior to transplantation. Transplantation conditioning is very common before bone marrow transplantation. [NIH]

Transplantation Tolerance: An induced state of non-reactivity to grafted tissue from a donor organism that would ordinarily trigger a cell-mediated or humoral immune response. [NIH]

Transversion: A base-pair substitution mutation in which a purine-pyrimidine pair is replaced by the equivalent pyrimidine-purine pair, i. e. A-T becomes T-A. [NIH]

Trauma: Any injury, wound, or shock, must frequently physical or structural shock, producing a disturbance. [NIH]

Trees: Woody, usually tall, perennial higher plants (Angiosperms, Gymnosperms, and some Pterophyta) having usually a main stem and numerous branches. [NIH]

Tricuspid Valve: The valve consisting of three cusps situated between the right atrium and right ventricle of the heart. [NIH]

Triglyceride: A lipid carried through the blood stream to tissues. Most of the body's fat tissue is in the form of triglycerides, stored for use as energy. Triglycerides are obtained primarily from fat in foods. [NIH]

Trimetrexate: A nonclassical folic acid inhibitor through its inhibition of the enzyme dihydrofolate reductase. It is being tested for efficacy as an antineoplastic agent and as an antiparasitic agent against Pneumocystis carinii pneumonia in AIDS patients. Myelosuppression is its dose-limiting toxic effect. [NIH]

Trypsin: A serine endopeptidase that is formed from trypsinogen in the pancreas. It is converted into its active form by enteropeptidase in the small intestine. It catalyzes hydrolysis of the carboxyl group of either arginine or lysine. EC 3.4.21.4. [NIH]

Tuberculosis: Any of the infectious diseases of man and other animals caused by species of Mycobacterium. [NIH]

Tuberous Sclerosis: A rare congenital disease in which the essential pathology is the appearance of multiple tumors in the cerebrum and in other organs, such as the heart or kidneys. [NIH]

Tumor Necrosis Factor: Serum glycoprotein produced by activated macrophages and other mammalian mononuclear leukocytes which has necrotizing activity against tumor cell lines and increases ability to reject tumor transplants. It mimics the action of endotoxin but differs from it. It has a molecular weight of less than 70,000 kDa. [NIH]

Tympanic membrane: A thin, tense membrane forming the greater part of the outer wall of the tympanic cavity and separating it from the external auditory meatus; it constitutes the boundary between the external and middle ear. [NIH]

Ulcer: A localized necrotic lesion of the skin or a mucous surface. [NIH]

Ulceration: 1. The formation or development of an ulcer. 2. An ulcer. [EU]

Ultrasonography: The visualization of deep structures of the body by recording the reflections of echoes of pulses of ultrasonic waves directed into the tissues. Use of ultrasound for imaging or diagnostic purposes employs frequencies ranging from 1.6 to 10 megahertz. [NIH]

Ultrasound test: A test that bounces sound waves off tissues and internal organs and changes the echoes into pictures (sonograms). [NIH]

Umbilical Arteries: Either of a pair of arteries originating from the internal iliac artery and passing through the umbilical cord to carry blood from the fetus to the placenta. [NIH]

Umbilical Cord: The flexible structure, giving passage to the umbilical arteries and vein, which connects the embryo or fetus to the placenta. [NIH]

Umbilical cord blood: Blood from the placenta (afterbirth) that contains high concentrations of stem cells needed to produce new blood cells. [NIH]

Unconscious: Experience which was once conscious, but was subsequently rejected, as the "personal unconscious". [NIH]

Univalent: Pertaining to an unpaired chromosome during the zygotene stage of prophase to first metaphase in meiosis. [NIH]

Uracil: An anticancer drug that belongs to the family of drugs called alkylating agents. [NIH]

Urea: A compound (CO(NH2)2), formed in the liver from ammonia produced by the deamination of amino acids. It is the principal end product of protein catabolism and constitutes about one half of the total urinary solids. [NIH]

Uremia: The illness associated with the buildup of urea in the blood because the kidneys are not working effectively. Symptoms include nausea, vomiting, loss of appetite, weakness, and mental confusion. [NIH]

Ureters: Tubes that carry urine from the kidneys to the bladder. [NIH]

Urethra: The tube through which urine leaves the body. It empties urine from the bladder. [NIH]

Uric: A kidney stone that may result from a diet high in animal protein. When the body breaks down this protein, uric acid levels rise and can form stones. [NIH]

Uridine Diphosphate: A uracil nucleotide containing a pyrophosphate group esterified to C5 of the sugar moiety. [NIH]

Urinary: Having to do with urine or the organs of the body that produce and get rid of urine. [NIH]

Urinary Plasminogen Activator: A proteolytic enzyme that converts plasminogen to plasmin where the preferential cleavage is between arginine and valine. It was isolated originally from human urine, but is found in most tissues of most vertebrates. EC 3.4.21.73. [NIH]

Urinary tract: The organs of the body that produce and discharge urine. These include the kidneys, ureters, bladder, and urethra. [NIH]

Urine: Fluid containing water and waste products. Urine is made by the kidneys, stored in the bladder, and leaves the body through the urethra. [NIH]

Urogenital: Pertaining to the urinary and genital apparatus; genitourinary. [EU]

Urokinase: A drug that dissolves blood clots or prevents them from forming. [NIH]

Urticaria: A vascular reaction of the skin characterized by erythema and wheal formation due to localized increase of vascular permeability. The causative mechanism may be allergy, infection, or stress. [NIH]

Uterus: The small, hollow, pear-shaped organ in a woman's pelvis. This is the organ in which a fetus develops. Also called the womb. [NIH]

Vaccine: A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. [NIH]

Vagina: The muscular canal extending from the uterus to the exterior of the body. Also called the birth canal. [NIH]

Vaginitis: Inflammation of the vagina characterized by pain and a purulent discharge. [NIH]

Valine: A branched-chain essential amino acid that has stimulant activity. It promotes muscle growth and tissue repair. It is a precursor in the penicillin biosynthetic pathway. [NIH]

Varicose: The common ulcer in the lower third of the leg or near the ankle. [NIH]

Vascular: Pertaining to blood vessels or indicative of a copious blood supply. [EU]

Vasoactive: Exerting an effect upon the calibre of blood vessels. [EU]

Vasoconstriction: Narrowing of the blood vessels without anatomic change, for which constriction, pathologic is used. [NIH]

Vasodilation: Physiological dilation of the blood vessels without anatomic change. For dilation with anatomic change, dilatation, pathologic or aneurysm (or specific aneurysm) is used. [NIH]

Vasodilator: An agent that widens blood vessels. [NIH]

VE: The total volume of gas either inspired or expired in one minute. [NIH]

Vector: Plasmid or other self-replicating DNA molecule that transfers DNA between cells in nature or in recombinant DNA technology. [NIH]

Vein: Vessel-carrying blood from various parts of the body to the heart. [NIH]

Venous: Of or pertaining to the veins. [EU]

Venous blood: Blood that has given up its oxygen to the tissues and carries carbon dioxide back for gas exchange. [NIH]

Venous Thrombosis: The formation or presence of a thrombus within a vein. [NIH]

Ventricle: One of the two pumping chambers of the heart. The right ventricle receives oxygen-poor blood from the right atrium and pumps it to the lungs through the pulmonary artery. The left ventricle receives oxygen-rich blood from the left atrium and pumps it to the body through the aorta. [NIH]

Ventricular: Pertaining to a ventricle. [EU]

Venules: The minute vessels that collect blood from the capillary plexuses and join together to form veins. [NIH]

Vertebrae: A bony unit of the segmented spinal column. [NIH]

Vertebral: Of or pertaining to a vertebra. [EU]

Vertigo: An illusion of movement; a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo). The term is sometimes erroneously used to mean any form of dizziness. [EU]

Vesicular: 1. Composed of or relating to small, saclike bodies. 2. Pertaining to or made up of vesicles on the skin. [EU]

Vestibular: Pertaining to or toward a vestibule. In dental anatomy, used to refer to the tooth surface directed toward the vestibule of the mouth. [EU]

Vestibule: A small, oval, bony chamber of the labyrinth. The vestibule contains the utricle and saccule, organs which are part of the balancing apparatus of the ear. [NIH]

Veterinary Medicine: The medical science concerned with the prevention, diagnosis, and treatment of diseases in animals. [NIH]

Villi: The tiny, fingerlike projections on the surface of the small intestine. Villi help absorb nutrients. [NIH]

Viral: Pertaining to, caused by, or of the nature of virus. [EU]

Viral vector: A type of virus used in cancer therapy. The virus is changed in the laboratory and cannot cause disease. Viral vectors produce tumor antigens (proteins found on a tumor cell) and can stimulate an antitumor immune response in the body. Viral vectors may also be used to carry genes that can change cancer cells back to normal cells. [NIH]

Virulence: The degree of pathogenicity within a group or species of microorganisms or viruses as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. [NIH]

Virus: Submicroscopic organism that causes infectious disease. In cancer therapy, some viruses may be made into vaccines that help the body build an immune response to, and kill, tumor cells. [NIH]

Viscera: Any of the large interior organs in any one of the three great cavities of the body, especially in the abdomen. [NIH]

Viscosity: A physical property of fluids that determines the internal resistance to shear forces. [EU]

Vitamin A: A substance used in cancer prevention; it belongs to the family of drugs called retinoids. [NIH]

Vitreous Body: The transparent, semigelatinous substance that fills the cavity behind the crystalline lens of the eye and in front of the retina. It is contained in a thin hyoid membrane and forms about four fifths of the optic globe. [NIH]

Vitreous Hemorrhage: Hemorrhage into the vitreous body. [NIH]

Vitreous Humor: The transparent, colorless mass of gel that lies behind the lens and in front of the retina and fills the center of the eyeball. [NIH]

Vitro: Descriptive of an event or enzyme reaction under experimental investigation occurring outside a living organism. Parts of an organism or microorganism are used together with artificial substrates and/or conditions. [NIH]

Vivo: Outside of or removed from the body of a living organism. [NIH]

Warfarin: An anticoagulant that acts by inhibiting the synthesis of vitamin K-dependent coagulation factors. Warfarin is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, pulmonary embolism, and atrial fibrillation with embolization. It is also used as an adjunct in the prophylaxis of systemic embolism after myocardial infarction. Warfarin is also used as a rodenticide. [NIH]

Weight Gain: Increase in body weight over existing weight. [NIH]

White blood cell: A type of cell in the immune system that helps the body fight infection and disease. White blood cells include lymphocytes, granulocytes, macrophages, and others. [NIH]

Windpipe: A rigid tube, 10 cm long, extending from the cricoid cartilage to the upper border of the fifth thoracic vertebra. [NIH]

Wound Healing: Restoration of integrity to traumatized tissue. [NIH]

Xanthine: An urinary calculus. [NIH]

Xanthine Oxidase: An iron-molybdenum flavoprotein containing FAD that oxidizes hypoxanthine, some other purines and pterins, and aldehydes. Deficiency of the enzyme, an autosomal recessive trait, causes xanthinuria. EC 1.1.3.22. [NIH]

Xenograft: The cells of one species transplanted to another species. [NIH]

X-ray: High-energy radiation used in low doses to diagnose diseases and in high doses to treat cancer. [NIH]

X-ray therapy: The use of high-energy radiation from x-rays to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy) or from materials called radioisotopes. Radioisotopes produce radiation and can be placed in or near the tumor or in the area near cancer cells. This type of radiation treatment is called internal radiation therapy, implant radiation, interstitial radiation, or brachytherapy. Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. X-ray therapy is also called radiation therapy, radiotherapy, and irradiation. [NIH]

Yeasts: A general term for single-celled rounded fungi that reproduce by budding. Brewers' and bakers' yeasts are Saccharomyces cerevisiae; therapeutic dried yeast is dried yeast. [NIH]

Zymogen: Inactive form of an enzyme which can then be converted to the active form, usually by excision of a polypeptide, e. g. trypsinogen is the zymogen of trypsin. [NIH]

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