THALASSEMIA

A MEDICAL DICTIONARY, BIBLIOGRAPHY,
AND ANNOTATED RESEARCH GUIDE TO
INTERNET REFERENCES

JAMES N. PARKER, M.D.
AND PHILIP M. PARKER, PH.D., EDITORS

ICON Health Publications
ICON Group International, Inc.
4370 La Jolla Village Drive, 4th Floor
San Diego, CA 92122 USA

Printed in the United States of America.

Last digit indicates print number: 10 9 8 7 6 4 5 3 2 1

Publisher, Health Care: Philip Parker, Ph.D.
Editor(s): James Parker, M.D., Philip Parker, Ph.D.

Cataloging-in-Publication Data

Parker, James N., 1961-
Parker, Philip M., 1960-

Thalassemia: A Medical Dictionary, Bibliography, and Annotated Research Guide to Internet References / James N. Parker and Philip M. Parker, editors
p. cm.
Includes bibliographical references, glossary, and index.
ISBN: 0-597-84652-9
1. Thalassemia-Popular works. I. Title.

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Acknowledgements

The collective knowledge generated from academic and applied research summarized in various references has been critical in the creation of this book which is best viewed as a comprehensive compilation and collection of information prepared by various official agencies which produce publications on thalassemia. Books in this series draw from various agencies and institutions associated with the United States Department of Health and Human Services, and in particular, the Office of the Secretary of Health and Human Services (OS), the Administration for Children and Families (ACF), the Administration on Aging (AOA), the Agency for Healthcare Research and Quality (AHRQ), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Healthcare Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), the institutions of the National Institutes of Health (NIH), the Program Support Center (PSC), and the Substance Abuse and Mental Health Services Administration (SAMHSA). In addition to these sources, information gathered from the National Library of Medicine, the United States Patent Office, the European Union, and their related organizations has been invaluable in the creation of this book. Some of the work represented was financially supported by the Research and Development Committee at INSEAD. This support is gratefully acknowledged. Finally, special thanks are owed to Tiffany Freeman for her excellent editorial support.

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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 thalassemia 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 thalassemia, 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 thalassemia, 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 thalassemia. 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 thalassemia, 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 thalassemia.

The Editors

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

CHAPTER 1. STUDIES ON THALASSEMIA

Overview

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

The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and thalassemia, 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 "thalassemia" (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:

- **Unilateral Trismus in a Patient with Trigeminal Neuralgia Due to Microvascular Compression of the Trigeminal Motor Root**

  Source: Journal of Oral and Maxillofacial Surgery. 57(1): 90-92. January 1999.

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

  Summary: In this article, the authors report a case of unilateral trismus (difficulty opening the mouth) associated with typical trigeminal neuralgia (facial nerve pain), refractory to medical therapy, alleviated by microvascular decompression. The case study is of a 33 year old right handed woman with a significant medical history of hypertension, asthma, depression, and beta **thalassemia** who presented with a 14 month history of intermittent right ear pain, followed by right masseter muscle spasm with jaw

deviation to the left. There was no history of trauma, joint noises, or episodes of closed or open lock of the mandible. The patient subsequently developed intermittent, sharp, lancinating, right facial pain in the second and third dermatomes of the trigeminal nerve. The patient's facial and ear pain was sharp, intermittent, and nonpositional, triggered by touching the face, eating, cold temperatures, and wind. The authors describe the drug management of the patient and the move to a surgical microvascular decompression of the trigeminal nerve. The authors discuss the relevant anatomy of the trigeminal nerve, along with the pathophysiology and differential diagnosis. Postoperatively, the patient remained off all medications. She noted some preauricular (in front of the ear) hints of trigeminal neuralgia, but this was minimal. 3 figures. 13 references.

- **The Racial Divide: The Effect of Race on Treating HIV**

  Source: Positively Aware; Spring 1994.

  Contact: Test Positive Aware Network, 5537 N Broadway, Chicago, IL, 60640, (773) 989-9400, http://www.tpan.com.

  Summary: This article looks at racial and ethnic differences that affect the progression of HIV in whites and African Americans in the United States. The biology of HIV disease is no different for African Americans than for any other ethnic group. However, several race-specific health considerations affect the way physicians treat African Americans for HIV disease. Special health concerns of African Americans that may affect their treatment include sickle cell anemia, **thalassemia,** kidney problems, hypertension, G6PD enzyme deficiency, and skin problems.

- **'Common' Uncommon Anemias**

  Source: American Family Physician. 59(4): 851-858. February 15, 1999.

  Contact: Available from American Academy of Family Physicians. 11400 Tomahawk Creek Parkway, Leawood, KS 66211-2672. (800) 274-2237. Website: www.aafp.org.

  Summary: This article reviews the more often seen diagnoses among the uncommon anemias'; these include the anemia of renal disease, **thalassemia,** myelodysplastic syndrome, and the anemia of chronic disease. These conditions may be suggested by the clinical presentation, laboratory test values, and peripheral blood smear, or by failure of the anemia to respond to iron supplements or nutrient replacement. The principal cause of the anemia of renal disease is a decreased production of red blood cells related to a relative deficiency or erythropoietin. When treatment is required, erythropoietin is administered, often with iron supplementation. In the anemia of chronic disease, impaired iron transport decreases red blood cell production. Treatment is predominantly directed at the underlying condition. Since iron stores are usually normal, iron administration is not beneficial. **Thalassemia** minor results from a congenital abnormality of hemoglobin synthesis. The disorder may masquerade as mild iron deficiency anemia, but iron therapy and transfusions are often not indicated. In the myelodysplastic syndrome, blood cell components fail to mature, and the condition may progress to acute nonlymphocytic leukemia. The rate of progression depends on the subtype of myelodysplasia, but the leukemia is usually resistant to therapy. 5 figures. 3 tables. 16 references. (AA-M).

- **Viral Hepatitis in Children**

  Source: Seminars in Liver Disease. 14(3): 289-302. August 1994.

Contact: Available from Thieme Medical Publishers, Inc. 381 Park Avenue South, New York, NY 10016. (800) 782-3488.

Summary: This article reviews viral hepatitis in children, focusing on hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). The authors note that, despite the unrelatedness among these viruses in replication strategy, genetic structure, and pathogenetic mechanisms, there is remarkable similarity among them in clinical presentation. Topics include the epidemiology and prevention of hepatitis A; the development of HAV vaccines; the use of inactivated vaccine for HAV; a future HAV vaccination policy; the epidemiology and transmission of HBV; the consequences of HBV infection during childhood; HBV and primary hepatocellular carcinoma during childhood; mechanisms of immune tolerance; fulminant hepatitis B infection in neonates; therapy for chronic HBV infection in children; liver transplantation and HBV; HBV vaccine; the molecular basis for diagnostic tests of HCV infection; the epidemiology of HCV in children; HCV and particular conditions, including hemophilia, **thalassemia,** cancer survival, transplant recipients, hemodialysis, and cryptogenic pediatric liver disease; vertical transmission of HCV; and the natural history and therapy of HCV. 3 tables. 169 references. (AA-M).

- **Recurrent Oral Blood Blisters**

  Source: Archives of Dermatology. 135(5): 593-594, 596-597. May 1999.

  Contact: Available from American Medical Association. Subscriber Services Center, P.O. Box 10945, Chicago, IL 60610. (800) 262-2350 or (312) 670-7827. Fax (312) 464-5831. E-mail: ama-subs@ama-assn.org.

  Summary: This brief article is one of three cases presented in a column that highlights clinical cases of special interest and challenges readers to determine the diagnosis. In this case, a 52 year old woman presented with recurrent oral blood blisters. She had a history of **thalassemia** minor and idiopathic vulvar pruritis; she had also undergone a hysterectomy because of a leiomyoma. For the past 6 years, painful blood blisters had been occurring on the lateral borders of her tongue and buccal mucosa, 8 to 10 times per year. The lesions ruptured in a few hours, leaving superficial ulcers that healed in 2 or 3 days. The patient reported no other mucosal or skin lesions or any bleeding tendency. She had used a dental prosthesis for the last 11 years. The diagnosis was angina bullosa hemorrhagica (ABH), a term used to describe blood blisters occurring in the oral, pharyngeal, and esophageal mucosa that seemed to be unrelated to an identifiable cause or systemic disorder. ABH is a benign phenomenon with characteristic clinical features; the cause is unknown. There is no treatment for ABH other than symptomatic care. Patients should be reassured of the benignity of their disease. 2 figures. 8 references.

- **Association Between Hepatitis C Virus Infection and Type 2 Diabetes Mellitus: What Is the Connection? (editorial)**

  Source: Annals of Internal Medicine. 133(8): 650-652. October 17, 2000.

  Contact: Available from American College of Physicians. American Society of Internal Medicine. 190 North Independence Mall West, Philadelphia, PA 19106-1572. Website: www.acponline.org.

  Summary: This editorial reviews the evidence demonstrating the association between hepatitis C virus (HCV) infection and type 2 diabetes. One study found that, among patients with cirrhosis awaiting transplantation, those who were infected with HCV were five times more likely to have type 2 diabetes than those who were not, regardless

of gender, body mass index, or severity of liver disease. A large retrospective survey conducted in Italy found that type 2 diabetes was present in 23.6 percent of those with HCV infection. A study of patients undergoing transplantation for HCV related cirrhosis found that 29 percent of patients had diabetes before transplantation, 37 percent had diabetes at 1 year, and 41 percent had diabetes at 5 years. Another study found that the prevalence of type 2 diabetes was increased fourfold in patients with **thalassemia** and HCV infection, independent of cirrhosis, body mass index, or iron overload. A study examining the prevalence of HCV infection in selected patients with type 2 diabetes found that a substantial proportion of patients with abnormal alanine aminotransferase levels had HCV infection. Other studies found that patients with type 2 diabetes were more likely than controls to be positive for HCV antibodies. In addition, the editorial discusses a study that provides strong evidence for the association between HCV infection and type 2 diabetes and offers possible explanations for this association. 19 references.

Federally Funded Research on Thalassemia

The U.S. Government supports a variety of research studies relating to thalassemia. 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 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 thalassemia.

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 thalassemia. The following is typical of the type of information found when searching the CRISP database for thalassemia:

- **Project Title: 14TH INTERNATIONAL CONGRESS ON FLAVINS AND FLAVOPROTEINS**

  Principal Investigator & Institution: Matthews, Rowena G.; Professor; Biological Chemistry; University of Michigan at Ann Arbor 3003 South State, Room 1040 Ann Arbor, Mi 481091274

  Timing: Fiscal Year 2002; Project Start 01-JUN-2002; Project End 31-MAY-2003

  Summary: (provided by applicant): This Congress will be the fourteenth in a continuing series of International Flavin Symposia, held every three years. The most recent conference was held in Konstanz Germany on August 29-September 4, 1999. The meeting for which funding is requested will be held from July 14-18, 2002 in St. John's College, Cambridge University, Cambridge, UK. These meetings offer an opportunity for students, postdoctoral fellows, and senior researchers to hold intensive discussions on current research in flavins and flavoproteins, and to present their own work in

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

posters and talks. The Proceedings are published as a symposium volume which provides a useful reference for all participants. Sessions are planned on the following topics: New structures and mechanistic implication of simple flavoproteins; Electron transfer in complex flavoprotein systems; Flavins:light and biology; and New families--catalysis based on the fumarate reductase framework. Plenary lectures will be presented by Maria Vanoni (structure-function studies of glutamate synthases), Denis Stuehr (The NO synthase flavorptoein-kinetic and strucural studies to reveal its unique mechanisms of regulation), Sunny Xie (Single-molecule studies of flavoenzymes), and Gary Cecchini (Structural insights into the function and physiology of complex II). In addition, a session has been reserved for presentations to be selected from posters presented at the meeting. The afternoons are reserved for poster sessions, to ensure maximal interaction at these sessions, which have been traditionally very popular with participants. Tea will be served at each poster session. Presentations were selected by an International Organizing Committee with an eye to a diverse representation of speakers at the meeting.

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

- **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: A QTL FOR FETAL HEMOGLOBIN AND F CELLS ON CHROMOSOME 8Q**

  Principal Investigator & Institution: Thein, Swee L.; U of L King's College London London, Wc2r 2Ls

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

  Summary: (provided by applicant): Current treatment for Sickle cell disease (SCD) and beta **thalassemia** is, at best, symptomatic involving blood transfusions, the use of drugs to remove iron and to control pain, and in cases with HLA-compatible siblings, bone marrow transplantation. Our studies and others, have shown that in both disorders, high levels of fetal hemoglobin (Hb F, alpha1gamma2) have a major beneficial effect. The ability to produce Hb F in response to disease varies enormously from patient to patient, and is one of the major factors underlying the remarkable diversity in the severity of these disorders. This has prompted an intense search for approaches to augment fetal hemoglobin production in patients with SCD and beta **thalassemia,** one of which involves the use of drugs such as hydroxyurea and butyrate analogues. However, these agents are limited by their toxicity and they are effective in only a proportion of patients. The long term objective of this proposal is to obtain a better understanding of the genetic factors which modify fetal hemoglobin and F cell (FC) levels in normal adults and in response to disease. We have demonstrated for the first time that Hb F and F cell levels are highly heritable and transmitted as a complex genetic trait, influenced by several factors including a common sequence variant (C to T) in the Ggamma-promoter region, referred to as the Xmn1-Ggamma site. In earlier studies, as part of a systematic search for loci that may regulate gamma globin gene expression in beta **thalassemia** and SCD, we have identified an extensive kindred which includes individuals with beta **thalassemia** and hereditary persistence of fetal hemoglobin (HPFH). A quantitative trait locus (QTL) modifying fetal Hb production has been mapped to chromosome 6q23 in this kindred but variance components analysis revealed that a significant amount of FC variance remained unaccounted for. Furthermore, other QTLs for Hb F and FC have been implicated in different family studies. The presence of the Xmn1-Ggamma site is a major determinant for FC levels, and its location suggests that it is involved in transcriptional activation of the Ggamma globin gene. A linkage re-analysis of the genome-wide data in the kindred was carried out under a two-locus genetic model, with one of the loci being the Xmn1-Ggamma site. A new locus on chromosome 8q has now been identified using this method. Now, in an integrated program, we propose to isolate and characterize the 8q QTL by three approaches: (1) positional (candidate) gene cloning, (2) functional cloning by complementation assays in transgenic mice, and (3) differential gene expression analysis, in parallel with the 6q project. The delineation of these genetic factors should increase our understanding of the trans-acting factors for the fine tuning in the control of Hb F production after birth in normal adults and in response to disease with implications for pharmacogenomics. The discovery of these factors may also suggest new approaches for therapeutic augmentation of fetal hemoglobin production in patients with SCD and beta **thalassemia.**

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

- **Project Title: A3: HUMAN MOLECULAR GENETICS: SICKLE CELL, THALASSEMIA, HEMOPHILIA**

  Principal Investigator & Institution: Cadilla, Carmen L.; University of Puerto Rico Med Sciences Medical Sciences Campus San Juan, Pr 00936

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

Summary: This abstract is not available.

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

- **Project Title: ABNORMAL HEMOGLOBIN SYNTHESIS -- MECHANISM AND DETECTION**

  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 01-AUG-1976; Project End 31-JUL-2006

  Summary: (provided by applicant): This application is a continuation on our studies of normal and abnormal hemoglobin synthesis in sickle cell anemia and **thalassemia.** The project in the previous grant period consisted of three aims. 1) DNA diagnosis of sickle cell anemia and **thalassemia.** 2) Control of globin gene expression. 3) Globin gene transfer. Because the topics in Aim 2 will now be carried on by previous trainees who have become independent investigators, this proposal will continue to pursue only the first and third aims. hi Aim 1 we have completed our studies on dot blot hybridization for the diagnosis of the mutations in hemoglobinopathies and **thalassemia** that are commonly found in the American population. We propose to develop and refine methods of prenatal diagnosis from fetal cells isolated using maternal blood. Our preliminary studies show that this is a promising approach, but much more work is needed to make this test practical. We will use phage display to isolate single chain antibodies specific for fetal nucleated red cells and human embryonic hemoglobin. We will investigate the use of image analysis and laser capture microdissections to facilitate the retrieval of fetal nucleated red cells. These developments will greatly enhance the usefulness of this procedure. The second aim of this proposal is to explore the possibility of in utero gene delivery alpha-thalassemia is a good model for in utero gene therapy because pathological changes in homozygous alpha-thalassemia usually appear before birth. In our laboratory, we have made mouse models of alpha-thalassemia by knocking out the endogenous mouse alpha-globin genes. By crossing various strains, we have mice that have 3,2,1 or no alpha-globin gene and they mimic the clinical manifestation of human alpha-thalassemia. We will use AAV vectors and lentiviral vectors containing the beta-g1obin LCR controlling the human a-globin gene to inject into fetal mice at the 15th week of gestation. We will follow these mice to observe the expression of the. alpha-globin gene and the rescue the disease phenotype. Such an approach could be useful not only for alpha-thalassemia but also for other genetic disorders such as OTC deficiency where the disease begins in utero.

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

- **Project Title: ACTIVATION OF GAMMA GLOBIN EXPRESSION BY TRANSACTIVATORS**

  Principal Investigator & Institution: Song, Chao-Zhong; Medicine; University of Washington Grant & Contract Services Seattle, Wa 98105

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

  Summary: (provided by applicant): The chain hemoglobinopathies such as sickle cell disease and **thalassemia** are among the most common inherited diseases in humans. Reactivation of chain expression can cure the diseases by compensating for the loss of the chain activity. The identification of transcription activators that activate globin gene expression and understanding the mechanisms by which they activate globin gene expression will provide new targets and strategies for the treatment of sickle cell disease

and **thalassemia.** The long-term objectives of this proposal are to validate the in vivo role of the candidate globin transactivators FKLF1 and FKLF2 in globin gene expression, study the mechanisms by which they activate globin gene expression and identify transcription factors that activate endogenous globin expression through the CACCC box of the promoter. Our specific aims are: 1) To determine the in vivo role of FKLF1 and FKLF2 in globin gene activation; 2) To characterize FKLF1 and FKLF2 proteins; 3) To study the regulation of FKLF1 and FKLF2 transcriptional activation of globin gene by acetylation; 4) To study the regulation of FKLF1 and FKLF2 transcriptional activation of globin gene by phosphorylation; 5) To identify target genes of FKLF1 and FKLF2 in fetal erythroid cells; 6) To study the regulation of FKLF1 and FKLF2 gene expression; 7) If the studies in specific aim 1 show that FKLF1 or FKLF2 can not activate endogenous globin in vivo, we will then clone new factors that interact with the CACCC box and activate the globin gene. We will use the experimental approaches based on cell culture, genetic assays and molecular and biochemical methods to achieve our goals.

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

- **Project Title: APOLIPOPROTEIN E 4/4 PROTECTS AGAINST FALCIPARUM MALARIA**

  Principal Investigator & Institution: Fujioka, Hisashi; Pathology; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

  Timing: Fiscal Year 2004; Project Start 15-FEB-2004; Project End 31-JAN-2006

  Summary: (provided by the applicant): Since hominization the human genome has been under selective pressure to develop resistance against infectious diseases. For example, it is thought that malaria infection has been an important evolutionary force in the selection of various hemoglobinopathies and other red blood cell disorders (thalassemia, glucose-6-phosphate dehydrogenase deficiency, sickle cell trait, and hemoglobin C etc.) and their observed overlapping geographic distributions support this hypothesis. Similarly, the frequency of human apolipoprotein E (apo E: protein component of triglyceride-rich lipoprotein) epsilon 4 allele is extremely high in the malaria endemic areas of sub-Saharan Africa and in Papua New Guinea, suggesting that apo E phenotype E4/4 protects against malaria infection. An in vitro growth inhibition assay was used to test the hypothesis and provided evidence for an association between apo E4/4 and impaired infection of red blood cells by the human malarial parasite Plasmodium falciparum. Apo E4 allele of the spo E gene has been linked to the pathogenesis of Alzheimer's disease, cardiovascular disease and atherosclerosis, but the studies proposed herein are the first to investigate the role of human apo E4/4 in protecting against malaria infection. A preliminary ultrastructural study of P. falciparum blood stage parasites exposed to human plasma containing native Apo E4/4 has revealed that this molecule disrupts parasite cell membranes. It is not known if apo E4/4 produces these cytopathic effects merely by making contact with the parasite plasma membrane or whether it needs to be internalized in order to act. Consequently, a major aim of this proposal is to determine the precise site of interaction between apo E4/4 and the parasite by immunocytochemistry. Further to this, the study will be extended to at least 8 other lines of P. falciparum parasites originating from a variety of geographical locations in order to better characterize the role of apo E4 during malaria infection and will ultimately be repeated using highly purified apo E4/4, rather than plasma. These studies represent a unique approach in the battle against malaria and could provide the basis for the design of an entirely new class of anti-malarial drugs.

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

- **Project Title: AUGMENTATION OF FETAL HEMOGLOBIN IN THALASSEMIA**

  Principal Investigator & Institution: Olivieri, Nancy F.; Hospital for Sick Chldrn (Toronto) 555 University Ave Toronto, On

  Timing: Fiscal Year 2002; Project Start 01-JUL-2002; Project End 30-JUN-2003

  Summary: This research study is designed to compare the effectiveness of the iron-chelating agent deferoxamine, when administered using two different routes: subcutaneous bolus infections, and 8-hour subcutaneous infusions (standard therapy), in patients with **thalassemia** major. While a few studies to date have measured urinary iron excretion achieved with these two regimens of deferoxamine, their relative effectiveness as not been compared. Despite its effectiveness, the use of deferoxamine is complicated by a requirement for prolonged parenteral infusion and, as a consequence considerable expense and poor patient compliance. Because most patients affected with **thalassemia** live in emerging countries which cannot afford this expense associated with infusion pumps, this life- saving therapy is available to a small fraction of the world's thalassemics. The primary hypothesis of this study is that subcutaneous bolus injections of deferoxamine, administered twice daily over a period of 12 months, will reduce or maintain body storage iron at concentrations equivalent to those in a cohort of patients treated with nightly 8-hour subcutaneous infusions of deferoxamine over the same period. The specific aims of the proposed research are to compare: the short-term efficacy of twice-daily bolus injections, and 8-hour infusions of deferoxamine, as determined by urinary iron excretion and reduction in toxic fractions of serum iron and its metabolites; the relative effectiveness of these regimens, as determined by reduction of hepatic iron concentration; and patient compliance with these regimens. The primary endpoint of this trial is hepatic iron concentration, the most quantitative, specific and sensitive method for determining body iron burden, to be determined in each patient at baseline and after 12 months, in all patients. If the effectiveness of twice- daily bolus injections is demonstrated to be equal to that of conventional infusions of deferoxamine, this new regimen will offer to all patients with **thalassemia,** worldwide, a cost-effective and convenient infusions of deferoxamine, this new regimen will offer to all patients with **thalassemia,** worldwide, a cost-effective and convenient alternative to prolonged infusions of deferoxamine, currently the only method of administration of this life-saving drug.

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

- **Project Title: BETA GLOBIN GENE REGULATION AND BETA THALASSEMIA DISEASE**

  Principal Investigator & Institution: Lewis, Brian A.; Biochemistry; Univ of Med/Dent Nj-R W Johnson Med Sch Robert Wood Johnson Medical Sch Piscataway, Nj 088545635

  Timing: Fiscal Year 2002; Project Start 01-AUG-2001; Project End 31-JUL-2004

  Summary: (provided by applicant) This grant is intended to support Dr. Lewis' additional postdoctoral training and serve as a transition period leading towards a career as an academic research professor. Dr. Reinberg's laboratory provides an excellent research and intellectual environment, and the laboratory's expertise in transcriptional biochemistry will complete Dr. Lewis' training. Dr. Lewis' research aim is to understand the regulation of the human beta -globin promoter at the transcriptional level. His immediate goals entail a more detailed study of the beta-globin promoter. His previous work identified two human beta-thalassemia mutations as defects in a novel beta-globin downstream core promoter element. Research is now directed at obtaining a mechanistic understanding of the downstream core promoter element, including its role

in beta-globin regulation and the proteins necessary for its activity. Lastly, the research will study the function of the beta-globin core promoter elements in a more physiological chromatin context. This work will make important and novel contribution to our understanding of tissue-specific regulation, core promoter, and downstream element function, and promoter activity in a chromatin context.

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- **Project Title: BETA-GLOBIN MRNA DECAY IN ERYTHROID CELLS**

  Principal Investigator & Institution: Schoenberg, Daniel R.; Professor; Molecular & Cellular Biochemistry; Ohio State University 1960 Kenny Road Columbus, Oh 43210

  Timing: Fiscal Year 2004; Project Start 01-JUN-2004; Project End 31-MAR-2006

  Summary: (provided by applicant): The beta-thalassemias are common genetic disorders that result from mutations in the beta globin gene. Many of these mutations introduce a premature termination codon (PTC) that results in the degradation of mRNA encoded by the affected allele. Individuals inheriting mutations in both beta-globin alleles have severe anemia, hemolysis, and secondary pathology resulting from expansion of the bone marrow. Most PTC containing mRNAs are degraded through a nucleus-associated surveillance pathway termed nonsense mediated mRNA decay (NMD). Previous work demonstrated that a PTC in exon 2 of the human beta-globin gene activated the cytoplasmic degradation of beta-globin mRNA, with the production of metastable decay intermediates. We replicated this in a model system using murine erythroleukemia cells, and determined that mRNA decay results from endonucleolytic cleavage. The degradation of both normal and PTC-containing beta-globin mRNA is catalyzed by a polysome-associated ribonuclease whose properties are similar to a polysome-associated endonuclease identified in Xenopus termed xPMR1. We propose that the endonuclease-catalyzed degradation of PTC-containing beta-globin mRNA in erythroid cells is a specialized form of NMD. Aim 1 will use transcription pulse-chase and a new, sensitive FRET-based assay to examine details of the mRNA decay process and how they relate to structural features of beta-globin mRNA. Aim 2 will examine the relationship between the PTC-stimulated degradation of beta-globin mRNA and NMD by RNAi of Upfl, expression of dominant negative proteins, examining the relationship of this process to downstream intron splicing, and by examining its relationship to the pioneer round of translation. Aim 3 will characterize the beta-globin mRNA, focusing on a recently identified unique gene believed to encode this enzyme. This will entail expression of recombinant protein, characterization of its biochemical properties, and experiments studying the impact of inactivating mPMR1 by RNA interference on the PTC-stimulated degradation of beta-globin mRNA. The long-term goal is to identify new therapeutic targets for treating beta-thalassemia and other diseases caused by PTCs by better understanding the enzymatic mechanisms responsible for the degradation of PTC-containing mRNAs.

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

- **Project Title: CARDIAC DISEASE IN COOLEYS ANEMIA--MOLE AND CLIN STUDIES**

  Principal Investigator & Institution: Brittenham, Gary M.; Professor of Medicine; Anatomy and Cell Biology; Columbia University Health Sciences Po Box 49 New York, Ny 10032

  Timing: Fiscal Year 2002; Project Start 30-SEP-1998; Project End 31-JUL-2004

Summary: The proposed research project is designed to characterize the molecular pathophysiology and clinical consequences of iron-induced cardiac disease using a coordinated series of studies of cardiac myocytes in culture, of the first animal model of the cardiomyopathy of iron overload, and of patients with **thalassemia** major. Iron-induced myocardial disease is the most frequent cause of death in **thalassemia** major and is a major life-limiting complication of other transfusion- dependent refractory anemias hereditary hemochromatosis and other forms of iron overload. We hypothesize that (i) the body iron burden is a principal determinant of the magnitude of cardiac iron deposition in patients with **thalassemia** major, (ii) the nonuniform pattern of iron deposition in the heart results in variability in iron concentrations within cardiac myocytes, and (iii) the increased intracellular iron selectively affects specific ion channels in cardiac myocytes, producing abnormalities in sodium and potassium currents that result in aberrant ventricular repolarization and contribute to arrhythmogenesis. The proposed research has three specific aims: (1) to determine the pathophysiologic mechanisms responsible for iron-induced abnormalities of Na+ and K+ currents in cultured neonatal rat cardiac myocytes and the effects of iron chelators, antiarrhythmic drugs and other agents; (2) to examine the effects of excess iron, iron chelators, antiarrhythmic drugs and other agents on cardiac electrophysiology and function in a gerbil model of iron overload both in the intact animal and in isolated heart preparations; and (3) to determine the relationship in patients with **thalassemia** major between body iron burden, as measured by non- invasive magnetic susceptometry, and abnormalities of cardiac rhythm and function, as assessed as assessed by the signal-averaged electrocardiogram, T wave alternans, dynamic measures of the QT interval and echocardiography. This research will result in new fundamental information about the molecular basis for the effects of iron on cardiac ion channels, will provide the first electrophysiolgical and functional studies in a new animal model of iron overload, and will develop new non-invasive means of identifying those patients at the highest risk for iron-induced cardiac disease to permit intensive iron chelation therapy and other preventive interventions.

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

- **Project Title: CELL THERAPIES FOR COOLEY'S ANEMIA**

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

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 30-JUN-2007

  Summary: (provided by applicant): **Cooley's anemia** (CA) will be cured in an animal model of beta **thalassemia** major by therapeutic cloning, genome modification, and replacement cell therapy Therapeutic cloning will be used to derive primary beta/0 thalassemic embryonic stem (ES) cell lines that will be genetically modified to correct their defect. Corrected thalassemic ES cells will be used for replacement cell therapy after differentiation into hematopoietic progenitors and transplantation back into CA animals. Initial experiments will utilize a knockout mouse model of primary beta-thalassemia that reproduces most of the pathology of the disorder (PNAS 92 9259-9263). The model was created by targeted deletion of 16 kilobases of DNA that removes both adult mouse beta-globin genes. Later experiments will utilize a novel mouse model of CA generated by targeted gene replacement of the adult murine alpha-globin genes with human alpha-globin and the adult mouse beta-globin genes with a human gamma- to beta-globin gene switching cassette that contains a primary beta thalassemic allele. Newborn mice homozygous for the knockin allele will survive solely on human fetal hemoglobin at birth. The mice will succumb to CA during the first weeks of life once the

fetal to adult hemoglobin switch is complete. **Cooley's anemia** ES cell lines will be established from developing blastocysts isolated from either heterozygous mating pairs or from nuclear transfer of fibroblast nuclei isolated from newborn CA mice into enucleated mouse eggs. Identical **Cooley's anemia** mice will be cloned from these ES cells by injection of CA ES cells into tetraploid blastocysts. Cloning after modification of the CA ES cells will be utilized to test genetic therapies designed to correct the **thalassemia.** Therapeutic benefit will be assessed by a direct comparison of the anemia in mice cloned from the modified ES cells to clones produced from the unmodified CA ES cells. Hematopoietic stem cells (HSCs) isolated from the bone marrow of cloned mice generated from the corrected CA ES cells will be used to cure sublethally conditioned isogeneic mice cloned from the diseased ES cells Finally, in vitro differentiation of the corrected CA ES cells will be used to generate hematopoietic progenitors in cell culture Conditioned CA mouse clones will be cured by the injection of these isogeneic corrected hematopoietic progenitors. Successful completion of these studies will delineate the basic steps required for curing many heritable hematopoietic disorders in humans, namely, therapeutic cloning to establish autologous ES cell lines, correction of diseased allele(s) in the ES cells, and hematopoietic progenitor replacement cell therapy.

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- **Project Title: CHARACTERIZATION OF A ALPHA-GLOBIN CHAPERONE PROTEIN**

  Principal Investigator & Institution: Weiss, Mitchell J.; Children's Hospital of Philadelphia 34Th St and Civic Ctr Blvd Philadelphia, Pa 191044399

  Timing: Fiscal Year 2002; Project Start 01-APR-2002; Project End 31-MAR-2007

  Summary: Recent discoveries in our laboratory offer new insights into normal erythroid biology and beta-thalassemia. The high- level production of hemoglobin that occurs during erythroid maturation is tightly coordinated so as to minimize toxicities caused by accumulation of individual alpha- and beta- globin subunits, which tend to precipitate in cells. Prior studies of normal and beta-thalassemic erythroid precursors predict that compensatory mechanisms exist to neutralize free alpha-globin. To learn more about the control of hemoglobin production, we isolated RNA transcripts that are induced by the essential transcription factor GATA-1, a global regulator of erythropoiesis. We identified Erythroid Differentiation Related Factor (EDRF), a small, abundant highly erythroid-specific protein that is strongly upregulated during terminal erythroid maturation and appears to be a direct GATA-1 target gene. We determined that alpha-globin is a specific EDRF binding partner in two independent protein interaction screens. EDRF interacts with free alpha-globin but not with beta-globin or hemoglobin A (alpha2beta2). Moreover, EDRF markedly inhibits precipitation of free alpha-globin in solution and in mammalian cells. Our findings raise the possibility that EDRF acts as a chaperone protein to prevent precipitation and subsequent toxicity of free alpha-globin in erythroid cells. Now that we have established a physical and functional connection between EDRF and alpha-globin in vitro and in heterologous cells, we will study the significance of this association in normal erythropoiesis. Structure-function analyses in Aim 1 will define the domains that are required for physical and functional interactions between EDRF and alpha-globin. In Aim 2, we will assess the biological role of EDRF and its association with alpha-globin in established cell lines and in primary erythroid cells derived from in vitro culture of EDRF gene-targeted embryonic stem (ES) cells. To this end, we have developed EDRF heterozygous and homozygous-null ES cells. In Aim 3, we will determine the hematopoietic consequences of altered EDRF expression in mice. By genetically manipulating EDRF

and free alpha-globin levels, we will determine how their relative stoichiometry affects viability and differentiation of erythroid cells. Specifically, we will establish whether EDRF-null animals exhibit excessive alpha- globin precipitation in erythroid precursors, and whether altered EDRF gene expression affects the severity of beta-thalassemia, a disorder that is distinguished by alpha-globin precipitation. Our studies to characterize a highly expressed erythroid specific protein that prevents aggregation of free alpha-globin are important for understanding how hemoglobin chain balance is modulated by non-globin proteins during normal erythropoiesis and might provide a novel approach to alleviate the deleterious effects of excessive alpha-globin in beta-thalassemia.

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- **Project Title: CORE--PATIENT SERVICES CORE**

  Principal Investigator & Institution: Mcmahon, Lillian E.; Director; 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: The Patient Service Core brings to our patients, their families, community members, physicians and other health professionals, state-of-the-art educational, counseling, and diagnostic services made available because of the core of physician-scientists and allied health professionals associated with the Boston Comprehensive Sickle Cell Center. Through our outreach programs, we make services of the Boston Comprehensive Sickle Cell Center available to community members not receiving primary care at our major teaching hospitals. Professional counseling is provided to patients and families at risk for sickle cell disease and related disorders. We provide education to health professionals about sickle cell disease and related disorders. Education is also provided to patients and families at risk for sickle cell disease and related disorders. We also have established a hemoglobin diagnosis laboratoryproviding hemoglobinopathy screening using innovative technology and definitive hemoglobin diagnosis by mass spectrometry. A major limitation of HPLC for hemoglobinopathy detection is present during the study of sickle hemoglobinopathies where a clinically important interference exists between HbA2 and an adduct of HbS when using the Bio Rad Variant II method. Capillary zone electrophoresis, an alternative to isoelectric focusing, has found many uses in the research laboratory due to its simplicity, superior resolution, linearity, precision, reproducibility, speed of analysis, and automated operation. Using capillary zone electrophoresis the quantitation of HbA2 is not affected by the presence of HbS and capillary zone electrophoresis can resolve HbA1c from carbamylated HbA1a, A1b, A1d, F, C, and O-Arab. We will explore and develop the use of capillary zone electrophoresis for routine hemoglobinopathy and **thalassemia** detection.

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- **Project Title: CRYSTALLOGRAPHIC STUDIES OF EUKARYOTIC POLY(A)POLYMERASE**

  Principal Investigator & Institution: Doublie, Sylvie; Microbiol & Molecular Genetics; University of Vermont & St Agric College 340 Waterman Building Burlington, Vt 05405

  Timing: Fiscal Year 2002; Project Start 18-DEC-2000; Project End 31-MAY-2006

  Summary: (From the applicant's abstract) The long-term goal of this project is to understand the molecular mechanisms of eukaryotic mRNA polyadenylation. mRNA polyadenylation plays an essential role in the initiation step of protein synthesis, in the export of mRNAs from the nucleus to the cytoplasm, and in the control of mRNA

stability. Polyadenylation is a key regulatory step in the expression of many genes. Aberrant polyadenylation has been shown to cause diseases such as **thalassemia** and lysosomal storage disorder. Moreover, oculopharyngeal muscular dystrophy is the result of the insertion of short GCG repeats in the gene encoding one of the polyadenylation factors, poly(A) binding protein 2 (PABP 2). We are investigating the crystal structure of the enzyme at the heart of the polyadenylation machinery, poly(A) polymerase (PAP), its interaction with substrates, and its association with proteins playing a part in mRNA 3'-end processing. There are no structural data to date for any of the mammalian polyadenylation factors. The specific aims are as follows: 1. The X-ray crystal structure of bovine PAP with its substrates ATP and poly(A) RNA will be determined using a combination of multiwavelength anomalous diffraction (MAD) and multiple isomorphous replacement. The structure of PAP complexed with substrates will guide additional structural and functional studies. 2. PABP 2 is required for processive synthesis and control of the poly(A) tail length. PABP2 is known to bind both the poly(A) tail and PAP. We will work towards the structure determination of the ternary complex of PABP2, PAP, and poly(A), using either the intact proteins or the interacting domains of each protein. 3. Phosphorylation of target sites located in the C-terminal domain of PAP results in strong repression of PAP activity. The down regulation of PAP via hyperphosphorylation is reminiscent of the inhibitory effect of U1A, which has been shown to inhibit polyadenylation of its own mRNA by binding to PAP. We will work towards the crystallization of the complex between PAP and U1A, using either the intact proteins, or the C-termini of each protein. We will concurrently attempt to crystallize phosphorylated, full-length bovine PAP. A comparison of the phosphorylated PAP structure with that of the PAP-U1A complex should elucidate whether both situations use a similar mechanism of repression. It is expected that these results will not only provide a sound structural basis for understanding the mechanism of polyadenylation at the molecular level but will also shed light on the mechanisms of processivity and repression.

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- **Project Title: CYCLIC NUCLEOTIDES AND FETAL GLOBIN GENE EXPRESSION**

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

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

  Summary: (provided by applicant): Pharmacological stimulation of fetal hemoglobin (Hb F) has been attracting great concerns for many years, but the molecular mechanisms by which expression of the g-globin gene is induced in the adult stage still remain unclear. The long-term goal of this proposal is to develop "novel Hb F inducers" by clarifying intracellular pathways that regulate g-globin gene expression. We showed that expression of the g-globin gene is induced in erythroleukemic cells as well as in primary erythroblasts by activating an intracellular pathway comprising soluble guanylate cyclase (sGC) and cGMP-dependent protein kinase (PKG). This pathway was also found to be essential for the induced expression of the g-globin gene by hemin or butyrate. In the first specific aim, we will study the molecular mechanisms by which the sGC-PKG pathway induces g-globin gene expression. First, we will identify and characterize within the b-globin locus cis-acting and trans-acting elements that mediate molecular effects of the pathway to the g-globin gene. Next, we will examine whether the sGC-PKG pathway contributes to the expression of the gamma-globin gene in beta-thalassemia. In the second specific aim, we will test using transgenic mice the hypothesis that expression of the g-globin gene is induced in the adult stage by over-

expressing or activating sGC, which is an obligate heterodimer of a- and b- subunits. We will first create transgenic mice with DNA constructs carrying sGC subunit genes driven by the b-globin gene promoter and the LCR, and breed them with mice carrying the human b-globin locus. Second, we will examine whether the phenotype of sickle cell mice can be alleviated by expressing sGC subunits at high levels. Recently we found two normal subjects with no mutations in the b-globin locus who express 30% Hb F and have high levels of porphyrins such as protoporphyrin IX (PPIX) and ZnPP, both of which are sGC activators. Third, we will examine whether g-globin gene expression can be induced by increasing PPIX concentrations in red cells. This will be performed by breeding mice carrying the human b-globin locus with those of ferrochelatase deficiency. If successfully implemented, this proposal should not only enhance our understanding of the molecular mechanisms that regulate the expression of the g-globin gene during development, but also provide important information to develop novel Hb F inducers for treating the b-globin disorders.

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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: ENHANCING PATIENT PRENATAL EDUCATION-A FEASIBILITY STUDY**

  Principal Investigator & Institution: Sorenson, James R.; Professor and Chair; Health Behavior and Hlth Educ; University of North Carolina Chapel Hill Aob 104 Airport Drive Cb#1350 Chapel Hill, Nc 27599

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

  Summary: (provided by applicant): An increasing number of genetic carrier screening tests pose a challenge to adequate prenatal patient education. Clinic based computer patient education programs may be an effective response to this challenge. Before mounting a RCT to assess their effectiveness it is essential to study the feasibility of operating such programs in clinic settings. We propose a feasibility study. Our first specific aim is to develop an interactive computer assisted instruction (ICAI) patient education program for six prenatal genetic carrier screening tests (Multiple-Marker, Advanced Maternal Age, Sickle Cell, **Thalassemia,** Cystic Fibrosis, and Tay Sachs/Canavan). Our second aim is to collect data on the impact of the ICAI program on patient knowledge and anxiety, as well as patient and provider acceptance of the ICAI program. Our third aim is to assess the impact of the ICAI program on clinic activities. Our fourth aim is to estimate the likely effect size of the ICAI on patient knowledge and anxiety and to develop study methods for a RCT of ICAI effectiveness. To accomplish this we propose first, to develop the ICAI program using Cognitive Response Interviewing and Usability Testing methodologies with pregnant patients, as well as provider interviews. Next we will measure patient knowledge and anxiety prior to and after completing the ICAI. We will also ascertain patient and provider assessment of the ICAI as a clinic based educational tool. Third, we will employ Patient Time Flow Analysis to assess the impact of the ICAI on clinic activities. Based on these data, we will design a RCT to assess ICAI program effectiveness in public health prenatal clinics and private obstetrical practices.

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

- **Project Title: FETAL GLOBIN INDUCTION IN BETA THALASSEMIA**

  Principal Investigator & Institution: Perrine, Susan P.; Associate Professor of Medicine; None; Boston University Medical Campus 715 Albany St, 560 Boston, Ma 02118

  Timing: Fiscal Year 2002; Project Start 30-SEP-1998; Project End 31-JUL-2004

  Summary: The beta thalassemias are characterized by a deficiency of adult (beta) globin chains of adult hemoglobin (Hb), an excess of toxic, unmatched alpha globin chains, and intramedullary hemolysis. The resulting anemia develops only after fetal (gamma) globin synthesis and Hb F is suppressed in infancy. Induction of fetal (gamma) globin to levels which improve globin chain balance by even 10 percent can prolong red blood cell survival and diminish clinical morbidity. 5-Azacytidine has increased hemoglobin (Hb) levels by 1.8-3 gmd/d1 in **thalassemia,** but also causes general cytopenias and carries carcinogenicity risks. Fatty acids induce (gamma) globin experimentally. Arginine Butyrate, a prototype fatty acid, has been most effective when given intermittently or Pulsed, inducing Hb F to a mean level of 22 percent in 7/9 adults with sickle cell disease and increasing total hemoglobin by 3 gm/dl over baseline levels in 5/6 beta **thalassemia** patients. Two clinical pilot studies are proposed to test the hypotheses that therapy with

Pulsed Butyrate, or rhu-EP0 + Pulsed Butyrate, will induce gamma globin chain synthesis sufficiently to improve non alpha: alpha globin chain balance and red blood cell survival, and increase total Hb in a significant proportion of patients with beta **thalassemia** intermedia. Baseline hematologic levels will be assayed four times over a two-month period. Butyrate will then be administered during an Induction Phase, to determine a patient's optimal dose, followed by a "Maintenance Phase" of therapy for 3 months. Pulsed Butyrate will also be tested with rhu-EPO. The proportions of patients on each study in whom the following endpoints are achieved, compared to baseline levels, will be analyzed: 1) an increase in total Hb of at least 2.0 grams/dl, 2) an increase in hematocrit of at least 5 percent, 3) a decrease in hemolysis, measured by LDH and bilirubin, 4) improvement in globin chain synthesis by 10 percent. Whether specific genotypes and in vitro response to Butyrate correlate with clinical responses will also be analyzed. These studies should determine the proportion and some genotypes of beta **thalassemia** patients which can benefit from Pulsed Butyrate plus/minus rhu-EP0 therapy.

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

- **Project Title: FETAL STEM CELL GENE THERAPY**

  Principal Investigator & Institution: Muench, Marcus O.; Surgery; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747

  Timing: Fiscal Year 2002; Project Start 01-SEP-2001; Project End 31-AUG-2004

  Summary: (adapted from the application) A growing number of hematological diseases can be diagnosed before birth. In some cases, early treatment may benefit the health and survival of the fetus. Either in utero stem cell transplantation (IUT) or fetal gene therapy may treat diseases such as the hemaglobinopathies. This application aims to determine the best method for the introduction of genes into fetal hematopoietic stem cells (HSCs). Fetal HSCs are more proliferative than their adult counterparts and are, therefore, hypothesized to be more susceptible to transduction by retroviral vectors based on murine leukemia virus or human immunodeficiency virus. IUT offers another means of curing a number of hematological diseases by generating a state of hematopoietic chimerism. However, in the absence of any advantage for the donor HSCs, the levels of chimerism that can be achieved by IUT are low. This limits the use of this therapy to very few diseases. Our aim is to extend the use of IUT to the treatment of diseases, such as **thalassemia** and sickle cell anemia, by engineering HSCs to have a proliferative advantage over normal HSCs. This application will test if introduction of the erythropoietin receptor (EpoR) into HSCs will render these altered cells responsive to erythropoietin (EPO). This will in turn result in the altered HSCs and their progeny having a proliferative advantage over normal progenitors. Truncated forms of EpoR (tEpoR) will also be tested. These tEpoR, having deletions in the negative regulatory region of their cytoplasmic domains, deliver stronger proliferative signals than EpoR. The effects of introducing the EpoR genes on the proliferation and differentiation of HSCs and their progenitor progeny will be determined using various in vitro culture systems. It is hypothesized that ectopic expression of either EpoR or tEpoR will confer the ability of HSCs and early progenitors to proliferate in response to EPO with minimal effect on the differentiation program of these cells. To test if ectopic EpoR or tEpoR expression on HSCs can make these cells more competitive than their normal counterparts, modified HSCs will be tested against control HSCs in a mouse model of human hematopoiesis. The ability of HSCs expressing ectopic EpoR to engraft bone marrow after no or only minimal cytoablation will also be tested. These in vivo experiments will further determine if making HSCs responsive to EPO will have any

detrimental effect on the long‑term reconstituting‑ and multilineage‑ potential of HSCs. A positive outcome from the proposed studies would aid in developing treatments for hemoglobinopathies based on generating hematopoietic allochimerism.

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

- **Project Title: GAMMA GLOBIN VECTORS FOR TREATMENT OF HEMOGLOBINOPATHIES**

  Principal Investigator & Institution: Persons, Derek A.; St. Jude Children's Research Hospital Memphis, Tn 381052794

  Timing: Fiscal Year 2002; Project Start 01-FEB-2000; Project End 31-JAN-2004

  Summary: This application is focused on the candidate's immediate career goal, which is to enhance and further his laboratory-based training to date by acquiring new skills in the development, testing and use of globin vectors designed for gene therapy approaches to the beta-chain hemoglobinopathies. With the applicant's clinical background, previous doctoral research experience and three years of post-doctoral work in the laboratory of Dr. Arthur Nienhuis at St. Jude Children's Research Hospital (SJCRH) most recently, the candidate is now entering a transitional phase in his career with the goal of becoming an independent investigator as a clinician-scientist. However, the candidate and the sponsor strongly believe that further training involving the new vectors and animal models outlined in this application will facilitate this transition and greatly enhance the potential for early success as an independent investigator. As an independent faculty member in an academic medical setting, it is the candidate's long-term career goal to continue in the area of gene therapy for hematologic disorders with specific interest in developing a research program compatible with the translation of successful preclinical gene therapy approaches to the clinic. In this application, the candidate proposes to obtain additional training and specific expertise in the development and testing of new therapeutic globin vectors with his current mentor, Dr. Arthur Nienhuis, at SJCRH. Within the Div. of Experimental Hematology in which Dr. Nienhuis is a member and Chief, there is significant expertise in retroviral and lentiviral vector development, in techniques of gene transfer into murine and human hematopoietic stem cells, in animal models of **thalassemia,** and in the use of the NOD/SCID murine transplant model for human stem cells. Thus, the further training the applicant requires for the execution of the proposed research is readily available. The proposed research project is based on the need for the development of improved globin vectors for use in a gene therapy approach to both **thalassemia** and sickle cell anemia. The focus of this project involves a gene addition strategy based on the hypothesis that delivery of an optimized gamma-globin gene cassette can achieve a sufficient level of expression in developing erythroid cells to reverse the thalassemic or sickle cell disease phenotype. The project contains 3 specific aims: 1) to design and test novel gamma-globin retroviral and lentiviral vectors, 2) to use a murine model of beta-thalassemia to model gene therapy approaches using optimized gamma-globin vectors. and 3) to characterize and use primitive hematopoietic cells from patients with beta-thalassemia to evaluate the therapeutic potential of optimized gamma-globin vectors.

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- **Project Title: GAMMA-GLOBIN GENE SILENCING IN HUMAN RED CELLS**

  Principal Investigator & Institution: Tuan, Dorothy Y.; Biochem and Molecular Biology; Medical College of Georgia 1120 15Th St Augusta, Ga 30912

Timing: Fiscal Year 2003; Project Start 01-SEP-2003; Project End 31-MAY-2007

Summary: (provided by applicant): In **thalassemia** and sickle cell disease the severity of symptoms can be ameliorated by enhanced expression of the fetal gamma-globin genes in adult erythroid cells in which the gamma-genes are normally silenced. This application proposes to test the hypothesis that the intergenic DNA between the Agamma- and delta-globin genes including the psi/beta-globin gene enhancer and promoter and the Alu repetitive DNAs as well as the beta-globin promoter participates in the silencing of gamma-genes by competing with the gamma-promoter for binding with specific transcription factors (TFs) present in limited amounts in adult erythroid cells. Two new systems will be used for the study: in vitro culture of human erythroid progenitor CFU-E cells obtained from adult blood and transgenic (Tg) zebrafish harboring 100 kb of BAC DNA spanning the entire human beta-globin gene locus, in which the gamma-globin genes undergo silencing during erythroid differentiation and development. The specific aims are: (1). Identification of TFs that regulate gamma-globin gene inactivation and assess their relative abundance during human erythropoiesis from CFU-E to erythroblast cells by i) microarray analysis to identify known and also new and unknown TFs differentially expressed in CFU-E and erythroblast cells, ii) over-expressing these TFs in CFU-E cells to determine their activities on y-gene expression, iii) gel mobility shift assays with nuclear extracts of CFU-E and erythroblast cells to study the binding affinities of the TFs to cognate DNA motifs in the globin promoters and the intergenic DNAs, and iv) Chromatin immunoprecipitation (CHIP) to map in vivo changes in the assembly of these TFs into pol II or pol III transcriptional machinery in the beta-globin gene locus. 2). Identification of cis-DNA elements that regulate inactivation of human gamma-globin genes during ontogeny in Tg zebrafish. Interginic DNA and globin promoters will be deleted in vivo from the integrated human BAC DNA by Cre-loxP mediated recombination. The effects of the deletions on gamma-gene expression and on the assembly of the TFs into transcriptional machinery at the human globin gene locus will be studied by quantitative RTPCR and CHIP. Establishing and understanding the in vitro human adult erythropoiesis and Tg zebrafish models of gamma-globin gene silencing will provide new targets and new systems to test pharmacological compounds designed to regulated gamma-globin.

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- **Project Title: GENE THERAPY FOR COOLEY'S ANEMIA IN A NEW MOUSE MODEL**

  Principal Investigator & Institution: Rivella, Stefano; Pediatrics; Weill Medical College of Cornell Univ New York, Ny 10021

  Timing: Fiscal Year 2004; Project Start 01-MAY-2004; Project End 31-MAR-2009

  Summary: (provided by applicant): Stem cell-based gene therapy offers a potential means to cure congenital severe hemoglobinopathies such as beta-thalassemia. For this reason we have constructed a lentiviral vector (TNS9) carrying the human beta-globin gene and demonstrated that with this vector we can obtain long-term correction of a mouse model affected by beta-thalassemia intermedia. Furthermore, this vector rescues a new lethal mouse model affected by beta-thalassemia major. However, in these mice the level of correction of the anemia and hemoglobin produced are not yet optimal. We believe that in order to unveil completely the potential of this gene therapy approach, we need to investigate, in this new mouse model of **Cooley's anemia,** (Aim 1) the correlation between the fraction of lentiviral transduced hematopoietic stem cells (HSC), the degree of BM chimerism and the corresponding level of anemia correction. For this

purpose, we will generate a new lentiviral vector that combines expression of a reporter gene, such as the humanized red-shifted green fluorescent protein (hrGFP), in all the hematopoietic lineages and expression of the human beta-globin gene in erythroid cells (TNS9+GFP). To increase human beta-globin expression (Aim 2) we propose to generate new lentiviral vectors that could potentially increase hemoglobin production. We believe that we can raise hemoglobin production from TNS9 by extending the beta-globin promoter by 1 Kb and inserting a 1 Kb genomic region corresponding to the HS1 of the LCR. Another genomic element that could raise the level of hemoglobin production by diminishing the variability of expression at different genomic integration sites is the cHS4 insulator element. The production of new therapeutic vectors requires efficient strategies to compare and identify the best beta-globin encoding lentivirus. For this purpose we propose (Aim 3) to investigate the average level of expression of TNS9 versus the new lentiviral vectors (proposed in Aim 2) in BM chimeras. In addition, we propose (Aim 4) to generate transgenic mice from lentiviral transduced single copy ES cells to study the level of and variability in expression for each vector. Finally, insertion of selective drug resistance genes, dihydrofolate reductase (DHFR) versus methylguanine-DNA-methyltransferase (MGMT), will be evaluated (Aim 5) to enhance competitive repopulation of transduced stem cells expressing the human beta-globin gene.

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- **Project Title: GENE THERAPY OF SICKLE CELL ANEMIA & BETA-THALASSEMIA**

  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-1995; Project End 31-AUG-2005

  Summary: (provided by applicant) This supplement proposal to our Gene Therapy Program Grant has been prompted by the unanticipated success, ahead of schedule, of the correction of sickle transgenic mice and severe transgenic B- thalassemic mice with our lentivirus vector. The present proposal aims at accelerating, as much as it is possible and safe, the advent of clinical trials. In the absence of unanticipated set backs, we estimate that within 2 years we should be in a position of contemplating clinical trials. Hence, this proposal includes expansion and retargeting of previous Aims but also completely new experimental Aims. The specific reasons for a supplemental proposal are the following: 1) The effort, initially centered on sickle cell anemia, has been significantly expanded recently, to the gene therapy of B-thalassemia, with aspects not included in the original proposal; 2) We have significantly expanded our strategy of anti-sickling in order to improve even further the antisickling properties of our vector, including improvement of the thalassemia-targeted vector by adding an increased capacity of delivering oxygen. Recently data from our laboratory suggest the need to pursue a novel anti-sickling globin construct, involving simultaneously vertical, lateral and inter-double strand contact site mutations. These new objectives have as background our grossly underestimation of the animal facility cost of our large transgenic mice colony. 3) As a completely new aspect of the project is the use of a Primate model. Since they are significant differences in the behavior of murine and human hematopoietic stem cells, it is, therefore, imperative to test gene therapy strategies in an animal model system which closely resembles man before considering clinical trials. The objectives include the assessment of: a) Potential toxicity of genetically modify marrow repopulating cells, b)The efficacy and duration of transgene expression, c)The various sources and doses of hematopoietic stem cells required for clinically

achievable levels of genetic modification will be evaluated, d) The conditioning regimen required for engraftment of the genetically modified stem cell graft. 4) Another area of novel expansion is the extension to testing of B-globin therapeutic vectors and gene transfer strategies to human thalassemia-patient hematopoietic cells assessed both in vitro and in in vivo immunodeficient mouse models. Also, we plan to extend to the **thalassemia** model studies to developing effective procedures for transplantation under non-myeloablative conditions including assessment of selective expansion of genetically modified stem cells. In the expansion to primate models, the Vancouver site will optimize and carry out clinical scale transductions of non-human primate hematopoietic stem cells. Additionally, we will exploit the recently developed nude-NOD/SCID mouse model to enable long term (over 1 year follow-up) comparative studies of the recovery and repopulating function of transduced non-human primate hematopoietic stem cells.

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- **Project Title: GENE THERAPY USING HEMATOPOIETIC STEM CELLS**

  Principal Investigator & Institution: Kohn, Donald B.; Professor of Pediatrics and Microbiology; Children's Hospital Los Angeles 4650 Sunset Blvd Los Angeles, Ca 900276062

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

  Summary: (provided by applicant): The central theme of this Program is gene transfer to hematopoietic stem cells (HSC) or progenitor cells to correct genetic diseases affecting the production and/or function of blood cells. While the concept of gene therapy using HSC to provide safe and effective methods to treat congenital disorders has been under study for at least two decades, there have been only a few rare cases of successful clinical application. The techniques currently in use for gene transfer and expression in HSC are inadequate in most cases to yield clinical benefits. The goal of this Program is to investigate the mechanisms limiting successful clinical applications of gene transfer and to develop improved techniques which will broaden the range of diseases which may be treated effectively. The Project leaders have complementary expertise in the relevant areas of experimental hematology, immunology, signal transduction, and gene therapy and have a long-standing record of interactive collaborations. These advances can only be realized by combining each of these individual projects into a unified Program. This Program has five projects: 1. Transduction of human stem and progenitor cells, 2. Minimal Lentiviral Vectors for Gene Therapy of beta-thalassemia, 3. Optimized Gene Therapy for Human X-linked Agammaglobulinemia, 4. Gene Therapy for SCID due to Cytokine Receptor Defects, and 5. Gene Therapy for ADA-deficient SCID. Four Cores (Administrative, Cell Isolation and Analysis, Vectors and Animals) will support the projects with integrated services for optimal quality and efficiency. The information generated by these investigations will provide valuable knowledge to the field to increase the effectiveness of gene therapy interventions for hematologic disorders.

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- **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.

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- **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.

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- **Project Title: GENETIC MODIFIERS IN CHILDREN WITH SICKLE CELL ANEMIA**

  Principal Investigator & Institution: Ware, Russell E.; Professor of Pediatrics; Pediatrics; Duke University Durham, Nc 27710

  Timing: Fiscal Year 2002; Project Start 01-JUL-2001; Project End 30-JUN-2006

  Summary: (provided by applicant) The beta6 (Glu toVal) mutation in the beta globin gene that leads to sickle cell anemia (SCA) has been known for many years, and the biophysical characteristics of intracellular sickling are well described, but the clinical heterogeneity in patients with SCA is poorly understood. Patients with SCA have a wide variability of clinical disease expression that is puzzling, despite efforts to identify globin gene modifiers such as alpha **thalassemia,** beta globin haplotype, or enhanced gamma globin expression. Our preliminary data suggest that genetic modifiers outside the globin gene loci can alter clinical disease expression in SCA, and we hypothesize that these genetic modifiers can predict the development of cerebrovascular and hepatobiliary disease in children with SCA. To test our hypothesis, we will analyze DNA samples from over 400 pediatric patients enrolled in two completed NHLBI-sponsored multicenter trials: (1) the Cooperative Study of Sickle Cell Disease (CSSCD) and (2) the Study to Prevent Stroke (STOP). We also include the upcoming Phase III infant hydroxyurea trial (BABY-HUG) that will add 200 additional DNA samples and the opportunity for direct patient contact and clinical research experience by trainees. We will test DNA samples from these unique pediatric cohorts for genetic polymorphisms (DNA mutations) in genes that collectively are important in thrombosis (e.g. methylenetetrahydrofolate reductase, platelet glycoprotein IIIa, plasminogen activator inhibitor, prothrombin, Factor V, and Factor VII genes), brain injury repair (apolipoprotein E), bilirubin metabolism (the UDP-glucuronosyltransferase), and iron accumulation (hereditary hemochromatosis gene). After determining the prevalence of each DNA mutation, we will correlate specific polymorphisms with patient data including laboratory measurements, clinical events, and radiological studies. The long-

term goal is to identify genetic risk factors that influence the development of cerebrovascular and hepatobiliary disease, and to develop a prospective interventional clinical trial for children with SCA. Trainees will study laboratory techniques, statistical analysis, IRB protocol design, informed consent, ethical issues related to participation in clinical trials, and have direct patient contact with families participating in BABY-HUG.

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- **Project Title: GENOMEWIDE SEARCH FOR MODIFIERS OF SEVERITY IN BETA-THA***

  Principal Investigator & Institution: Braun, Andreas; Sequenom, Inc. 3595 John Hopkins Ct San Diego, Ca 921211121

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

  Summary: (provided by applicant): Beta-thalassemias are extremely common in SouthEast Asia. Many of the molecular defects accounting for the beta-chain deficiencies in these patients have been characterized, and are attributed to adult beta-globin gene mutations resulting in reduced levels (beta+-thalassemia) or complete inactivation (beta0-thalassemia) of the encoded beta-chains. The great numbers of individuals with **thalassemia** trait or disease have overwhelmed the medical service communities in this region, where the expense and/or limited availability precludes access to needed resources for many if not most of the patients. Due to recent worldwide migrations, these abnormal alleles and associated disorders are becoming more common in other regions, including the U.S. One mutant allele, HbE, identified as a G>A substitution in codon 26 of beta-globin, may be the most common beta-thalassemia allele worldwide. This allele is unusual in that it combines two forms of deficiency: one is qualitative, in that this substitution leads to a Glu>Lys amino acid change in the encoded protein, and the other is quantitative, in that the mutation alters normal splicing. A most puzzling feature of HbE is the variable disease presentation in heterozygotes with another beta-thalassemia allele, for example in beta0-thalassemia/ HbE disorder. Patients with seemingly identical "functional genotypes" at this locus, i.e. expression only of betaE-globin from one allele, show a remarkable variability in disease severity, ranging from nearly asymptomatic (MILD disease) to transfusion-dependent anemia with additional complications (SEVERE disease). There exists a great and immediate need to identify the modifying factors, which may represent either novel therapeutic targets or the focus of diagnostic assays to help identify at-risk individuals. To address this need, we intend to perform a genomewide search for genetic polymorphisms associated with disease severity. SEQUENOM's platform for genetic analysis, DNA MassArray, has been developed to provide accurate and high throughput scoring of genetic variations in a highly automated setting. We intend to test the feasibility of genomwide association studies by taking a "brute-force", unbiased approach to identifying modifiers of severity in patients with beta 0-thalassemia/HbE disease. It's anticipated this "non-hypothesis-driven" approach may also reveal genes that might have been overlooked because of expectations based on current understanding of biology. To our knowledge, using 100,000 gene-based SNPs, this will be the largest genomewide association study ever undertaken in an attempt to identify disease susceptibility or protective alleles.

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- **Project Title: HBF VARIANTS FOR GENE THERAPY OF SICKLE CELL DISEASE**

  Principal Investigator & Institution: Adachi, Kazuhiko; Children's Hospital of Philadelphia 34Th St and Civic Ctr Blvd Philadelphia, Pa 191044399

Timing: Fiscal Year 2002; Project Start 01-APR-1998; Project End 31-MAR-2006

Summary: (provided by applicant): Despite extensive research on the Hb molecule, the mechanism by which heme and globin subunits coordinately assemble and how misfolded and unstable unassembled globin chains are removed from erythrocytes are not known. In addition, the basic mechanism by which Hb F inhibits polymerization and ameliorates the clinical course of SCD is not completely understood. Elucidating such mechanisms can contribute to the development of strategies for gene therapy in the treatment of diseases of altered globin chains or those associated with decreased globin synthesis. In this proposal we aim (1) gamma-chain assembly with a chains to form functional human fetal Hb, (2) Ubiquitin-mediated degradation of excess non-alpha globin chains in vivo, and (3) Engineered Hb F variants having low oxygen affinity and inhibitory properties on Rb S polymerization. The long-range goal is to identify and design optimal Rb F variants for use in gene therapy of sickle cell disease (SCD) andthalassemia. In Specific Aims (1) we will test two related hypotheses; (i) Folded alpha-globin chains assemble with intermediately folded nascent gamma-chains prior to or soon after the release from polyribosomes. (ii) The amino acids at G-10, 14 and 18, which have been shown by x-ray crystallographic analysis to be at the alpha1gamma1 interaction sites on the G helix, are critical for assembly of alpha- and gamma-globin chains in vivo as well as in vitro. In Specific Aim (2), we hypothesize that purified non-alpha chain tetramers, like Hb hetero-tetramers, are not substrates for ubiquitination since Beta4 and gamma4 structures are very similar to the alpha2Beta2 heterotetramer structure. Using a rabbit reticulocyte cell free system, we will measure degradation of non-alpha chain in the absence of a chain during translation in the presence of ubiquitin. In specific Aim (3), we will continue to investigate the inhibitory mechanism of Hb S polymerization by Hb F. We hypothesize that Hb F variants (e.g., Hb F gamma 73 His, Rb F gamma 6Val & 73 His) can be engineered that have inhibitory properties exceeding those of Hb F and we will seek such variants. We will also continue to seek Rb F variants with lower oxygen affinity than Hb S through not only enhancement of 2,3-BPG interaction but also amino acid substitution at the alyl interaction sites on the G helix. Because of their lower oxygen affinity, these hemoglobin variants in addition to having anti-nucleation properties would effectively inhibit sickling at lower levels than would native Rb F, such as about 10 percent vs. 20 percent. The understanding of the assembly of gamma and alpha chain and the mechanism of degradation of excess globin will provide a basis for determining the most appropriate gamma chain mutant for gene therapy, which should be one that can be introduced by viral vectors at significantly lower levels than native Rb F. Furthermore, these studies will be of general interest to researchers who study protein biosynthesis and will help identify why some mutant globin chains are incorporated into hemoglobin more or less efficiently than wild type chains as well as how separately translated alpha and non-alpha chain are quality controlled during hemoglobin formation to preserve functional erythrocytes.

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- **Project Title: HEMOCHROMATOSIS--MECHANISMS AND NOVEL THERAPIES**

  Principal Investigator & Institution: Powell, Lawrie W.; Queensland Institute of Medical Research Herston Brisbane Qld, 4006

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

  Summary: (adapted from the application) The broad long-term objectives of this project are to gain a greater understanding of the biology of iron absorption (uptake and transfer) with a view to the development of novel therapeutic approaches to iron overload diseases. Recent exciting discoveries including the hemochromatosis gene HFE

and the metal transporters DMT1, hephaestin and SFT have provided the opportunity to study the steps in the pathway of iron uptake and transport across the intestinal cell as well as intracellular signaling pathways involved. In the first instance it is proposed to examine the distribution of both HFE mRNA and proteins in normal individuals, patients with hemochromatosis, other forms of iron overload and iron deficiency as well as in several animal models. In addition, this project will investigate the distribution and expression of DMT1, hephaestin, Ireg1 and SFT in these human subjects and animal models. These studies will be integrated with a more detailed analysis of HFE trafficking and processing, including the precise nature of the assembly, localization, transport and degradation of the HFE molecule. This knowledge will provide an avenue for the development of therapeutics aimed at increasing the secretion and transport of the mutated form of HFE to the compartment where it is active. The experiments in the various animal models should allow the elucidation of the relative contributions of brush border uptake and basolateral transfer in normal and abnormal iron homeostasis and the responses to various stimuli known to modulate iron absorption. A novel aspect of the experimental protocol involves hepatocyte transplantation to examine the role of the liver in regulating iron absorption. A major aspect of this study is the determination of the three dimensional structure of hephaestin and DMT1 and to use these in structure based design studies to develop novel therapeutic agents that inhibit intestinal iron absorption. Such agents will be particularly applicable to the treatment of disorders in which iron absorption is elevated, such as hemochromatosis and **thalassemia.** In the former this should reduce or even abolish the requirement for prolonged phlebotomy therapy which is time-consuming, expensive and often poorly tolerated by patients. The approach is a multidisciplinary one combining the expertise of members of the Clinical Sciences Unit of QIMR in iron metabolism with that of x-ray crystallography and structure-based drug design studies at the Centre for Drug Design and Development in the University of Queensland.

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 Po Box 49 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.

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- **Project Title: IMAGING OF APOPTOSIS**

  Principal Investigator & Institution: Ross, Brian D.; University of Michigan at Ann Arbor 3003 South State, Room 1040 Ann Arbor, Mi 481091274

  Timing: Fiscal Year 2002; Project Start 14-JUN-2002; Project End 31-MAR-2007

  Summary: (provided by applicant): The goal of the proposed project is to develop a transgenic rodent wherein activation of apoptosis can be imaged non-invasively. Strict coordination of proliferation and apoptosis is essential for normal physiology. An imbalance in these two opposing processes results in various diseases including AIDS, neurdegenerative disorders (Alzheimer's disease), myelodysplastic syndromes (Aplastic anemia, thalassemia), ischemia/reperfusion injury, cancer and autoimmune disease among others. Objective imaging of apoptosis will be a major advancement not only in the screening and validation of novel therapeutic molecules for the above diseases but also in the evaluation of therapeutic success or failure of current and future therapeutic treatment paradigms. We have over the last year of our P20 (pre-ICMIC) award developed a reporter cassette which when transfected into mammalian cells results in a polypeptide that has significantly attenuated levels of reporter activity. When this molecule is being expressed in cells undergoing apoptosis, a caspase (proteases activated during apoptosis) specific cleavage of the reporter gene occurs resulting in activation of the reporter thus enabling imaging of apoptosis. In the present proposal we will optimize this novel molecular construct and conduct in vitro (Specific Aim 1) and in vivo (Specific Aim 2) studies. Finally, a transgenic rodent model will be developed wherein the activation of apoptosis within the skin in response to sunlight can be imaged (Specific Aim 3). The ability to image apoptosis non-invasively and dynamically over time will be an invaluable resource to pharmaceutical industry and scientists for in vitro high throughput screening of compounds with pro- and anti-apoptotic activity and also for target validation in vivo.

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- **Project Title: IN UTERO GENE THERAPY TO FETAL HEMATOPOIETIC STEM CELLS**

  Principal Investigator & Institution: Mahler, Wendy R.; Medicine; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747

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

  Summary: (provided by applicant): The goal of this proposal is to use in utero gene delivery to target highly proliferative hematopoietic stem cells (HSC) in the fetal liver. Current limitations to successful gene therapy for hematopoietic disorders include low

efficiency of transduction of long term repopulating cells, gene silencing in transduced clones of cells, and the lack of a selective advantage to allow preferential growth and expansion of the transgene. Targeting HSC populations from the mid-gestation fetal liver, at a time when the cells are rapidly expanding, has the potential to transduce large numbers of HSC. This group and others have been successful at in utero gene transfer. We will enrich for transduced cells by applying postnatal selection for the presence of a specific methylguanine methyltransferase (P140K MGMT) included in gene transfer vectors. Finally, we will use this approach to transduce and select HSC expressing P140K MGMT and human a globin in a murine model of beta **thalassemia.**

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

- **Project Title: INDUCTION OF HBF BY PROLYL HYDROXYLASE INHIBITORS**

  Principal Investigator & Institution: Klaus, Stephen J.; Fibrogen, Inc. 225 Gateway Blvd South San Francisco, Ca 94080

  Timing: Fiscal Year 2004; Project Start 13-APR-2004; Project End 30-SEP-2004

  Summary: (provided by applicant): Sickle cell disease (SCD) and beta-thalassemia are mostly inherited beta-hemoglobinopathies that lead to chronic anemia. Both diseases are characterized by insufficient or defective expression of the beta chain of adult hemoglobin (Hb), leading to insufficient oxygen delivery to peripheral tissues. Inadequate oxygen levels in tissues causes the episodic vasoocclusive crises that cause ischemic pain and damage, often necessitating blood transfusions. It has been recognized for decades that a means to mitigate the pathophysiology of these diseases, and in particular SCD, is to substitute the mutant adult Hb with fetal Hb (HbF). HbF is normally not expressed during adulthood due to silencing. The ability to induce fetal hemoglobin expression during adulthood has recently been achieved by pharmacological means, and led to the approval of hydroxyurea (HU) to treat patients with SCD. Although HU is the current standard of care for SCD, it has an unclear mechanism of action, and the use of HU is hindered by dose-limiting toxicity and the fact that many SCD patients respond poorly or not at all. Furthermore, HU displays little efficacy for beta-thalassemia. Therapeutic options to treat beta-hemoglobinopathy remain a large, unmet medical need worldwide. FibroGen has proprietary libraries of prolyl hydroxylase (PH) inhibitors that activate the transcription factor hypoxia-inducible factor, which may play a role in regulating expression of the gamma-globin gene that comprises HbF. Preliminary data shows that PH inhibitors lead to increased HbF expression in vitro and are additive to the HbF-inducing effects of HU. We propose to screen our existing libraries of PH inhibitors to identify and optimize the pharmacophore associated with induction of HbF expression. The ultimate goal is to select and test lead candidates in non-human primates for induction of HbF in vivo. Ultimately, this will enable identification of an HbF-inducing compound that can be tested alone or in combination with HU to mitigate the pathophysiology associated with SCD and other beta-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: IRON INDUCED CONGESTIVE HEART FAILURE**

  Principal Investigator & Institution: Brown, Arthur M.; Professor and Chairman; Physiology and Biophysics; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

  Timing: Fiscal Year 2002; Project Start 30-SEP-1998; Project End 31-AUG-2004

  Summary: (Adapted from the applicant's abstract) This multidisciplinary research project is designed to characterize the pathophysiology of iron-induced congestive heart failure using a systematic series of studies of the cardiomyopathy of iron overload in a new animal model, the Mongolian gerbil. Iron-induced myocardial disease is the most frequent cause of death in **thalassemia** major and is a major life-limiting complication of other transfusion-dependent refractory anemias, hereditary hemochromatosis and other forms of iron overload. The investigators hypothesize that (I) the body iron burden is a principal determinant of the magnitude of cardiac iron deposition in patients with **thalassemia** major, (ii) the nonuniform pattern of iron deposition in the heart results in variability in iron concentrations within cardiac myocytes, and (iii) increased intracellular iron selectively affects specific ion channels in cardiac myocytes, producing abnormalities in sodium and potassium currents, and damages other cellular components, producing cardiomyocyte dysfunction and heart failure. The proposed research has three specific aims: (1) to determine the effects of chronic iron overload on cardiac function during the development and progression of iron-induced heart failure in the gerbil model of iron overload, using miniaturized assessment of cardiac physiology in vivo in the intact animal, physiological studies of the isolated heart, and cellular studies of freshly isolated cardiomyocytes; (2) to determine the effects of iron-chelating therapy and other pharmacological interventions on the progression and regression of iron-induced heart failure in the gerbil model of iron overload, using

similar methods; and (3) to determine the molecular mechanisms by which cardiac Na+ currents are decreased and Ca2+-independent transient outward cardiac K+ currents are increased in iron-induced heart failure, using both freshly isolated cardiomyocytes from the gerbil model of iron-induced cardiomyopathy and rat neonatal cardiomyocytes in culture. This research will furnish the first electrophysiological and functional data from a new experimental model of heart failure. The results will provide fundamental information about the molecular basis for the effects of iron on cardiac ion channels and cardiomyocyte function in the heart failure of iron overload. (End of Abstract)

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

- **Project Title: LENTIVIRAL VECTORS FOR GENE THERAPY FOR BETA-THALASSEMIA**

  Principal Investigator & Institution: Malik, Punam; Assistant Professor of Pediatrics and Pa; Children's Hospital Los Angeles 4650 Sunset Blvd Los Angeles, Ca 900276062

  Timing: Fiscal Year 2002; Project Start 08-MAY-2002; Project End 31-MAR-2007

  Summary: (provided by applicant): The B-thalassemias are the most common single gene defect in humans and result from absent or decreased B-globin synthesis, leading to severe anemia. Patients with B-thalassemia major are treated with life-long transfusions. Bone marrow transplantation can be curative, but is limited to a few with matched donors, and has potentially serious complications. Replacement of a normal B-globin gene into hematopoietic stem cells (HSCs) can potentially correct the disorder permanently, avoiding the complications associated with a transplant. 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 diseases like SCID and hemophilia B. 'Globin' gene therapy has suffered from problems of vector instability, low titers and variable expression. The recently developed lentiviral vectors transduce the non-dividing HSCs and stably export large genomic fragments by unique RNA export mechanisms, imparting stability to globin vectors. Self-inactivating (SIN) lentiviral vectors are even more advantageous: the viral LTR is deleted upon integration into cells, completely inactivating viral transcription. This feature is ideal for the expression of a highly lineage-restricted gene such as globin, and additionally improves their bio-safety. We have recently shown remarkably lineage-specific and long-term expression of GFP and gamma-globin from SIN lentiviral vectors in mouse erythroleukemia (MEL) cells, primary murine and human cells. We propose to capitalize on these findings by examining the capabilities of SIN lentiviral vectors to carry the human B-globin gene and erythroid regulatory elements for gene transfer into HSCs that results in stable, lineage-specific and sustained expression of B-globin in RBCs. The aims of the study are to: 1) Develop SIN-lentiviral vectors carrying the human B-globin gene under control of 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 B-globin SIN lentiviral vectors in vivo, in thalassemic mice. 3) Determine the gene transfer capacity and efficacy of B-globin SIN lentiviral vectors in the RBC progeny of human **thalassemia** progenitor cells, using a unique model of human RBC production developed in our laboratory from hematopoietic progenitor cells. Together, these aims comprise a focussed research program to produce therapeutic and sustained levels of B-globin in human **thalassemia** RBCs, and form the basis for future preclinical studies.

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

- **Project Title: MALDI-TOF MASS SPECTROMETER**

  Principal Investigator & Institution: Ames, Bruce N.; Professor; Children's Hospital & Res Ctr at Oakland Research Center at Oakland Oakland, Ca 946091809

  Timing: Fiscal Year 2002; Project Start 01-MAY-2002; Project End 30-APR-2003

  Summary: The proposal requests support to purchase a Matrix Assisted Laser Desorption Ionization-Time of Flight-Mass Spectrometer (MALDI-TOF MS) for use at Children's Hospital Oakland Research Institute (CHORI) to facilitate an array of projects involving single nucleotide polymorphism (SNP) and proteome analysis. We emphasize the appropriateness of the MALDI-TOF MS approach compared to other technologies, the value of this addition to enhancing our research efforts, and the timeliness in the adoption of this technology to the proposed research applications. MALDI-TOF MS offers an efficient means of identifying SNPs, the most common type of DNA sequence variations in human populations, using high throughput multiplex technology populations. Multiplex analysis, allows simultaneous genotyping of a single sample at multi loci, and requires a system that is easily adaptable to the changing needs of research. Although alternative approaches to multiplex SNP-based genotyping exist, most of these are considerably more time consuming and less flexible. Use the multiplex SNP analysis technique afforded by MALDI-TOF MS, large panels of samples can be typed efficiently, accurately, specifically, and reliably. Acquisition of this instrument will benefit a consortium of users at CHORI who are engaged in a search for genes that modulate disease susceptibility and severity and sensitivity to environmental toxins. Among the diseases under study are sickle cell anemia, **thalassemia,** nutritional deficiencies, tuberculosis, diabetes, asthma, birth defects, sexually transmitted disease, and trachoma. In a broader context access to MALDI-TOF MS at CHORI will facilitate the application of knowledge regarding the role of genetic variations in human health. Proteomics, the large scale analysis of proteins, complements genomics by focusing on the gene products responsible for mediating cellular function. Proteomics focuses on several aspects of protein analysis: the identification of proteins and their post-translational modifications, the "differential display" utilized in comparing protein expression in health and disease states, and the studies of protein-protein interactions required to elucidate structure and function. MALDI-TOF MS is a well- established and robust which fulfills all of the proteomic functions described above. The availability of a MALDI-TOF MS instrument with the capabilities to perform these tasks, as well as quantitative analysis using isotope coded affinity tags (ICAT), will greatly enhance our ability to simultaneously characterize multiple proteins potentially involved mitochondrial function and other physiological states involved in health and disease.

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

- **Project Title: MECHANISMS CONTROLLING CELLULAR FETAL HEMOGLOBIN CONTENT**

  Principal Investigator & Institution: Dover, George J.; Professor of Pediatrics; Pediatrics; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 01-JAN-1982; Project End 31-DEC-2004

  Summary: This abstract is not available.

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

- **Project Title: MENTORED PATIENT ORIENTED HEMATOLOGY RESEARCH TRAINING**

  Principal Investigator & Institution: Sheth, Sujit S.; Pediatrics; Columbia University Health Sciences Po Box 49 New York, Ny 10032

  Timing: Fiscal Year 2002; Project Start 01-JUL-2000; Project End 30-JUN-2005

  Summary: The applicant's overall commitment is to an academic research career in clinical investigative hematology, primarily devoted to the improvement of the care of patients with hemoglobinopathies, including those with sickle cell disease and the thalassemias. His long-term goals are to acquire the research skills and experience needed to become an independent investigator able to carry out the clinical studies that will be needed to make available to patients the new diagnostic technologies and therapeutic interventions now in development, including gene therapy, the manipulation of fetal hemoglobin production, stem-cell transplantation and other advances. With the support of the K23 Mentored Patient-Oriented Research Career Development Award, the applicant's immediate objectives are (i) completion of a two-year program of didactic exercises leading to a Master's Degree in Patient-Oriented Research from the School of Public Health of Columbia University, (ii) mentored involvement in the clinical studies required for the development of new methods for the assessment and management of transfusional iron overload in patients with hemoglobinopathies, and (iii) mentored participation as the leader of the Columbia University component of the **Thalassemia** Clinical Research Network. In order to achieve these objectives, the applicant will draw upon the vast resources for clinical research and training that are available at the Columbia University College of Physicians and Surgeons. All clinical research activity will be carried out through the NIH sponsored GCRC at the New York Presbyterian Hospital. The ultimate objectives are to enable the applicant to gain the training and expertise to be able to develop into an independent clinical investigator with a focus on patient-oriented research, in the setting of an academic institution.

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

- **Project Title: MIXED CHIMERISM FOLLOWING PRENATAL TOLERANCE INDUCTION**

  Principal Investigator & Institution: Carrier, Ewa; Cancer Center; University of California San Diego La Jolla, Ca 920930934

  Timing: Fiscal Year 2002; Project Start 15-SEP-1999; Project End 31-AUG-2004

  Summary: This research project is designed to establish low toxicity approaches for maintaining mixed chimerism in beta-thalassemic mouse with the ultimate goal of developing myeloablative regimens to treat humans with congenital hemoglobinopathies. It will utilize 3 strategies developed in our laboratory: 1) murine model of in utero transplantation in beta-thalassemic mice, 2) prenatal tolerance induction and 3) high dose postnatal boots. The In utero transplantation provides excellent opportunity to introduce allogeneic cells into the developing fetal immune system with the goal of inducing tolerance to these cells From the experiments performed in different labs, it appears that the kind and relative number of cells injected defines the degree of tolerance induced. We are therefore proposing a research program in which 3 aims will be addressed: 1) establishment of optimal cell preparation for induction of high degree of tolerance following in utero transplantation; 2) establishment of strategies for maintenance of mixed chimerism. Our hypothesis is that lack of potent antigen presenting cells such as dendritic cells as well as specific B/T cell

ratio in injected population are important factors for induction of high degree of tolerance. Specifically designed experiments aimed t induction of tolerance will be performed. Depending on the degree of tolerance induced, mini-myeloablative regimens will be designed and minimal level of microchimerism sufficient for correction of hemolytic anemia will be established. Additionally, protocols for postnatal boots to maintain the level of chimerism will be designed. This research will lead directly to the establishment of successful human protocols for early treatment of hemoglobinopathies in non-toxic and inexpensive manner.

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

- **Project Title: MIXED CHIMERISM IN THE HEMOGLOBINOPATHIES**

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

  Timing: Fiscal Year 2002; Project Start 30-SEP-1999; Project End 31-AUG-2004

  Summary: The investigators of this proposal have developed two tools that may be of value in establishing stable mixed chimerism of patients with sickle cell anemia and beta **thalassemia.** The first tool is directed toward developing a minimally toxic method for producing stem cell depletion using the combination of flt-3 ligand (FL) and 5-fluorouracil (5-FU). This approach may be a useful component of transplant conditioning regimens that are directed at achieving mixed chimerism. The second tool uses chemical inducers of dimerization (CIDs) to specifically deliver a mitogenic signal to genetically modified cells. Transfer of a gene that encodes a CID-responsive protein may render normal donor stem cell responsive to CID-mediated proliferation. This approach may allow the proliferative status of normal donor stem cells in mixed chimeras to come under direct pharmacological control. Specific Aim 1 tests whether CIDs can expand genetically modified stem and progenitor cells in vivo. Specific Aim 2 develops a mouse model of mixed chimerism in beta **thalassemia,** and seeks to determine the level of normal donor stem cell engraftment needed to reverse the thalassemic phenotype. Specific Aim 3 tests whether CID-mediated in vivo expansion of normal donor stem cells can correct the thalassemic phenotype of mice with mixed chimerism. Specific Aim 4 evaluates whether FL can sensitize stem ells to 5-FU. In Specific Aim 5, the FL/5-FU combination is added to an immunosuppressive condition regimen for studies in allogeneic models of mixed chimerism. In Specific Aim 6, findings from the previous specific aims are combined to test CID-mediated in vivo expansion of normal donor stem cells in an allogeneic model of mixed chimerism.

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

- **Project Title: MOLECULAR ANALYSIS OF A YEAST TRANSCRIPTIONAL REGULATOR**

  Principal Investigator & Institution: Auble, David T.; Associate Professor; Biochem & Molecular Genetics; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2002; Project Start 01-MAY-1997; Project End 30-APR-2006

  Summary: (provided by applicant): The long-term objectives of the proposed project are to elucidate the mechanism of action and in vivo function of Mot1, an essential yeast transcriptional regulator that can activate or repress transcription. Mot1 is a member of a large family of evolutionarily conserved nuclear ATPases (the Snf2/Swi2 family) involved in transcription, DNA repair, and recombination. Defects in human Snf2/Swi2-related protein complexes are known to contribute to certain pediatric

cancers, Cockayne's Syndrome, a-thalassemia, and the most common form of X-linked mental retardation. Despite the ubiquitous occurrence of Snf2/Swi2 family members, the molecular mechanisms of action of these proteins are not understood in detail, nor is it understood what roles many of these proteins play in vivo. Mot1 's ATPase activity is required to activate or repress transcription of specific genes in vivo. Consistent with its role as a repressor, Mot1 can dissociate TATA-binding protein (TBP)-DNA complexes in an ATP-dependent reaction. Motl's mechanism of ATP-dependent transcriptional activation is unknown. Biochemical, molecular biological, and genetic approaches will be used to define how Mot1 regulates transcription in vivo and how the Mot1 response of particular promoters is determined. These approaches will also be used to understand how ATP hydrolysis by Mot1 drives TBP/DNA disruption. The proposed analysis of Mot1 function will lead to a better understanding of the role of Motl in transcriptional control as well as a better understanding of the functions of Snf2/Swi2 family members in general.

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

- **Project Title: MOLECULAR ANALYSIS OF NORMAL AND THALASSEMIC DNA**

  Principal Investigator & Institution: Orkin, Stuart H.; Professor; Children's Hospital (Boston) Boston, Ma 021155737

  Timing: Fiscal Year 2002; Project Start 01-APR-1982; Project End 31-MAR-2004

  Summary: Understanding the mechanisms by which globin genes are regulated in vivo is relevant to the design of novel approaches to management of **thalassemia** and hemoglobinopathies by drug or somatic gene therapy. Moreover, elucidating the basis of erythroid expression will lead to fundamental insights into the development of hematopoietic cells. Recent studies have implicated an abundant DNA-binding protein, GATA-1, as a central regulator of gene expression in erythroid cells. Gene targeting in mouse embryonic stem (ES) has established GATA-1 as an essential protein for erythroid cells to accomplish its proposed roles. This research plan is directed toward resolution of these outstanding issues. First, two approaches will be undertaken to define the cis-regulatory elements of the mouse GATA-1 gene: (i) GATA-1/lacZ gene constructs will be used to delineate sequences required for gen activation in transgenic mice; (ii) a two-step procedure involving gene targeting and Cre-mediated site-specific excision in ES cells will be used to test the role of upstream and intronic regions. By these approaches, the critical cis- regulatory sequences of the GATA-1 gene will be mapped. A long-range goal is identification of the regulatory proteins involved in turning-on GATA-1 in progenitors and maintaining its expression. Study of the structure and function of GATA-1 will include (i) x-ray crystallography of the novel two-finger DNA-binding domain complexed to DNA; (ii) analysis of the role of phosphorylation at multiple ser residues in the protein in DNA-binding, cellular localization, and its capacity to direct differentiation either in the 416B megakaryocytic differentiation assay or in rescue of GATA-1 minus ES cells; (iii) detection of protein-protein interactions of GATA-1 with other transcription factors (SP1, EKLF) and with itself in vitro in a GST-pull down assay and in "two-hybrid" assays in mammalian cells and yeast; and (iv) the search for novel erythroid proteins that interact wit GATA-1 or components of the basal transcription complex (TFIID and TFIIB) by cloning of cDNAs in yeast using GATA-1 as the tethered protein and in vitro using a protein interaction screen of gammagt11 MEL cDNAs. A long-range goal is the discovery of novel proteins that are critical to the establishment of an erythroid transcriptional complex, but which do not themselves directly contact DNA.

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

- **Project Title: MOLECULAR BASIS OF HUMAN GAMMA-GLOBIN GENE ACTIVATION.**

  Principal Investigator & Institution: Grosveld, Franklin G.; Erasmus University of Rotterdam Box 1738, 3000 Dr Rotterdam Rotterdam,

  Timing: Fiscal Year 2003; Project Start 25-JUL-2003; Project End 30-JUN-2007

  Summary: (provided by applicant): The long-term objective of the research is to develop reagents that activate human gamma globin gene transcription in the adult for treatment of beta-thalassemia and sickle cell anemia. It is known that expression of the fetal gamma globin genes greatly ameliorates the effects of these diseases, however it is not known how the human gamma globin genes are normally suppressed (or expressed at very low levels) when the expression of the human gamma globin genes switches to that of the delta and beta globin genes. It could be the result of an absence of transcription factors required for gamma globin gene expression or the presence of active suppressors of gamma globin expression or both. The aim of this application is therefore twofold: the characterization of the stage specific factors that are required for gamma globin gene expression and/or the stage specific factors that suppress gamma globin gene expression. Two independent in vivo approaches will be used. One uses chromatin precipitation to directly purify and sequence the proteins bound to the gamma globin gene promoters in the fetal stage and adult stage. The other is a functional assay to obtain single chain antibodies that switch on the gamma globin genes in the adult stage.

  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 MECHANISMS OF GLOBIN GENE EXPRESSION**

  Principal Investigator & Institution: Cunningham, John J.; St. Jude Children's Research Hospital Memphis, Tn 381052794

  Timing: Fiscal Year 2002; Project Start 01-JUL-2002; Project End 30-JUN-2003

  Summary: (provided by applicant): The long term objectives of this project are to determine the mechanisms by which erythroid Kruppel-like factor (EKLF) contributes specifically to the developmental control of beta-globin gene expression and more generally to erythropoiesis in vivo. Utilizing an EKLF-dependent erythroblast model, studies of the structural determinants of EKLF function have identified separable chromatin remodeling and transactivation domains. Moreover, these experiments demonstrate that additional sequences outside the previously defined in vitro remodeling domain are required for modulation of beta-globin promoter structure. In contrast to studies utilizing transient reporter assays, a novel internal activation domain, which is sufficient for induction of endogenous beta-globin gene expression to wild type levels was observed. To extend these observations, the first specific aim will assess the ability of the defined domains to modulate local and regional chromatin remodeling, transcription and globin gene switching in the context of an intact animal. This will be accomplished by deriving knock-in mouse strains that express various EKLF domains. Two of these mouse lines will test the hypothesis that an EKLF domain which can mediated chromatin remodeling but lacks transactivation potential, is sufficient to recruit the distal locus control region enhancer to the beta-globin promoter in definitive erythroid cells. In complementary experiments, a similarly derived knock-in EKLF mutant encoding the novel transactivation domain but lacking a second previously described amino terminal transactivation region will be tested for its ability to rescue normal erythropoiesis. The determination that additional polypeptide sequences are required for remodeling of the endogenous beta-globin promoter has resulted in a working hypothesis that additional as yet unidentified factors are necessary for this process. Studies in the second specific aim focus on the identification and characterization of these factors. Biochemical approaches utilizing reagents already in hand will be exploited to identify the components of this complex. Long-term, the genes identified will be studied by deriving mice in which the corresponding genomic loci are targeted. Together, the studies will provide important insights into the critical functions of EKLF that are essential for erythropoiesis. This fundamental knowledge is likely to expand our understanding of the molecular mechanisms regulating the gamma- to beta-switch in globin gene expression, potentially identifying therapeutic targets for the treatment of sickle cell disease and B-thalassemia.

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

- **Project Title: MOLECULAR/CHEMISTRY CHAPERONES AND HEMOGLOBINOPATHIES**

  Principal Investigator & Institution: Welch, William J.; Professor; Surgery; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747

  Timing: Fiscal Year 2003; Project Start 01-JAN-2003; Project End 30-SEP-2003

  Summary: (provided by applicant): Protein folding abnormalities resulting from mutations in the coding regions of many genes represent the molecular basis for a large

number of disease states. The solubility and stability of globin chains are altered by hundreds of mutations in the a- and b-globins. Therefore, diseases involving abnormal globin biogenesis are numerous (5% of the world's population are carriers of an inherited variant of hemoglobin). While the structure of the final folded state of each individual protein is largely determined by the primary amino acid sequence specified by the nucleotide sequence of the gene encoding it, it has become clear that a class of protein molecules known as molecular chaperones can modulate the rate of proper protein folding events and determine the degree to which polypeptides enter into non-productive pathways of folding. Furthermore, the rate of turnover of the wild-type (wt) and mutant forms of protein species by the cellular proteolytic machinery can be influenced by the action of various molecular chaperones. Finally, small nonprotein molecules acting as chemical chaperones can affect changes in the disposition of mutant gene products as they partition between non-native and native states. The action of the chemical chaperones on the polypeptide substrate or upon the protein folding environment often results in changes in the maturation rate, half-life and function of the mutant protein to where they approach that of the wild type species. We propose to examine folding pathway and assembly of globin chains during and after translation of the wild type and a number of mutant globin polypeptides. Special focus will be placed on study of the interactions with and actions of molecular chaperones with regard to final folded structure, solubility, stability and function of the globin chain variants. We will determine whether abnormally folded globin chains have any impact upon the levels and activities of the various molecular chaperones. Finally, through systematically changing the protein folding environment via small chemical chaperones, we will attempt to alter the fate of mutant globin chains. While the proposed research is of a basic biochemical nature, we believe it should facilitate the translation to approaches likely to have an immediate clinical impact.

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

- **Project Title: MR OF HEART IRON: T2*/T2 CALIBRATION & APPLICATION**

  Principal Investigator & Institution: Pennell, Dudley J.; U of L Imperial Col of Sci/Technlgy/Med of Science/Technology/Medicine London,

  Timing: Fiscal Year 2003; Project Start 15-SEP-2003; Project End 30-JUN-2007

  Summary: (provided by applicant): Beta-Thalassemia major (**thalassemia**) is a common genetic condition causing profound anemia which is very widespread in the world, particularly in countries where malaria has been prevalent, because single copies of the gene, which are insufficient to cause the major disease, offer protection against malaria. Some 93 million worldwide carry one copy of this gene, and one-quarter of children will inherit the major condition if 2 carriers reproduce. About 60,000 children are born annually with **thalassemia** and treatment is invasive and expensive. Regular blood transfusions are required to keep the children alive, but this leads to iron overload in the tissues which causes death at a young age in many sufferers. Treatment with iron chelation is helpful, but requires sometimes daily injections and is very expensive especially in developing countries. In 70% of cases, death is due to heart failure, the onset of which is difficult to predict and often has a rapid downhill course. Therefore our long term aim is to prevent death from heart failure caused by myocardial iron overload in **thalassemia** by using magnetic resonance (MR) imaging to identify early iron loading, and establish effective and well tolerated myocardial chelation regimes. Thus there is great scope for helping large numbers of sufferers, and also finding more acceptable and cost-effective treatments. In this grant application, we have 4 major aims: first, to understand how iron affects the signal from the MR scanner; second, to optimize

MR acquisition sequences so that measurements taken from the images accurately reflect the magnetic relaxation in the tissues; third, to calibrate the MR relaxation measurements against both heart and liver, so that we understand how the measurements made by the scanner relate to the amount of iron in these organs; fourth, to roll-out MR sequences to 6 sites world-wide and validate their use, so that these sites can in principle act as local distributors of the expertise within their own regions, whilst promoting research into improved care in **thalassemia.** These centers are Philadelphia (USA), Cagliari (Italy), Athens (Greece), Nicosia (Cyprus), Mumbai (India) and Singapore.

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

- **Project Title: MRI QUANTITATION OF TISSUE IRON IN HEMATOLOGIC DISORDERS**

  Principal Investigator & Institution: Song, Hee K.; Radiology; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104

  Timing: Fiscal Year 2003; Project Start 15-SEP-2003; Project End 30-JUN-2007

  Summary: (provided by applicant): Chronic iron overload leads to increased iron deposition in tissues. In chronically-transfused **thalassemia** patients, exogenous iron is stored in the spleen, liver, endocrine organs and heart. By contrast, in hereditary hemochromatosis iron overload occurs as a result of excessive absorption of iron from the diet. In both diseases, control of iron levels below the toxic threshold is essential. Further, since serum ferritin levels do not parallel tissue iron levels, periodic liver biopsies have to be performed. The invasive nature of this procedure calls for alternative, less traumatic approaches for multi-organ iron screening. Here we propose to implement, validate and apply to patients with **thalassemia,** a MRI-based quantitative tissue iron mapping technique focusing on the liver and heart, to evaluate the hypothesis that tissue iron levels can be measured accurately and reproducibly. The method is based on the GESFIDE imaging technique developed in the investigators' laboratory. This method allows efficient measurement of T2'and T2, the RF-reversible and RF-irreversible transverse relaxation times, both known to be reduced at elevated tissue iron levels. The following specific aims will be pursued: 1. We shall fully develop and implement improved GESFIDE MRI iron mapping technique at 1.5 and 3T and examine its performance in human volunteers. 2. We shall evaluate the method's accuracy on specimens of a murine model of **thalassemia** in comparison to chemical assay. 3. We shall, in a pilot study of 30 patients with **thalassemia,** measure iron levels in the heart and liver at three time points during a three-year observation period and compare the results with liver biopsy data and to results in age- and gender-matched controls. 4. We shall, in the patients of specific aim #3, evaluate cardiac function by MR to test the hypothesis that the severity of impaired function is associated with the degree of cardiac iron overload.

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- **Project Title: NEW YORK REGION THALASSEMIA CENTER**

  Principal Investigator & Institution: Giardina, Patricia J.; Pediatrics; Weill Medical College of Cornell Univ New York, Ny 10021

  Timing: Fiscal Year 2002; Project Start 01-JUL-2000; Project End 30-JUN-2005

  Summary: (Adapted from the applicant's abstract) The overall objective of this proposal is to establish a New York Regional **Thalassemia** Center (NYRTC) that could participate in the development and establishment of the NIH **Thalassemia** Clinical Research

Network (TCRN). Key research in **thalassemia** and the meaningful evaluation of new therapies would be greatly enhanced by the creation of this network. In preliminary work, the investigators have developed a group of 12 regional institutions caring for more than 200 patients and have begun compiling a patient database. Members of the NYRTC have identified two central subjects for investigation as models for collaborative trials: hepatitis C(HCV) infection and osteoporosis. The first study proposes combination therapy to treat HCV, a complication common among patients transfused before blood screening which leads to increased risk of liver disease (fibrosis, cirrhosis, cancer) from both iron overload and HCV. Interferon alone is effective in only 10% of cases. Pilot studies combining interferon and ribavirin show promise. The investigators propose to include analysis of iron status patient and host specific disease modifiers, including mutations of the HFE gene. These mutations affect gastrointestinal iron absorption and the investigators have found are associated with low CD8 immunotype. The second study centers on evaluation and treatment of osteoporosis. Iron overload influences bone metabolism both directly and indirectly through effects on the immune, endocrine and hematopoietic systems. Markers of bone formation and resorption will be correlated with bone mineral density and a variety of iron-related parameters as well as the above mentioned host specific disease modifiers. A clinical trial will be undertaken to assess the effectiveness of pamidronate, a drug that inhibits bone resorption. Again, the impact of iron and the disease modifiers will be examined. These studies are ideally suited to multicenter collaborations.

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- **Project Title: NON TRANSFERRIN BOUND PLASMA IRON & DEFEROXAMINE THERAPY**

  Principal Investigator & Institution: Porter, John B.; U of L University College London University College London London,

  Timing: Fiscal Year 2002; Project Start 15-AUG-1999; Project End 31-JUL-2004

  Summary: This abstract is not available.

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

- **Project Title: ORAL THERAPEUTIC FOR BETA-THALASSEMIA**

  Principal Investigator & Institution: Faller, Douglas V.; Director, Cancer Research Center; Gene Regulation Laboratories 233 Needham St, Ste 300 Newton, Ma 02464

  Timing: Fiscal Year 2003; Project Start 01-SEP-2003; Project End 31-AUG-2004

  Summary: (provided by applicant): The beta thalassemias are genetic disorders caused by molecular mutations affecting the genes for adult hemoglobin and are among the most common genetic diseases worldwide, although they comprise an orphan condition in the U.S. The beta **thalassemia** syndromes are characterized by excess alpha globin chains, which are toxic to the developing red blood cell and cause rapid apoptosis, resulting in severe anemia and early mortality from complications of blood transfusions, including infections and iron overload. Pharmacologic reactivation of the genes for fetal globin can compensate for the deficient beta globin chains, and this approach has been successfully demonstrated with a short chain fatty acid, arginine butyrate, given intravenously, and a derivative, sodium phenylbutyrate, which requires large drug quantities that are difficult for patient to tolerate. A more tolerable oral therapeutic which both stimulate fetal globin and erythropoiesis is needed for long-term therapy of most patients. The investigators have developed a new-generation short chain fatty acid derivative (ST7), which stimulates both fetal globin gene expression and erythropoiesis

in anemic and non-anemic animal models, and enhances proliferation and survival of erythroid cells, including cultured thalassemic erythroid progenitor cells. This lead candidate is orally-bioavailable with PK profiles at low oral doses which are superior to previous short chain fatty acid therapies. The investigators propose in this application: 1) to perform the medicinal formulation required for a new IND; and 2) to refine low-dose regimens for subsequent clinical trials in humans. These are tasks required for development of ST7 as a new oral therapeutic for treatment of patients with beta thalassemia

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- **Project Title: OUTCOME MODIFYING GENES IN SICKLE CELL DISEASE**

  Principal Investigator & Institution: Telen, Marilyn J.; Chief, Division of Hematology; Medicine; Duke University Durham, Nc 27710

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

  Summary: (provided by applicant): Sickle cell disease (SCD) is caused by homozygosity for a single mutation of the beta hemoglobin gene. Despite the constancy of this genetic abnormality, the clinical course of patients with SCD is remarkably variable. SCD can affect the function and cause the failure of multiple organ systems through the process of vaso-occlusion. However, we as yet do not understand why the clinical course of SCD and the organs affected are so variable among patients. The process of vaso-occlusion itself appears both complex, involving multiple pathophysiological processes, as well as possibly variable from one organ system to another. This study, therefore, is designed to identify genetic factors that predispose SCD patients to develop specific end-organ complications and to experience more or less severe clinical courses. We will0 enroll 1000 patients with Hb SS and Hb S-beta **thalassemia** being followed at three regional institutions (Duke University Medical Center, University of North Carolina Medical Center, and Emory University Medical Center). Medical information obtained will identify the presence or absence of specific targeted outcomes (overall disease severity as well as specific types of end organ damage). All clinical data will be managed and stored on the PEDIGENE system and will include medical status (history, physical examination, and laboratory results) and information regarding potentially confounding environmental factors. We will also obtain blood for DNA analysis, and plasma samples potentially useful for later correlative studies (e.g. of cytokine levels or coagulation activation) will also be stored. Information on sample quality and quantity will be stored in the PEDIGENE system and linked to the clinical data obtained. Identification and development of SNPs for the candidate target genes will be performed, and the DNA samples will be analyzed for these, with results entered into the PEDIGENE system. State-of-the-art statistical methods will be used to examine the relationship between specific clinical outcomes with the SNPs, to determine which genetic characteristics predispose patients with SCD to a more or less severe overall clinical course as well as to individual organ-specific complications. Identification of such genetic factors will reveal new targets for development of therapy individualized to specific complications of SCD, thus leading eventually to improved outcomes and increased life expectancy for patients with SCD.

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

- **Project Title: PARVOVIRUS VECTORS FOR HUMAN GENE THERAPY**

  Principal Investigator & Institution: Srivastava, Arun; Professor; Microbiology and Immunology; Indiana Univ-Purdue Univ at Indianapolis 620 Union Drive, Room 618 Indianapolis, in 462025167

Timing: Fiscal Year 2002; Project Start 01-SEP-1997; Project End 30-JUN-2005

Summary: (provided by applicant): Human hemoglobinopathies, such as beta-thalassemia and sickle-cell disease, are among the likely diseases amenable to gene therapy. The adeno-associated virus 2 (AAV2), a non-pathogenic human parvovirus, has gained attention as a potentially useful vector. Although significant progress has been made in understanding the initial steps in the AAV2 infection pathway, the precise role of the cellular proteins involved in these processes has not been elucidated. For example, cell surface heparan sulfate proteoglycan (HSPG) has been shown to be the primary receptor for AAV2 binding, but the mechanism of viral entry into the cell is not completely understood. Also, other serotypes, such as AAV4 and AAV5, have not been evaluated for hematopoietic stem cell transduction. Similarly, although a second human parvovirus, designated parvovirus B19, known to possess a remarkable tropism for human hematopoietic cells in the erythroid lineage, has been developed as a vector, the precise steps in the virus host cell-interaction are not fully understood. We have documented that in addition to HSPG as a receptor, AAV2 also requires a co-receptor, fibroblast growth factor receptor 1 (FGFR1), for successful infection. We have also documented that cell surface expression of erythrocyte P antigen, reported to be a receptor for parvovirus B19, is necessary but not sufficient for a successful infection by parvovirus B19. Using recombinant AAV2-, AAV4-, AAV5-, and parvovirus B19-globin vectors, we will test the following hypotheses: 1. Efficient transduction of primary human hematopoietic stem/progenitor cells can be mediated by AAV2, AAV4 and/or AAV5 vectors, 2. Efficient entry of parvovirus B19 in primary human hematopoietic cells is mediated by a putative cellular co-receptor, and 3. Parvovirus vectors will prove to be safe and effective for therapeutic correction of hemoglobinopathies in animal models in vivo. The following four Specific Aims will be pursued: 1. Elucidation of underlying mechanisms of differential transduction of primary human hematopoietic stem cells from bone marrow and umbilical cord blood by AAV2-, AAV4-, and AAV5-globin vectors. 2. AAV-mediated erythroid lineage-restricted expression of human globin genes in human hematopoietic cells in vitro, and therapeutic correction in homozygous beta-thalassemic mice in vivo. 3. Identification and characterization of the putative cellular co-receptor for efficient transduction of primary human hematopoietic progenitor cells by parvovirus B19-globin vectors. 4. AAV- and parvovirus B19-mediated transduction and long-term, regulated expression of human globin genes in hematopoietic progenitor cells in non-human primates in vivo. The knowledge gained from these studies will be applicable in further development of AAV and parvovirus B19 vectors and their optimal use in gene therapy of beta-thalassemia and sickle-cell disease.

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- **Project Title: POLYMORPHISMS AND SEVERITY IN SICKLE CELL DISEASE**

  Principal Investigator & Institution: Fisher, Timothy C.; 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 believed that much of the clinical variability among patients with sickle cell disease (SCD) may be genetically determined, resulting from the co-inheritanceof "epistatic" genes which interact with the basic sickling defect to modify the disease pathophysiology. We recently conducted a pilot study comparing the inheritance of several common blood group polymorphisms with SCD severity in 103 children and found that the Lewis negative Le(a-b-) phenotype was associated with a 2-fold higher hospitalization rate for SCD-related complications compared to Le(a+b-) and Le(a-b+)

patients. The Le(a-b-) phenotype is also known be associated with a 2-fold increased risk of ischemic heart disease (IHD). No mechanism has yet been identified, but we hypothesize that the association between Lewis RBC phenotype and SCD severity may be mediated by differences in the plasma levels of sialyI-Lewis a (sLea), a high-affinity selectin ligand.The objectives of this proposed multi-center collaborative study are: a) to confirm our initial findings in a larger group of children drawn from multiple centers; b) to determine whether the Lewis(a-b-) phenotype is also associated with disease severity in adults; c) to determine whether the Lewis phenotype or plasma sLea level predict specific types of complication (e.g. stroke, ACS); d) to establish whether Lewis acts independently of HbF, beta-globin haplotypes and alpha **thalassemia;** e) to look for any link between other blood group polymorphisms (e.g., Duffy, MNS) and SCD disease severity. Lewis antigen status will be determined serologically, along with 20 other blood group antigens. We will also perform Se and Le genotyping by PCR-RFLP and quantify plasma sLea by ELISA. Disease severity data will be collected via standardized report forms and entered into the CSCC Common Database. It is anticipated that retrospective data will be available from the Database for many patients. The participation of multiple centers in this project is essential, since it requires the collection of high-quality clinical data on large numbers of patients. Given the large increment in hospitalizations associated with Le(a-b-) in our pilot study, we believe that this marker may be useful as an early predictor of severity in SCD, and may help with the targeting of aggressive interventions (BMT, chronic transfusion) to higher-risk SCD patients.

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- **Project Title: PROMOTER CHROMATIN STRUCTURE IN FETAL GLOBIN SILENCING**

  Principal Investigator & Institution: Lowrey, Christopher H.; Associate Professor; Medicine; Dartmouth College 11 Rope Ferry Rd. #6210 Hanover, Nh 03755

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

  Summary: (provided by applicant): The human hemoglobinopathies comprise the largest class of human genetic diseases. Those involving the b-locus include b-thalassemia and sickle cell disease. Experimental results from a variety of approaches indicate clinical strategies designed to achieve increased levels of fetal hemoglobin in the erythrocytes of people with these diseases would achieve significant clinical benefits. While several - strategies have been employed or are under development, no routinely applicable safe and effective method for activating g-globin gene expression has been devised. A clear understanding of the mechanisms by which the g-globin gene is silenced during development or reactivated in specific genetic conditions is a direct route to identifying targets for the rational design of therapies directed at g-globin gene re-expression. For the development of this project we have chosen to focus on the role of chromatin structure. Strong evidence has been developed over the last three decades implicating chromatin structural changes in gene silencing in general and within the b-globin locus in particular. Recent advances in the field of chromatin structure have made this an opportune time to begin to investigate the mechanisms behind the changes in chromatin structure associated with g-globin gene silencing. By precisely identifying the changes that occur and the molecules that mediate these changes, it is our goal to identify molecular targets for future pharmacologic or genetic treatments of the b-hemoglobinopathies. In this application we propose to take a focused approach to documenting and understanding the chromatin structural changes which occur within the g-globin gene promoter during the silencing of the human g-globin gene. AIM 1: To comprehensively characterize g-globin promoter chromatin structure in human fetal

liver in adult erythroid cells. AIM 2: To determine whether a human b-globin YAC transgenic mouse accurately recapitulates the chromatin structural changes associated with g-globin gene silencing seen in human cells. AIM 3: To begin to determine the molecular mechanisms which mediate changes in the chromatin structure of the g-globin promoter during gene silencing.

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- **Project Title: QUANTITATIVE ASSESSMENT OF IRON OVERLOAD BY MRI**

  Principal Investigator & Institution: Wang, Zhiyue J.; Assistant Professor; Radiology; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

  Timing: Fiscal Year 2000; Project Start 30-SEP-1998; Project End 31-JUL-2004

  Summary: (Adapted from applicant's abstract) The long-term objective of this proposal is to develop in vivo magnetic resonance (MR) techniques for a reliable non-invasive assessment of iron stores in patients with iron overload due to chronic transfusion therapy for diseases such as **thalassemia,** sickle cell disease and other blood disorders. The specific aims of the project are: 1a) to study the T2 of liver tissue under iron overload conditions in vivo and correlate with biopsy determined iron level; 1b) to measure T2 of cardiac tissue from autopsied human hearts and an iron overload gerbil model in vitro and correlate with a chemically determined iron level; 2) to assess a new, non-invasive magnetic susceptibility measurement technique, "the contact reference method," that will be applicable for outer myocardium; (3) to develop a non-invasive susceptibility measurement technique for the liver using blood vessel signal as internal reference. An accurate assessment of body iron stores plays a central role in the management of chronically-transfused patients. Current body iron assessment methods are limited to liver biopsy or superconducting quantum interference device (SQUID) susceptometry, but neither is convenient for routine use, and there is no non-invasive technique to evaluate the heart. The focus of this application centers on developing techniques for the liver examination, and characterizing MR properties of heart tissue under iron overload conditions. A spectroscopy sequence with minimum TE 1.5 ms will be used to measure the liver T2 in a 3x3x3 cm3 volume in 30 patients, and correlate the results with biopsy determine iron level; In vitro T2 of 108 specimens from 9 human autopsy hearts and 192 specimens from 48 gerbil hearts will be measured and correlated with the tissue iron level. The magnetic susceptibility of the same human autopsy hearts and gerbil hearts will be evaluated by a contact reference technique: the resonant frequency differences across the interface of tissue and saline reference, obtained by using 3-dimensional gradient echo imaging, will be used to qualify the tissue susceptibility. Finally, an in vivo liver susceptibility measurement technique will be developed: sequential 2-dimensional navigator echo imaging will be used to measure frequency offset, the magnetic susceptibility of the liver will be obtained. For each aim, statistical analysis using linear regression will be done to assess the reliability of iron level predicted by the MR technique.

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- **Project Title: RED CELL MEMBRANE STUDIES**

  Principal Investigator & Institution: Narla, Mohandas; Vice President, Research; Cancer Biology; University of Calif-Lawrenc Berkeley Lab Lawrence Berkeley National Laboratory Berkeley, Ca 94720

  Timing: Fiscal Year 2002; Project Start 01-MAY-1983; Project End 31-MAR-2002

Summary: The overall objectives of this program focus on the genesis and assembly of the red cell, with emphasis on the membrane skeleton. A continuing long term objective is to understand the pathophysiologic mechanisms of hemolytic anemia. New emphasis is placed on exploring novel role(s) of prototypical red cell skeletal proteins in intracellular structures in erythroid progenitors and in nonerythroid cells. New perspectives on skeletal assembly and function include model studies of kidney epithelial cells, and of the budding yeast, S.cerevisiae. To achieve these broad goals, six complementary approaches are proposed: 1. Characterize the structure and function of a complex repertoire of developmentally-regulated skeletal protein 4.1 isoforms, by molecular studies of the gene and its multiple alternative transcripts, and via use of transgenic mouse technology; 2. Explore the role of skeletal proteins in plasma membrane remodeling and in nuclear and centrosomal function during erythropoiesis, and study the role of interactions between erythroid progenitors and marrow microenvironment in regulating erythroid differentiation; 3. Characterize a novel spectrin-based skeletal protein complex of the Golgi, and investigate its dynamics of assembly and its function in model kidney epithelial cells; 4. Explore general principles of skeletal assembly and function by cloning conserved homologs from yeast and mammals, and investigating function by uniquely combining powerful yeast genetics with biophysical techniques developed in this program for analysis of red cell membranes; 5. Analyze pathophysiologic mechanisms of red cell loss in **thalassemia,** using murine models developed in this program to explore the hypothesis that a-globin chain accumulation, by provoking oxidant damage at the membrane, activates an apoptotic program ultimately manifested as ineffective erythropoiesis; 6. Examine functional consequences of specific interactions between red cell membrane proteins and proteins elaborated by intraerythrocytic stages of the malarial parasite, Plasmodium falciparum, especially as they affect red cell deformability and cytoadherence. Finally, supporting the projects is a mouse core which will prepare transgenic and knockout mice, as well as maintain mouse lines. Application of this broad range of expertise in molecular biology, genetics, biochemistry, cell biology, and biophysics should provide a better understanding of fundamental principles of membrane organization in eukaryotic cells, and may eventually provide in sights into management of hemolytic anemias in which membrane structure, function, and development are deranged.

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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 2002; Project Start 01-APR-1999; Project End 31-MAR-2003

  Summary: Human epsilon-globin is a beta-like globin whose expression is developmentally restricted to primitive erythroblasts in the blood islands of the embryonic yolk sac. In contrast to fetal and adult globins, the mechanistic bases for epsilon-globin gene regulation and the function of its encoded protein are poorly understood. Although transcriptional downregulation is a major effector of embryonic globin gene silencing, recent studies indicate that other, post-transcriptional events also play an important and previously unanticipated role in this process. Neither the specific post-transcriptional mechanisms involved, nor their ultimate contribution to epsilon-globin regulation have been established. Likewise, the physiologic properties of hemoglobins assembling from epsilon-globin subunits are incompletely described. The importance of fully defining the molecular controls and function of epsilon globin is

magnified by the possibility that its reactivated expression might be therapeutically beneficial to adults with genetic defects in beta-globin expression. The feasibility and clinical potential of this approach cannot be judged without a comprehensive understanding of epsilon-globin regulation and function, which the current proposal will provide. First, key physiologically-important properties will be determined for hemoglobins that will assemble in definitive erythrocytes expressing epsilon globin. These studies, which will be done both in vitro and in transgenic mice, will include determinations of the O2 affinity and the anti-sickling characteristics of Hb alpha2epsilon2, of particular importance to individuals with beta **thalassemia** and sickle cell anemia. Second, the effect of specific post-transcriptional mechanisms on the expression of epsilon globin in definitive erythrocytes will be established. The specific processes that will be studied (mRNA stability, mRNA translational efficiency, and globin subunit stability, among others) are known to affect the expression of other human globins. As a group, these studies will begin to bring what is known about embryonic epsilon globin into parity with what is known about other fetal and adult globins. Moreover, the information provided by these studies will permit a reasoned approach to the design of molecular therapies aimed at epsilon-globin reactivation as well as an informed expectation of the likelihood that such an approach will be therapeutically beneficial.

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- **Project Title: REGULATION OF FETAL AND ADULT HUMAN HEMOGLOBIN PRODUCTI**

  Principal Investigator & Institution: Ley, Timothy J.; Medicine; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2002; Project Start 01-MAY-1987; Project End 30-APR-2004

  Summary: One of the long term goals of this laboratory is to develop genetically-based strategies for the treatment of sickle cell anemia and beta-thalassemia. The goal of this study is to determine whether homologous recombination can be developed as a strategy to repair mutant beta-globin genes in embryonic stem cells and primary hematopoietic progenitors. To accomplish these goals, we propose the following specific aims. Specific Aim 1: We will develop mice with a mutation similar to the betas globin mutation of humans by creating a beta6 mutation in the mouse beta-major globin gene using homologous recombination in embryonic stem cells. We will create embryonic stem cells lines that contain a mutation that causes an alanine yields isoleucine substitution in position 6 of the murine beta-major globin gene (beta6I), and that have a selectable marker cassette (PGK-neo) either retained or excised (via Cre-Lox mediated recombination) downstream from beta-major. These ES cells will be the starting material for Specific Aim 2, and will be used to make mice that bear the mutations. The hematopoietic cells of heterozygous mice with beta6I (and the excised PGK-neo cassette) form the starting material for Specific Aim 3. Specific Aim 2: We will define the efficiency of homologous recombination-mediated repair of the beta6 mutation in embryonic stem cells using targeting vectors of different sizes. To explore the relationship of targeting arm size and homologous recombination efficiency, we will create targeting vectors that contain a total of 8, 16, 60, or 110 kb of wild-type targeting DNA from the mouse beta-globin cluster, and compare the abilities of these vectors to correct the beta6I mutation in ES cells via homologous recombination. Specific Aim 3: We will determine whether hematopoietic progenitors have the ability to correct the beta6I mutation via homologous recombination, using the targeting vectors defined in Specific Aim 2. Functional targeting vectors defined in Specific Aim 2 will be used to

determine whether hematopoietic progenitors and/or stem cells have the machinery to perform homologous recombination events within the beta-globin locus. Bone marrow cells purified from mice heterozygous for the beta6I mutation (and PGK-neo deleted) will be transfected with the targeting vectors using physical means of DNA delivery (i.e. electroporation or lipofection). These cells will be selected using either neomycin phosphotransferase or GFP expression (or both), and individual colonies derived from hematopoietic progenitors (LTC-IC and CFU-C) will be analyzed for the frequency of correction of the beta6I mutation using PCR-based techniques. These studies should allow us to determine whether homologous recombination can be rationally developed as a method for correcting mutations in the beta-globin locus within primary hematopoietic progenitor cells.

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- **Project Title: REGULATION OF PROTEIN SYNTHESIS AND ERYTHROPOIESIS**

  Principal Investigator & Institution: Chen, Jane-Jane; Principal Research Scientist; None; Massachusetts Institute of Technology Room E19-750 Cambridge, Ma 02139

  Timing: Fiscal Year 2003; Project Start 01-JAN-1979; Project End 30-NOV-2007

  Summary: (provided by applicant): Our long-term objective is to contribute to the understanding of the regulation of hemoglobin synthesis and erythroid differentiation in normal and abnormal hematological conditions, with particular emphasis on the roles of heme and protein synthesis in these processes. Protein synthesis in intact reticulocytes and their lysates is dependent on the availability of heme. Heme serves as the prosthetic group of the hemoglobin, the predominant protein in red blood cell (RBC) and its late precursor cells. Biochemical studies have shown that, under conditions of heme-deficiency or iron-deficiency, protein synthesis is inhibited at the level of initiation due to the activation of the heme-regulated translational inhibitor (HRI). HRI is a heme-regulated protein kinase that phosphorylates the a-subunit of eukaryotic initiation factor 2 (eIF2a). Phosphorylation of the a-subunit of eIF2 impairs its recycling in translational initiation and results in the cessation of protein synthesis. The research designs are (1) To Elucidate the Molecular Mechanism by which HRI Regulates Red Blood Cell Production, (2) To Assess the Protective Role of HRI in Red Blood Cell Disorders, and (3) To Delineate the Molecular Mechanism of Stress-Activation of HRI. The methods to be employed are the generation of genetically modified mice, hematological analysis, histological and electron microscopic examinations, colony culture assays for erythroid progenitors, Western-blot analysis and protein kinase assays, cell culture, phenotypic examination of mouse embryos, recombinant DNA techniques. Our recent study indicates that HRI is not only necessary for globin synthesis, but also for heme biosynthesis. HRI is also important for the survival of mice with **thalassemia** and erythropoietic protoporphria. Our proposed study may lead to potential application of HRI in treating human patients with red cell diseases.

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

- **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: RESTORATION OF GLOBIN GENE EXPRESSION IN THALASSEMIA**

  Principal Investigator & Institution: Kole, Ryszard; Professor; Comprehensive Cancer Center; University of North Carolina Chapel Hill Aob 104 Airport Drive Cb#1350 Chapel Hill, Nc 27599

  Timing: Fiscal Year 2002; Project Start 01-DEC-1994; Project End 30-NOV-2003

  Summary: The long term goal of this project is application of antisense oligonucleotides and antisense vectors in treatment of **thalassemia.** The project is based on a unique application of antisense oligonucleotides in which these compounds are used to restore correct functioning of a defective gene rather than to inhibit the expression of an undesirable gene, as commonly applied. Specifically, antisense oligonucleotides are used to reverse aberrant splicing of human beta-globin pre-mRNA by blocking splice sites activated by the mutations in intron 2 of Beta- globin gene which cause **thalassemia.** The oligonucleotides not only inhibit aberrant splicing but, by forcing the spliceosome to form on the adjacent correct splice sites, restore correct splicing of beta-globin pre-mRNA and in consequence restore translation of beta-globin polypeptide. In the previous granting period the effective correction of splicing in a number of thalassemic mutants was accomplished both in the cell free splicing extracts and in model cell lines which expressed thalassemic beta-globin transcripts. The main thrust of the work proposed in this application will be to establish the conditions for antisense treatment of thalassemic erythroid cells in vitro and in vivo in animal model. The

specific aims to accomplish these goals are: 1) To optimize the correction of splicing of human thalassemic beta-globin pre-mRNAs by antisense oligonucleotides in K562 cells expressing IVS2-654, IVS2-705 and IVS2-745 mutants. 2) To optimize the effects of antisense oligonucleotides on human beta-globin expression in bone marrow of the IVS2-654 mouse. 3) To treat the IVS2-654 thalassemic mice with antisense oligonucleotides either in a free form or with the aid of delivery agents. 4) To test in K-562 cell lines the correction of splicing of thalassemic beta-globin pre-mRNA by antisense vectors targeted to the aberrant splice sites. 5) To test the antisense snRNA vectors developed in Specific Aim 4 in IVS2-654 mice. To provide high level of expression and to explore the possibility of tissue tropic delivery of antisense sequences the snRNA genes will be incorporated into adeno-associated virus.

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

- **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: ROLE OF LBP-1A AND P14 NF-E4 IN GAMMA GLOBIN GENE EXPRE***

  Principal Investigator & Institution: Jane, Stephen M.; Royal Melbourne Hospital Melbourne 3050, Australia Melbourne,

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

  Summary: (provided by applicant): Elevated levels of fetal hemoglobin lead to a significant amelioration of symptoms in patients with sickle cell disease and beta-thalassemia. This observation suggests that treatment strategies capable of re-activating fetal hemoglobin expression after birth should be explored. To achieve this goal we must first understand the mechanisms underlying the developmental regulation of the beta-globin locus, particularly the factors that can modulate gamma- globin expression. We have previously identified a candidate factor for this aim, the stage selector protein (SSP). The SSP is an erythroid-specific protein complex consisting of the ubiquitously expressed transcription factor CP2, and a tissue-restricted partner, p22 NF-E4. We have recently identified a second CP2-like gene, LBP-1a that also can form an SSP complex with NF-E4. We have also identified a 14 kD isoform of NF-E4 which acts in direct contrast to p22 NF-E4 and represses gamma-gene expression in a fetal/erythroid cell line. We have coupled these recent observations to our pre-existing knowledge of the SSP to develop three aims that will enhance our understanding of the mechanisms of action of this complex. The first specific aim focuses on the mechanistic roles of LBP-1a and p14 NF-E4 in regulating gamma-globin gene expression in the fetal erythroid environment and in hemoglobin switching models. These experiments will employ gene-targeting and transgenic strategies to elucidate the role of LBP-1a and p14 NF-E4 in vitro and in vivo. Specific aim 2 will expand on our observation that p14 NF-E4 fails to bind CP2/LBP-1a, full length NF-E4 or DNA and thus appears to exert is dominant negative effect through sequestration of a protein associating with the SSP. We will define the protein partners of both isoforms of NF-E4 using molecular and biochemical approaches. The work described in specific aim 3 will focus on the identification and characterisation of the core regions of the NF-E4 promoter using transcription assays in cell lines and transgenic mice. Taken together, these aims address many of the issues raised in the RFA. In particular, they seek to validate an existing trans-activator by direct function analysis and by investigation of mechanism of action. They also examine induction of the structural gene of such an activator with the emphasis on developing an assay system for high throughput drug screening. Finally, through protein interaction studies they may identify additional novel factors important in the activation (or repression) of gamma-globin gene expression.

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

- **Project Title: SECONDARY HEMOCHROMATOSIS IN BETA THALASSEMIA AND SCD**

  Principal Investigator & Institution: Vichinsky, Elliott P.; Director; Children's Hospital & Res Ctr at Oakland Research Center at Oakland Oakland, Ca 946091809

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

  Summary: (adapted from the application) The purpose of this study is to determine whether the pathologic effects of iron overload secondary to hypertransfusion are different in SCD and beta **thalassemia.** Iron-related organ injury and death are common in patients with beta **thalassemia.** Similar organ pathology and mortality have not been reported in SCD after hypertransfusion. Differences in organ and cellular iron localization, cellular processing of iron, inflammatory state, or the generation of reactive

low molecular weight iron might explain the differences in disease response. Pilot data shows that the severity of iron overload is similar in hypertransfused patients with SCD and beta **thalassemia,** yet the rate of organ dysfunction (heart, endocrine) is much greater in beta **thalassemia.** The primary hypothesis of this study is that hypertransfused patients with SCD show less organ damage than patients with beta **thalassemia.** The specific aims of the study are: 1) to determine the organ and cellular distribution of iron in hypertransfused patients with beta **thalassemia** and SCD, 2) to determine whether severe organ damage occurs less frequently in hypertransfused patients with SCD than in patients with beta **thalassemia** and to evaluate whether markers for early organ dysfunction can be identified and used to guide chelation therapy, 3) to determine the molecular differences in ferritin between SCD and beta **thalassemia** which could account for a difference in iron deposition in response to chronic RBC transfusion. Organ and cellular iron distribution will be determined 1) post-mortem by histologic and chemical analyses of tissues obtained from hypertransfused patients with SCD or beta-thalassemia matched for age, transfusion volume, sex, and 2) pre-mortem, at an earlier stage of morbidity, by quantitative and histologic analyses of liver biopsy and bone marrow aspirates. Quantitative CT will be used to compare the organ distribution of iron in the two diseases. The frequency of severe organ damage (heart disease, diabetes, spinal fracture) will be determined prospectively over 3 years in a multicenter study (200 patients) to confirm the primary hypothesis. Evidence for early organ dysfunction will be sought using sensitive markers in patients (20 patients) followed prospectively for 4 years at CHO. In summary, if this study is successful and demonstrates a strong difference in the toxicity of severe iron overload in SCD as compared to beta **thalassemia,** it will change the approach to chelation therapy in hypertransfused patients with SCD, lead to reduced chelator-related toxicity, and improve quality of life in these patients.

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- **Project Title: SEMI-SYNTHETIC, SITE-SPECIFICALLY INTEGRATING LENTIVIRUS**

  Principal Investigator & Institution: Leboulch, Philippe; Assistant Professor; Brigham and Women's Hospital 75 Francis Street Boston, Ma 02115

  Timing: Fiscal Year 2003; Project Start 19-SEP-2003; Project End 31-AUG-2005

  Summary: (provided by applicant): The overall goal of this project is the development of novel approaches that overcome the limitations of viral vectors. While recent years have seen the first cure of a genetic disease by retroviral transduction of hematepoietic stem cells in X-SCID children, the same trial has also resulted in leukemic syndromes upon activation of an oncogene by the randomly integrated Retrovirus. Preventing similar adverse events has now become a main goal of the field of gene therapy. Among Retroviruses, Lentiviruses offer unique advantages because they can provide long-term gene expression of complex genetic structures even in non-dividing cells. However, important safety concerns and manufacturing hurdles remain: (i) contamination with a replication-competent Lentivirus (RCL), (ii) oncogenesis by random insertional mutagenesis, and (iii) the unavailability of GMP-grade, high-titer, stable lentiviral packaging cell-lines. On the basis of extensive preliminary results, this proposal will attempt to remedy these important issues. In Specific Aim 1, we will build a semi-synthetic lentiviral vector in which recombinant envelope proteins or fusiogenic peptides are added to lentiviral particles packaged in the absence of any viral envelope gene. This approach virtually eliminates the possibility of RCL contamination and greatly facilitates the design of stable lentiviral packaging cell-lines by avoiding the

cytotoxicity of pseudotyping envelopes. This strategy was rendered efficient by the prior magnetization of virions by super-paramagnetic nanoparticles. In Specific Aim 2, we will test the hypothesis that lentiviral vectors can be engineered to integrate site-specifically at "non-dangerous" chromosomal sites of the human genome by substituting the lentiviral integrase with a site-specific integrase from the phiC31 bacteriophage, which has been shown to operate in human cells. In Specific Aim 3, we will apply the engineering principles of "in-vitro evolution" together with the power of lentiviral libraries and selection screens to derive mutants of the phiC31 integrase with greater intrinsic activity and integration specificity within human cells. In Specific Aim 4, we will combine the previous findings to build step-by-step under GMP conditions, a packaging cell-line that produces high-titer semi-synthetic lentiviral vectors capable of non-dangerous site-specific integration in human cells. These approaches will be ultimately evaluated for their capacity to transfer a complex beta-globin gene into murine and human hematopoietic stem cells.

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- **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 946091809

  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.

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- **Project Title: TARGETED ACTIVATION OF FETAL HEMOGLOBIN**

  Principal Investigator & Institution: Barbas, Carlos F.; Professor; Scripps Research Institute Tpc7 La Jolla, Ca 92037

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

  Summary: (provided by applicant): This project seeks to clarify molecular pathways that activate fetal hemoglobin or prevent its silencing as well as to define or develop novel transactivators of fetal hemoglobin. The net result of this study will be an increased understanding of globin regulation and novel molecular targets and therapeutic strategies to treat b-chain hemoglobinopathies. The ability to selectively manipulate the transcription of genes controlling the -globin locus is anticipated to have a significant impact on both our understanding of this locus as well as the treatment of diseases associated with mutations in this locus. The study proposed here capitalizes on our development of designed transcription factors that enable the transcription of endogenous genes to be either activated or repressed. Currently no other gene therapy strategy provides the means of effectively knocking out the expression of an endogenous gene- for example knocking out a silencer of g-globin expression. Polydactyl zinc finger proteins can now be prepared that recognize 18 bp DNA target sequences with high affinity and specificity. When fused to activation or repression domains, these proteins become potent regulators of the transcriptional activity of the target gene. This proposal focuses on the use of our transcriptional regulators to specifically modulate transcription of the b-globin locus with the aim of up-regulating fetal hemoglobin. We aim to explore the potential of targeted gene modulation as a gene-based therapeutic strategy for the treatment of b-hemoglobinopathies as well as a unique gene discovery tool for the identification of novel transcriptional modifiers of this locus and the validation of existing ones. A novel genome-wide transcriptional modulation strategy will be applied to the search for new targets for therapeutic intervention. With selective and potent transcriptional regulators we will address the therapeutic potential of controlling the globin locus in animal models. It is anticipated that the results of this work will provide a novel approach to study the molecular mechanisms of hemoglobinopathies as well as new strategies to treat them.

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

- **Project Title: TARGETED CORRECTION OF FAULTY BETA GLOBIN GENES**

  Principal Investigator & Institution: Smithies, Oliver; Pathology and Lab Medicine; University of North Carolina Chapel Hill Aob 104 Airport Drive Cb#1350 Chapel Hill, Nc 27599

  Timing: Fiscal Year 2002; Project Start 01-JUL-1988; Project End 30-JUN-2005

  Summary: Gene therapy would ideally correct a mutant gene precisely without causing changes elsewhere in the genome. Homologous recombination has this potential, but has not yet been successfully used in this context. During the last grant period, we demonstrated correction of a faulty HPRT gene by homologous recombination in clonogenic hematopoietic progenitor cells, and showed that a truncated erythropoietin receptor transgene introduced into the HPRT locus of ES cells can give hematopoietic

stem cells (HSC) from the resulting mice an advantage over wild type cells in competitive bone marrow transplantation. Building on this work, we have chosen three aims directed towards correcting mutant human globin genes in mice, but equally applicable to other defects treatable via HSC correction. Specific aim (i1) will test whether ex vivo homologous recombination in HSC can correct mutant genes at (A) the HPRT and (B) the B globin locus. Specific aim (ii) will develop a transgene able to give a controllable in vivo transplantation advantage specifically to HSC when inserted at and site in the genome. Including but not limited to the globin locus. Specific aim (iii) will combine the targeting procedures developed in aim (i) with an advantage sequence developed under aim (ii) to attempt therapy in mice carrying a mutant human beta globin gene (B-O or B-S). Correcting a mutant gene in HSC by homologous recombination, and showing that the simultaneous co-introduction of an advantage transgene into HSC can facilitate their engraftment in an affected donor, would constitute substantial advances both for gene therapy in particular and for bone marrow transplantation in general.

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- **Project Title: THALASSEMIA CLINICAL RESEARCH NETWORK**

  Principal Investigator & Institution: Neufeld, Ellis J.; Associate Professor of Pediatrics; Children's Hospital (Boston) Boston, Ma 021155737

  Timing: Fiscal Year 2002; Project Start 15-JUL-2000; Project End 30-JUN-2005

  Summary: Large-scale clinical studies in **thalassemia** have been limited by the small numbers of patients followed at any Center in North America. The establishment of a Clinical Research Network, as proposed in the current RFA, opens the way to important new studies for better diagnosis and management of **thalassemia,** and the prevention of long-term complications of the disease. Cardiac disease remains the major cause of early death among patients with transfusion-dependent beta-thalassemia major, and is often related to poor compliance with prescribed chelation regimens. Hepatitis C virus infections are also common in patients born before universal screening of the blood supply, and are a significant cause of morbidity. The two studies in this Proposal will address important aspects of these diseases. It has been observed that patients who present with significant cardiac disease, chiefly left ventricular dysfunction, improve rapidly after being started on an intensive chelation program. The rate of improvement is often too rapid to be accounted for by clearance of substantial amounts of iron from the body. This observation has led to the hypothesis that the cardiac toxicity of iron is not due to tissue deposition per se, but to a local depressant effect. This hypothesis has found experimental support in studies of non transferrin-bound plasma iron (NTBPI), which is highly toxic to cardiac and liver cells. Levels of NTBPI are are frequently elevated in inadequately chelated patients, and normalize rapidly after institution of adequate chelation regimens. We propose to evaluate the effectiveness of aggressive chelation therapy in reversing myocardial dysfunction, as determined clinically and by specialized echocardiographic measures, and correlating the improvement in function with changes in NTBPI and hepatic iron concentration (which is the most accurate correlate of total body iron burden). These studies will provide direct insight into mechanisms of myocardial dysfunction in patients with **thalassemia,** and will also allow us to prospectively evaluate the efficacy of aggressive chelation regimens. The second protocol is designed to assess the efficacy of a new drug regimen in treatment of chronic Hepatitis C virus infections. The most effective drug regimen for treatment of Hepatitis C (interferon-alpha + ribavirin) is quite toxic in **thalassemia** patients, as ribavirin causes significant red cell breakdown. A chemically-modified form of interferon (PEG-IFN),

which persists in the circulation for much longer than conventional interferon, has recently been developed. Preliminary clinical studies suggest that therapy with PEG-IFN alone is as effective as current combination therapy, and has fewer toxicities. We therefore propose to evaluate the response of Hepatitis C-infected **thalassemia** patients to treatment with PEG-IFN alone, lend to treat patients who do not respond to PEG- IFN monotherapy with this drug in combination with ribavirin. Endpoints of this study will include end-of-treatment and sustained viral elimination, and changes in measures of hepatic inflammation. This study, when carried out in the context of a clinical trials network, will allow us to evaluate a promising new therapy more rapidly and with greater statistical power than would otherwise be possible.

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- **Project Title: THALASSEMIA CLINICAL RESEARCH NETWORK - DCC**

  Principal Investigator & Institution: Wright, Elizabeth C.; New England Research Institutes, Inc. 9 Galen St Watertown, Ma 02472

  Timing: Fiscal Year 2002; Project Start 01-JUL-2000; Project End 30-JUN-2005

  Summary: New England Research Institutes (NERI) proposes to serve as the Data Coordinating Center for the **Thalassemia** Clinical Research Network to accomplish the following goals: To collaborate with the Steering Committee in the selection of protocols and the design of the clinical trials, specifically providing statistical advice relevant to design, conduct, and analysis; To develop and maintain a data management system for the Network; To develop and maintain a system for tracking all central laboratory specimens; To train trial personnel in all aspects of the trials, conduct site visits, and monitor and document the quality of all data collected; To compile edit, report on, and analyze trial data and collaborate in scientific presentations and publications; and To provide administrative support. Important features of NERI's proposal include: our extensive, highly relevant expertise in multi-site studies of sickle cell disease; clinical trials involving transfusion therapy of patients with sickle cell anemia and interferon treatment for patients with hepatitis C; our in-house expertise in quality of life, health care utilization and cost measurement; our proprietary ADEPT web-based data management system which fully integrates data entry with automated, centralized randomization and protocol and patient tracking; our modular approach to all study protocols; and finally, our proposal to establish in, Year 01, a registry of all **thalassemia** patients identified, during the funding period, at each of the clinical centers to fully inform all proposed clinical trials in terms of feasibility target population, and science.

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

- **Project Title: THE MID-ATLANTIC THALASSEMIA CONSORTIUM**

  Principal Investigator & Institution: Cohen, Alan R.; Professor and Chairman; Children's Hospital of Philadelphia 34Th St and Civic Ctr Blvd Philadelphia, Pa 191044399

  Timing: Fiscal Year 2002; Project Start 01-JUL-2000; Project End 30-JUN-2005

  Summary: Significant advances in the treatment of **thalassemia** in the past three decades have been accompanied by many new clinical research questions that can only be answered by multi-center trials with a sufficient number of eligible patients. To this end, the long- term objective of this proposal is to develop and participate in a Clinical **Thalassemia** Network that will design and implement collaborative research studies in **thalassemia.** The major specific aim related to this objective is to create the Mid- Atlantic **Thalassemia** Consortium that includes the Children's Hospital of Philadelphia, Thomas Jefferson Hospital/Alfred I. duPont Hospital for Children, St. Christopher's Hospital for

Children, Johns Hopkins Hospital, and the Children's National Medical Center of Washington DC. This Consortium, which includes 82 patients with clinically significant **thalassemia** syndromes, takes advantage of the experience and expertise that exists in the five **thalassemia** programs. The Principal Investigator and the four co-investigators have a combined experience in clinical research in hemoglobinopathies of more than 100 years. The application proposes one short-term and one long-term clinical trial that are well suited for multi-center research within the **Thalassemia** Network. The goal of the short-term trial is to develop fetal hemoglobin enhancing agents as a safe and effective therapy of **thalassemia** intermedia. The specific aim is to conduct a one-year, randomized, placebo-controlled multi-center trial of a pulse-dose regimen of sodium phenylbutyrate to determine the effect on hemoglobin level and other hematologic parameters. The goal of the long-term trial is to determine the effect of storage time of donor red cells on the transfusion requirements and rate of iron loading in patients with **thalassemia** major, and to correlate these differences with findings using radiolabeled red cells. The specific aim is to conduct a three-year, randomized, crossover clinical trial of AS- 1 and AS-3 donor red cells stored for either 0-14 days or 21-35 days and to evaluate blood requirements and donor unit utilization. 51Cr studies of 24-hour red cell recovery, post-24- hour red cell survival and red cell availability in a subset of patients will complement the clinical trial. Both the short-term and long-term study take advantage of the specific expertise of investigators in the Mid-Atlantic **Thalassemia** Consortium. Moreover, both studies require the number of patients that can only be achieved through multi-center research as proposed for the **Thalassemia** Clinical Network. The successful development of the Clinical **Thalassemia** Network will provide a unique opportunity to address some of the most important problems affecting the length and quality of life of patients with **thalassemia,** and will serve as a model for the study of other diseases.

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- **Project Title: THE UNIQUE HEMOGLOBIN I OF L. PECTINATA--HEME (FE(IV)=O)**

  Principal Investigator & Institution: Lopez-Garriga, Juan; University of Puerto Rico Mayaguez Mayaguez, Pr 00709

  Timing: Fiscal Year 2003; Project Start 01-MAY-2003; Project End 30-APR-2007

  Summary: The peroxidative reactions of hemoglobin (Hb) and myoglobin (Mb) constrain delivery and turnover of oxygen to cells. The reactions of these proteins with hydrogen peroxide (H2O2) and its superoxide anions are detrimental in red cell pathological conditions, i.e. sickle cell anemia, **thalassemia,** and red cell aging. These reactions limit the development of proteins for oxygen carrying therapeutics. The formation of ferryl (hemeFe(IV)=O) species have been identified as one of the main reaction intermediates. Interactions of these species with a number of Hb and Mb heme pocket amino acids are also known. Despite the efforts, concerns persist about the transient structure, mechanism, kinetics, dynamics, and reactivity of Hb and Mb with H202. The relationship between the structure, reactivity, and function of these Hb and Mb ferryl derivatives is not clearly understood. An answer to these problems will unravel the nature of the ferryl species and their relationship to heme peroxidative reactions. Our preliminary studies show that we will achieve this goal by taking advantage of the ability of hemoglobin I (Hbl) from L. pectinata to stabilize, through its unusual heme pocket configuration (Gin64, Phe29, and Phe68), the ferryl (hemeFe(IV)=O) compound I a thousand times more than Mb. This suggest that the interplay between the proximal transligand effect, the distal heme pocket polarizability, and the absence of hydrogen bonding between the distal amino and the ferryl are also

responsible for such behavior. Here we will address these issues by continuing our previous work on mutated Hbl species and following the formation of their heme-ferryl derivative by time resolved resonance Raman. These techniques can detect the transient ferryl species in times shorter than milliseconds and can help resolve questions such as: How does H2O2 ligand stabilization occur? Which conformational and structural changes are important in the stabilization of HblFe(IV)=O ferryl? What control heme and H202 reactivity in this unique protein? How do the heme pocket aromatic residues contribute or modulate the association and dissociation rate constants for ferryl intermediates in Hbl or Hbll?

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- **Project Title: THERAPEUTIC MULTIDENTATE IRON SEQUESTERING AGENTS**

  Principal Investigator & Institution: Raymond, Kenneth N.; Professor; Chemistry; University of California Berkeley Berkeley, Ca 947205940

  Timing: Fiscal Year 2002; Project Start 01-JUN-2000; Project End 30-APR-2005

  Summary: (adapted from the application) Current strategies to prevent iron toxicity associated with transfusion induced hemosiderosis have a number of limitations. Desferrioxamine (Desferal) a tri-hydroxamate, is the most commonly used iron chelator. Desferal, is expensive, has a short half-life in vivo, does not efficiently remove iron from transferrin, must be given on a regular, frequent basis by a subcutaneous or intravenous route and its use can result in significant, irreversible toxicity. The bidentate dimethyl-3-hydroxypyridine-4-one, known as L1, DMHP, CP20 or Deferiprone, can catalyze iron removal from transferrin and has been shown to be effective when given orally. However, toxicity results with this agent, due in part to its thermodynamic instability and high concentration required to obtain a therapeutic effect. This application describes a plan to develop and evaluate a series of new iron chelating agents that are effective when administered orally and have no toxicity. Our hypothesis is that multidentate, rather than bidentate, hydroxypyridonate ligands will be effective as oral iron chelating agents and will not be toxic. Our specific aims will be to synthesize a variety of multidentate hydroxypyridonate ligands that are structurally designed so that they can decorporate iron from transferrin at low concentrations, have a long half-life in vivo, are therapeutically effective at removing excess iron when administered orally and are not toxic. Using a number of synthetic chemical steps, a series of novel iron chelating compounds with unique chemical structures, which have the potential to meet the above criteria, will be synthesized. The thermodynamics stability and kinetics of removal of iron from human transferrin will be determined for each compound. Two iron overloaded animal models will be used to evaluate toxicity, biological routes of iron excretion, and ability to remove iron from tissue stores. Our ultimate goal is to develop a safe, oral, clinically effective iron-chelating agent that will prevent the toxicity of iron accumulation in patients who require chronic red cell transfusions.

  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: WEILL CORNELL PROGRAM OF EXCELLENCE IN GENE THERAPY**

  Principal Investigator & Institution: Crystal, Ronald G.; Chief; None; Weill Medical College of Cornell Univ New York, Ny 10021

  Timing: Fiscal Year 2002; Project Start 28-SEP-2000; Project End 31-AUG-2005

  Summary: The unifying theme of the Weill Cornell PEGT is the challenge of adapting the technology of ex vivo and in vivo gene transfer to treat and prevent disorders of heart, lung and blood. This challenge can be met by understanding the biology of gene transfer to cells and experimental animals and applying that understanding the biology of gene transfer to cells and experimental animals and applying that understanding to the design of clinical studies. The Weill Cornel PEGT combines extensive gene therapy core facilities with 6 NIH funded Principal Investigators at Weill Cornell, Memorial-Sloan Kettering, and Evanston Northwestern, with overlapping interests and ongoing collaborations including 2 NIH Program Projects and 5 shared R01 grants. The proposed PEGT comprises 4 pre-clinical projects, 2 clinical projects, 8 cores, and a data management program. The projects include: (1) Genetic Treatment of - **thalassemia** by lentivirus-mediated transfer of a regulated human-globin gene (M. Sadelain), (2) In vivo expansion, mobilization and recovery of bone marrow-derived stem cells by regional delivery of adenoviral vectors expressing cytokines (S. Rafii), (3) Manipulation of hematopoietic and endothelial stem cell self-renewal and proliferation by adeno- and retroviral gene transfer (M. Moore); (4) Development of a anti-Pseudomonas vaccine using dendritic cells modified to express CD40L and pulsed with Pseudomonas (R.

Crystal); (5) retroviral mediated transfer of the glucose-6-phosphate dehydrogenase gene into human hematopoietic progenitor cells for the treatment of patients with chronic non-spherocytic hemolytic anemia (L. Luzzato), myocardial angiogenesis therapy as an adjunct to off-pump coronary artery bypass surgery (T. Rosengart). The supporting cores include: DNA vector, RNA vector; Stem cell; Analysis; Clinical Operations and Regulatory Affairs; Experimental Animal; Training and Education; Administration; and PEGT Data Management.

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

- **Project Title: WORKSHOP ON BIOLRON IN THALASSEMIA & SICKLE CELL DISEASE**

  Principal Investigator & Institution: Theil, Elizabeth C.; Senior Scientist; Children's Hospital & Res Ctr at Oakland Research Center at Oakland Oakland, Ca 946091809

  Timing: Fiscal Year 2002; Project Start 15-MAY-2002; Project End 30-APR-2003

  Summary: (provided by applicant): Biolron, the study of the molecular and cellular basis of iron homeostasis in health and disease, is a rapidly expanding field and a fertile ground for translational research. Several of the genes which alter iron homeostasis, such as Sickle Cell Disease and the Thalassemias were defined almost half a century ago, whereas other new genes that alter iron homeostasis are still being discovered, e.g. DMT1 for iron uptake, mitochondrial ferritin and ferroportin for iron exit and HFE for hemochromatosis. The importance of the new field is the recent founding of IBIS, the International Society for Biolron Research. The CHORI (Children's Hospital Oakland Research Institute) Center for Biolron Research is sponsoring a Workshop on Biolron in Health and Disease to bring together a small group of Senior Scientists and Physicians with Junior Scientists and Trainees working in the area of Biolron related to Sickle Cell Disease, **Thalassemia,** novel aspects of iron deficiency and iron chelation. CHORI has an unusually strong focus in Biolron Research and Postdoctoral Training Program in Hematology/Immunology.Children's Hospital Oakland has large numbers of patients in transfusion programs for Sickle Cell Disease and **Thalassemia** and a Hematology Fellows Program. The workshop has three goals: 1-Sharpen the focus on coupling basic and clinical research; 2-Develop and strengthen collaborations; 3-Broaden knowledge of Trainees in Biolron research (Students and Postdoctoral Fellows) outside their more narrow individual basic or clinical research areas. The results of the workshop will enhance the development of Biolron Research in the areas of Sickle Cell Disease and **Thalassemia,** increase awareness of impact of iron nutrition and chelation on the two diseases, and facilitate the transfer of basic and clinical research to the clinic.

  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

[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.

unrestricted.[5] To search, go to **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Pmc**, and type "thalassemia" (or synonyms) into the search box. This search gives you access to full-text articles. The following is a sample of items found for thalassemia in the PubMed Central database:

- **"Silent" nucleotide substitution in a beta+-thalassemia globin gene activates splice site in coding sequence RNA.** by Goldsmith ME, Humphries RK, Ley T, Cline A, Kantor JA, Nienhuis AW.; 1983 Apr;
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- **[alpha]-Thalassemia in the American Negro.** by Schwartz E, Atwater J.; 1972 Feb;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=302140
- **[beta]-Thalassemia in the American Negro.** by Friedman S, Hamilton RW, Schwartz E.; 1973 Jun;
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- **A 5' splice-region G----C mutation in exon 1 of the human beta-globin gene inhibits pre-mRNA splicing: a mechanism for beta+-thalassemia.** by Vidaud M, Gattoni R, Stevenin J, Vidaud D, Amselem S, Chibani J, Rosa J, Goossens M.; 1989 Feb;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=286617
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  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=326534
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  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=40451
- **A normal [beta]-globin allele as a modifier gene ameliorating the severity of [alpha]-thalassemia in mice.** by Leder A, Wiener E, Lee MJ, Wickramasinghe SN, Leder P.; 1999 May 25;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=26874

[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.

- **A novel beta thalassemia gene with a single base mutation in the conserved polypyrimidine sequence at the 3' end of IVS 2.** by Beldjord C, Lapoumeroulie C, Pagnier J, Benabadji M, Krishnamoorthy R, Labie D, Bank A.; 1988 Jun 10; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=336707
- **A nucleotide change at a splice junction in the human beta-globin gene is associated with beta 0-thalassemia.** by Baird M, Driscoll C, Schreiner H, Sciarratta GV, Sansone G, Niazi G, Ramirez F, Bank A.; 1981 Jul; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=319760
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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 thalassemia, simply go to the PubMed Web site at **http://www.ncbi.nlm.nih.gov/pubmed**. Type "thalassemia" (or synonyms) into the search box, and click "Go." The following is the type of output you can expect from PubMed for thalassemia (hyperlinks lead to article summaries):

[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.

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- **Variable severity of beta-thalassemia patients of eastern India: effect of alpha-thalassemia and xmnI polymorphism.**
  Author(s): Bandyopadhyay S, Roychowdhury K, Chandra S, Das M, Dasgupta UB.
  Source: Clinical and Experimental Medicine. 2001 September; 1(3): 155-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11833853

- **Very mild pathology in a case of Hb S/beta0-thalassemia in combination with a homozygosity for the alpha-thalassemia 3.7 kb deletion.**
  Author(s): Kerkhoffs JL, Harteveld CL, Wijermans P, van Delft P, Haak HL, Bernini LF, Giordano PC.
  Source: Hemoglobin. 2000 August; 24(3): 259-63.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10975447

- **Viremia, genetic heterogeneity, and immunity to hepatitis G/GB-C virus in multiply transfused patients with thalassemia.**
  Author(s): Zemel R, Dickman R, Tamary H, Bukh J, Zaizov R, Tur-Kaspa R.
  Source: Transfusion. 1998 March; 38(3): 301-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9563412

- **Visual failure caused by suprasellar extramedullary hematopoiesis in beta thalassemia: case report.**
  Author(s): Aarabi B, Haghshenas M, Rakeii V.
  Source: Neurosurgery. 1998 April; 42(4): 922-5; Discussion 925-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9574659

- **Vitamin E status, glutathione peroxidase activity and the effect of vitamin E supplementation in children with thalassemia.**
  Author(s): Suthutvoravut U, Hathirat P, Sirichakwal P, Sasanakul W, Tassaneeyakul A, Feungpean B.
  Source: J Med Assoc Thai. 1993 October; 76 Suppl 2: 146-52.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7822984

- **Why are hemoglobin F levels increased in HbE/beta thalassemia?**
  Author(s): Rees DC, Porter JB, Clegg JB, Weatherall DJ.
  Source: Blood. 1999 November 1; 94(9): 3199-204.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10556208

- **X-linked alpha-thalassemia/mental retardation (ATR-X) syndrome. Report of three male patients in a large French family.**
  Author(s): Lefort G, Taib J, Toutain A, Houdayer C, Moraine CI, Humeau C, Sarda P.
  Source: Annales De Genetique. 1993; 36(4): 200-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8166424

- **X-linked alpha-thalassemia/mental retardation (ATR-X) syndrome: a new kindred with severe genital anomalies and mild hematologic expression.**
  Author(s): McPherson EW, Clemens MM, Gibbons RJ, Higgs DR.
  Source: American Journal of Medical Genetics. 1995 January 30; 55(3): 302-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7726227

- **X-linked alpha-thalassemia/mental retardation (ATR-X) syndrome: localization to Xq12-q21.31 by X inactivation and linkage analysis.**
  Author(s): Gibbons RJ, Suthers GK, Wilkie AO, Buckle VJ, Higgs DR.
  Source: American Journal of Human Genetics. 1992 November; 51(5): 1136-49.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1415255

- **X-linked alpha-thalassemia/mental retardation syndrome. Linkage analysis in a new family further supports localization in proximal Xq.**
  Author(s): Houdayer CI, Toutain A, Ronce N, Lefort G, Sarda P, Taib J, Briault S, Lambert JC, Moraine CI.
  Source: Annales De Genetique. 1993; 36(4): 194-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8166423

- **X-linked thrombocytopenia with thalassemia from a mutation in the amino finger of GATA-1 affecting DNA binding rather than FOG-1 interaction.**
  Author(s): Yu C, Niakan KK, Matsushita M, Stamatoyannopoulos G, Orkin SH, Raskind WH.
  Source: Blood. 2002 September 15; 100(6): 2040-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12200364

- **Yersinia enterocolitica infection in a boy with beta thalassemia major.**
  Author(s): Monno R, Valenza MA, Quarto M, Sabato V, De Mattia D, Paradies G, Montinaro L, Fumarola D.
  Source: The Pediatric Infectious Disease Journal. 1994 March; 13(3): 233-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8177635

CHAPTER 2. NUTRITION AND THALASSEMIA

Overview

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

Finding Nutrition Studies on Thalassemia

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 "thalassemia" (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 is a typical result when searching for recently indexed consumer information on thalassemia:

- **Diabetic nephropathy in hypertransfused patients with beta-thalassemia. The role of oxidative stress.**
  Author(s): Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, Ontario, Canada.
  Source: Loebstein, R Lehotay, D C Luo, X Bartfay, W Tyler, B Sher, G D Diabetes-Care. 1998 August; 21(8): 1306-9 0149-5992

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

- **An algorithm to aid in the investigation of thalassemia trait in multicultural populations.**
  Author(s): University Health Network/The Princess Margaret Hospital, Toronto, Ontario, Canada.
  Source: Kiss, T L Ali, M A Levine, M Lafferty, J D Arch-Pathol-Lab-Med. 2000 September; 124(9): 1320-3 0003-9985
- **An investigation into variability in the therapeutic response to deferiprone in patients with thalassemia major.**
  Author(s): The Hospital for Sick Children, and Department of Pediatrics, Pharmacology, Pharmacy, and Medicine, The University of Toronto, Ontario, Canada.
  Source: Diav Citrin, O Atanackovic, G Koren, G Ther-Drug-Monit. 1999 February; 21(1): 74-81 0163-4356
- **Analysis of folate and vitamin B12 in beta thalassemia minor.**
  Author(s): Emergency Service, St. Anna Hospital, USL 31, Ferrara, Italy.
  Source: Gallerani, M Cicognani, I Ballardini, P Martinelli, L Ricci, A Dall'Ara, G Faggioli, M Riv-Eur-Sci-Med-Farmacol. 1990 Aug-October; 12(4-5): 247-50 0392-291X
- **Antihistone and other autoantibodies in beta-thalassemia major patients receiving iron chelators.**
  Author(s): Institute of Immunohaematology (ICMR), KEM Hospital Campus, Parel, Mumbai, India.
  Source: Pradhan, V Badakere, S Ghosh, K Acta-Haematol. 2003; 109(1): 35-9 0001-5792
- **Application of a discriminant function distinguishing iron deficiency anemia and heterozygous beta-thalassemia from other genetic abnormalities.**
  Author(s): Department of Pathology, Phamongkudklao Hospital, Bangkok, Thailand.
  Source: Kaewborworn, U Bunyaratvej, A Ravivongse, R Thuvasethakul, P Hathirat, P Birth-Defects-Orig-Artic-Ser. 1987; 23(5A): 177-80 0547-6844
- **Biochemical and clinical effects of vitamin E administration in homozygous beta-thalassemia.**
  Source: Giardini, O. Cantani, A. Donfrancesco, A. Martino, F. Mannarino, O. D'Eufemia, P. Miano, C. Ruberto, U. Lubrano, R. Acta-Vitaminol-Enzymol. Milano : Acta Vitaminologica et Enzymologica 1985. volume 7 (1/2) page 55-60. 0300-8924
- **Bone marrow transplantation for children with thalassemia: two years' experience with low-dose busulfan, citoxan and GM-CSF.**
  Author(s): Department of Pediatrics, University of Turin, Italy.
  Source: Miniero, R Vassallo, E Busca, A Piga, A Perugini, L Madon, E Bone-Marrow-Transplant. 1993; 12 Suppl 151-3 0268-3369

- **Clinical experience using the Androderm testosterone transdermal system in hypogonadal adolescents and young men with beta-thalassemia major.**
  Author(s): Department of Pediatrics, Hospital S. Anna, Ferrara, Italy.
  Source: De Sanctis, V Vullo, C Urso, L Rigolin, F Cavallini, A Caramelli, K Daugherty, C Mazer, N J-Pediatr-Endocrinol-Metab. 1998; 11 Suppl 3891-900

- **Comparison between deferoxamine and deferiprone (L1) in iron-loaded thalassemia patients.**
  Author(s): The Chronic Care Centre, The American University of Beirut Medical Centre, Beirut, Lebanon. ataher@aub.edu.lb
  Source: Taher, A Sheikh Taha, M Koussa, S Inati, A Neeman, R Mourad, F Eur-J-Haematol. 2001 July; 67(1): 30-4 0902-4441

- **Comparison of a transfusion preparation of newly formed red cells and standard washed red cell transfusions in patients with homozygous beta-thalassemia.**
  Author(s): Canadian Red Cross, Toronto Center, Ontario, Canada.
  Source: Collins, A F Goncalves Dias, C Haddad, S Talbot, R Herst, R Tyler, B J Zuber, E Blanchette, V S Olivieri, N F Transfusion. 1994 June; 34(6): 517-20 0041-1132

- **Effects of hormonal replacement therapy on bone metabolism in young adults with beta-thalassemia major.**
  Author(s): Department of Internal Medicine, University of Messina, Italy. alasco@unime.it
  Source: Lasco, A Morabito, N Gaudio, A Buemi, M Wasniewska, M Frisina, N Osteoporos-Int. 2001; 12(7): 570-5 0937-941X

- **Electroretinographic and visual-evoked potential abnormalities in patients with beta-thalassemia major.**
  Author(s): Department of Ophthalmology, University of Pavia, Italy.
  Source: Gelmi, C Borgna Pignatti, C Franchin, S Tacchini, M Trimarchi, F Ophthalmologica. 1988; 196(1): 29-34 0030-3755

- **Endocrine complications of thalassemia.**
  Author(s): Department of Pediatrics, Rambam Medical Center, Haifa, Israel. D_tiosano@rambam.health.gov.il
  Source: Tiosano, D Hochberg, Z J-Endocrinol-Invest. 2001 October; 24(9): 716-23 0391-4097

- **Growth hormone release by the novel GH releasing peptide hexarelin in patients with homozygous beta-thalassemia.**
  Author(s): University of Athens, Greece.
  Source: Tolis, G Karydis, I Markousis, V Karagiorga, M Mesimeris, T Lenaerts, V Deghenghi, R J-Pediatr-Endocrinol-Metab. 1997 Jan-February; 10(1): 35-40

- **Growth hormone response following growth hormone releasing hormone injection in thalassemia major: influence of pubertal development.**
  Author(s): Service de Medecine Infantile 1, Hopital d'Enfants, CHR de Nancy, Vandoeuvre les Nancy, France.
  Source: Leheup, B P Cisternino, M Bozzola, M Dousset, B Marradi, P L Antoniazzi, F Tato, L Severi, F Sommelet, D Pierson, M J-Endocrinol-Invest. 1991 January; 14(1): 37-40 0391-4097

- **Growth plate injury of the long bones in treated beta-thalassemia.**
  Author(s): Department of Radiology, St. Anna Hospital, Ferrara, Italy.
  Source: Orzincolo, C Scutellari, P N Castaldi, G Skeletal-Radiol. 1992; 21(1): 39-44 0364-2348

- **Hematologic disorders including sickle-cell syndromes, hemophilia, and beta-thalassemia.**
  Author(s): Division of Rheumatology, University of Alabama at Birmingham 35294-3296, USA.
  Source: Bastian, H M Curr-Opin-Rheumatol. 1995 January; 7(1): 70-2 1040-8711
- **High prevalence of thyroid dysfunction in adult patients with beta-thalassemia major submitted to amiodarone treatment.**
  Author(s): Dipartimento di Scienze Mediche M. Aresu, Universita di Cagliari, Italy.
  Source: Mariotti, S Loviselli, A Murenu, S Sau, F Valentino, L Mandas, A Vacquer, S Martino, E Balestrieri, A Lai, M E J-Endocrinol-Invest. 1999 January; 22(1): 55-63 0391-4097
- **Incidence and treatment of fractures in thalassemia.**
  Author(s): Department of Pediatric Orthopaedic Surgery, Children's Hospital of Philadelphia, Pennsylvania.
  Source: Michelson, J Cohen, A J-Orthop-Trauma. 1988; 2(1): 29-32 0890-5339
- **Induction of puberty in patients with beta-thalassemia major.**
  Author(s): University College Hospital, London, England.
  Source: Chatterjee, R Katz, M Wonke, B Hoffbrand, A V Politis, D Birth-Defects-Orig-Artic-Ser. 1987; 23(5A): 453-8 0547-6844
- **Liver injury due to iron overload in thalassemia: histopathologic and ultrastructural studies.**
  Author(s): Department of Pathology, Mahidol University, Bangkok, Thailand.
  Source: Thakerngpol, K Fucharoen, S Boonyaphipat, P Srisook, K Sahaphong, S Vathanophas, V Stitnimankarn, T Biometals. 1996 April; 9(2): 177-83 0966-0844
- **Malnutrition and growth abnormalities in children with beta thalassemia major.**
  Author(s): Department of Pediatrics, Chiang Mai University, Thailand.
  Source: Tienboon, P Sanguansermsri, T Fuchs, G J Southeast-Asian-J-Trop-Med-Public-Health. 1996 June; 27(2): 356-61 0038-3619
- **Management of cardiac complications in patients with thalassemia major.**
  Author(s): E.O. Ospedali Galliera, Cardiology Division, Genova, Italy.
  Source: Vecchio, C Derchi, G Semin-Hematol. 1995 October; 32(4): 288-96 0037-1963
- **Management of thalassemias: growth and development, hormone substitution, vitamin supplementation, and vaccination.**
  Author(s): 1st Department of Pediatrics, Medical School, University of Athens, St. Sophia Children's Hospital, Greece.
  Source: Kattamis, C A Kattamis, A C Semin-Hematol. 1995 October; 32(4): 269-79 0037-1963
- **Oral iron chelation with 1,2-dimethyl-3-hydroxypyrid-4-one (L1) in iron loaded thalassemia patients.**
  Author(s): Department of Pediatrics and Clinical Biochemistry, Hospital for Sick Children, Toronto, Canada.
  Source: Olivieri, N F Matsui, D Liu, P P Blendis, L Cameron, R McClelland, R A Templeton, D M Koren, G Bone-Marrow-Transplant. 1993; 12 Suppl 19-11 0268-3369
- **Overview of the beta thalassemias: genetic and clinical aspects.**
  Author(s): Children's Hospital of Philadelphia, Department of Pediatrics, University of Pennsylvania School of Medicine 19104.
  Source: Schwartz, E Cohen, A Surrey, S Hemoglobin. 1988; 12(5-6): 551-64 0363-0269

- **Pulmonary iron overload in thalassemia major presenting as small airway disease.**
  Author(s): Department of Diagnostic Radiology, University of Hong Kong, Queen Mary Hospital, Hong Kong, China. cgcooi@hkucc.hku.hk
  Source: Ooi, G C Khong, P L Lam, W K Trendell Smith, N J Tsang, K W T Acta-Haematol. 2002; 108(1): 43-6 0001-5792

- **Reactivation of fetal hemoglobin in patients with beta-thalassemia.**
  Author(s): Hospital for Sick Children, Toronto, Ontario, Canada.
  Source: Olivieri, N F Semin-Hematol. 1996 January; 33(1): 24-42 0037-1963

- **Recombinant growth hormone treatment in short patients with thalassemia major: results after 24 and 36 months.**
  Author(s): Dipartimento di Biomedicina dell'Eta Evolutiva-Universita di Bari, Italy. lucicava@tin.it
  Source: Cavallo, L Acquafredda, A Zecchino, C De Sanctis, V Cisternino, M Caruso Nicoletti, M Galati, M Massolo, F J-Pediatr-Endocrinol-Metab. 2001 Sep-October; 14(8): 1133-7

- **Recombinant human growth hormone treatment in children with thalassemia major.**
  Author(s): Department of Pediatrics, Faculty of Medicine, Ankara University, Turkey.
  Source: Arcasoy, A Ocal, G Kemahli, S Berberoglu, M Yildirmak, Y Canatan, D Akcurin, S Akar, N Uysal, Z Adiyaman, P Cetinkaya, E Pediatr-Int. 1999 December; 41(6): 655-61 1328-8067

- **Relationship of serum vitamin E, erythrocyte nonheme iron, and malonyldialdehyde (lipid membrane peroxidation product) in thalassemia.**
  Author(s): Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.
  Source: Vatanavicharn, S Anuwatanakulchai, M Yenchitsomanus, P Siddhikol, C Birth-Defects-Orig-Artic-Ser. 1987; 23(5A): 207-11 0547-6844

- **Renal lesions and clinical findings in thalassemia major and other chronic anemias with hemosiderosis.**
  Author(s): Department of Pathology, Childrens Hospital of Los Angeles, California 90027.
  Source: Landing, B H Gonick, H C Nadorra, R L Hyman, C B Wells, T R Villarreal Engelhardt, G Mersch, J Agness, C L Pediatr-Pathol. 1989; 9(5): 479-500 0277-0938

- **Role of lipid peroxidation and antioxidants in aging process and thalassemia.**
  Author(s): Department of Clinical Chemistry, Faculty of Associated Medical Sciences, Chiang Mai University, Thailand.
  Source: Chanarat, N Kitasato-Arch-Exp-Med. 1992 December; 65(4): 245-9 0023-1924

- **The effect of 3 years of recombinant growth hormone therapy on glucose metabolism in short Chinese children with beta-thalassemia major.**
  Author(s): Department of Paediatrics, Queen Mary Hospital, University of Hong Kong, China.
  Source: Kwan, E Y Tam, S C Cheung, P T Low, L C J-Pediatr-Endocrinol-Metab. 2000 May; 13(5): 545-52

- **The effect of bu shen sheng xue fang on beta-thalassemia at gene level.**
  Author(s): Guang'anmen Hospital of China Academy of TCM, Beijing.
  Source: Wu, Z Jiang, B Cui, J Ji, X Huang, X Cai, H Chen, P Wang, R Huang, Y J-Tradit-Chin-Med. 1998 December; 18(4): 300-3 0254-6272

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 thalassemia; 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

- **Minerals**

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

  L-carnitine
  Source: Healthnotes, Inc.; www.healthnotes.com

CHAPTER 3. ALTERNATIVE MEDICINE AND THALASSEMIA

Overview

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

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 thalassemia 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 "thalassemia" (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 thalassemia:

- **A controlled trial of long-term chelation therapy in homozygous beta-thalassemia.**
  Author(s): Letsky EA.
  Source: Birth Defects Orig Artic Ser. 1976; 12(8): 31-41. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1009233

- **A moderate transfusion regimen may reduce iron loading in beta-thalassemia major without producing excessive expansion of erythropoiesis.**
  Author(s): Cazzola M, Borgna-Pignatti C, Locatelli F, Ponchio L, Beguin Y, De Stefano P.
  Source: Transfusion. 1997 February; 37(2): 135-40.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9051086

- **A prospective evaluation of iron chelation therapy in children with severe beta-thalassemia. A six-year study.**
  Author(s): Maurer HS, Lloyd-Still JD, Ingrisano C, Gonzalez-Crussi F, Honig GR.

Source: Am J Dis Child. 1988 March; 142(3): 287-92.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3344715

- **Absence of hemoglobin A in a double heterozygote for F-thalassemia and hemoglobin S.**
Author(s): Stamatoyannopoulos G, Sofroniadou C, Akrivakis A.
Source: Blood. 1967 December; 30(6): 772-6.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=4965621

- **Adrenal function in thalassemia major following long-term treatment with multiple transfusions and chelation therapy. Evidence for dissociation of cortisol and adrenal androgen secretion.**
Author(s): Sklar CA, Lew LQ, Yoon DJ, David R.
Source: Am J Dis Child. 1987 March; 141(3): 327-30.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3028128

- **An international survey of patients with thalassemia major and their views about sustaining life-long desferrioxamine use.**
Author(s): Ward A, Caro JJ, Green T, Huybrechts K, Arana A, Wait S, Eleftheriou A.
Source: Bmc Clinical Pharmacology [electronic Resource]. 2002 April 23; 2(1): 3.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12015817

- **An oral treatment for iron overload in thalassemia?**
Author(s): Kowdley KV, Tavill AS.
Source: Hepatology (Baltimore, Md.). 1996 February; 23(2): 380-2.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8591869

- **Angioid streaks in homozygous beta thalassemia.**
Author(s): Aessopos A, Stamatelos G, Savvides P, Kavouklis E, Gabriel L, Rombos I, Karagiorga M, Kaklamanis P.
Source: American Journal of Ophthalmology. 1989 October 15; 108(4): 356-9.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2801854

- **Apolipoprotein E epsilon4 allele as a genetic risk factor for left ventricular failure in homozygous beta-thalassemia.**
Author(s): Economou-Petersen E, Aessopos A, Kladi A, Flevari P, Karabatsos F, Fragodimitri C, Nicolaidis P, Vrettou H, Vassilopoulos D, Karagiorga-Lagana M, Kremastinos DT, Petersen MB.
Source: Blood. 1998 November 1; 92(9): 3455-9.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9787187

- **Arterial calcifications in beta-thalassemia.**
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  Source: Acta Haematologica. 2002; 108(1): 43-6.
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- **Rapid removal of excessive iron in thalassemia by high-dose intravenous chelation therapy.**
  Author(s): Sabatino D.
  Source: The Journal of Pediatrics. 1990 January; 116(1): 157-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2334479

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  Author(s): Gumruk F, Gurgey A, Duru F, Altay C.
  Source: Pediatric Hematology and Oncology. 1992 October-December; 9(4): 359-63.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1467169

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  Author(s): Sumboonnanonda A, Malasit P, Tanphaichitr VS, Ong-ajyooth S, Petrarat S, Vongjirad A.
  Source: Pediatric Nephrology (Berlin, Germany). 2003 March; 18(3): 257-60. Epub 2003 February 26.
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  Author(s): Dimitriou P, Giamouris J, Nicolaidou P, Antipas SE, Fretzayas A, Messaropoulos T, Karpathios T.
  Source: Scand J Haematol. 1986 November; 37(5): 417-20.
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- **Response to long-term deferoxamine therapy in thalassemia.**
  Author(s): Cohen A, Martin M, Schwartz E.
  Source: The Journal of Pediatrics. 1981 November; 99(5): 689-94.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7299539

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  Author(s): Spirito P, Lupi G, Melevendi C, Vecchio C.

Source: Circulation. 1990 July; 82(1): 88-94.
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- **Results of therapy for beta-thalassemia major.**
Author(s): Lin KH, Lin KS.
Source: J Formos Med Assoc. 1992 February; 91(2): 126-30.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1364206

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Author(s): Dore F, Cianciulli P, Oggiano L, Pardini S, Bonfigli S, Ganau A, Piga G, Trua G, Papa G, Longinotti M.
Source: Haematologica. 1990 September-October; 75 Suppl 5: 9-25. Review.
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- **Reversal of cardiac complications in thalassemia major by long-term intermittent daily intensive iron chelation.**
Author(s): Miskin H, Yaniv I, Berant M, Hershko C, Tamary H.
Source: European Journal of Haematology. 2003 June; 70(6): 398-403.
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Author(s): Jiang C, Hansen RM, Gee BE, Kurth SS, Fulton AB.
Source: Documenta Ophthalmologica. Advances in Ophthalmology. 1998-99; 96(4): 333-45.
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Author(s): Peng CT, Chow KC, Chen JH, Chiang YP, Lin TY, Tsai CH.
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Author(s): Gaziev D, Polchi P, Lucarelli G, Galimberti M, Sodani P, Angelucci E, Giardini C, Baronciani D, Erer B.
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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11393640

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  Author(s): Kontzoglou G, Koussi A, Tsatra J, Noussios G, Vital V, Sagarakis G, Athanassiou M.
  Source: International Journal of Pediatric Otorhinolaryngology. 1996 May; 35(3): 223-30.
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  Source: Pediatric Hematology and Oncology. 1998 July-August; 15(4): 371-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9658440

- **Short stature and truncal shortening in transfusion dependent thalassemia patients: results from a thalassemia center in Malaysia.**
  Author(s): Hamidah A, Rahmah R, Azmi T, Aziz J, Jamal R.
  Source: Southeast Asian J Trop Med Public Health. 2001 September; 32(3): 625-30.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11944728

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  Author(s): Borgna-Pignatti C, De Stefano P, Bongo IG, Avato F, Cazzola M.
  Source: Am J Pediatr Hematol Oncol. 1984 Fall; 6(3): 340-3.
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  Author(s): Olivieri NF, Koren G, St Louis P, Freedman MH, McClelland RA, Templeton DM.
  Source: Semin Hematol. 1990 April; 27(2): 101-4. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2190316

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  Author(s): Maioli M, Pacifico A, Frulio T, Longinotti M.
  Source: Acta Diabetol Lat. 1983 April-June; 20(2): 143-52.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=6349202

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  Author(s): Olivieri NF, Nathan DG, MacMillan JH, Wayne AS, Liu PP, McGee A, Martin M, Koren G, Cohen AR.

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Author(s): Lo L, Singer ST.
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Source: J Pediatr Endocrinol Metab. 2000 May; 13(5): 545-52.
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Author(s): Wu Z, Jiang B, Cui J, Ji X, Huang X, Cai H, Chen P, Wang R, Huang Y.

Source: J Tradit Chin Med. 1998 December; 18(4): 300-3.
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Author(s): Longo F, Zecchina G, Sbaiz L, Fischer R, Piga A, Camaschella C.
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Author(s): Agarwal MB, Shah S, Vishwanathan C, Rajadhyaksha G, Bhave AA, Dube SR, Billa V, Malkan G, Bajan K.
Source: Indian Pediatrics. 1992 August; 29(8): 997-102.
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- **Treatment of beta-thalassemia patients with recombinant human erythropoietin: effect on transfusion requirements and soluble adhesion molecules.**
Author(s): Chaidos A, Makis A, Hatzimichael E, Tsiara S, Gouva M, Tzouvara E, Bourantas KL.
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Author(s): Giardini C.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9107523

- **Turner's syndrome and hypogonadotrophic hypogonadism: thalassemia major and hemochromatosis.**
Author(s): Afonso Lopes L, Benador D, Wacker P, Wyss M, Sizonenko PC.
Source: J Pediatr Endocrinol Metab. 1995 January-March; 8(1): 73-7.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7584702

- **Type 3 hemochromatosis and beta-thalassemia trait.**
Author(s): Riva A, Mariani R, Bovo G, Pelucchi S, Arosio C, Salvioni A, Vergani A, Piperno A.
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- **Umbilical cord blood transplantation in Chinese children with beta-thalassemia.**
Author(s): Fang J, Huang S, Chen C, Zhou D, Li CK, Li Y, Huang K.
Source: Journal of Pediatric Hematology/Oncology : Official Journal of the American Society of Pediatric Hematology/Oncology. 2004 March; 26(3): 185-9.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15125611

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Author(s): Giardina PJ, Hilgartner MW.
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Author(s): Boturao-Neto E, Marcopito LF, Zago MA.
Source: Brazilian Journal of Medical and Biological Research = Revista Brasileira De Pesquisas Medicas E Biologicas / Sociedade Brasileira De Biofisica. [et Al.]. 2002 November; 35(11): 1319-28.
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- **Vitamin E status, glutathione peroxidase activity and the effect of vitamin E supplementation in children with thalassemia.**
Author(s): Suthutvoravut U, Hathirat P, Sirichakwal P, Sasanakul W, Tassaneeyakul A, Feungpean B.
Source: J Med Assoc Thai. 1993 October; 76 Suppl 2: 146-52.
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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/**

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 THALASSEMIA

Overview

In this chapter, we will give you a bibliography on recent dissertations relating to thalassemia. 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 "thalassemia" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on thalassemia, we have not necessarily excluded non-medical dissertations in this bibliography.

Dissertations on Thalassemia

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 thalassemia. 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:

- **DNA diagnosis of thalassemia from ancient Italian skeletons** by Yang, Dongya; PhD from Mcmaster University (Canada), 1998, 211 pages
  http://wwwlib.umi.com/dissertations/fullcit/NQ42773
- **Molecular characterization of an atypical beta-thalassemia** by Popovich, Bradley W; PhD from Mcgill University (Canada), 1986
  http://wwwlib.umi.com/dissertations/fullcit/NL34418
- **THALASSEMIA: AN ANTHROPOLOGICAL STUDY OF 86 PATIENTS AND THEIR FAMILIES IN CYPRUS** by BOOK, PATRICIA ANN, PHD from The University of Connecticut, 1980, 341 pages
  http://wwwlib.umi.com/dissertations/fullcit/8025344

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. PATENTS ON THALASSEMIA

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.[8] 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 "thalassemia" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on thalassemia, we have not necessarily excluded non-medical patents in this bibliography.

Patents on Thalassemia

By performing a patent search focusing on thalassemia, 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. The following is an

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

example of the type of information that you can expect to obtain from a patent search on thalassemia:

- **Butyrate prodrugs derived from lactic acid**

  Inventor(s): Li; Bigin (Bedford, MA), Tung; Roger D. (Cambridge, MA)

  Assignee(s): Vertex Pharmaceuticals, Inc. (Cambridge, MA)

  Patent Number: 5,880,152

  Date filed: March 10, 1997

  Abstract: This invention relates to butyrate prodrugs derived from lactic acid and pharmaceutical compositions and methods employing them, either alone or in combination with other agents, for increasing gamma globin and fetal hemoglobin in a patient. These compounds, compositions and methods are particularly effective in treating.beta.-hemoglobinopathies, including sickle cell syndromes and.beta.-thalassemia syndromes. This invention relates to the use of these prodrugs, alone or in combination with other agents, to stimulate cell differentiation which prevents proliferation of malignant cells. These methods are particularly useful in treating cancer, especially malignant hematological disorders. In addition, this invention relates to the use of these prodrugs in treating inflammatory bowel diseases.

  Excerpt(s):.beta.-hemoglobinopathies are a group of inherited disorders of.beta.-globin biosynthesis. Although efforts have concentrated on a variety of therapeutic regimens, feasible clinical treatments for these debilitating diseases remain scarce. Various therapies have been utilized in the treatment of.beta.-hemoglobinopathies, each accompanied by drawbacks. G. P. Rogers et. al., "Current and Future Strategies for the Management of Hemoglobinopathies and Thalassemia", Hematology 1994, Education Program American Society of Hematology, pp. 9-20 (1994). Although the chemotherapeutic agent hydroxyurea stimulates fetal hemoglobin production and reduces sickling crisis in sickle cell anemia patients, its use in monotherapy is potentially limited by myelotoxicity and the risk of carcinogenesis. Potential long term carcinogenicity is also a drawback of 5-azacytidine-based therapies. Red blood cell transfusions expose patients to the potential of a wide range of infectious viral agents, as well as alloimmunization. Bone marrow transplants are not a readily available option for a large number of patients. Erythropoietin-based therapies have not proved consistent among a range of patient populations. Such varying drawbacks contraindicate the long term use of such agents or therapies.

  Web site: http://www.delphion.com/details?pn=US05880152__

- **Butyric ester cyto-differtiating agents**

  Inventor(s): Newmark; Harold L. (Maplewood, NJ)

  Assignee(s): Sloan-kettering Institute for Cancer Research (New York, NY)

  Patent Number: 5,645,852

  Date filed: September 13, 1995

  Abstract: This invention provides a method of inducing cell differentiation in a subject and methods of treating leukemia, **thalassemia,** or sickle cell anemia by administration to the subject of one or more oral bolus doses of a pharmaceutical composition comprising an effective amount of one or more butyryl glycerides and a

pharmaceutically acceptable carrier. This invention also provides a method of treating a surface or skin disorder in a subject by topical administration to the subject of a pharmaceutical composition comprising an effective amount of one or more butyryl glycerides and a pharmaceutically acceptable carrier.

Excerpt(s): Throughout this application, various publications are referenced in parentheses. Full citations for these publications can be found immediately preceding the claims. The disclosures of these publications in their entirety are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein. It has long been well known that the salts of butyric acid, particularly the sodium salt, act in vitro on many abnormal or transformed cell lines to cause these cells to change to a more normal state, including phenotype and function. This "differentiation" action is also shown by a number of agents with no readily obvious structure-activity relationship. In vitro, butyrate acts on some cancer or leukemia cancer cell lines such as HT-29, or HL-60 in this fashion, when maintained at concentrations of about 0.3 to 5 millimolar (mM). Desirable changes of the aberrant blood cells of sickle cell anemia and **thalassemia** can be obtained in vitro at lower concentrations of about 0.05 mM [Perrine S. P., et al., N. Engl. J. Med., Vol. 328, pages 81-86, (1993); Perfine, S. P., et al., Blood, Vol. 74, pages 454-459 (1989)]. Attempts to utilize butyrate salts in therapy have not generally been successful. An early attempt at using intravenous infusions of sodium butyrate at 500 mg/kg body weight per day for several days produced only a short-lived remission in a child with leukemia [Novogrodsky, A., et al., Cancer, Vol. 51, pages 9-14]. A larger study [Miller, A. A., et al., Eur. J. Cancer Clin. Oncol., Vol. 23, pages 1283-1287 (1987)], using the same infusion rate showed no clinical response, but also demonstrated that the infused butyrate had a very short metabolic half-life of about 6 minutes, resulting in peak blood levels below 0.05 mM, considered ineffective for leukemia. Higher rates of intravenous infusions could not be considered because of the risk of toxicity from sodium overload, and achieved success in treating **thalassemia** and sickle cell patients by continuous intravenous infusions of 500 mg/kg/day or higher doses, if needed, for several days. In these studies also, blood levels of butyrate did not exceed 0.05 mM and the butyrate was apparently rapidly metabolized [Perrine, et al. (1993)].

Web site: http://www.delphion.com/details?pn=US05645852__

- **Composition and method for treatment of hemoglobinopathies**

  Inventor(s): Fadulu; Sunday O. (20115 Wickham Ct., Katy, TX 77450)

  Assignee(s): Fadulu; Sunday O. (Katy, TX)

  Patent Number: 5,447,720

  Date filed: July 6, 1993

  Abstract: A composition and method of treatment of hemoglobinopathies, such as, for example, sickle cell disease and **thalassemia,** wherein an inventive extract used in such treatment is obtained from alfalfa and other certain plant materials, preferably using a hydroxide base and hexane. In the most preferred embodiment, the plant material is first extracted with 1,1,1-trichloroethane and a hydroxide base, followed by extraction with hexane. The polar acidic compounds present in alfalfa and other plant materials selectively dissolve in the hexane phase and exhibit good antisickling activity in vitro. Further, these active compounds which comprise the inventive extract are effective in

vivo by significantly alleviating the many clinical manifestations of sickle cell disease and **thalassemia** experienced by the affected patients.

Excerpt(s): The present invention relates to the treatment of blood disorders; and in particular, to a method and composition for the treatment of hemoglobinopathies, including.alpha.-thalassemia,.beta.-thalassemia, sickle cell diseases such as sickle cell SC (i.e., HbSC), sickle cell anemia (i.e., HbSS), and sickle cell trait (i.e., HbAS), for example, and combination hemoglobinopathies such as HbSS/.beta.-thalassemia, for example. Sickle cell disease is an inherited disease wherein the patient carries two abnormal.beta.sup.s genes, at least one of which codes for an abnormal type of hemoglobin molecule hemoglobin S (HbS). The disease itself stems from inadequate oxygen transport by red blood cells due to the presence of HbS. In sickle cell disease, HbS replaces normal hemoglobin, hemoglobin A (HbA), and differs from HbA only in that glutamic acid is substituted for valine at position 6 of the beta chain of the globin molecule. This one variation results in HbS being less soluble than HbA, especially in the reduced state, where it forms long, crystalline masses to cause the red blood cells to distort into the shape of sickles. HbS is inherited as a mendelian dominant such that there are both homozygous and heterozygous states. The most common and most severe form of the disease is HbSS, the homozygous state, (also referred to as sickle cell anemia). HbSS makes up from 80% to 100% of the total hemoglobin in individuals affected with sickle cell disease. Sickle cell trait carriers (HbAS) are heterozygous for HbS and usually show no sign of the disease. However, since about 25% to 40% of the total hemoglobin in trait carriers is HbS, sickle cell trait carriers risk hemolysis when exposed to low oxygen tension, such as during anesthesia, for example. Statistically, the marriage of two trait carriers results in a 25% chance that one of their children will be afflicted with sickle cell disease (i.e., homozygous) and a 50% chance that their children will have the sickle cell trait (i.e., heterozygous). Other sickle hemoglobinopathies related to HbSS include HbSC, HbSD, and HbSE.

Web site: http://www.delphion.com/details?pn=US05447720__

- **Compositions and methods for reducing adhesiveness of defective red blood cells**

  Inventor(s): Crandall; Ian Edward (Riverside, CA), Sherman; Irwin William (Riverside, CA), Shohet; Stephen Byron (San Francisco, CA), Thevenin; Bernard Jean-Marie (San Francisco, CA)

  Assignee(s): The Regents of the University of California (Oakland, CA)

  Patent Number: 6,124,262

  Date filed: March 17, 1995

  Abstract: Peptide sequences and analogs thereof based on amino acid motifs in band 3 which are effective in reducing the adhesiveness of pathologically adhesive red blood cells. One class of peptide sequences are characterized by the sequence motif Z.sup.1 xKxxx+ (SEQ ID NO:45), wherein Z.sup.1 is selected from the group consisting of tyrosine, phenylalanine and alanine; x is an unobstructive residue and + is a positively charged residue (e.g., K or P--H). These peptides are used to reduce adhesiveness in the treatment of sickle cell disease, **thalassemia** and diabetes. A second class of peptide sequences are characterized by the sequence motif Z.sup.2 Z.sup.3 Z.sup.2 -x-xxxx- (SEQ ID NO:46), wherein Z.sup.2 represents a hydrophobic residue, x is an unobstructive residue and - is a negatively charged residue. These peptides can be used to reduce adhesiveness in the treatment of malria, sickle cell disease, **thalassemia** and diabetes.

Excerpt(s): The present invention relates to compositions and methods for use in reducing the adhesiveness of pathologically adhesive red blood cells (as hereinafter defined). In particular, the present invention is directed to compositions and methods for treatment of various conditions involving red blood cells with pathologically increased adhesiveness, for example as a result of malaria, sickle cell disease, **thalassemia** or diabetes. This invention was made with Government support under Grant No. R01 AJ32995 and R01 DK16095, awarded by the National Institutes of Health. The Government has certain rights in this invention. Sickle cell disease is a result of the presence of the altered gene product hemoglobin S. This disease is characterized by hemolytic anemia and complications resulting from episodic vaso-occlusive events, and despite the fact that more than 50 years have elapsed since the existence of a "vicious cycle" of sickling and erythrostasis was reported [Ham and Castle (1940) Trans. Assoc. Am. Physicians 55, 127-132], there still remain significant gaps in understanding of the mechanisms whereby sickle hemoglobin leads to the various manifestations of this disorder. Although the tendency of hemoglobin S to polymerize with reduced oxygen tension is the fundamental abnormality in sickle cell disease, polymerization and sickling itself do not entirely explain the pathophysiology of this disorder. In particular, membrane alterations in the sickle red cell contribute to sickle cell disease. The well-recognized complications of this syndrome such as recurrent and episodic painful crises, ischemic damage to tissues and organs, increased infections, and stroke presumably result from local disturbances in blood flow. The debilitating episodes of sickle cell crisis have been difficult to manage other than with hydration and analgesia.

Web site: http://www.delphion.com/details?pn=US06124262__

- **Compositions for the treatment of blood disorders**

  Inventor(s): Faller; Douglas V. (27 Harding Ave., Braintree, MA 02184), Perrine; Susan P. (27 Harding Ave., Braintree, MA 02184)

  Assignee(s): None Reported

  Patent Number: 6,011,000

  Date filed: June 6, 1995

  Abstract: The invention relates to compositions containing chemical compounds and compositions containing steel factor which stimulate the expression of hemoglobin or globin protein such as embryonic or fetal globin, or the proliferation of hemoglobin expressing and other cells. These compositions can be used to treat or prevent the symptoms associated with anemia, sickle cell diseases, **thalassemia** and other blood disorders. The invention also relates to methods for administering these compositions to patients and to medical aids for the treatment and prevention of blood and other disorders.

  Excerpt(s): The invention relates to compositions useful in the treatment and prevention of blood disorders such as anemia, **thalassemia** and sickle cell disease. Compositions comprise proteins or chemicals that stimulate the specific expression of a globin protein or the proliferation or development of hemoglobin expressing or other myeloid cells. The invention also relates to methods and medical aids which utilize these compositions to ameliorate symptoms associated with blood disorders. Hematopoiesis, or the formation of blood cells, begins in the developing human embryo as clusters of stem cells called blood islands. These cells appear in the yolk sac at about the third week of development and, at about the third month, migrate to the developing liver which becomes the principal site of blood cell formation. Although the spleen, lymph nodes

and bone marrow all make small contributions to blood cell development, not until the fourth month does the bone marrow become the principal site of hematopoiesis. At birth, virtually all blood cells originate from the bone marrow. Although small foci of blood-forming cells sometimes persist in the liver for longer periods of time, hepatic blood cell formation has decreased to a trickle. At this time, all of the marrow is actively forming blood cells and continues to do so until after puberty when, at about 18 years of age, the principal sites of blood cell formation become the marrow of the vertebrae, ribs, sternum, skull, pelvis and the proximal epiphyseal regions of the femur and humerus. These areas represent only about half of the available marrow. The cavities which remain are filled with yellow-fatty tissues. In the adult, hematopoiesis involves the bone marrow, the lymph nodes and the spleen. These organs and associated tissues are traditionally divided into myeloid and lymphoid tissue-types. Myeloid tissues and the cells derived from the myeloid tissue include the erythrocytes, platelets, granulocytes and monocytes. Lymphoid and lymphoid-derived tissues include the thymus, lymph nodes and spleen. The myeloid/lymphoid division is somewhat artificial as these two types of tissues are believed to originate from a single pluripotent stem cell.

Web site: http://www.delphion.com/details?pn=US06011000__

- **Cyclic tetrapeptide compound and use thereof**

  Inventor(s): Hino; Motohiro (Tsuchiura, JP), Mori; Hiroaki (Suita, JP), Sakamoto; Kazutoshi (Tsuchiura, JP), Takase; Shigehiro (Ishioka, JP), Tsurumi; Yasuhisa (Tsukuba, JP)

  Assignee(s): Fujisawa Pharmaceutical Co., Ltd. (Osaka, JP)

  Patent Number: 6,656,905

  Date filed: May 4, 2001

  Abstract: A cyclic tetrapeptide compound and use thereof. Especially, a compound WF27082, a process for production of the compound by culturing, in a nutrient medium, a WF27082-producing strain belonging to Acremonium and recovering the compound from a culture broth, a pharmaceutical composition containing the compound as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient, the compound for use as a medicament, a use of the compound for manufacture of a medicament for inhibiting histone deacetylase, a use of the compound for manufacture of a medicament for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous **thalassemia,** fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), protozoal infections, organ transplant rejections, autoimmune diseases, or tumors, a use of histone deacetylase inhibitors as an immunosuppressant or an antitumor agent, and a use of histone deacetylase inhibitors for manufacture of a medicament for treating or preventing organ transplant rejections, autoimmune diseases or tumors are described.

  Excerpt(s): The present invention relates to a cyclic tetrapeptide compound which is useful as a medicament, to a process for producing the same and to a pharmaceutical composition comprising the same. Histone deacetylases are known to play an essential role in the transcriptional machinery for regulating gene expression, and histone deacetylase inhibitors induce histone hyperacetylation and affect the gene expression. Therefore, a histone deacetylase inhibitor is useful as a therapeutical or prophylactic agent for several diseases caused by abnormal gene expression, such as inflammatory disorders, diabetes, diabetic complications, homozygous **thalassemia,** fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), protozoal infection, or the like. In this connection,

a cyclic tetrapeptide compound that can be used as an anti-tumor agent is disclosed in JP-A-7-196686 but this publication is silent on the action against histone deacetylases and the effect against the above-mentioned various diseases.

Web site: http://www.delphion.com/details?pn=US06656905__

- **Detection of human.alpha.-thalassemia mutations and their use as predictors of blood-related disorders**

  Inventor(s): Bowie; Lemuel J. (Evanston, IL)

  Assignee(s): Evanston Hospital Corporation (Evanston, IL)

  Patent Number: 5,750,345

  Date filed: October 31, 1995

  Abstract: The invention is based on the discovery that adults having a genotype comprising a hemoglobin.alpha.-gene deletion are significantly more likely to be hypertensive than adults having a normal (.alpha.alpha./.alpha.alpha.) gentoype. The invention provides an improved method for determining a human subject's genotype at the.alpha.-gene loci; a method of screening a human subject for an increased potential of developing hypertension and other blood-related disorders; and provides an apparatus/kit for screening a human subject for a risk of developing hypertension and other blood-related disorders.

  Excerpt(s): The present invention relates in general to a method and to a kit of materials for performing assays for blood-related disorders, and more particularly to a method and kit for predicting whether a human subject has a mild.alpha.-thalassemia genotype, and whether a human subject will develop hypertension. The modern development of molecular biological techniques has permitted investigation into the genetic abnormalities that cause, or correlate with, specific human disease states and conditions. For example, restriction fragment length polymorphism (RFLP) analysis facilitates the identification of genetic defects which cause or are correlated with disease states, and facilitates the identification of individuals possessing the genetic defects. RFLP procedures involve digesting DNA with one or more restriction enzymes and analyzing the restriction fragments using, e.g., Southern blot hybridizations employing selected gene probes. See Alberts et al., Molecular Biology of the Cell, Second Edition, New York: Garland Publishing (1989), pp. 270-71. The polymerase chain reaction (PCR) and its many variations are particularly useful tools for investigation into genetic abnormalities that underlie disease states and conditions. (See, e.g., Erlich et al., Current Communications in Molecular Biology: Polymerase Chain Reaction, Cold Spring Harbor: Cold Spring Harbor Press (1989); Innis et al., PCR Protocols: A Guide to Methods and Applications. San Diego: Academic Press (1990).) PCR is used to amplify a DNA or one or more portions thereof that are of particular interest, to facilitate further characterization of the amplified portion. Such further characterization includes gel electrophoresis to determine size, nucleotide sequencing, hybridization studies using particular probes, and the like. See generally, Sambrook et al., Molecular Cloning--A Laboratory Manual, Second Edition, Cold Spring Harbor: Cold Spring Harbor Press (1989).

  Web site: http://www.delphion.com/details?pn=US05750345__

- **Formulation for treating thalassemia and a process for preparing the same**

  Inventor(s): Ghansham; Dass (Delhi, IN), Harsh; Priyadarshi (Allahabad, IN), Kumar; Sarkar Ajit (New Delhi, IN), Rattan; Khanna Sushil (Delhi, IN), Sudarshan; Kumar (New Delhi, IN)

  Assignee(s): Council of Scientific and Industrial Research (New Delhi, IN)

  Patent Number: 5,665,392

  Date filed: July 11, 1995

  Abstract: A pharmaceutical formulation useful for treating patients suffering from **thalassemia,** which comprises powder of Anemonin Pretensis in an amount in the range of 0.02 to 0.12 wt % of the formulation, quinine sulphate in an amount in the range of 0.0005 to 0.003 wt % of the formulation, distilled or demineralised water in an amount in the range of 0 to 40 wt % of the formulation and, ethanol in an amount in the range of 99.88 to 60 wt % of the formulation; and a process for preparing the formulation by mixing the above ingredients.

  Excerpt(s): This invention relates to a formulation for iron-chelation. The formulation of the present invention is useful for treating patients suffering from the disease of **Thalassemia.** This invention relates particularly to a formulation having increased therapeutic efficacy useful for the treatment of patients suffering from the disease of **Thalassemia.** Thalassemia is a dreaded disease among children. The disease is caused due to hereditary disorders connected with defective hemoglobin synthesis, characterised by hypochromia, microcytosis, haemolysis and a variable degree of anaemia. **Thalassemia** involves a heterogeneous group of molecular defects with a wide spectrum of clinical expressions.

  Web site: http://www.delphion.com/details?pn=US05665392__

- **Gallium complexes for the treatment of free radical-induced diseases**

  Inventor(s): Berenshtein; Edward (Jerusalem, IL), Chevion; Mordechai (Jerusalem, IL)

  Assignee(s): Yissum Research Development Company of the Hebrew University of Jerusalem (Jerusalem, IL)

  Patent Number: 5,618,838

  Date filed: February 29, 1996

  Abstract: A pharmaceutical composition comprises a gallium complex of desferrioxamine r penicillamine as active ingredients therein, in combination with a pharmacologically acceptable carrier. The gallium desferrioxamine or gallium penicillamine complex are useful in the treatment of free radical-induced pathological conditions; the treatment of injury resulting from ischemic insult to the heart, brain or kidney; the treatment of **thalassemia;** the treatment of hemochromatosis; the treatment of Wilson's disease; the treatment of paraquat toxicity; or for exchanging gallium for iron.

  Excerpt(s): This application is a 371 of PCT/US 94/06878 filed Jun. 17, 1994. The present invention relates to a pharmaceutical composition containing a gallium complex (Ga) as active ingredient therein, or a combination of Ga complex with zinc (Zn) and/or manganese (Mn) complexes, therein. More particularly, the present invention relates to pharmaceutical preparations which are effective against iron-mediated and copper-mediated damage, said preparations being based on Gallium complexes with

desferrioxamine B (desferrioxamine=DFO) or with penicillamine and preparations based on combinations of Ga, Zn and Mn complexes with DFO or with penicillamine.

Web site: http://www.delphion.com/details?pn=US05618838__

- **Hematological parameter**

  Inventor(s): Telmissani; Omar A. (Dahram, SA)

  Assignee(s): EMT & Associates, Inc. (New York, NY)

  Patent Number: 6,030,838

  Date filed: September 24, 1998

  Abstract: A new hematological parameter, namely mean hemoglobin density in one liter of blood (MDHL), is based on the new index of mean cell density of hemoglobin, MCHD, or more particularly, MDHL is provided as an advantageous screening parameter to distinguish between Iron Deficiency Anemia (IDA) and **Thalassemia** Trait TT. The MDHL parameter showed superior sensitivity, specificity, predictive value and efficacy of as high as 100%. The new screening test also entails significantly lower costs involving the evaluation of patients with hypochromic microcytosis.

  Excerpt(s): The invention is related to a novel screening parameter for hypochromic microcytosis, or more particularly a parameter based on a new red blood cell index for distinguishing between an iron deficiency anemia and a **Thalassemia** Trait. Within this application several publications are referenced by Arabic numerals within parentheses. Full citations for these references may be found at the end of the specification immediately preceding the claims. The disclosures of these publications in their entirety are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. Iron deficiency anemia (IDA) and **Thalassemia** Trait (TT) are the common causes of hypochromic microcytosis. Differentiation between these diseases is based on the measurement of serum iron, total iron binding capacity and/or the serum ferritin for IDA; and when the iron status is normal, estimation of Hb fractions, by electrophoresis for example, is required for TT. However, these procedures are complicated and expensive, especially when, in addition, alpha (.alpha.) **Thalassemia** Trait (.alpha.-thal) is considered. In some cases, it may require globin chain synthesis rate determination or even.alpha. globin gene analysis.

  Web site: http://www.delphion.com/details?pn=US06030838__

- **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__

- **Inducers of gamma globin gene expression and screening assays therefor**

  Inventor(s): Caron; Connie (Westborough, MA), Voss; Jeffrey W. (West Boylston, MA)

  Assignee(s): Basf Aktiengesellschaft (DE)

  Patent Number: 5,700,640

  Date filed: September 16, 1994

  Abstract: Methods for stimulating gamma globin gene expression in a mammalian cell comprising contacting the cell with a compound selected from valeric acid and certain isomers, derivatives or salts thereof, including isovaleric acid, 4-pentynoic acid and methylthioacetic acid, or an inhibitor of a short chain fatty acyl CoA dehydrogenase, or an activator of protein kinase C are disclosed. The methods of the invention are particularly useful for ameliorating.beta.-globin disorders, such as sickle cell anemia or.beta.-thalassemia. The method of the invention can also be used to prevent or ameliorate malaria in a mammal. The compounds of the invention can also be used to stimulate differentiation of a cell. Pharmaceutical compositions of the active compounds of the invention are also disclosed. Screening assays for identifying agents that stimulate gamma globin gene expression in an erythroid cell, stimulate cell differentiation or stimulate transport of a short chain fatty acid, or derivative or salt thereof, into cells are also disclosed.

  Excerpt(s): Human.beta.-like globin genes are encoded in a cluster located on chromosome 11. This cluster includes two genes encoding gamma, or fetal, globin (.gamma.sup.G and.gamma.sup.A) and one gene encoding beta, or adult globin. Expression of globin genes is tightly regulated during ontogeny. A developmental switch from production of predominantly fetal hemoglobin (HbF;.alpha.sub.2.gamma.2) to production of adult hemoglobin (HbA;.alpha.sub.2.gamma.2) occurs beginning at about 28 to 34 weeks of gestation and continuing shortly after birth until HbA becomes predominant. This switch results primarily from decreased transcription of the gamma globin genes and increased transcription of the beta globin gene. The basis for many congenital hematological diseases is a defect in the structure or production of beta globin. For example, sickle cell anemia results from a point mutation in the beta globin structural gene, leading to production of abnormal HbS.beta.-thalassemias result from a partial or complete defect in the expression of the beta globin gene, leading to deficient or absent HbA. Certain populations of adult patients with beta chain abnormalities have higher than normal levels of HbF and have been observed to have a milder clinical course of disease than patients with normal adult levels of HbF. For example, a group of

Saudi Arabian sickle cell anemia patients who express 20-30% HbF have only mild clinical manifestations of the disease (Pembrey, M. E. et al. (1978) Br. J. Haematol. 40:415; Miller, B. A. et al. (1986) Blood 67:1404). There are also a variety of distinct genetic mutations which cause hereditary persistence of fetal hemoglobin, in which gamma globin gene expression is not downregulated during development. This condition has been shown to significantly decrease the severity of sickle cell anemia or.beta.-thalassemia in individuals simultaneously afflicted with both traits (see e.g., Wood, W. G. and Weatherall, D. J. (1983) Biochem. J. 215:1-10). Genetic mutations leading to persistence of gamma globin gene expression have been assigned to at least three distinct loci, making it very unlikely that the ameliorating effect observed in individuals afflicted with both traits is due to a genetically linked trait unrelated to, but co-segregating with, hereditary persistence of fetal hemoglobin. The beneficial effect of gamma globin gene expression as compensation for a defect in beta globin expression or structure has also been studied biochemically. Gamma globin has been shown to function as a chain terminator of the polymerization of deoxygenated Hb S that causes the pathology of sickle cell anemia (Poillon, W. N. et al. (1993) Proc. Natl. Acad. Sci. USA 90:5039-5043). Moreover, the maturation of malarial parasites is inhibited in erythrocytes that express fetal hemoglobin (Pasvol, G. et al. (1976) Lancet 1(7972):1269-1272; Luzzatto, L. et al. (1976) Lancet 1(7984):523-524; Cao, A. et al. (1977) Lancet 1(8004):202). Thus, there is both genetic and biochemical evidence that gamma globin gene expression can be therapeutically beneficial in a variety of clinical disorders.

Web site: http://www.delphion.com/details?pn=US05700640__

- **L-glutamine therapy for sickle cell diseases and thalassemia**

  Inventor(s): Niihara; Yukaka (Rolling Hills Estates, CA), Tanaka; Kouichi R. (Rancho Palos Verdes, CA), Zerez; Charles R. (Culver City, CA)

  Assignee(s): Harbor-UCLA Research and Education Institute (Torrance, CA)

  Patent Number: 5,693,671

  Date filed: May 1, 1996

  Abstract: A method and kit for treating patients suffering from sickle cell disease and **thalassemia.** The method includes regularly administering a safe and pharmacologically effective amount of L-glutamine based compound to a patient to reduce pain, requirement for pain killers, and increase energy and activity levels.

  Excerpt(s): This invention relates to treatments and therapies for anemia conditions and diseases of the blood, and more particular is a therapy for sickle cell diseases and **thalassemia** by administration of L-glutamine and L-glutamine based compounds. Sickle cell diseases and **thalassemia** are some of the most common and devastating hereditary disorders of the blood. Sickle cell disease include diseases which cause sickling of the red blood cells, and includes sickle cell anemia (which results from two hemoglobin S genes), sickle.beta.-thalassemia (one hemoglobin S and one.beta.-thalassemia gene), and hemoglobin SC disease (one hemoglobin S and one hemoglobin C), and the somewhat rare disease hemoglobin C Harlem. **Thalassemia** includes.alpha.-thalassemia and.beta.-thalassemia. These hereditary diseases have significant morbidity and mortality and affect individuals of African American heritage, as well as those of Mediterranean, Middle Eastern, and South East Asian descent.beta.-thalassemia (also known as **Cooley's anemia,** erythroblastic anemia, **hereditary leptocytosis** and Mediterranean disease) in particular affects Eastern descent. These diseases commonly cause severe pain in sufferers in part due to ischemia caused by the damaged red blood

cells blocking free flow through the circulatory system. No safe and effective therapies for these diseases are available. In the past several years, hydroxyurea has been used in an increasing number of sickle cell anemia patients. However, hydroxyurea is a chemotherapeutic agent with myleosuppressive effects and its long term safety is still unknown. An ideal agent would be one that is readily available, affordable, effective and safe even with chronic use.

Web site: http://www.delphion.com/details?pn=US05693671__

- **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 and compounds for curing diseases caused by mutations**

  Inventor(s): Cole-Strauss; Allyson (Philadelphia, PA), Kmiec; Eric B. (Malvern, PA), Yoon; Kyonggeun (Berwyn, PA)

  Assignee(s): Thomas Jefferson University (Philadelphia, PA)

  Patent Number: 5,760,012

  Date filed: May 1, 1996

  Abstract: The invention concerns the use of duplex oligonucleotides having both 2'-deoxyribonucleotides and ribonucleotides, wherein there is base pairing between the two types of nucleotides. The sequence of the oligonucleotide is selected so that the 3' and 5' most regions of the oligonucleotide are homologous with (identical to) the sequence of a preselected target gene of a cell. The two regions of homology embrace a region that is heterologous with the target sequence. The introduction of the oligonucleotide into the nucleus of the cell causes the alteration of the target gene such that the sequence of the altered target gene is the sequence of the heterologous region. Consequently, the oligonucleotides of the invention are termed Chimeric Repair Vectors (CRV). In one embodiment of the invention the target gene is a globin gene and the target cell is a hematopoietic stem cell. This embodiment can be used to correct certain hemoglobinopathies such as Sickle Cell Disease,.beta.-thalassemia, and also Gaucher Disease. The rate of correction of the globin gene is high enough so that no selection of the treated hematopoietic stem cells is required to obtain a therapeutically significant effect. In one embodiment the ribose moieties of the nucleotides of the CRV contain methylated 2'-oxygens.

  Excerpt(s): The field of the invention concerns cures for diseases caused by mutations that result abnormal levels of or products of the mutated gene in hematopoietic cells or any other cell-type that can be removed from a subject, cultured and reimplanted. The cure is effected by pairing the mutated gene of the subject by homologous recombination between the mutated gene and a chimeric repair vector (CRV), which is an nucleic acid having both deoxyribonucleotides and ribonucleotides. More particularly, the field concerns the repair of the mutations that cause Sickle Cell Disease,.beta.-thalassemia and Gaucher Disease. There are over 500 known structural variants of hemoglobin. Most persons having a variant hemoglobin are asymptomatic or only mildly affected. Three common variants are associated with significant disease. Two, HbS (Sickle Hemoglobin) and HbC, are point mutations in the codon encoding Glu.sup.6 of.beta.-globin and are found in Africans and their descendants. HbC results from the substitution G.fwdarw.A in the first position of codon 6 and HbS results from the substitution A.fwdarw.T in the second position of codon 6, producing Lys.sup.6 and Val.sup.6 respectively. The third common structural variant of hemoglobin associated with disease, HbE, results from the substitution G.fwdarw.A in the first position of codon 26, encoding Glu.sup.26 resulting in a Lys.sup.26 and is found primarily in the Southeast Asian population and their descendants. Persons heterozygous for HbS, HbC

or HbE do not have significant symptoms. However, HbS homozygotes, HbS/HbC heterozygotes, and heterozygotes for HbC or HbE and an allele of.beta.-thalassemia are severely effected and require frequent medical attention.

Web site: http://www.delphion.com/details?pn=US05760012__

- **Methods for in vivo reduction of iron levels and compositions useful therefor**

  Inventor(s): Lai; Ching-San (Encinitas, CA)

  Assignee(s): Medinox, Inc. (San Diego, CA)

  Patent Number: 5,922,761

  Date filed: September 6, 1996

  Abstract: In accordance with the present invention, there are provided methods for the in vivo reduction of free iron ion levels in a mammalian subject. The present invention employs a scavenging approach whereby free iron ions are bound in vivo to a suitable physiologically compatible scavenger. The resulting complex renders the free iron ions harmless, and is eventually excreted in the urine of the host. Further in accordance with the present invention, there are provided compositions and formulations useful for carrying out the above-described methods. An exemplary scavenger contemplated for use in the practice of the present invention is a dithiocarbamate-containing composition. This material binds to free iron ions, forming a stable, water-soluble dithiocarbamate-iron complex. The present invention relates to methods for reducing in vivo levels of free iron ions as a means of treating subjects afflicted with iron overload and non-iron overload diseases and/or conditions, such as **thalassemia,** anemia hereditary hemochromatosis, hemodialysis, stroke and rheumatoid arthritis. Dithiocarbamate-containing scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo forming a stable dithiocarbamate-metal complex, which is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject, thereby reducing in vivo levels of free iron ions.

  Excerpt(s): The present invention relates to methods for reducing iron levels in mammals. In a particular aspect, the present invention relates to methods for reducing free iron ion levels in mammals by administration of dithiocarbamates as scavengers of free iron ions in hosts undergoing anthracycline chemotherapy, as well as hosts suffering from iron overload or non-iron overload diseases and/or conditions, such as **thalassemia,** anemia, hereditary hemochromatosis, hemodialysis, stroke and rheumatoid arthritis. In a further aspect, the present invention relates to compositions and formulations useful in the methods disclosed herein. Iron is crucial for maintaining normal structure and function of virtually all mammalian cells (see, for example, Voest et al., in Ann. Intern. Med. 120:490-499 (1994) and Kontoghiorghes, G. J., in Toxicol. Letters 80:1-18 (1995)) Adult humans contain 3-5 g of iron, mainly in the form of hemoglobin (58%), ferritin/hemosiderin (30%),. myoglobin (9%) and other heme or nonheme enzyme proteins (Harrison and Hoare, in Metals in Biochemistry, Chapman and Hall, New York, 1980). Total iron levels in the body are regulated mainly through absorption from the intestine and the erythropoietic activity of the bone marrow. Upon absorption, iron is transported to various tissues and organs by the serum protein transferrin. Once transported to the target tissue or organ, iron is transported and stored intracellularly in the form of ferritin/hemosiderin. Under normal conditions, transferrin is about 30% saturated with iron in healthy individuals, and an equilibrium is maintained between the sites of iron absorption, storage and utilization. The presence of

these homeostatic controls ensures the maintenance of physiological levels of not only iron, but also other essential metal ions such as copper, zinc and cobalt.

Web site: http://www.delphion.com/details?pn=US05922761__

- **Pharmaceutical compositions and methods using isobutyramide for treating betaglobin disorders**

  Inventor(s): Perrine; Susan P. (Richmond, CA)

  Assignee(s): Children's Hospital Medical Center of Northern California (Oakland, CA)

  Patent Number: 5,439,939

  Date filed: March 17, 1992

  Abstract: This invention relates to treatment of betaglobin disorders, such as sickle-cell anemia and beta-thalassemia, by administering compositions of isobutyramide.

  Excerpt(s): Betaglobin is a polypeptide subunit of hemoglobin A, the principal hemoglobin in adult humans. Hemoglobin A is the principal oxygen carrier in blood. Hemoglobin A is made up of four subunits, two alphaglobin chains and two betaglobin chains. Several diseases are characterized by the production of abnormal betaglobin and impaired hemoglobin S, as in sickle-cell anemia, or from the production of no or deficient amounts of betaglobin and hemoglobin A, as in beta-thalassemia. These diseases have long been recognized to arise from genetic defects, such as a single mutation in the betaglobin gene in sickle-cell anemia. There is no pharmaceutical composition or method in use for the effective treatment of betaglobin disorders. This invention is directed to pharmaceutical compositions and methods employing isobutyramide for treating disorders arising from betaglobin deficiencies. This invention relates to use of isobutyramide to treat these disorders by stimulating production of fetal hemoglobin, hemoglobin F.

  Web site: http://www.delphion.com/details?pn=US05439939__

- **Pulsed administration of compositions for the treatment of blood disorders**

  Inventor(s): Perrine; Susan P. (27 Harding Ave., Braintree, MA 02184)

  Assignee(s): None Reported

  Patent Number: 5,939,456

  Date filed: July 26, 1996

  Abstract: The invention relates to novel compositions and to methods for the pulsed administration of compositions to a patient or to cells in vitro for the treatment of human blood disorders. Compositions contain chemical compounds that stimulate the expression of fetal hemoglobin and/or stimulate the proliferation of red blood cells, white blood cells and platelets in patients and ex vivo for reconstitution of hematopoiesis in vivo. These methods are useful to treat or prevent the symptoms associated with anemia, sickle cell disease, **thalassemia** and other blood disorders. The invention also relates to methods for the pulsed administration of compositions to patients for the treatment and prevention of cell proliferative disorders including deficiencies such as cytopenia and malignancies such as viral-induced tumors, other forms of neoplasia and for expansion of cells for hematopoietic transplantation. Pulsed

administration has been shown to be more effective than continuous therapy in patients tested.

Excerpt(s): The invention relates to methods for the treatment and prevention of blood disorders such as anemia, neutropenia, thrombocytopenia, **thalassemia** and sickle cell disease. These methods comprise the administration of compositions that stimulate the expression of a globin protein and, in particular, fetal hemoglobin, or the proliferation or development of hemoglobin expressing, myeloid cells or megakaryocytic cells. The major function of red blood cells is to transport oxygen to tissues of the body. Minor functions include the transportation of nutrients, intercellular messages and cytokines, and the absorption of cellular metabolites. Anemia, or a loss of red blood cells or red blood cell capacity, can be grossly defined as a reduction in the ability of blood to transport oxygen. Anemia can be measured by determining a patient's red blood cell mass or hematocrit. Hematocrit values are indirect, but fairly accurate measures of the total hemoglobin concentration of a blood sample. Anemia, as measured by a reduced hematocrit, may be chronic or acute. Chronic anemia may be caused by extrinsic red blood cell abnormalities, intrinsic abnormalities or impaired production of red blood cells. Extrinsic or extra-corpuscular abnormalities include antibody-mediated disorders such as transfusion reactions and erythroblastosis, mechanical trauma to red cells such as micro-angiopathic hemolytic anemias, thrombotic thrombocytopenic purpura and disseminated intravascular coagulation. In addition, infections by parasites such as Plasmodium, chemical injuries from, for example, lead poisoning, and sequestration in the mononuclear system such as by hypersplenism can result in red blood cell disorders and deficiencies. Impaired red blood cell production can occur by disturbing the proliferation and differentiation of the stem cells or committed cells. Some of the more common diseases of red cell production include aplastic anemia, hypoplastic anemia, pure red cell aplasia and anemia associated with renal failure or endocrine disorders. Disturbances of the proliferation and differentiation of erythroblasts include defects in DNA synthesis such as impaired utilization of vitamin B.sub.12 or folic acid and the megaloblastic anemias, defects in heme or globin synthesis, and anemias of unknown origins such as sideroblastic anemia, anemia associated with chronic infections such as malaria, trypanosomiasis, HIV, hepatitis virus or other viruses, and myelophthisic anemias caused by marrow deficiencies.

Web site: http://www.delphion.com/details?pn=US05939456__

- **Screening test for beta-thalassemia trait and a diagnostic kit for its individualization**

  Inventor(s): De Matteis; Maria C. (Piazza Isotta Nogarola, 15 - 37131 Verona, IT)

  Assignee(s): None Reported

  Patent Number: 4,604,350

  Date filed: April 15, 1983

  Abstract: A screening test for beta-thalassemia trait carriers is carried out by mixing 10.mu.l of blood of the patient with 2 ml of an aqueous solution prepared from glycerol, sodium chloride, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium azide, Acid Green 5 to obtain a suspension. A well cluster, having several wells is used. The suspension is formed in one well and the turbidity is determined by placing a reading scale under the cluster.

  Excerpt(s): Hemolysis of the erythrocytes by glycerol has been studied by many authors, among whom: M. H. Jacobs, et al, J. Exper. Zool. 113, 272, (1950); J. Kroes, et al, Biochim.

Biophys. Acta 249, 647, (1971); T. J. Moore, J. Lipid Res. 9, 642 (1968); J. De Gier, et al, Biochim. Biophis, Acta 49, 286 (1961) and Experientia 22, 20 (1966); J. M. C. Wessels, et al, Biochim. Biophys. Acta 291, 178-196 (1973). E. L. Gottfried and N. A. Robertson, Blood 40, 940 (1972), J. Lab. Clin. Med. 83, 323-333 (1974) and 84, 746-751, describe methods for screening erythrocyte abnormalities like the **thalassemia** trait carriers, iron deficiency anemia, hereditary spherocytosis, sickle-cell anemia, based on the lysis time of the erythrocytes suspended in a 0.3M aqueous buffered solution of glycerol (glycerol lysis test, GLT). The present invention is based on a similar principle bar is far more reliable and simpler. A. Zanella et al, British Journal of Haematology, 45, 481-6 (1980), describes a modification of GLT, named Acidified Glycerol Lysis Test (AGLT) as a screening test for hereditary spherocytosis. The object of the present invention is to provide a screening test for beta-thalassemia trait carriers with a diagnostic kit for its diagnosis.

Web site: http://www.delphion.com/details?pn=US04604350__

- **Simple, rapid and reliable method for detecting thalassemia**

  Inventor(s): Huang; Shu-Zhen (Shanghai, CN), Rodgers; Griffin P. (Silver Spring, MD), Schechter; Alan N. (Bethesda, MD)

  Assignee(s): The United States of America AS Represented by the Department of Health (Washington, DC)

  Patent Number: 5,281,519

  Date filed: October 23, 1992

  Abstract: A simple, rapid and reliable method for diagnosis of **thalassemia** is described. The method comprises amplification of the cDNA by polymerase chain reaction and determining the ratio between.alpha. and.beta. hemoglobin chain mRNAs.

  Excerpt(s): The present invention is related generally to diagnostic methodologies. More particularly, the present invention is related to a simple, inexpensive and rapid method for detecting thalassemias and monitoring therapeutic effects on the disease. The thalassemias represent a heterogeneous group of diseases, characterized by the absence or diminished synthesis of one or the other of the globin chains of hemoglobin A. In.alpha.-thalassemia,.alpha.-chain synthesis is decreased or absent; whereas in.beta.-thalassemia,.beta.-chain synthesis is diminished or absent. Numerous molecular defects account for the various thalassemias. The degree of clinical expression is generally dictated by the nature and severity of the underlying globin gene (DNA) defect. **Thalassemia** major (homozygous.beta.-thalassemia) defines the most severe variety of the disease. **Thalassemia** intermedia and **thalassemia** minor refer to the heterozygous state, generally associated with milder clinical manifestations. Beta-thalassemia is an autosomal recessive disorder characterized by absent (.beta.sup.o) or decreased (.beta.sup.+) synthesis of the.beta.-globin chain. **Thalassemia** is found in almost all population and ethnic groups around the world. It has been estimated that 3% of the world's population or 150 million people carry.beta.-thalassemia genes. Indeed, it is among the most common genetic diseases in the world. Alpha **thalassemia,** the corresponding disorder of.alpha. hemoglobin chain is also of great prevalence, especially in the Orient.

  Web site: http://www.delphion.com/details?pn=US05281519__

- **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 Thalassemia

As of December 2000, U.S. patent applications are open to public viewing.[9] 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 thalassemia:

[9] This has been a common practice outside the United States prior to December 2000.

- **Compositions and administration of compositions for the treatment of blood disorders**

  Inventor(s): Perrine, Susan P.; (Weston, MA)

  Correspondence: Nixon Peabody Llp; Attention: David Resnick; 101 Federal Street; Boston; MA; 02110; US

  Patent Application Number: 20010027215

  Date filed: April 30, 2001

  Abstract: The invention relates to novel compositions and to methods for the pulsed administration of compositions to a patient or to cells in vitro for the treatment of human blood disorders. Compositions contain chemical compounds that stimulate the expression of fetal hemoglobin and/or stimulate the proliferation of red blood cells, white blood cells and platelets in patients and ex vivo for reconstitution of hematopoiesis in vivo. These methods are useful to treat or prevent the symptoms associated with anemia, sickle cell disease, **thalassemia,** blood loss, and other blood disorders. The invention also relates to methods for the pulsed administration of compositions to patients for the treatment and prevention of cell proliferative disorders including deficiencies such as cytopenia and malignancies and for expansion of cells for hematopoietic transplantation. Pulsed administration has been shown to be more effective than continuous therapy in patients tested.

  Excerpt(s): The invention relates to composition methods for the treatment and prevention of blood disorders such as anemia, neutropenia, thrombocytopenia, **thalassemia** and sickle cell disease using such compositions. The compositions include C.sub.1-C.sub.4 substituted and/or phenyl substituted carboylic acids such as dimethyl substitutions onto carboxylic acids. The methods comprise the administration of compositions that stimulate the expression of a globin protein and, in particular, fetal hemoglobin, or the proliferation or development of hemoglobin expressing, myeloid cells or megakaryocytic cells. The major function of red blood cells is to transport oxygen to tissues of the body. Minor functions include the transportation of nutrients, intercellular messages and cytoldnes, and the absorption of cellular metabolites. Anemia, or a loss of red blood cells or red blood cell capacity, can be grossly defined as a reduction in the ability of blood to transport oxygen. Anemia can be measured by determining a patient's red blood cell mass or hematocrit. Hematocrit values are indirect, but fairly accurate measures of the total hemoglobin concentration of a blood sample. Anemia, as measured by a reduced hematocrit, may be chronic or acute. Chronic anemia may be caused by extrinsic red blood cell abnormalities, intrinsic abnormalities or impaired production of red blood cells. Extrinsic or extra-corpuscular abnormalities include antibody-mediated disorders such as transfusion reactions and erythroblastosis, mechanical trauma to red cells such as micro-angiopathic hemolytic anemias, thrombotic thrombocytopenic purpura and disseminated intravascular coagulation. In addition, infections by parasites such as Plasmodium, chemical injuries from, for example, lead poisoning, and sequestration in the mononuclear system such as by hypersplenism can result in red blood cell disorders and deficiencies. Impaired red blood cell production can occur by disturbing the proliferation and differentiation of the stem cells or committed cells. Some of the more common diseases of red cell production include aplastic anemia, hypoplastic anemia, pure red cell aplasia and anemia associated with renal failure or endocrine disorders. Disturbances of the proliferation and differentiation of erythroblasts include defects in DNA synthesis such as impaired utilization of vitamin B.sub.12 or folic acid and the megaloblastic anemias, defects in heme or globin synthesis, and anemias of unknown origins such as sideroblastic anemia,

anemia associated with chronic infections such as malaria, trypanosomiasis, HIV, hepatitis virus or other viruses, and myelophthisic anemias caused by marrow deficiencies.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Medium and low density gene chips**

Inventor(s): Bangce, Ye; (Shanghai, CN)

Correspondence: Patrea L. Pabst; Holland & Knight Llp; Suite 2000, One Atlantic Center; 1201 West Peachtree Street, N.E.; Atlanta; GA; 30309-3400; US

Patent Application Number: 20030186230

Date filed: July 23, 2001

Abstract: This invention makes public a kind of DNA chip for diagnosing the mutation of the hereditary anemia related genes with the character of fixed specific NA probes for testing the mutation of hereditary anemia related gent on the glass slide, silica plate, membrane and macromolecular materials. In comparison with current techniques, in this invention a 70.times.4 DNA probe is fixed on the surface of a carrier the size of a microscope slide, and this probe can detect hereditary anemia such as.alpha.-, or.beta.-thalassemia, and hemoglobin abnormality caused by related gent mutation. The invention has the statistic characteristics of parallel analysis and multiple analysis. Under the specific elution conditions, the completely matched and single-base-non-matched hybridization can be distinguished. Consequently, this DNA chip is appropriate for early diagnosis and prenatal screening of hereditary anemia.

Excerpt(s): This invention is a kind of DNA chip for diagnosing the mutation of the hereditary anemia related genes. China is a big country where a large part of the population is afflicted with the hereditary disease. The hereditary disease is a kind of disease caused by the modification of the genetic materials in human germ cells or fertilized ova and transferred from parental generation to progeny, and usually include 3 big groups: monogenic hereditary disease, chromosome hereditary disease and polygenic hereditary disease. Considering the whole world, at least 2% of newborns are afflicted with evident congenital abnormality. Though the incidence of most hereditary diseases (except polygenic hereditary disease) is low, there are a great variety of hereditary diseases. There are more than 4000 monogenic hereditary diseases, more than 100 chromosome hereditary diseases, and no less than 100 polygenic diseases. Moreover, on the average more than 100 new monogenic hereditary diseases have been being found per years in the world, which reflects the severity of the problems hereditary diseases have brought to medicine, society and families. For most of the hereditary diseases, there is no effective treatment at present, and hence the prevention seems particularly important. If fetuses can be diagnosed to determine whether they are afflicted with hereditary diseases, artificial abortion can be conducted on ill fetuses to prevent their coming into the world. Prenatal genetic screening supplemented with artificial abortion has been approved to be an effective method for preventing hereditary diseases that seriously harm health. Presently there are about 50,000,000 disabled persons in our country, a considerable number of which are caused by hereditary diseases. Because the rate of consanguineous marriage is high in remote regions and some rural areas, the incidence of hereditary diseases still tends to increase. Therefore, widely implementing prenatal genetic screening to eliminate the birth of congenitally defected infants and lower disease incidence plays an important role in ensuring eugenically superior birth and rearing, and improving population quality.

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

- **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

- **Use for deferiprone**

  Inventor(s): Piga, Antonio; (Moncalieri, IT), Spino, Michael; (Pickering, CA)

  Correspondence: Ivor M. Hughes, Barrister & Solicitor,; Patent & Trademark Agents; 175 Commerce Valley Drive West; Suite 200; Thornhill; ON; L3t 7p6; CA

  Patent Application Number: 20030158234

  Date filed: April 4, 2003

  Abstract: A method of treating iron induced cardiac disease in a patient with iron overload, such as in **thalassemia** or the like comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

  Excerpt(s): The invention relates to the use of deferiprone for the prevention/stabilization/reduction of the risk of heart disease, such as heart failure, in patients having an iron overload condition such as is found in those suffering from for example, **thalassemia,** hemochromatosis, and myelodysplasia, and corresponding methods of treatment involving deferiprone therefor. Although reference is made in the following discussion to **thalassemia** specifically, the invention is not intended to be interpreted as limited only to the treatment thereof. Any chronic iron overload condition would benefit from treatment by utilizing the method described herein as well as the other aspects of the invention. For example, those suffering from hemochromatosis and transfused sickle cell anemia would also benefit. Thalassemia, among other afflictions, must be treated by regular transfusions of red blood cells in order to extend the life of the patient. However, transfusions create a widespread iron overload in the patient. Iron overload is dangerous since the excessive iron can cause toxic degenerative changes in the heart, liver and endocrine organs.

  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 thalassemia, 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 "thalassemia" (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 thalassemia.

You can also use this procedure to view pending patent applications concerning thalassemia. 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 6. BOOKS ON THALASSEMIA

Overview

This chapter provides bibliographic book references relating to thalassemia. In addition to online booksellers such as **www.amazon.com** and **www.bn.com**, excellent sources for book titles on thalassemia 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: Federal Agencies

The Combined Health Information Database collects various book abstracts from a variety of healthcare institutions and federal agencies. To access these summaries, go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. You will need to use the "Detailed Search" option. To find book summaries, 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. For the format option, select "Monograph/Book." Now type "thalassemia" (or synonyms) into the "For these words:" box. You should check back periodically with this database which is updated every three months. The following is a typical result when searching for books on thalassemia:

- **Epidemiology -- Serology. III International Conference on Acquired Immunodeficiency Syndrome (AIDS); Washington, D.C., June 1-5, 1987**

  Contact: InfoMedix, 12800 Garden Grove Blvd, Ste F, Garden Grove, CA, 92643, (714) 530-3454.

  Summary: This sound recording of proceedings from the III International Conference on AIDS, held June 1-5, 1987, in Washington, D.C., deals with the epidemiology of the Human immunodeficiency virus (HIV). Detecting HIV antibodies in early stages of the infection, using a variety of tests, is discussed. HIV anti-envelope antibody and how it changes from early HIV infection to later infection and Acquired immunodeficiency syndrome (AIDS) is also described. Case studies of several homosexual and bisexual men who became HIV positive and then seroreverted to HIV negative were also discussed. Correlations between an individual's antibody levels and his prognosis are also discussed. Several studies of this correlation in children, **thalassemia** patients, and homosexuals are described.

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 "thalassemia" at online booksellers' Web sites, you may discover non-medical books that use the generic term "thalassemia" (or a synonym) in their titles. The following is indicative of the results you might find when searching for "thalassemia" (sorted alphabetically by title; follow the hyperlink to view more details at Amazon.com):

- **21st Century Complete Medical Guide to Anemia, Thalassemia, Cooley¿s Anemia, Authoritative CDC, NIH, and FDA Documents, Clinical References, and Practical Information for Patients and Physicians (CD-ROM)** by PM Medical Health News; ISBN: 1592486746; http://www.amazon.com/exec/obidos/ASIN/1592486746/icongroupinterna
- **Advances & Controversies in Thalassemia Therapy: Bone Marrow Transplantation & Other Approaches** by C. Dean Buckner (Editor), et al; ISBN: 047151599X; http://www.amazon.com/exec/obidos/ASIN/047151599X/icongroupinterna
- **Advances and Controversies in Thalassemia Therapy: Bone Marrow Transplantation and Other Approaches: Proceedings of an International Symposium on B** by International Symposium on Bone Marrow Transplantation and Related Pro, et al; ISBN: 0845151592; http://www.amazon.com/exec/obidos/ASIN/0845151592/icongroupinterna
- **BERGSMA IRON METABOLISM AND THALASSEMIA** by D BERGSMA; ISBN: 0471562939; http://www.amazon.com/exec/obidos/ASIN/0471562939/icongroupinterna
- **Cooley's Anemia: Seventh Symposium (Annals of the New York Academy of Sciences, V. 850)** by Alan Cohen (Editor), Mass.) Cooley's Anemia Symposium 1997 Cambridge; ISBN: 1573311219; http://www.amazon.com/exec/obidos/ASIN/1573311219/icongroupinterna
- **Endocrine Disorders in Thalassemia** by S. Ando, et al; ISBN: 3540583904; http://www.amazon.com/exec/obidos/ASIN/3540583904/icongroupinterna
- **Fifth Cooley's Anemia Symposium**; ISBN: 0897662857; http://www.amazon.com/exec/obidos/ASIN/0897662857/icongroupinterna
- **Fifth Cooley's Anemia Symposium (Annals of the New York Academy of Sciences, Vol 445)** by N.Y.)/ Cooley's Anemia Symposium / Bank, Arthur/ Anderson, W. French/ Zaino, Edward C./ New York Academy of Sciences Cooley's Anemia Symposium 1984 New York, Arthur Bank; ISBN: 0897662849; http://www.amazon.com/exec/obidos/ASIN/0897662849/icongroupinterna
- **Fourth Cooley's Anemia Symposium**; ISBN: 0897660765; http://www.amazon.com/exec/obidos/ASIN/0897660765/icongroupinterna
- **Frequencies of Hemoglobin Variants: Thalassemia, the Glucose-6-Phosphate Dehydrogenase Deficiency, G6Pd Variants & Ovalocytosis in Human Populations** by Frank B. Livingstone; ISBN: 0195036344; http://www.amazon.com/exec/obidos/ASIN/0195036344/icongroupinterna

- **Iron metabolism and thalassemia : conference held at Key Biscayne, Florida, November 1975**; ISBN: 0845110063; http://www.amazon.com/exec/obidos/ASIN/0845110063/icongroupinterna
- **Prenatal Diagnosis of Thalassemia and the Hemoglobinopathies** by Dimitris Loukopoulos (Editor); ISBN: 0849359724; http://www.amazon.com/exec/obidos/ASIN/0849359724/icongroupinterna
- **Radiology of Thalassemia** by C. Papavasiliou, et al; ISBN: 0387176888; http://www.amazon.com/exec/obidos/ASIN/0387176888/icongroupinterna
- **Sickle Cell Disease and Thalassemias: New Trends in Therapies** by Y. Beuzard (Editor), et al; ISBN: 2855985781; http://www.amazon.com/exec/obidos/ASIN/2855985781/icongroupinterna
- **Sickle-Cell Anemia and Thalassemia: A Primer for Health Care Professionals** by R.G. Huntsman; ISBN: 0921037007; http://www.amazon.com/exec/obidos/ASIN/0921037007/icongroupinterna
- **Sixth Cooley's Anemia Symposium**; ISBN: 0897666364; http://www.amazon.com/exec/obidos/ASIN/0897666364/icongroupinterna
- **Sixth Cooley's Anemia Symposium (Annals of the New York Academy of Sciences, Vol 612)** by Arthur Bank (Editor); ISBN: 0897666356; http://www.amazon.com/exec/obidos/ASIN/0897666356/icongroupinterna
- **Thalassemia** by John Chirban (Editor); ISBN: 0819156752; http://www.amazon.com/exec/obidos/ASIN/0819156752/icongroupinterna
- **Thalassemia : pathophysiology and management**; ISBN: 0845110675; http://www.amazon.com/exec/obidos/ASIN/0845110675/icongroupinterna
- **Thalassemia : recent advances in detection and treatment : international symposium held June 7-11, 1981 in S. Margherita di Pula, Cagliari Sardinia, Italy**; ISBN: 0845110519; http://www.amazon.com/exec/obidos/ASIN/0845110519/icongroupinterna
- **Thalassemia: Pathophysiology and Management, Part a (Birth Defects: Original Article Series, Vol 23, No 5A, 1987)** by Suthat Fucharoen (Editor), et al; ISBN: 0471606383; http://www.amazon.com/exec/obidos/ASIN/0471606383/icongroupinterna
- **Thalassemia: Pathophysiology and Management, Part B (Birth Defects: Original Article Series, Vol 23 No 5B)** by Suthat Funcharoen (Editor), Rowley; ISBN: 0471610437; http://www.amazon.com/exec/obidos/ASIN/0471610437/icongroupinterna
- **Thalassemia: Recent Advances in Detection and Treatment** by Antonio Cao (Editor), Liss; ISBN: 0471613959; http://www.amazon.com/exec/obidos/ASIN/0471613959/icongroupinterna
- **The molecular genetics of □ga□s-thalassemia : structure and expression of the □ga□s-globin gene cluster** by Cornelis Leonard Harteveld Harteveld; ISBN: 9090111999; http://www.amazon.com/exec/obidos/ASIN/9090111999/icongroupinterna
- **The Thalassemias** by D.J. Weatherall (Editor); ISBN: 0443025657; http://www.amazon.com/exec/obidos/ASIN/0443025657/icongroupinterna

Chapters on Thalassemia

In order to find chapters that specifically relate to thalassemia, an excellent source of abstracts is the Combined Health Information Database. You will need to limit your search to book chapters and thalassemia 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 "thalassemia" (or synonyms) into the "For these words:" box. The following is a typical result when searching for book chapters on thalassemia:

- **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 7. MULTIMEDIA ON THALASSEMIA

Overview

In this chapter, we show you how to keep current on multimedia sources of information on thalassemia. We start with sources that have been summarized by federal agencies, and then show you how to find bibliographic information catalogued by the National Library of Medicine.

Video Recordings

An excellent source of multimedia information on thalassemia is the Combined Health Information Database. You will need to limit your search to "Videorecording" and "thalassemia" using the "Detailed Search" option. Go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find video productions, 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 "Videorecording (videotape, videocassette, etc.)." Type "thalassemia" (or synonyms) into the "For these words:" box. The following is a typical result when searching for video recordings on thalassemia:

- **HGB E, anemia and basic genetics**

  Source: Providence, RI: Providence Ambulatory Health Care Foundation. n.d. 1 videotape.

  Contact: Available from Media Consultants, 18 Stillwater Road, Smithfield, RI 02917. Telephone: (401) 232-0412 / fax: (401) 231-4462. $8.00 plus $2.00 shipping and handling.

  Summary: This videotape provides information on hemoglobin E, anemia, and basic genetics. It is supplemented by three pamphlets: 'Questions about **Thalassemia,**' Questions about Hemoglobin E,' and 'Genetics: The story of genes.' The tapes and pamphlets are available in English, Laotian, and Cambodian. [Funded by the Maternal and Child Health Bureau].

CHAPTER 8. PERIODICALS AND NEWS ON THALASSEMIA

Overview

In this chapter, we suggest a number of news sources and present various periodicals that cover thalassemia.

News Services and Press Releases

One of the simplest ways of tracking press releases on thalassemia 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 "thalassemia" (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 thalassemia. 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 "thalassemia" (or synonyms). The following was recently listed in this archive for thalassemia:

- **ICL670 selectively chelates iron in patients with thalassemia**
  Source: Reuters Industry Breifing
  Date: May 13, 2003
- **Lentivirus-based gene repair feasible as treatment for beta-thalassemia**
  Source: Reuters Medical News
  Date: January 31, 2003

- **Iron overload, HCV infection predict hepatic fibrosis worsening in thalassemia**
  Source: Reuters Medical News
  Date: July 18, 2002
- **Unrelated-donor bone marrow feasible for patients with beta-thalassemia major**
  Source: Reuters Medical News
  Date: July 16, 2002
- **Growth improves in children with thalassemia major following L-carnitine therapy**
  Source: Reuters Industry Breifing
  Date: September 04, 2000
- **Hepatic iron level indicates total body iron stores in patients with thalassemia major**
  Source: Reuters Medical News
  Date: August 04, 2000
- **Antenatal screening for thalassemia risk inadequate in UK**
  Source: Reuters Medical News
  Date: February 04, 2000
- **Expression of human embryonic globins can reverse lethal thalassemias in mice**
  Source: Reuters Medical News
  Date: November 10, 1998
- **Deferiprone not efficacious for treatment of iron overload in thalassemia major patients**
  Source: Reuters Medical News
  Date: August 13, 1998
- **Alpha Thalassemia May Predispose To Natural Malaria "Vaccination"**
  Source: Reuters Medical News
  Date: October 10, 1996
- **Researchers Cautiously Optimistic About New Iron-Chelation Agent For Treatment Of Thalassemia Major**
  Source: Reuters Medical News
  Date: April 06, 1995
- **Cord-Blood Stem Cell Transplantation Successful In Child With Severe Thalassemia**
  Source: Reuters Medical News
  Date: February 15, 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 "thalassemia" (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 "thalassemia" (or synonyms). If you know the name of a company that is relevant to thalassemia, 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 "thalassemia" (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 "thalassemia" (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 thalassemia:

- **Statement of the Alzheimer's Association Regarding a Research Paper on Desferrioxamine (Desferal or DFO)**

  Source: Advocate. Alzheimer's Association of Greater Washington, DC Chapter. [Newsletter] 1, 7. June 1991.

  Contact: Available from Alzheimer's Association of Greater Washington, DC Chapter. 7910 Woodmont Avenue, Suite 1100, Bethesda, MD 20814. (301) 652-6446. PRICE: Call for price information.

  Summary: This article discusses the response of the Alzheimer's Association to a research paper on desferrioxamine (Desferal or DFO). Desferal is a drug that is currently approved only for the treatment of iron intoxication or to remove iron overload following repeated blood transfusions in patients with **thalassemia.** In the current study, the drug was administered only to healthy, younger patients. It is not clear what effect Desferal might have on older patients with Alzheimer's disease and other medical conditions. Because there are significant questions about the design of the research study and the mode of action and potential toxicity of Desferal, further studies are required to decide whether Desferal has any potential for the treatment of Alzheimer's Disease.

- **Genetic Factors in Alzheimer's Disease**

  Source: Global Perspective. [Newsletter] 2(1): 6-7. April 1991.

  Contact: Alzheimer's Disease International. 919 North Michigan Avenue, Suite 1000, Chicago, IL 60611-1676. (800) 272-3900; (312) 335-8882 (TDD); (312) 335-1110 (FAX). PRICE: Call for price information.

  Summary: This newsletter article discusses a genetic theory for Alzheimer's disease, focusing on formal genetics and population genetic studies. Neither epidemiology studies nor small pedigrees support the suggestion that Alzheimer's Disease is inherited. Further, cross-cultural studies of patients from the nineteenth versus the twentieth centuries who lived in Europe or America found no age-related differences in onset of Alzheimer's disease. However, detailed, extensive pedigree studies that have examined at least three generations of affected families indicate that two types of heritable Alzheimer's disease may exist: an early onset, dominant form of the disease, and a late onset, sporadic form also referred to as senile dementia of the Alzheimer type (SDAT). When data from a large pedigree study of more than 6,000 members of a family with a pattern of early onset Alzheimer's disease were adjusted for late-onset disease (i.e., onset at age 80 rather than 42), statistical analysis revealed that most late-onset carriers, about 80 percent, will die before developing the disease. Formal genetic research studies indicate a possible linkage between early onset Alzheimer's disease and some genes on chromosome 21, including one gene defined as the familial Alzheimer's disease (FAD) gene, but no definitive genetic markers of the disease have been found yet. The author of the study concludes that genetically, based on accumulating evidence, Alzheimer's is a disease similar to **thalassemia** major (Cooley's anemia). The use of formal genetics is considered a futile route to study the late-onset form of the disease, and systemic cross-cultural, or cross-population studies of founder effect and rare alleles (hereditary characteristics) are recommended for understanding the natural history of Alzheimer's disease.

Academic Periodicals covering Thalassemia

Numerous periodicals are currently indexed within the National Library of Medicine's PubMed database that are known to publish articles relating to thalassemia. In addition to these sources, you can search for articles covering thalassemia 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 thalassemia. 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 thalassemia. 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 thalassemia:

Deferoxamine

- **Systemic - U.S. Brands:** Desferal
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/203185.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 thalassemia 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 "thalassemia" (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 thalassemia:

- **Isobutyramide (trade name: Isobutyramide oral solution)**
  http://www.rarediseases.org/nord/search/nodd_full?code=157
- **Isobutyramide**
  http://www.rarediseases.org/nord/search/nodd_full?code=161
- **Sodium phenylbutyrate**
  http://www.rarediseases.org/nord/search/nodd_full?code=191
- **Arginine butyrate**
  http://www.rarediseases.org/nord/search/nodd_full?code=673
- **Arginine Butyrate**
  http://www.rarediseases.org/nord/search/nodd_full?code=674
- **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[10]:

- 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/**

[10] 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.[11] 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:[12]

- **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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[11] 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**).

[12] 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[13]

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.[14] To use the NLM Gateway, simply go to the search site at **http://gateway.nlm.nih.gov/gw/Cmd**. Type "thalassemia" (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	14960
Books / Periodicals / Audio Visual	138
Consumer Health	180
Meeting Abstracts	12
Other Collections	105
Total	15395

HSTAT[15]

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.[16] 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.[17] Simply search by "thalassemia" (or synonyms) at the following Web site: **http://text.nlm.nih.gov**.

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[13] Adapted from NLM: **http://gateway.nlm.nih.gov/gw/Cmd?Overview.x**.

[14] 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).

[15] Adapted from HSTAT: **http://www.nlm.nih.gov/pubs/factsheets/hstat.html**.

[16] The HSTAT URL is **http://hstat.nlm.nih.gov/**.

[17] 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[18]

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.[19] 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.[20] 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/**.

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[18] Adapted from **http://www.ncbi.nlm.nih.gov/Coffeebreak/Archive/FAQ.html**.

[19] 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.

[20] 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.

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 thalassemia 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 thalassemia. 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 thalassemia. 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 "thalassemia":

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

Genetic Disorders
http://www.nlm.nih.gov/medlineplus/geneticdisorders.html

High Risk Pregnancy
http://www.nlm.nih.gov/medlineplus/highriskpregnancy.html

Sickle Cell Anemia
http://www.nlm.nih.gov/medlineplus/sicklecellanemia.html

Within the health topic page dedicated to thalassemia, the following was listed:

- General/Overviews

Anemia
Source: Mayo Foundation for Medical Education and Research
http://www.mayoclinic.com/invoke.cfm?id=DS00321

Anemia: When Low Iron Is the Cause
Source: American Academy of Family Physicians
http://familydoctor.org/009.xml

- Diagnosis/Symptoms

Ferritin Test
Source: American Association for Clinical Chemistry
http://www.labtestsonline.org/understanding/analytes/ferritin/test.html

Hematocrit
Source: American Association for Clinical Chemistry
http://www.labtestsonline.org/understanding/analytes/hematocrit/test.html

Hemoglobin
Source: American Association for Clinical Chemistry
http://www.labtestsonline.org/understanding/analytes/hemoglobin/test.html

Serum Iron Test
Source: American Association for Clinical Chemistry
http://www.labtestsonline.org/understanding/analytes/serum_iron/test.html

TIBC (Total Iron-Binding Capacity) & Transferrin
Source: American Association for Clinical Chemistry
http://www.labtestsonline.org/understanding/analytes/tibc/test.html

Understanding Your Complete Blood Count
Source: National Institutes of Health, Clinical Center
http://www.cc.nih.gov/ccc/patient_education/pepubs/cbc97.pdf

- Treatment

  Blood and Marrow Stem Cell Transplantation
  Source: Leukemia & Lymphoma Society
  http://www.leukemia-lymphoma.org/all_mat_toc.adp?item_id=2443

  Cord Blood FAQs
  Source: National Marrow Donor Program
  http://www.marrow.org/FAQS/cord_blood_faqs.html

  Epoetin Treatment
  Source: American Society of Clinical Oncology
  http://www.asco.org/ac/1%2C1003%2C_12-002214-00_18-0024517-00_19-0024518-00_20-001%2C00.asp

  How Is Fanconi Anemia Treated?
  Source: Fanconi Anemia Research Fund
  http://www.fanconi.org/TREATMENT.HTML

- Nutrition

  Iron
  Source: National Institutes of Health, Office of Dietary Supplements
  http://www.cc.nih.gov/ccc/supplements/iron.html

- Specific Conditions/Aspects

  Acquired Aplastic Anemia: Basic Explanations
  Source: Aplastic Anemia & MDS International Foundation
  http://www.aplastic.org/cgi-bin/byteserver.pl/pdfs/ACQUIRED-APLASTIC-ANEMIA-BASIC-EXPLANATIONS.pdf

  Anemia (Normocytic Anemia)
  Source: American Academy of Family Physicians
  http://familydoctor.org/639.xml

  Anemia in Kidney Disease and Dialysis
  Source: National Kidney and Urologic Diseases Information Clearinghouse
  http://kidney.niddk.nih.gov/kudiseases/pubs/anemia/index.htm

  Aplastic Anemia
  Source: Mayo Foundation for Medical Education and Research
  http://www.mayoclinic.com/invoke.cfm?id=DS00322

  Diamond-Blackfan Anemia (DBA)
  Source: National Cancer Institute
  http://marrowfailure.cancer.gov/DBA.html

  Iron Deficiency Anemia
  Source: Mayo Foundation for Medical Education and Research
  http://www.mayoclinic.com/invoke.cfm?id=DS00323

  Vitamin Deficiency Anemia
  Source: Mayo Foundation for Medical Education and Research
  http://www.mayoclinic.com/invoke.cfm?id=DS00325

What Is Fanconi Anemia and How Is It Diagnosed?
Source: Fanconi Anemia Research Fund
http://www.fanconi.org/WhatisFA.html

- Children

About Anemia
Source: Nemours Foundation
http://kidshealth.org/kid/health_problems/blood/anemia.html

Anemia
Source: Nemours Foundation
http://kidshealth.org/parent/medical/heart/anemia.html

Anemia and Iron Status
Source: Centers for Disease Control and Prevention
http://www.cdc.gov/nccdphp/dnpa/anemiron.htm

Iron-Deficiency Anemia
Source: Nemours Foundation
http://kidshealth.org/parent/medical/heart/ida.html

- Latest News

Anemia Linked with Heart Disease in Women
Source: 06/01/2004, Reuters Health
http://www.nlm.nih.gov//www.nlm.nih.gov/medlineplus/news/fullstory_18092.html

Iron Deficient Infants Lag Behind
Source: 05/07/2004, United Press International
http://www.nlm.nih.gov//www.nlm.nih.gov/medlineplus/news/fullstory_17588.html

- Organizations

Fanconi Anemia Research Fund
http://www.fanconi.org/

National Heart, Lung, and Blood Institute
http://www.nhlbi.nih.gov/

National Institute of Diabetes and Digestive and Kidney Diseases
http://www.niddk.nih.gov/

- Research

Anemia Elevates Risk of Physical Decline in Older People
Source: National Institute on Aging
http://www.nih.gov/news/pr/jul2003/nia-25.htm

Enzyme Discovery Sheds Light on Causes of Rare Disease, Cancer
Source: National Institute on Aging
http://www.nia.nih.gov/news/pr/2003/0914.htm

- Statistics

  FASTATS: Anemia/Iron Deficiency
  Source: National Center for Health Statistics
  http://www.cdc.gov/nchs/fastats/anemia.htm

- Teenagers

  Understanding Anemia
  Source: Nemours Foundation
  http://kidshealth.org/teen/diseases_conditions/blood/anemia.html

- Women

  Anemia
  Source: National Women's Health Information Center
  http://www.4woman.gov/faq/anemia.htm

  Keeping the Blood and Lymphatic System Healthy
  Source: American Medical Women's Association
  http://www.amwa-doc.org/publications/WCHealthbook/bloodamwa-ch29.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 thalassemia. 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:

- **Thalassemia Among Asians**

  Source: Oakland, CA: Association of Asian Pacific Community Health Organizations. 1992. 2 p.

  Contact: National Maternal and Child Health Clearinghouse. 2070 Chain Bridge Road, Suite 450, Vienna, VA 22182-2536. (703) 821-8955. Fax (703) 821-2098. PRICE: Single copy free.

  Summary: This brochure provides readers with information about **thalassemia,** an inherited blood disorder that has a high prevalence in Asians, particularly Southeast Asians. The brochure discusses how **thalassemia** is inherited, the two main types of **thalassemia** disease (alpha and beta), the **thalassemia** trait, screening tests, how to minimize concerns about **thalassemia,** and where to get more information. The

brochure emphasizes the importance of early diagnosis of **thalassemia** in infants. Culturally appropriate line drawings illustrate the brochure.

- **Thalassemia**

  Source: White Plains, NY: March of Dimes Birth Defects Foundation. 1994. 2 p.

  Contact: Available from March of Dimes Birth Defects Foundation. Fulfillment Center, P.O. Box 1657, Wilkes-Barre, PA 18703. (800) 367-6630 or (717) 820-8104. Fax (717) 825-1987. PRICE: $4.00 for package of 50 fact sheets, plus $4.50 shipping and handling (as of 1996). Order Number 09-041-00. For a free single copy, call (914) 428-7100.

  Summary: This fact sheet provides information about **thalassemia,** a group of inherited diseases of the blood. Topics include the different kinds of **thalassemia,** how **thalassemia** affects a child, treatment options, how the disease is transmitted, diagnostic tests and genetic screening for **thalassemia,** the prevention of **thalassemia,** and current research on the disease. 3 figures.

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:

- **FAQ - About Thalassemia**

  Summary: This online document answers questions consumers frequently have about this group of genetic blood disorders. Topics covered include symptoms, treatment and management of the disorder.

  Source: Cooley's Anemia Foundation

  http://www.healthfinder.gov/scripts/recordpass.asp?RecordType=0&RecordID=5143

- **Thalassemia**

  Source: March of Dimes Birth Defects Foundation

  http://www.healthfinder.gov/scripts/recordpass.asp?RecordType=0&RecordID=3272

- **What is Thalassemia?**

  Summary: A description of thalassemia -- a fatal blood disease that is found predominantly among people of Mediterranean and Asian Indian, South Asian and Chinese ancestry.
  Source: Cooley's Anemia Foundation
  http://www.healthfinder.gov/scripts/recordpass.asp?RecordType=0&RecordID=2567

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 thalassemia. 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 Thalassemia

The following is a list of associations that provide information on and resources relating to thalassemia:

- **Cooley's Anemia Foundation, Inc**

  Telephone: (718) 321-2873 Toll-free: (800) 522-7222

  Fax: (718) 321-3340

  Email: info@cooleysanemia.org

  Web Site: http://www.cooleysanemia.org

  Background: The **Cooley's Anemia** Foundation, Inc. is a national not-for-profit organization dedicated to advancing the treatment and cure of **Cooley's Anemia,** an inherited blood disorder. Established in 1954, the Foundation conducts national programs that promote medical research and provides a variety of patient services and educational programs. The Foundation has more than 15 chapters throughout the United States and supports the **Thalassemia** Action Group (TAG), a support group for affected individuals and their families. Services provided by the **Cooley's Anemia** Foundation include: information on **thalassemia,** referrals to local medical sources and emergency medical supplies to people in need. Informational materials available from the Foundation including video tapes, brochures, and regular newsletters.

  Relevant area(s) of interest: Thalassemia

Finding Associations

There are several Internet directories that provide lists of medical associations with information on or resources relating to thalassemia. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with thalassemia.

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 thalassemia. 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 "thalassemia" (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 "thalassemia". 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 "thalassemia" (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 "thalassemia" (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.[21]

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

[21] 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)[22]:

- **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/**

[22] 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**).

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**

THALASSEMIA DICTIONARY

The definitions below are derived from official public sources, including the National Institutes of Health [NIH] and the European Union [EU].

3-dimensional: 3-D. A graphic display of depth, width, and height. Three-dimensional radiation therapy uses computers to create a 3-dimensional picture of the tumor. This allows doctors to give the highest possible dose of radiation to the tumor, while sparing the normal tissue as much as possible. [NIH]

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]

Abducens: A striated, extrinsic muscle of the eyeball that originates from the annulus of Zinn. [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]

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]

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]

Activities of Daily Living: The performance of the basic activities of self care, such as dressing, ambulation, eating, etc., in rehabilitation. [NIH]

Acute leukemia: A rapidly progressing cancer of the blood-forming tissue (bone marrow). [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]

Acyl: Chemical signal used by bacteria to communicate. [NIH]

Adaptability: Ability to develop some form of tolerance to conditions extremely different from those under which a living organism evolved. [NIH]

Adduct: Complex formed when a carcinogen combines with DNA or a protein. [NIH]

Adenocarcinoma: A malignant epithelial tumor with a glandular organization. [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]

Adipocytes: Fat-storing cells found mostly in the abdominal cavity and subcutaneous tissue. Fat is usually stored in the form of tryglycerides. [NIH]

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 Cortex: The outer layer of the adrenal gland. It secretes mineralocorticoids, androgens, and glucocorticoids. [NIH]

Adrenal Medulla: The inner part of the adrenal gland; it synthesizes, stores and releases catecholamines. [NIH]

Adverse Effect: An unwanted side effect of treatment. [NIH]

Afferent: Concerned with the transmission of neural impulse toward the central part of the nervous system. [NIH]

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 Distribution: The frequency of different ages or age groups in a given population. The distribution may refer to either how many or what proportion of the group. The population is usually patients with a specific disease but the concept is not restricted to humans and is not restricted to medicine. [NIH]

Age Groups: Persons classified by age from birth (infant, newborn) to octogenarians and older (aged, 80 and over). [NIH]

Age of Onset: The age or period of life at which a disease or the initial symptoms or manifestations of a disease appear in an individual. [NIH]

Airway: A device for securing unobstructed passage of air into and out of the lungs during general anesthesia. [NIH]

Alanine: A non-essential amino acid that occurs in high levels in its free state in plasma. It is produced from pyruvate by transamination. It is involved in sugar and acid metabolism, increases immunity, and provides energy for muscle tissue, brain, and the central nervous system. [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]

Alkaloid: A member of a large group of chemicals that are made by plants and have

nitrogen in them. Some alkaloids have been shown to work against cancer. [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-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]

Alternans: Ipsilateral abducens palsy and facial paralysis and contralateral hemiplegia of the limbs, due to a nuclear or infranuclear lesion in the pons. [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]

Alveolar Process: The thickest and spongiest part of the maxilla and mandible hollowed out into deep cavities for the teeth. [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 Motifs: Commonly observed structural components of proteins formed by simple combinations of adjacent secondary structures. A commonly observed structure may be composed of a conserved sequence which can be represented by a consensus sequence. [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]

Amiodarone: An antianginal and antiarrhythmic drug. It increases the duration of ventricular and atrial muscle action by inhibiting Na,K-activated myocardial adenosine triphosphatase. There is a resulting decrease in heart rate and in vascular resistance. [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]

Anaemia: A reduction below normal in the number of erythrocytes per cu. mm., in the quantity of haemoglobin, or in the volume of packed red cells per 100 ml. of blood which occurs when the equilibrium between blood loss (through bleeding or destruction) and blood production is disturbed. [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]

Analgesic: An agent that alleviates pain without causing loss of consciousness. [EU]

Analog: In chemistry, a substance that is similar, but not identical, to another. [NIH]

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]

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]

Angina: Chest pain that originates in the heart. [NIH]

Angioid Streaks: Small breaks in the elastin-filled tissue of the retina. [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]

Anions: Negatively charged atoms, radicals or groups of atoms which travel to the anode or positive pole during electrolysis. [NIH]

Annealing: The spontaneous alignment of two single DNA strands to form a double helix. [NIH]

Anode: Electrode held at a positive potential with respect to a cathode. [NIH]

Anomalies: Birth defects; abnormalities. [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]

Anthracycline: A member of a family of anticancer drugs that are also antibiotics. [NIH]

Antianginal: Counteracting angina or anginal conditions. [EU]

Antiarrhythmic: An agent that prevents or alleviates cardiac arrhythmia. [EU]

Antibacterial: A substance that destroys bacteria or suppresses their growth or reproduction. [EU]

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]

Anticoagulant: A drug that helps prevent blood clots from forming. Also called a blood thinner. [NIH]

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]

Antigen-presenting cell: APC. A cell that shows antigen on its surface to other cells of the immune system. This is an important part of an immune response. [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]

Antimetabolite: A chemical that is very similar to one required in a normal biochemical reaction in cells. Antimetabolites can stop or slow down the reaction. [NIH]

Antineoplastic: Inhibiting or preventing the development of neoplasms, checking the

maturation and proliferation of malignant cells. [EU]

Antineoplastic Agents: Substances that inhibit or prevent the proliferation of neoplasms. [NIH]

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]

Antipyretic: An agent that relieves or reduces fever. Called also antifebrile, antithermic and febrifuge. [EU]

Antiviral: Destroying viruses or suppressing their replication. [EU]

Anus: The opening of the rectum to the outside of the body. [NIH]

Anxiety: Persistent feeling of dread, apprehension, and impending disaster. [NIH]

Aorta: The main trunk of the systemic arteries. [NIH]

Apheresis: Components being separated out, as leukapheresis, plasmapheresis, plateletpheresis. [NIH]

Aplasia: Lack of development of an organ or tissue, or of the cellular products from an organ or tissue. [EU]

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]

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]

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]

Artery: Vessel-carrying blood from the heart to various parts of the body. [NIH]

Articular: Of or pertaining to a joint. [EU]

Assay: Determination of the amount of a particular constituent of a mixture, or of the biological or pharmacological potency of a drug. [EU]

Astrocytes: The largest and most numerous neuroglial cells in the brain and spinal cord. Astrocytes (from "star" cells) are irregularly shaped with many long processes, including those with "end feet" which form the glial (limiting) membrane and directly and indirectly

contribute to the blood brain barrier. They regulate the extracellular ionic and chemical environment, and "reactive astrocytes" (along with microglia) respond to injury. Astrocytes have high- affinity transmitter uptake systems, voltage-dependent and transmitter-gated ion channels, and can release transmitter, but their role in signaling (as in many other functions) is not well understood. [NIH]

Asymptomatic: Having no signs or symptoms of disease. [NIH]

Atrial: Pertaining to an atrium. [EU]

Atrioventricular: Pertaining to an atrium of the heart and to a ventricle. [EU]

Attenuated: Strain with weakened or reduced virulence. [NIH]

Atypical: Irregular; not conformable to the type; in microbiology, applied specifically to strains of unusual type. [EU]

Autoantibodies: Antibodies that react with self-antigens (autoantigens) of the organism that produced them. [NIH]

Autoantigens: Endogenous tissue constituents that have the ability to interact with autoantibodies and cause an immune response. [NIH]

Autoimmune disease: A condition in which the body recognizes its own tissues as foreign and directs an immune response against them. [NIH]

Autoimmunity: Process whereby the immune system reacts against the body's own tissues. Autoimmunity may produce or be caused by autoimmune diseases. [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]

Autopsy: Postmortem examination of the body. [NIH]

Babesiosis: A group of tick-borne diseases of mammals including zoonoses in humans. They are caused by protozoans of the genus babesia, which parasitize erythrocytes, producing hemolysis. In the U.S., the organism's natural host is mice and transmission is by the deer tick ixodes scapularis. [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]

Bactericidal: Substance lethal to bacteria; substance capable of killing bacteria. [NIH]

Bacteriophage lambda: A temperate inducible phage and type species of the genus lambda-like Phages, in the family Siphoviridae. Its natural host is E. coli K12. Its virion contains linear double-stranded DNA, except for 12 complementary bases at the 5'-termini of the polynucleotide chains. The DNA circularizes on infection. [NIH]

Bacteriophages: Viruses whose host is a bacterial cell. [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]

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]

Base Pairing: Pairing of purine and pyrimidine bases by hydrogen bonding in double-stranded DNA or RNA. [NIH]

Base Sequence: The sequence of purines and pyrimidines in nucleic acids and polynucleotides. It is also called nucleotide or nucleoside sequence. [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]

Benign tumor: A noncancerous growth that 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]

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]

Bioavailable: The ability of a drug or other substance to be absorbed and used by the body. Orally bioavailable means that a drug or other substance that is taken by mouth can be absorbed and used by the body. [NIH]

Biochemical: Relating to biochemistry; characterized by, produced by, or involving chemical reactions in living organisms. [EU]

Biogenesis: The origin of life. It includes studies of the potential basis for life in organic compounds but excludes studies of the development of altered forms of life through mutation and natural selection, which is evolution. [NIH]

Biological response modifier: BRM. A substance that stimulates the body's response to infection and disease. [NIH]

Biophysics: The science of physical phenomena and processes in living organisms. [NIH]

Biopsy: Removal and pathologic examination of specimens in the form of small pieces of tissue from the living body. [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]

Biotransformation: The chemical alteration of an exogenous substance by or in a biological system. The alteration may inactivate the compound or it may result in the production of an active metabolite of an inactive parent compound. The alteration may be either non-synthetic (oxidation-reduction, hydrolysis) or synthetic (glucuronide formation, sulfate conjugation, acetylation, methylation). This also includes metabolic detoxication and

clearance. [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]

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 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]

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 Fluids: Liquid components of living organisms. [NIH]

Body Mass Index: One of the anthropometric measures of body mass; it has the highest correlation with skinfold thickness or body density. [NIH]

Bolus: A single dose of drug usually injected into a blood vessel over a short period of time. Also called bolus infusion. [NIH]

Bolus infusion: A single dose of drug usually injected into a blood vessel over a short period of time. Also called bolus. [NIH]

Bolus injection: The injection of a drug (or drugs) in a high quantity (called a bolus) at once, the opposite of gradual administration (as in intravenous infusion). [EU]

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 Resorption: Bone loss due to osteoclastic activity. [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]

Brachial: All the nerves from the arm are ripped from the spinal cord. [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]

Brain Diseases: Pathologic conditions affecting the brain, which is composed of the intracranial components of the central nervous system. This includes (but is not limited to) the cerebral cortex; intracranial white matter; basal ganglia; thalamus; hypothalamus; brain stem; and cerebellum. [NIH]

Brain Stem: The part of the brain that connects the cerebral hemispheres with the spinal cord. It consists of the mesencephalon, pons, and medulla oblongata. [NIH]

Breeding: The science or art of changing the constitution of a population of plants or animals through sexual reproduction. [NIH]

Buccal: Pertaining to or directed toward the cheek. In dental anatomy, used to refer to the buccal surface of a tooth. [EU]

Buccal mucosa: The inner lining of the cheeks and lips. [NIH]

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]

Butyric Acid: A four carbon acid, CH3CH2CH2COOH, with an unpleasant odor that occurs in butter and animal fat as the glycerol ester. [NIH]

Calcification: Deposits of calcium in the tissues of the breast. Calcification in the breast can be seen on a mammogram, but cannot be detected by touch. There are two types of breast calcification, macrocalcification and microcalcification. Macrocalcifications are large deposits and are usually not related to cancer. Microcalcifications are specks of calcium that may be found in an area of rapidly dividing cells. Many microcalcifications clustered together may be a sign of cancer. [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]

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]

Carbohydrate: An aldehyde or ketone derivative of a polyhydric alcohol, particularly of the pentahydric and hexahydric alcohols. They are so named because the hydrogen and oxygen are usually in the proportion to form water, (CH2O)n. The most important carbohydrates are the starches, sugars, celluloses, and gums. They are classified into mono-, di-, tri-, poly- and heterosaccharides. [EU]

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]

Carboxy: Cannabinoid. [NIH]

Carboxylic Acids: Organic compounds containing the carboxy group (-COOH). This group of compounds includes amino acids and fatty acids. Carboxylic acids can be saturated, unsaturated, or aromatic. [NIH]

Carcinogen: Any substance that causes cancer. [NIH]

Carcinogenesis: The process by which normal cells are transformed into cancer cells. [NIH]

Carcinogenic: Producing carcinoma. [EU]

Carcinogenicity: The ability to cause cancer. [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]

Cardiomyopathy: A general diagnostic term designating primary myocardial disease, often of obscure or unknown etiology. [EU]

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]

Cardiovascular System: The heart and the blood vessels by which blood is pumped and circulated through the body. [NIH]

Carnitine: Constituent of striated muscle and liver. It is used therapeutically to stimulate gastric and pancreatic secretions and in the treatment of hyperlipoproteinemias. [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]

Caspase: Enzyme released by the cell at a crucial stage in apoptosis in order to shred all cellular proteins. [NIH]

Catecholamine: A group of chemical substances manufactured by the adrenal medulla and secreted during physiological stress. [NIH]

Catheters: A small, flexible tube that may be inserted into various parts of the body to inject or remove liquids. [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]

Cause of Death: Factors which produce cessation of all vital bodily functions. They can be analyzed from an epidemiologic viewpoint. [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 Aging: The decrease in the cell's ability to proliferate with the passing of time. Each cell is programmed for a certain number of cell divisions and at the end of that time

proliferation halts. The cell enters a quiescent state after which it experiences cell death via the process of apoptosis. [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 Differentiation: Progressive restriction of the developmental potential and increasing specialization of function which takes place during the development of the embryo and leads to the formation of specialized cells, tissues, and organs. [NIH]

Cell Division: The fission of a cell. [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]

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]

Cerebral: Of or pertaining of the cerebrum or the brain. [EU]

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]

Chaperonins: A class of sequence-related molecular chaperones found in bacteria, mitochondria, and plastids. Chaperonins are abundant constitutive proteins that increase in amount after stresses such as heat shock, bacterial infection of macrophages, and an increase in the cellular content of unfolded proteins. Bacterial chaperonins are major immunogens in human bacterial infections because of their accumulation during the stress of infection. Two members of this class of chaperones are chaperonin 10 and chaperonin 60. [NIH]

Character: In current usage, approximately equivalent to personality. The sum of the relatively fixed personality traits and habitual modes of response of an individual. [NIH]

Chelating Agents: Organic chemicals that form two or more coordination bonds with a central metal ion. Heterocyclic rings are formed with the central metal atom as part of the ring. Some biological systems form metal chelates, e.g., the iron-binding porphyrin group of

hemoglobin and the magnesium-binding chlorophyll of plants. (From Hawley's Condensed Chemical Dictionary, 12th ed) They are used chemically to remove ions from solutions, medicinally against microorganisms, to treat metal poisoning, and in chemotherapy protocols. [NIH]

Chelation: Combination with a metal in complexes in which the metal is part of a ring. [EU]

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]

Chemotherapeutic agent: A drug used to treat cancer. [NIH]

Chemotherapy: Treatment with anticancer drugs. [NIH]

Chimeras: Organism that contains a mixture of genetically different cells. [NIH]

Chin: The anatomical frontal portion of the mandible, also known as the mentum, that contains the line of fusion of the two separate halves of the mandible (symphysis menti). This line of fusion divides inferiorly to enclose a triangular area called the mental protuberance. On each side, inferior to the second premolar tooth, is the mental foramen for the passage of blood vessels and a nerve. [NIH]

Chlorophyll: Porphyrin derivatives containing magnesium that act to convert light energy in photosynthetic organisms. [NIH]

Cholecystectomy: Surgical removal of the gallbladder. [NIH]

Cholera: An acute diarrheal disease endemic in India and Southeast Asia whose causative agent is vibrio cholerae. This condition can lead to severe dehydration in a matter of hours unless quickly treated. [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]

Chondrocytes: Polymorphic cells that form cartilage. [NIH]

Chordae Tendineae: The tendinous cords that connect each cusp of the two atrioventricular valves to appropriate papillary muscles in the heart ventricles, preventing the valves from reversing themselves when the ventricles contract. [NIH]

Choroid: The thin, highly vascular membrane covering most of the posterior of the eye between the retina and sclera. [NIH]

Choroid Plexus: A villous structure of tangled masses of blood vessels contained within the third, lateral, and fourth ventricles of the brain. It regulates part of the production and composition of cerebrospinal fluid. [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]

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 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]

Cinchona: A genus of rubiaceous South American trees that yields the toxic cinchona alkaloids from their bark; quinine, quinidine, chinconine, cinchonidine and others are used to treat malaria and cardiac arrhythmias. [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]

Cirrhosis: A type of chronic, progressive liver disease. [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]

Clinical Medicine: The study and practice of medicine by direct examination of the patient. [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]

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]

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]

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]

Cofactor: A substance, microorganism or environmental factor that activates or enhances the action of another entity such as a disease-causing agent. [NIH]

Colitis: Inflammation of the colon. [NIH]

Colloidal: Of the nature of a colloid. [EU]

Colon: The long, coiled, tubelike organ that removes water from digested food. The remaining material, solid waste called stool, moves through the colon to the rectum and leaves the body through the anus. [NIH]

Combination Therapy: Association of 3 drugs to treat AIDS (AZT + DDC or DDI + protease inhibitor). [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]

Complete remission: The disappearance of all signs of cancer. Also called a complete response. [NIH]

Compliance: Distensibility measure of a chamber such as the lungs (lung compliance) or bladder. Compliance is expressed as a change in volume per unit change in pressure. [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]

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]

Confounding: Extraneous variables resulting in outcome effects that obscure or exaggerate the "true" effect of an intervention. [NIH]

Congenita: Displacement, subluxation, or malposition of the crystalline lens. [NIH]

Congestive heart failure: Weakness of the heart muscle that leads to a buildup of fluid in body tissues. [NIH]

Conjugated: Acting or operating as if joined; simultaneous. [EU]

Conjunctiva: The mucous membrane that lines the inner surface of the eyelids and the anterior part of the sclera. [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]

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]

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]

Constriction: The act of constricting. [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]

Contralateral: Having to do with the opposite side of the body. [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]

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 Artery Bypass: Surgical therapy of ischemic coronary artery disease achieved by grafting a section of saphenous vein, internal mammary artery, or other substitute between the aorta and the obstructed coronary artery distal to the obstructive lesion. [NIH]

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]

Corpuscle: A small mass or body; a sensory nerve end bulb; a cell, especially that of the blood or the lymph. [NIH]

Cortisol: A steroid hormone secreted by the adrenal cortex as part of the body's response to stress. [NIH]

Cranial: Pertaining to the cranium, or to the anterior (in animals) or superior (in humans) end of the body. [EU]

Crossing-over: The exchange of corresponding segments between chromatids of homologous chromosomes during meiosia, forming a chiasma. [NIH]

Crystallization: The formation of crystals; conversion to a crystalline form. [EU]

Curative: Tending to overcome disease and promote recovery. [EU]

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]

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]

Cytopenia: A reduction in the number of blood cells. [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]

De novo: In cancer, the first occurrence of cancer in the body. [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]

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]

Deletion: A genetic rearrangement through loss of segments of DNA (chromosomes), bringing sequences, which are normally separated, into close proximity. [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]

Dendritic: 1. Branched like a tree. 2. Pertaining to or possessing dendrites. [EU]

Dendritic cell: A special type of antigen-presenting cell (APC) that activates T lymphocytes. [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]

Deoxyribonucleotides: A purine or pyrimidine base bonded to a deoxyribose containing a bond to a phosphate group. [NIH]

Depolarization: The process or act of neutralizing polarity. In neurophysiology, the reversal of the resting potential in excitable cell membranes when stimulated, i.e., the tendency of the cell membrane potential to become positive with respect to the potential outside the cell. [EU]

Dermis: A layer of vascular connective tissue underneath the epidermis. The surface of the dermis contains sensitive papillae. Embedded in or beneath the dermis are sweat glands, hair follicles, and sebaceous glands. [NIH]

Deuterium: Deuterium. The stable isotope of hydrogen. It has one neutron and one proton in the nucleus. [NIH]

Developing Countries: Countries in the process of change directed toward economic growth, that is, an increase in production, per capita consumption, and income. The process of economic growth involves better utilization of natural and human resources, which results in a change in the social, political, and economic structures. [NIH]

Diabetes Mellitus: A heterogeneous group of disorders that share glucose intolerance in

common. [NIH]

Diagnostic procedure: A method used to identify a disease. [NIH]

Diagnostic Services: Organized services for the purpose of providing diagnosis to promote and maintain health. [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]

Diastole: Period of relaxation of the heart, especially the ventricles. [NIH]

Diastolic: Of or pertaining to the diastole. [EU]

Digestion: The process of breakdown of food for metabolism and use by the body. [NIH]

Digestive tract: The organs through which food passes when food is eaten. These organs are the mouth, esophagus, stomach, small and large intestines, and rectum. [NIH]

Dihydrotestosterone: Anabolic agent. [NIH]

Dimerization: The process by which two molecules of the same chemical composition form a condensation product or polymer. [NIH]

Dimethyl: A volatile metabolite of the amino acid methionine. [NIH]

Diploid: Having two sets of chromosomes. [NIH]

Direct: 1. Straight; in a straight line. 2. Performed immediately and without the intervention of subsidiary means. [EU]

Disabled Persons: Persons with physical or mental disabilities that affect or limit their activities of daily living and that may require special accommodations. [NIH]

Discrete: Made up of separate parts or characterized by lesions which do not become blended; not running together; separate. [NIH]

Disease Susceptibility: A constitution or condition of the body which makes the tissues react in special ways to certain extrinsic stimuli and thus tends to make the individual more than usually susceptible to certain diseases. [NIH]

Disinfectant: An agent that disinfects; applied particularly to agents used on inanimate objects. [EU]

Disposition: A tendency either physical or mental toward certain diseases. [EU]

Dissection: Cutting up of an organism for study. [NIH]

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]

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]

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]

Dura mater: The outermost, toughest, and most fibrous of the three membranes (meninges) covering the brain and spinal cord; called also pachymeninx. [EU]

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]

Effector: It is often an enzyme that converts an inactive precursor molecule into an active second messenger. [NIH]

Efferent: Nerve fibers which conduct impulses from the central nervous system to muscles and glands. [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]

Elastic: Susceptible of resisting and recovering from stretching, compression or distortion applied by a force. [EU]

Elastin: The protein that gives flexibility to tissues. [NIH]

Elective: Subject to the choice or decision of the patient or physician; applied to procedures that are advantageous to the patient but not urgent. [EU]

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]

Electroporation: A technique in which electric pulses of intensity in kilovolts per centimeter and of microsecond-to-millisecond duration cause a temporary loss of the semipermeability of cell membranes, thus leading to ion leakage, escape of metabolites, and increased uptake by cells of drugs, molecular probes, and DNA. Some applications of electroporation include introduction of plasmids or foreign DNA into living cells for transfection, fusion of cells to prepare hybridomas, and insertion of proteins into cell membranes. [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]

Emollient: Softening or soothing; called also malactic. [EU]

Endemic: Present or usually prevalent in a population or geographical area at all times; said of a disease or agent. Called also endemial. [EU]

Endoderm: The inner of the three germ layers of the embryo. [NIH]

Endogenous: Produced inside an organism or cell. The opposite is external (exogenous) production. [NIH]

Endothelial cell: The main type of cell found in the inside lining of blood vessels, lymph vessels, and the heart. [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]

Energy balance: Energy is the capacity of a body or a physical system for doing work. Energy balance is the state in which the total energy intake equals total energy needs. [NIH]

Enhancer: Transcriptional element in the virus genome. [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-Linked Immunosorbent Assay: An immunoassay utilizing an antibody labeled with an enzyme marker such as horseradish peroxidase. While either the enzyme or the antibody is bound to an immunosorbent substrate, they both retain their biologic activity; the change in enzyme activity as a result of the enzyme-antibody-antigen reaction is proportional to the concentration of the antigen and can be measured spectrophotometrically or with the naked eye. Many variations of the method have been developed. [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]

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]

Epidural: The space between the wall of the spinal canal and the covering of the spinal cord. An epidural injection is given into this space. [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]

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]

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 Membrane: The semipermeable outer portion of the red corpuscle. It is known as a 'ghost' after hemolysis. [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]

Erythroleukemia: Cancer of the blood-forming tissues in which large numbers of immature, abnormal red blood cells are found in the blood and bone marrow. [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]

Esophageal: Having to do with the esophagus, the muscular tube through which food passes from the throat to the stomach. [NIH]

Esophagus: The muscular tube through which food passes from the throat to the stomach. [NIH]

Estrogens: A class of sex hormones associated with the development and maintenance of secondary female sex characteristics and control of the cyclical changes in the reproductive cycle. They are also required for pregnancy maintenance and have an anabolic effect on protein metabolism and water retention. [NIH]

Ethanol: A clear, colorless liquid rapidly absorbed from the gastrointestinal tract and distributed throughout the body. It has bactericidal activity and is used often as a topical disinfectant. It is widely used as a solvent and preservative in pharmaceutical preparations as well as serving as the primary ingredient in alcoholic beverages. [NIH]

Ethnic Groups: A group of people with a common cultural heritage that sets them apart from others in a variety of social relationships. [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]

Excipient: Any more or less inert substance added to a prescription in order to confer a suitable consistency or form to the drug; a vehicle. [EU]

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]

Exhaustion: The feeling of weariness of mind and body. [NIH]

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]

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]

Extraction: The process or act of pulling or drawing out. [EU]

Extravasation: A discharge or escape, as of blood, from a vessel into the tissues. [EU]

Extremity: A limb; an arm or leg (membrum); sometimes applied specifically to a hand or foot. [EU]

Facial: Of or pertaining to the face. [EU]

Facial Expression: Observable changes of expression in the face in response to emotional stimuli. [NIH]

Facial Nerve: The 7th cranial nerve. The facial nerve has two parts, the larger motor root which may be called the facial nerve proper, and the smaller intermediate or sensory root. Together they provide efferent innervation to the muscles of facial expression and to the

lacrimal and salivary glands, and convey afferent information for taste from the anterior two-thirds of the tongue and for touch from the external ear. [NIH]

Facial Pain: Pain in the facial region including orofacial pain and craniofacial pain. Associated conditions include local inflammatory and neoplastic disorders and neuralgic syndromes involving the trigeminal, facial, and glossopharyngeal nerves. Conditions which feature recurrent or persistent facial pain as the primary manifestation of disease are referred to as facial pain syndromes. [NIH]

Facial Paralysis: Severe or complete loss of facial muscle motor function. This condition may result from central or peripheral lesions. Damage to CNS motor pathways from the cerebral cortex to the facial nuclei in the pons leads to facial weakness that generally spares the forehead muscles. Facial nerve diseases generally results in generalized hemifacial weakness. Neuromuscular junction diseases and muscular diseases may also cause facial paralysis or paresis. [NIH]

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]

Fatigue: The state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli. [NIH]

Fatty acids: A major component of fats that are used by the body for energy and tissue development. [NIH]

Femur: The longest and largest bone of the skeleton, it is situated between the hip and the knee. [NIH]

Ferritin: An iron-containing protein complex that is formed by a combination of ferric iron with the protein apoferritin. [NIH]

Ferrochelatase: An enzyme widely distributed in cells and tissues. It is located in the inner mitochondrial membrane and catalyzes the formation of heme from protoporphyrin IX and ferrous ions during the terminal step in the heme biosynthetic pathway. EC 4.99.1.1. [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]

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]

Fibroblast Growth Factor: Peptide isolated from the pituitary gland and from the brain. It is a potent mitogen which stimulates growth of a variety of mesodermal cells including chondrocytes, granulosa, and endothelial cells. The peptide may be active in wound healing and animal limb regeneration. [NIH]

Fibroid: A benign smooth muscle tumor, usually in the uterus or gastrointestinal tract. Also called leiomyoma. [NIH]

Fibrosis: Any pathological condition where fibrous connective tissue invades any organ, usually as a consequence of inflammation or other injury. [NIH]

Fine-needle aspiration: The removal of tissue or fluid with a needle for examination under a microscope. Also called needle biopsy. [NIH]

Fludarabine: An anticancer drug that belongs to the family of drugs called antimetabolites. [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]

Founder Effect: The principle that when a small subgroup of a larger population establishes itself as a separate and isolated entity, its gene pool carries only a fraction of the genetic diversity of the parental population. This may result in an increased frequency of certain diseases in the subgroup, especially those diseases known to be autosomal recessive. [NIH]

Fourth Ventricle: An irregularly shaped cavity in the rhombencephalon, between the medulla oblongata, the pons, and the isthmus in front, and the cerebellum behind. It is continuous with the central canal of the cord below and with the cerebral aqueduct above, and through its lateral and median apertures it communicates with the subarachnoid space. [NIH]

Frameshift: A type of mutation which causes out-of-phase transcription of the base sequence; such mutations arise from the addition or delection of nucleotide(s) in numbers other than 3 or multiples of 3. [NIH]

Frameshift Mutation: A type of mutation in which a number of nucleotides not divisible by three is deleted from or inserted into a coding sequence, thereby causing an alteration in the reading frame of the entire sequence downstream of the mutation. These mutations may be induced by certain types of mutagens or may occur spontaneously. [NIH]

Free Radicals: Highly reactive molecules with an unsatisfied electron valence pair. Free radicals are produced in both normal and pathological processes. They are proven or suspected agents of tissue damage in a wide variety of circumstances including radiation, damage from environment chemicals, and aging. Natural and pharmacological prevention of free radical damage is being actively investigated. [NIH]

Gallbladder: The pear-shaped organ that sits below the liver. Bile is concentrated and stored in the gallbladder. [NIH]

Gallium: A rare, metallic element designated by the symbol, Ga, atomic number 31, and atomic weight 69.72. [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]

Ganglion: 1. A knot, or knotlike mass. 2. A general term for a group of nerve cell bodies located outside the central nervous system; occasionally applied to certain nuclear groups

within the brain or spinal cord, e.g. basal ganglia. 3. A benign cystic tumour occurring on a aponeurosis or tendon, as in the wrist or dorsum of the foot; it consists of a thin fibrous capsule enclosing a clear mucinous fluid. [EU]

Gangrenous: A circumscribed, deep-seated, suppurative inflammation of the subcutaneous tissue of the eyelid discharging pus from several points. [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]

Gastric: Having to do with the stomach. [NIH]

Gastrin: A hormone released after eating. Gastrin causes the stomach to produce more acid. [NIH]

Gastrointestinal: Refers to the stomach and intestines. [NIH]

Gastrointestinal tract: The stomach and intestines. [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 Deletion: A genetic rearrangement through loss of segments of DNA or RNA, bringing sequences which are normally separated into close proximity. This deletion may be detected using cytogenetic techniques and can also be inferred from the phenotype, indicating a deletion at one specific locus. [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]

Gene Targeting: The integration of exogenous DNA into the genome of an organism at sites where its expression can be suitably controlled. This integration occurs as a result of homologous recombination. [NIH]

Gene Therapy: The introduction of new genes into cells for the purpose of treating disease by restoring or adding gene expression. Techniques include insertion of retroviral vectors, transfection, homologous recombination, and injection of new genes into the nuclei of single cell embryos. The entire gene therapy process may consist of multiple steps. The new genes may be introduced into proliferating cells in vivo (e.g., bone marrow) or in vitro (e.g., fibroblast cultures) and the modified cells transferred to the site where the gene expression is required. Gene therapy may be particularly useful for treating enzyme deficiency diseases, hemoglobinopathies, and leukemias and may also prove useful in restoring drug sensitivity, particularly for leukemia. [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 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 Markers: A phenotypically recognizable genetic trait which can be used to identify a genetic locus, a linkage group, or a recombination event. [NIH]

Genetic Screening: Searching a population or individuals for persons possessing certain genotypes or karyotypes that: (1) are already associated with disease or predispose to disease; (2) may lead to disease in their descendants; or (3) produce other variations not

known to be associated with disease. Genetic screening may be directed toward identifying phenotypic expression of genetic traits. It includes prenatal genetic screening. [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]

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]

Glossopharyngeal Nerve: The 9th cranial nerve. The glossopharyngeal nerve is a mixed motor and sensory nerve; it conveys somatic and autonomic efferents as well as general, special, and visceral afferents. Among the connections are motor fibers to the stylopharyngeus muscle, parasympathetic fibers to the parotid glands, general and taste afferents from the posterior third of the tongue, the nasopharynx, and the palate, and afferents from baroreceptors and chemoreceptors of the carotid sinus. [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]

Glutamate: Excitatory neurotransmitter of the brain. [NIH]

Glutamate Synthase: An enzyme that catalyzes the formation of 2 molecules of glutamate from glutamine plus alpha-ketoglutarate in the presence of NADPH. EC 1.4.1.13. [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]

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]

Glycoprotein: A protein that has sugar molecules attached to it. [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]

Gonadotropin: The water-soluble follicle stimulating substance, by some believed to originate in chorionic tissue, obtained from the serum of pregnant mares. It is used to supplement the action of estrogens. [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]

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]

Granule: A small pill made from sucrose. [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]

Gravidity: Pregnancy; the condition of being pregnant, without regard to the outcome. [EU]

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]

Habitual: Of the nature of a habit; according to habit; established by or repeated by force of habit, customary. [EU]

Haemolysis: Disruption of the integrity of the red cell membrane causing release of haemoglobin. Haemolysis may be caused by bacterial haemolysins, by antibodies that cause complement-dependent lysis, by placing red cells in a hyptonic solution, or by defects in the red cell membrane. [EU]

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]

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]

Heart attack: A seizure of weak or abnormal functioning of the heart. [NIH]

Heart failure: Loss of pumping ability by the heart, often accompanied by fatigue, breathlessness, and excess fluid accumulation in body tissues. [NIH]

Heat-Shock Proteins: Proteins which are synthesized in eukaryotic organisms and bacteria in response to hyperthermia and other environmental stresses. They increase thermal tolerance and perform functions essential to cell survival under these conditions. [NIH]

Heat-Shock Proteins 90: A class of molecular chaperones whose members act in the mechanism of signal transduction by steroid receptors. [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]

Hematoma: An extravasation of blood localized in an organ, space, or tissue. [NIH]

Hematopoiesis: The development and formation of various types of blood cells. [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]

Hematopoietic tissue: Tissue in which new blood cells are formed. [NIH]

Hemin: Chloro(7,12-diethenyl-3,8,13,17-tetramethyl-21H,23H-porphine-2,18-dipropanoato(4-)-N(21),N(22),N(23),N(24)) ferrate(2-) dihydrogen. [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]

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]

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]

Hemophilia: Refers to a group of hereditary disorders in which affected individuals fail to make enough of certain proteins needed to form blood clots. [NIH]

Hemorrhage: Bleeding or escape of blood from a vessel. [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]

Heparan Sulfate Proteoglycan: A substance released by astrocytes, which is critical in stopping nervous fibers in their tracks. [NIH]

Hepatic: Refers to the liver. [NIH]

Hepatitis: Inflammation of the liver and liver disease involving degenerative or necrotic alterations of hepatocytes. [NIH]

Hepatobiliary: Pertaining to the liver and the bile or the biliary ducts. [EU]

Hepatocellular: Pertaining to or affecting liver cells. [EU]

Hepatocellular carcinoma: A type of adenocarcinoma, the most common type of liver tumor. [NIH]

Hepatocyte: A liver cell. [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]

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 virus: A member of the herpes family of viruses. [NIH]

Herpes Zoster: Acute vesicular inflammation. [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]

Heterozygote: An individual having different alleles at one or more loci in homologous chromosome segments. [NIH]

Histology: The study of tissues and cells under a microscope. [NIH]

Histone Deacetylase: Hydrolyzes N-acetyl groups on histones. [NIH]

Histones: Small chromosomal proteins (approx 12-20 kD) possessing an open, unfolded structure and attached to the DNA in cell nuclei by ionic linkages. Classification into the various types (designated histone I, histone II, etc.) is based on the relative amounts of arginine and lysine in each. [NIH]

Homeostasis: The processes whereby the internal environment of an organism tends to remain balanced and stable. [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]

Hormone therapy: Treatment of cancer by removing, blocking, or adding hormones. Also called endocrine therapy. [NIH]

Horseradish Peroxidase: An enzyme isolated from horseradish which is able to act as an antigen. It is frequently used as a histochemical tracer for light and electron microscopy. Its antigenicity has permitted its use as a combined antigen and marker in experimental immunology. [NIH]

Human growth hormone: A protein hormone, secreted by the anterior lobe of the pituitary, which promotes growth of the whole body by stimulating protein synthesis. The human gene has already been cloned and successfully expressed in bacteria. [NIH]

Humeral: 1. Of, relating to, or situated in the region of the humerus: brachial. 2. Of or belonging to the shoulder. 3. Of, relating to, or being any of several body parts that are analogous in structure, function, or location to the humerus or shoulder. [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]

Hybridomas: Cells artificially created by fusion of activated lymphocytes with neoplastic cells. The resulting hybrid cells are cloned and produce pure or "monoclonal" antibodies or T-cell products, identical to those produced by the immunologically competent parent, and continually grow and divide as the neoplastic parent. [NIH]

Hydration: Combining with water. [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]

Hydroxyurea: An antineoplastic agent that inhibits DNA synthesis through the inhibition of ribonucleoside diphosphate reductase. [NIH]

Hypersensitivity: Altered reactivity to an antigen, which can result in pathologic reactions upon subsequent exposure to that particular antigen. [NIH]

Hypersplenism: Condition characterized by splenomegaly, some reduction in the number of circulating blood cells in the presence of a normal or hyperactive bone marrow, and the potential for reversal by splenectomy. [NIH]

Hypertension: Persistently high arterial blood pressure. Currently accepted threshold levels are 140 mm Hg systolic and 90 mm Hg diastolic pressure. [NIH]

Hypogonadism: Condition resulting from or characterized by abnormally decreased functional activity of the gonads, with retardation of growth and sexual development. [NIH]

Hypoplasia: Incomplete development or underdevelopment of an organ or tissue. [EU]

Hypoxia: Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood. [EU]

Hysterectomy: Excision of the uterus. [NIH]

Ida: An alkylating agent. [NIH]

Idiopathic: Describes a disease of unknown cause. [NIH]

Immune response: The activity of the immune system against foreign substances (antigens). [NIH]

Immune system: The organs, cells, and molecules responsible for the recognition and disposal of foreign ("non-self") material which enters the body. [NIH]

Immune Tolerance: The specific failure of a normally responsive individual to make an immune response to a known antigen. It results from previous contact with the antigen by an immunologically immature individual (fetus or neonate) or by an adult exposed to

extreme high-dose or low-dose antigen, or by exposure to radiation, antimetabolites, antilymphocytic serum, etc. [NIH]

Immunity: Nonsusceptibility to the invasive or pathogenic effects of foreign microorganisms or to the toxic effect of antigenic substances. [NIH]

Immunoassay: Immunochemical assay or detection of a substance by serologic or immunologic methods. Usually the substance being studied serves as antigen both in antibody production and in measurement of antibody by the test substance. [NIH]

Immunodeficiency: The decreased ability of the body to fight infection and disease. [NIH]

Immunodeficiency syndrome: The inability of the body to produce an immune response. [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]

Immunosuppressant: An agent capable of suppressing immune responses. [EU]

Immunosuppressive: Describes the ability to lower immune system responses. [NIH]

Impairment: In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [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]

Implantation: The insertion or grafting into the body of biological, living, inert, or radioactive material. [EU]

Impotence: The inability to perform sexual intercourse. [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]

Incision: A cut made in the body during surgery. [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]

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]

Infancy: The period of complete dependency prior to the acquisition of competence in walking, talking, and self-feeding. [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]

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]

Inflammatory bowel disease: A general term that refers to the inflammation of the colon and rectum. Inflammatory bowel disease includes ulcerative colitis and Crohn's disease. [NIH]

Informed Consent: Voluntary authorization, given to the physician by the patient, with full comprehension of the risks involved, for diagnostic or investigative procedures and medical and surgical treatment. [NIH]

Infuse: To pour (a liquid) into something. [EU]

Infusion: A method of putting fluids, including drugs, into the bloodstream. Also called intravenous infusion. [NIH]

Infusion Pumps: Fluid propulsion systems driven mechanically, electrically, or osmotically that are used to inject (or infuse) over time agents into a patient or experimental animal; used routinely in hospitals to maintain a patent intravenous line, to administer antineoplastic agents and other drugs in thromboembolism, heart disease, diabetes mellitus (insulin infusion systems is also available), and other disorders. [NIH]

Initiation: Mutation induced by a chemical reactive substance causing cell changes; being a step in a carcinogenic process. [NIH]

Innervation: 1. The distribution or supply of nerves to a part. 2. The supply of nervous energy or of nerve stimulus sent to a part. [EU]

Insertional: A technique in which foreign DNA is cloned into a restriction site which occupies a position within the coding sequence of a gene in the cloning vector molecule. Insertion interrupts the gene's sequence such that its original function is no longer expressed. [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 Infusion Systems: Portable or implantable devices for infusion of insulin. Includes open-loop systems which may be patient-operated or controlled by a pre-set program and are designed for constant delivery of small quantities of insulin, increased during food ingestion, and closed-loop systems which deliver quantities of insulin automatically based on an electronic glucose sensor. [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]

Integrase: An enzyme that inserts DNA into the host genome. It is encoded by the pol gene

of retroviruses and also by temperate bacteriophages, the best known being bacteriophage lambda. EC 2.7.7.-. [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]

Interferon: A biological response modifier (a substance that can improve the body's natural response to disease). Interferons interfere with the division of cancer cells and can slow tumor growth. There are several types of interferons, including interferon-alpha, -beta, and -gamma. These substances are normally produced by the body. They are also made in the laboratory for use in treating cancer and other diseases. [NIH]

Interferon-alpha: One of the type I interferons produced by peripheral blood leukocytes or lymphoblastoid cells when exposed to live or inactivated virus, double-stranded RNA, or bacterial products. It is the major interferon produced by virus-induced leukocyte cultures and, in addition to its pronounced antiviral activity, it causes activation of NK cells. [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]

Intestinal Mucosa: The surface lining of the intestines where the cells absorb nutrients. [NIH]

Intestine: A long, tube-shaped organ in the abdomen that completes the process of digestion. There is both a large intestine and a small intestine. Also called the bowel. [NIH]

Intoxication: Poisoning, the state of being poisoned. [EU]

Intracellular: Inside a cell. [NIH]

Intracellular Membranes: Membranes of subcellular structures. [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]

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]

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]

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]

Iron Chelating Agents: Organic chemicals that form two or more coordination links with an iron ion. Once coordination has occurred, the complex formed is called a chelate. The iron-binding porphyrin group of hemoglobin is an example of a metal chelate found in biological systems. [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]

Irreversible toxicity: Side effects that are caused by toxic substances or something harmful to the body and do not go away. [NIH]

Ischemia: Deficiency of blood in a part, due to functional constriction or actual obstruction of a blood vessel. [EU]

Isoelectric: Separation of amphoteric substances, dissolved in water, based on their isoelectric behavior. The amphoteric substances are a mixture of proteins to be separated and of auxiliary "carrier ampholytes". [NIH]

Isoelectric Focusing: Electrophoresis in which a pH gradient is established in a gel medium and proteins migrate until they reach the site (or focus) at which the pH is equal to their isoelectric point. [NIH]

Isoelectric Point: The pH in solutions of proteins and related compounds at which the dipolar ions are at a maximum. [NIH]

Isoleucine: An essential branched-chain amino acid found in many proteins. It is an isomer of LEUCINE. It is important in hemoglobin synthesis and regulation of blood sugar and energy levels. [NIH]

Karyotypes: The characteristic chromosome complement of an individual, race, or species as defined by their number, size, shape, etc. [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]

Ketoacidosis: Acidosis accompanied by the accumulation of ketone bodies (ketosis) in the body tissues and fluids, as in diabetic acidosis. [EU]

Ketone Bodies: Chemicals that the body makes when there is not enough insulin in the blood and it must break down fat for its energy. Ketone bodies can poison and even kill body cells. When the body does not have the help of insulin, the ketones build up in the blood and then "spill" over into the urine so that the body can get rid of them. The body can also rid itself of one type of ketone, called acetone, through the lungs. This gives the breath a

fruity odor. Ketones that build up in the body for a long time lead to serious illness and coma. [NIH]

Ketosis: A condition of having ketone bodies build up in body tissues and fluids. The signs of ketosis are nausea, vomiting, and stomach pain. Ketosis can lead to ketoacidosis. [NIH]

Kinetic: Pertaining to or producing motion. [EU]

Labile: 1. Gliding; moving from point to point over the surface; unstable; fluctuating. 2. Chemically unstable. [EU]

Lacrimal: Pertaining to the tears. [EU]

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]

Lead Poisoning: Disease caused by the gradual accumulation of a significant body burden of lead. [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]

Leiomyoma: A benign tumor derived from smooth muscle tissue, also known as a fibroid tumor. They rarely occur outside of the uterus and the gastrointestinal tract but can occur in the skin and subcutaneous tissues, probably arising from the smooth muscle of small blood vessels in these tissues. [NIH]

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]

Leptin: A 16-kD peptide hormone secreted from white adipocytes and implicated in the regulation of food intake and energy balance. Leptin provides the key afferent signal from fat cells in the feedback system that controls body fat stores. [NIH]

Lesion: An area of abnormal tissue change. [NIH]

Lethal: Deadly, fatal. [EU]

Leucocyte: All the white cells of the blood and their precursors (myeloid cell series, lymphoid cell series) but commonly used to indicate granulocytes exclusive of lymphocytes. [NIH]

Leukaemia: An acute or chronic disease of unknown cause in man and other warm-blooded animals that involves the blood-forming organs, is characterized by an abnormal increase in the number of leucocytes in the tissues of the body with or without a corresponding increase of those in the circulating blood, and is classified according of the type leucocyte most prominently involved. [EU]

Leukapheresis: The preparation of leukocyte concentrates with the return of red cells and leukocyte-poor plasma to the donor. [NIH]

Leukemia: Cancer of blood-forming tissue. [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]

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]

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]

Liver: A large, glandular organ located in the upper abdomen. The liver cleanses the blood and aids in digestion by secreting bile. [NIH]

Liver Transplantation: The transference of a part of or an entire liver from one human or animal to another. [NIH]

Lobe: A portion of an organ such as the liver, lung, breast, or brain. [NIH]

Localization: The process of determining or marking the location or site of a lesion or disease. May also refer to the process of keeping a lesion or disease in a specific location or site. [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]

Long-Term Care: Care over an extended period, usually for a chronic condition or disability, requiring periodic, intermittent, or continuous care. [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]

Lymph: The almost colorless fluid that travels through the lymphatic system and carries cells that help fight infection and disease. [NIH]

Lymph node: A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Also known as a lymph gland. Lymph nodes are spread out along lymphatic vessels and contain many lymphocytes, which filter the lymphatic fluid (lymph). [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]

Lymphocytes: White blood cells formed in the body's lymphoid tissue. The nucleus is round or ovoid with coarse, irregularly clumped chromatin while the cytoplasm is typically pale blue with azurophilic (if any) granules. Most lymphocytes can be classified as either T or B

(with subpopulations of each); those with characteristics of neither major class are called null cells. [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]

Lysine: An essential amino acid. It is often added to animal feed. [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]

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]

Mammary: Pertaining to the mamma, or breast. [EU]

Mammogram: An x-ray of the breast. [NIH]

Mandible: The largest and strongest bone of the face constituting the lower jaw. It supports the lower teeth. [NIH]

Mastication: The act and process of chewing and grinding food in the mouth. [NIH]

Mastitis: Inflammatory disease of the breast, or mammary gland. [NIH]

Maxillary: Pertaining to the maxilla : the irregularly shaped bone that with its fellow forms the upper jaw. [EU]

Maxillary Nerve: The intermediate sensory division of the trigeminal (5th cranial) nerve. The maxillary nerve carries general afferents from the intermediate region of the face including the lower eyelid, nose and upper lip, the maxillary teeth, and parts of the dura. [NIH]

Mediate: Indirect; accomplished by the aid of an intervening medium. [EU]

Medicament: A medicinal substance or agent. [EU]

MEDLINE: An online database of MEDLARS, the computerized bibliographic Medical Literature Analysis and Retrieval System of the National Library of Medicine. [NIH]

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]

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]

Meningitis: Inflammation of the meninges. When it affects the dura mater, the disease is termed pachymeningitis; when the arachnoid and pia mater are involved, it is called leptomeningitis, or meningitis proper. [EU]

Mental: Pertaining to the mind; psychic. 2. (L. mentum chin) pertaining to the chin. [EU]

Mental Health: The state wherein the person is well adjusted. [NIH]

Mental Processes: Conceptual functions or thinking in all its forms. [NIH]

Mental Retardation: Refers to sub-average general intellectual functioning which originated during the developmental period and is associated with impairment in adaptive behavior. [NIH]

Mesoderm: The middle germ layer of the embryo. [NIH]

Metabolite: Any substance produced by metabolism or by a metabolic process. [EU]

Methyltransferase: A drug-metabolizing enzyme. [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]

Microcalcifications: Tiny deposits of calcium in the breast that cannot be felt but can be detected on a mammogram. A cluster of these very small specks of calcium may indicate that cancer is present. [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]

Mineralization: The action of mineralizing; the state of being mineralized. [EU]

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]

Mobilization: The process of making a fixed part or stored substance mobile, as by separating a part from surrounding structures to make it accessible for an operative procedure or by causing release into the circulation for body use of a substance stored in the body. [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 Chaperones: A family of cellular proteins that mediate the correct assembly or disassembly of other polypeptides, and in some cases their assembly into oligomeric structures, but which are not components of those final structures. It is believed that chaperone proteins assist polypeptides to self-assemble by inhibiting alternative assembly pathways that produce nonfunctional structures. Some classes of molecular chaperones are the nucleoplasmins, the chaperonins, the heat-shock proteins 70, and the heat-shock proteins 90. [NIH]

Molecular Probes: A group of atoms or molecules attached to other molecules or cellular structures and used in studying the properties of these molecules and structures. Radioactive DNA or RNA sequences are used in molecular genetics to detect the presence of a complementary sequence by molecular hybridization. [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]

Monocytes: Large, phagocytic mononuclear leukocytes produced in the vertebrate bone marrow and released into the blood; contain a large, oval or somewhat indented nucleus surrounded by voluminous cytoplasm and numerous organelles. [NIH]

Monogenic: A human disease caused by a mutation in a single gene. [NIH]

Mononuclear: A cell with one nucleus. [NIH]

Monotherapy: A therapy which uses only one drug. [EU]

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]

Mucosa: A mucous membrane, or tunica mucosa. [EU]

Multicenter study: A clinical trial that is carried out at more than one medical institution. [NIH]

Muscular Diseases: Acquired, familial, and congenital disorders of skeletal muscle and smooth muscle. [NIH]

Mustard Gas: Severe irritant and vesicant of skin, eyes, and lungs. It may cause blindness and lethal lung edema and was formerly used as a war gas. The substance has been proposed as a cytostatic and for treatment of psoriasis. It has been listed as a known carcinogen in the Fourth Annual Report on Carcinogens (NTP-85-002, 1985) (Merck, 11th ed). [NIH]

Mutagen: Any agent, such as X-rays, gamma rays, mustard gas, TCDD, that can cause abnormal mutation in living cells; having the power to cause mutations. [NIH]

Mutagenesis: Process of generating genetic mutations. It may occur spontaneously or be induced by mutagens. [NIH]

Myelodysplasia: Abnormal bone marrow cells that may lead to myelogenous leukemia. [NIH]

Myelodysplastic Syndromes: Conditions in which the bone marrow shows qualitative and quantitative changes suggestive of a preleukemic process, but having a chronic course that does not necessarily terminate as acute leukemia. [NIH]

Myelogenous: Produced by, or originating in, the bone marrow. [NIH]

Myeloid Cells: Cells which include the monocytes and the granulocytes. [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]

Myocardial Reperfusion: Generally, restoration of blood supply to heart tissue which is ischemic due to decrease in normal blood supply. The decrease may result from any source including atherosclerotic obstruction, narrowing of the artery, or surgical clamping. Reperfusion can be induced to treat ischemia. Methods include chemical dissolution of an occluding thrombus, administration of vasodilator drugs, angioplasty, catheterization, and artery bypass graft surgery. However, it is thought that reperfusion can itself further damage the ischemic tissue, causing myocardial reperfusion injury. [NIH]

Myocardial Reperfusion Injury: Functional, metabolic, or structural changes in ischemic heart muscle thought to result from reperfusion to the ischemic areas. Changes can be fatal to muscle cells and may include edema with explosive cell swelling and disintegration, sarcolemma disruption, fragmentation of mitochondria, contraction band necrosis, enzyme washout, and calcium overload. Other damage may include hemorrhage and ventricular arrhythmias. One possible mechanism of damage is thought to be oxygen free radicals. Treatment currently includes the introduction of scavengers of oxygen free radicals, and injury is thought to be prevented by warm blood cardioplegic infusion prior to reperfusion. [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]

Myotonia: Prolonged failure of muscle relaxation after contraction. This may occur after voluntary contractions, muscle percussion, or electrical stimulation of the muscle. Myotonia is a characteristic feature of myotonic disorders. [NIH]

Natural selection: A part of the evolutionary process resulting in the survival and reproduction of the best adapted individuals. [NIH]

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]

Needle biopsy: The removal of tissue or fluid with a needle for examination under a microscope. Also called fine-needle aspiration. [NIH]

Neomycin: Antibiotic complex produced by Streptomyces fradiae. It is composed of neomycins A, B, and C. It acts by inhibiting translation during protein synthesis. [NIH]

Neonatal: Pertaining to the first four weeks after birth. [EU]

Neoplasia: Abnormal and uncontrolled cell growth. [NIH]

Neoplasm: A new growth of benign or malignant tissue. [NIH]

Nephropathy: Disease of the kidneys. [EU]

Neuralgia: Intense or aching pain that occurs along the course or distribution of a peripheral or cranial nerve. [NIH]

Neurologic: Having to do with nerves or the nervous system. [NIH]

Neuromuscular: Pertaining to muscles and nerves. [EU]

Neurotransmitter: Any of a group of substances that are released on excitation from the axon terminal of a presynaptic neuron of the central or peripheral nervous system and travel across the synaptic cleft to either excite or inhibit the target cell. Among the many substances that have the properties of a neurotransmitter are acetylcholine, norepinephrine, epinephrine, dopamine, glycine, y-aminobutyrate, glutamic acid, substance P, enkephalins, endorphins, and serotonin. [EU]

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]

Neutropenia: An abnormal decrease in the number of neutrophils, a type of white blood cell. [NIH]

Neutrophil: A type of white blood cell. [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]

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]

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]

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]

Ophthalmic: Pertaining to the eye. [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]

Orofacial: Of or relating to the mouth and face. [EU]

Osteomalacia: A condition marked by softening of the bones (due to impaired mineralization, with excess accumulation of osteoid), with pain, tenderness, muscular weakness, anorexia, and loss of weight, resulting from deficiency of vitamin D and calcium. [EU]

Osteonecrosis: Death of a bone or part of a bone, either atraumatic or posttraumatic. [NIH]

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]

Ovum: A female germ cell extruded from the ovary at ovulation. [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]

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]

Pachymeningitis: Inflammation of the dura mater of the brain, the spinal cord or the optic nerve. [NIH]

Palliative: 1. Affording relief, but not cure. 2. An alleviating medicine. [EU]

Palsy: Disease of the peripheral nervous system occurring usually after many years of increased lead absorption. [NIH]

Pamidronate: A drug that belongs to the family of drugs called bisphosphonates. Pamidronate is used as treatment for abnormally high levels of calcium in the blood. [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]

Papillary: Pertaining to or resembling papilla, or nipple. [EU]

Papillary Muscles: Conical muscular projections from the walls of the cardiac ventricles, attached to the cusps of the atrioventricular valves by the chordae tendineae. [NIH]

Paraplegia: Severe or complete loss of motor function in the lower extremities and lower portions of the trunk. This condition is most often associated with spinal cord diseases, although brain diseases; peripheral nervous system diseases; neuromuscular diseases; and muscular diseases may also cause bilateral leg weakness. [NIH]

Parasite: An animal or a plant that lives on or in an organism of another species and gets at least some of its nutrition from that other organism. [NIH]

Parathyroid: 1. Situated beside the thyroid gland. 2. One of the parathyroid glands. 3. A sterile preparation of the water-soluble principle(s) of the parathyroid glands, ad-ministered parenterally as an antihypocalcaemic, especially in the treatment of acute hypoparathyroidism with tetany. [EU]

Parathyroid Glands: Two small paired endocrine glands in the region of the thyroid gland. They secrete parathyroid hormone and are concerned with the metabolism of calcium and phosphorus. [NIH]

Parenteral: Not through the alimentary canal but rather by injection through some other route, as subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, etc. [EU]

Parity: The number of offspring a female has borne. It is contrasted with gravidity, which refers to the number of pregnancies, regardless of outcome. [NIH]

Partial remission: The shrinking, but not complete disappearance, of a tumor in response to therapy. Also called partial response. [NIH]

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]

Patch: A piece of material used to cover or protect a wound, an injured part, etc.: a patch over the eye. [NIH]

Pathogen: Any disease-producing microorganism. [EU]

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]

Pathophysiology: Altered functions in an individual or an organ due to disease. [NIH]

Patient Compliance: Voluntary cooperation of the patient in following a prescribed regimen. [NIH]

Patient Education: The teaching or training of patients concerning their own health needs. [NIH]

Pedigree: A record of one's ancestors, offspring, siblings, and their offspring that may be used to determine the pattern of certain genes or disease inheritance within a family. [NIH]

Pelvis: The lower part of the abdomen, located between the hip bones. [NIH]

Penicillamine: 3-Mercapto-D-valine. The most characteristic degradation product of the penicillin antibiotics. It is used as an antirheumatic and as a chelating agent in Wilson's disease. [NIH]

Penicillin: An antibiotic drug used to treat infection. [NIH]

Peptide: Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [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]

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]

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]

Phagocyte: An immune system cell that can surround and kill microorganisms and remove dead cells. Phagocytes include macrophages. [NIH]

Phagocytosis: The engulfing of microorganisms, other cells, and foreign particles by phagocytic cells. [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]

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]

Phlebotomy: The letting of blood from a vein. Although it is one of the techniques used in drawing blood to be used in diagnostic procedures, in modern medicine, it is used commonly in the treatment of erythrocytosis, hemochromocytosis, polycythemia vera, and porphyria cutanea tarda. Its historical counterpart is bloodletting. (From Cecil Textbook of Medicine, 19th ed & Wintrobe's Clinical Hematology, 9th ed) Venipuncture is not only for the letting of blood from a vein but also for the injecting of a drug into the vein for diagnostic analysis. [NIH]

Phospholipases: A class of enzymes that catalyze the hydrolysis of phosphoglycerides or glycerophosphatidates. EC 3.1.-. [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]

Phosphorylated: Attached to a phosphate group. [NIH]

Phosphorylates: Attached to a phosphate group. [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]

Physical Examination: Systematic and thorough inspection of the patient for physical signs of disease or abnormality. [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]

Pituitary Gland: A small, unpaired gland situated in the sella turcica tissue. It is connected to the hypothalamus by a short stalk. [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]

Placental blood transplantation: The transfer of blood from a placenta to an individual whose own blood production system is suppressed. Placental blood contains high levels of stem cells needed to produce new blood cells. It is being studied in the treatment of cancer and severe blood disorders such as aplastic anemia. Also called umbilical cord blood transplant. [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]

Plasmapheresis: Procedure whereby plasma is separated and extracted from anticoagulated whole blood and the red cells retransfused to the donor. Plasmapheresis is also employed for therapeutic use. [NIH]

Plasmids: Any extrachromosomal hereditary determinant. Plasmids are self-replicating circular molecules of DNA that are found in a variety of bacterial, archaeal, fungal, algal, and plant species. [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 Activation: A series of progressive, overlapping events triggered by exposure of the platelets to subendothelial tissue. These events include shape change, adhesiveness, aggregation, and release reactions. When carried through to completion, these events lead to the formation of a stable hemostatic plug. [NIH]

Plateletpheresis: The preparation of platelet concentrates with the return of red cells and platelet-poor plasma to the donor. [NIH]

Platelets: A type of blood cell that helps prevent bleeding by causing blood clots to form. Also called thrombocytes. [NIH]

Pneumonia: Inflammation of the lungs. [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]

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]

Pons: The part of the central nervous system lying between the medulla oblongata and the mesencephalon, ventral to the cerebellum, and consisting of a pars dorsalis and a pars ventralis. [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]

Porphyria Cutanea Tarda: A form of hepatic porphyria (porphyria, hepatic) characterized by photosensitivity resulting in bullae that rupture easily to form shallow ulcers. This condition occurs in two forms: a sporadic, nonfamilial form that begins in middle age and has normal amounts of uroporphyrinogen decarboxylase with diminished activity in the liver; and a familial form in which there is an autosomal dominant inherited deficiency of uroporphyrinogen decarboxylase in the liver and red blood cells. [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]

Postsynaptic: Nerve potential generated by an inhibitory hyperpolarizing stimulation. [NIH]

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]

Potentiation: An overall effect of two drugs taken together which is greater than the sum of the effects of each drug taken alone. [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]

Precipitation: The act or process of precipitating. [EU]

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]

Preimplantation Diagnosis: Determination of the nature of a pathological condition or disease in the ovum, zygote, or blastocyst prior to implantation. Cytogenetic analysis is performed to determine the presence or absence of genetic disease. [NIH]

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]

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]

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]

Prodrug: A substance that gives rise to a pharmacologically active metabolite, although not itself active (i. e. an inactive precursor). [NIH]

Progeny: The offspring produced in any generation. [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]

Proinsulin: The substance made first in the pancreas that is then made into insulin. When insulin is purified from the pancreas of pork or beef, all the proinsulin is not fully removed. When some people use these insulins, the proinsulin can cause the body to react with a rash, to resist the insulin, or even to make dents or lumps in the skin at the place where the insulin is injected. The purified insulins have less proinsulin and other impurities than the other types of insulins. [NIH]

Promoter: A chemical substance that increases the activity of a carcinogenic process. [NIH]

Prophylaxis: An attempt to prevent disease. [NIH]

Prosthesis: An artificial replacement of a part of the body. [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 Conformation: The characteristic 3-dimensional shape of a protein, including the secondary, supersecondary (motifs), tertiary (domains) and quaternary structure of the peptide chain. Quaternary protein structure describes the conformation assumed by multimeric proteins (aggregates of more than one polypeptide chain). [NIH]

Protein Folding: A rapid biochemical reaction involved in the formation of proteins. It begins even before a protein has been completely synthesized and proceeds through discrete intermediates (primary, secondary, and tertiary structures) before the final structure (quaternary structure) is developed. [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]

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]

Proteome: The protein complement of an organism coded for by its genome. [NIH]

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]

Protozoa: A subkingdom consisting of unicellular organisms that are the simplest in the animal kingdom. Most are free living. They range in size from submicroscopic to macroscopic. Protozoa are divided into seven phyla: Sarcomastigophora, Labyrinthomorpha, Apicomplexa, Microspora, Ascetospora, Myxozoa, and Ciliophora. [NIH]

Protozoal: Having to do with the simplest organisms in the animal kingdom. Protozoa are single-cell organisms, such as ameba, and are different from bacteria, which are not members of the animal kingdom. Some protozoa can be seen without a microscope. [NIH]

Protozoan: 1. Any individual of the protozoa; protozoon. 2. Of or pertaining to the protozoa; protozoal. [EU]

Proximal: Nearest; closer to any point of reference; opposed to distal. [EU]

Pseudoxanthoma: A rare disease of the skin characterized by the appearance of elevated yellowish papules or plaques, particularly on the neck, chest an abdomen and infrequently on the eyelids. [NIH]

Pseudoxanthoma Elasticum: A rare, progressive inherited disorder resulting from extensive basophilic degeneration of elastic tissue, usually presenting after puberty and involving the skin, eye, and cardiovascular system. Characteristic manifestations are small, circumscribed yellowish patches at sites of considerable movement of the skin, angioid streaks in the retina, and a tendency towards hemorrhage and arterial insufficiency. [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]

Puberty: The period during which the secondary sex characteristics begin to develop and the capability of sexual reproduction is attained. [EU]

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 hypertension: Abnormally high blood pressure in the arteries of the lungs. [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]

Purified Insulins: Insulins with much less of the impure proinsulin. It is thought that the use of purified insulins may help avoid or reduce some of the problems of people with diabetes such as allergic reactions. [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]

Purpura: Purplish or brownish red discoloration, easily visible through the epidermis, caused by hemorrhage into the tissues. [NIH]

Pyrimidines: A family of 6-membered heterocyclic compounds occurring in nature in a wide variety of forms. They include several nucleic acid constituents (cytosine, thymine, and uracil) and form the basic structure of the barbiturates. [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]

Quaternary: 1. Fourth in order. 2. Containing four elements or groups. [EU]

Quiescent: Marked by a state of inactivity or repose. [EU]

Quinine: An alkaloid derived from the bark of the cinchona tree. It is used as an antimalarial drug, and is the active ingredient in extracts of the cinchona that have been used for that purpose since before 1633. Quinine is also a mild antipyretic and analgesic and has been used in common cold preparations for that purpose. It was used commonly and as a bitter and flavoring agent, and is still useful for the treatment of babesiosis. Quinine is also useful in some muscular disorders, especially nocturnal leg cramps and myotonia congenita, because of its direct effects on muscle membrane and sodium channels. The mechanisms of its antimalarial effects are not well understood. [NIH]

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 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]

Radiolabeled: Any compound that has been joined with a radioactive substance. [NIH]

Radiological: Pertaining to radiodiagnostic and radiotherapeutic procedures, and interventional radiology or other planning and guiding medical radiology. [NIH]

Radiology: A specialty concerned with the use of x-ray and other forms of radiant energy in the diagnosis and treatment of disease. [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]

Random Allocation: A process involving chance used in therapeutic trials or other research endeavor for allocating experimental subjects, human or animal, between treatment and control groups, or among treatment groups. It may also apply to experiments on inanimate objects. [NIH]

Randomization: Also called random allocation. Is allocation of individuals to groups, e.g., for experimental and control regimens, by chance. Within the limits of chance variation, random allocation should make the control and experimental groups similar at the start of an investigation and ensure that personal judgment and prejudices of the investigator do not influence allocation. [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]

Randomized clinical trial: A study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best. It is the patient's choice to be in a randomized trial. [NIH]

Reactivation: The restoration of activity to something that has been inactivated. [EU]

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]

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]

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]

Reductase: Enzyme converting testosterone to dihydrotestosterone. [NIH]

Refer: To send or direct for treatment, aid, information, de decision. [NIH]

Refraction: A test to determine the best eyeglasses or contact lenses to correct a refractive error (myopia, hyperopia, or astigmatism). [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]

Reliability: Used technically, in a statistical sense, of consistency of a test with itself, i. e. the extent to which we can assume that it will yield the same result if repeated a second time. [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]

Reperfusion: Restoration of blood supply to tissue which is ischemic due to decrease in normal blood supply. The decrease may result from any source including atherosclerotic obstruction, narrowing of the artery, or surgical clamping. It is primarily a procedure for treating infarction or other ischemia, by enabling viable ischemic tissue to recover, thus limiting further necrosis. However, it is thought that reperfusion can itself further damage the ischemic tissue, causing reperfusion injury. [NIH]

Reperfusion Injury: Functional, metabolic, or structural changes, including necrosis, in ischemic tissues thought to result from reperfusion to ischemic areas of the tissue. The most common instance is myocardial reperfusion injury. [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]

Reproductive cells: Egg and sperm cells. Each mature reproductive cell carries a single set of 23 chromosomes. [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]

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]

Retrospective: Looking back at events that have already taken place. [NIH]

Retroviral vector: RNA from a virus that is used to insert genetic material into cells. [NIH]

Retrovirus: A member of a group of RNA viruses, the RNA of which is copied during viral replication into DNA by reverse transcriptase. The viral DNA is then able to be integrated into the host chromosomal DNA. [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]

Rhinitis: Inflammation of the mucous membrane of the nose. [NIH]

Ribavirin: 1-beta-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide. A nucleoside antimetabolite antiviral agent that blocks nucleic acid synthesis and is used against both RNA and DNA viruses. [NIH]

Ribonuclease: RNA-digesting enzyme. [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]

Ribosome: A granule of protein and RNA, synthesized in the nucleolus and found in the cytoplasm of cells. Ribosomes are the main sites of protein synthesis. Messenger RNA attaches to them and there receives molecules of transfer RNA bearing amino acids. [NIH]

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]

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]

Saphenous: Applied to certain structures in the leg, e. g. nerve vein. [NIH]

Saphenous Vein: The vein which drains the foot and leg. [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]

Screening: Checking for disease when there are no symptoms. [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]

Sedimentation: The act of causing the deposit of sediment, especially by the use of a centrifugal machine. [EU]

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]

Senile: Relating or belonging to old age; characteristic of old age; resulting from infirmity of old age. [NIH]

Sensory loss: A disease of the nerves whereby the myelin or insulating sheath of myelin on the nerves does not stay intact and the messages from the brain to the muscles through the nerves are not carried properly. [NIH]

Septicaemia: A term originally used to denote a putrefactive process in the body, but now usually referring to infection with pyogenic micro-organisms; a genus of Diptera; the severe type of infection in which the blood stream is invaded by large numbers of the causal. [NIH]

Septicemia: Systemic disease associated with the presence and persistence of pathogenic microorganisms or their toxins in the blood. Called also blood poisoning. [EU]

Sequence Analysis: A multistage process that includes the determination of a sequence (protein, carbohydrate, etc.), its fragmentation and analysis, and the interpretation of the resulting sequence information. [NIH]

Sequencing: The determination of the order of nucleotides in a DNA or RNA chain. [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]

Serologic: Analysis of a person's serum, especially specific immune or lytic serums. [NIH]

Serotypes: A cause of haemorrhagic septicaemia (in cattle, sheep and pigs), fowl cholera of birds, pasteurellosis of rabbits, and gangrenous mastitis of ewes. It is also commonly found in atrophic rhinitis of pigs. [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]

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]

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]

Signs and Symptoms: Clinical manifestations that can be either objective when observed by a physician, or subjective when perceived by the patient. [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]

Small intestine: The part of the digestive tract that is located between the stomach and the large intestine. [NIH]

Smooth muscle: Muscle that performs automatic tasks, such as constricting blood vessels. [NIH]

Social Environment: The aggregate of social and cultural institutions, forms, patterns, and processes that influence the life of an individual or community. [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]

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]

Soma: The body as distinct from the mind; all the body tissue except the germ cells; all the axial body. [NIH]

Somatic: 1. Pertaining to or characteristic of the soma or body. 2. Pertaining to the body wall in contrast to the viscera. [EU]

Somatic mutations: Alterations in DNA that occur after conception. Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. These alterations can (but do not always) cause cancer or other diseases. [NIH]

Spasm: An involuntary contraction of a muscle or group of muscles. Spasms may involve skeletal muscle or smooth muscle. [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]

Spectroscopic: The recognition of elements through their emission spectra. [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 Compression: Acute and chronic conditions characterized by external mechanical compression of the spinal cord due to extramedullary neoplasm; epidural abscess; spinal fractures; bony deformities of the vertebral bodies; and other conditions. Clinical manifestations vary with the anatomic site of the lesion and may include localized pain, weakness, sensory loss, incontinence, and impotence. [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]

Spinal Fractures: Broken bones in the vertebral column. [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]

Splenectomy: An operation to remove the spleen. [NIH]

Splenomegaly: Enlargement of the spleen. [NIH]

Sporadic: Neither endemic nor epidemic; occurring occasionally in a random or isolated manner. [EU]

Stabilization: The creation of a stable state. [EU]

Standard therapy: A currently accepted and widely used treatment for a certain type of cancer, based on the results of past research. [NIH]

Status Epilepticus: Repeated and prolonged epileptic seizures without recovery of consciousness between attacks. [NIH]

Steel: A tough, malleable, iron-based alloy containing up to, but no more than, two percent carbon and often other metals. It is used in medicine and dentistry in implants and instrumentation. [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]

Stool: The waste matter discharged in a bowel movement; feces. [NIH]

Strand: DNA normally exists in the bacterial nucleus in a helix, in which two strands are coiled together. [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]

Structure-Activity Relationship: The relationship between the chemical structure of a compound and its biological or pharmacological activity. Compounds are often classed together because they have structural characteristics in common including shape, size, stereochemical arrangement, and distribution of functional groups. Other factors contributing to structure-activity relationship include chemical reactivity, electronic effects, resonance, and inductive effects. [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]

Superoxide: Derivative of molecular oxygen that can damage cells. [NIH]

Superoxide Dismutase: An oxidoreductase that catalyzes the reaction between superoxide anions and hydrogen to yield molecular oxygen and hydrogen peroxide. The enzyme protects the cell against dangerous levels of superoxide. EC 1.15.1.1. [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]

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]

Symptomatic: Having to do with symptoms, which are signs of a condition or disease. [NIH]

Synaptic: Pertaining to or affecting a synapse (= site of functional apposition between neurons, at which an impulse is transmitted from one neuron to another by electrical or chemical means); pertaining to synapsis (= pairing off in point-for-point association of homologous chromosomes from the male and female pronuclei during the early prophase of meiosis). [EU]

Systemic: Affecting the entire body. [NIH]

Systolic: Indicating the maximum arterial pressure during contraction of the left ventricle of the heart. [EU]

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]

Tetanus: A disease caused by tetanospasmin, a powerful protein toxin produced by Clostridium tetani. Tetanus usually occurs after an acute injury, such as a puncture wound or laceration. Generalized tetanus, the most common form, is characterized by tetanic muscular contractions and hyperreflexia. Localized tetanus presents itself as a mild condition with manifestations restricted to muscles near the wound. It may progress to the generalized form. [NIH]

Tetany: 1. Hyperexcitability of nerves and muscles due to decrease in concentration of extracellular ionized calcium, which may be associated with such conditions as parathyroid hypofunction, vitamin D deficiency, and alkalosis or result from ingestion of alkaline salts; it is characterized by carpopedal spasm, muscular twitching and cramps, laryngospasm with inspiratory stridor, hyperreflexia and choreiform movements. 2. Tetanus. [EU]

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]

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]

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]

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]

Thymus: An organ that is part of the lymphatic system, in which T lymphocytes grow and multiply. The thymus is in the chest behind the breastbone. [NIH]

Thyroid: A gland located near the windpipe (trachea) that produces thyroid hormone, which helps regulate growth and metabolism. [NIH]

Thyroid Gland: A highly vascular endocrine gland consisting of two lobes, one on either side of the trachea, joined by a narrow isthmus; it produces the thyroid hormones which are concerned in regulating the metabolic rate of the body. [NIH]

Thyroxine: An amino acid of the thyroid gland which exerts a stimulating effect on thyroid metabolism. [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]

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]

Topical: On the surface of the body. [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]

Toxicokinetics: Study of the absorption, distribution, metabolism, and excretion of test substances. [NIH]

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]

Toxin: A poison; frequently used to refer specifically to a protein produced by some higher plants, certain animals, and pathogenic bacteria, which is highly toxic for other living organisms. Such substances are differentiated from the simple chemical poisons and the vegetable alkaloids by their high molecular weight and antigenicity. [EU]

Trace element: Substance or element essential to plant or animal life, but present in extremely small amounts. [NIH]

Trachea: The cartilaginous and membranous tube descending from the larynx and branching into the right and left main bronchi. [NIH]

Trachoma: A chronic infection of the conjunctiva and cornea caused by Chlamydia trachomatis. [NIH]

Transcriptase: An enzyme which catalyses the synthesis of a complementary mRNA molecule from a DNA template in the presence of a mixture of the four ribonucleotides (ATP, UTP, GTP and CTP). [NIH]

Transcription Factors: Endogenous substances, usually proteins, which are effective in the initiation, stimulation, or termination of the genetic transcription process. [NIH]

Transdermal: Entering through the dermis, or skin, as in administration of a drug applied to the skin in ointment or patch form. [EU]

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]

Transient Ischemic Attacks: Focal neurologic abnormalities of sudden onset and brief duration that reflect dysfunction in the distribution of the internal carotid-middle cerebral or the vertebrobasilar arterial system. [NIH]

Translation: The process whereby the genetic information present in the linear sequence of ribonucleotides in mRNA is converted into a corresponding sequence of amino acids in a protein. It occurs on the ribosome and is unidirectional. [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]

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]

Trigeminal: Cranial nerve V. It is sensory for the eyeball, the conjunctiva, the eyebrow, the skin of face and scalp, the teeth, the mucous membranes in the mouth and nose, and is motor to the muscles of mastication. [NIH]

Trigeminal Nerve: The 5th and largest cranial nerve. The trigeminal nerve is a mixed motor and sensory nerve. The larger sensory part forms the ophthalmic, mandibular, and maxillary nerves which carry afferents sensitive to external or internal stimuli from the skin, muscles, and joints of the face and mouth and from the teeth. Most of these fibers originate from cells of the trigeminal ganglion and project to the trigeminal nucleus of the brain stem. The smaller motor part arises from the brain stem trigeminal motor nucleus and innervates the muscles of mastication. [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]

Trismus: Spasmodic contraction of the masseter muscle resulting in forceful jaw closure. This may be seen with a variety of diseases, including tetanus, as a complication of radiation therapy, trauma, or in association with neoplastic conditions. [NIH]

Tropism: Directed movements and orientations found in plants, such as the turning of the sunflower to face the sun. [NIH]

Truncal: The bilateral dissection of the abdominal branches of the vagus nerve. [NIH]

Trypanosomiasis: Infection with protozoa of the genus Trypanosoma. [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]

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]

Tunica: A rather vague term to denote the lining coat of hollow organs, tubes, or cavities. [NIH]

Type 2 diabetes: Usually characterized by a gradual onset with minimal or no symptoms of metabolic disturbance and no requirement for exogenous insulin. The peak age of onset is 50 to 60 years. Obesity and possibly a genetic factor are usually present. [NIH]

Tyrosine: A non-essential amino acid. In animals it is synthesized from phenylalanine. It is also the precursor of epinephrine, thyroid hormones, and melanin. [NIH]

Ubiquitin: A highly conserved 76 amino acid-protein found in all eukaryotic cells. [NIH]

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]

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]

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]

Urethra: The tube through which urine leaves the body. It empties urine from the bladder. [NIH]

Urinary: Having to do with urine or the organs of the body that produce and get rid of urine. [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]

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]

Vaccination: Administration of vaccines to stimulate the host's immune response. This includes any preparation intended for active immunological prophylaxis. [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]

Vagus Nerve: The 10th cranial nerve. The vagus is a mixed nerve which contains somatic afferents (from skin in back of the ear and the external auditory meatus), visceral afferents (from the pharynx, larynx, thorax, and abdomen), parasympathetic efferents (to the thorax and abdomen), and efferents to striated muscle (of the larynx and pharynx). [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]

Valves: Flap-like structures that control the direction of blood flow through the heart. [NIH]

Vascular: Pertaining to blood vessels or indicative of a copious blood supply. [EU]

Vascular endothelial growth factor: VEGF. A substance made by cells that stimulates new blood vessel formation. [NIH]

Vascular Resistance: An expression of the resistance offered by the systemic arterioles, and to a lesser extent by the capillaries, to the flow of blood. [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]

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]

Ventricular Dysfunction: A condition in which the ventricles of the heart exhibit a decreased functionality. [NIH]

Ventricular Function: The hemodynamic and electrophysiological action of the ventricles. [NIH]

Ventricular Remodeling: The geometric and structural changes that the ventricle

undergoes, usually following myocardial infarction. It comprises expansion of the infarct and dilatation of the healthy ventricle segments. While most prevalent in the left ventricle, it can also occur in the right ventricle. [NIH]

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]

Veterinary Medicine: The medical science concerned with the prevention, diagnosis, and treatment of diseases in animals. [NIH]

Villous: Of a surface, covered with villi. [NIH]

Viral: Pertaining to, caused by, or of the nature of virus. [EU]

Viral Hepatitis: Hepatitis caused by a virus. Five different viruses (A, B, C, D, and E) most commonly cause this form of hepatitis. Other rare viruses may also cause hepatitis. [NIH]

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]

Vitelline Membrane: The plasma membrane of the egg. [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]

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]

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]

Yolk Sac: An embryonic membrane formed from endoderm and mesoderm. In reptiles and birds it incorporates the yolk into the digestive tract for nourishing the embryo. In placental mammals its nutritional function is vestigial; however, it is the source of most of the intestinal mucosa and the site of formation of the germ cells. It is sometimes called the vitelline sac, which should not be confused with the vitelline membrane of the egg. [NIH]

Zebrafish: A species of North American fishes of the family Cyprinidae. They are used in embryological studies and to study the effects of certain chemicals on development. [NIH]

Zygote: The fertilized ovum. [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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