PRIMARY PULMONARY HYPERTENSION

A 3-in-1 Medical Reference

A Bibliography and Dictionary
for Physicians, Patients,
and Genome Researchers

TO INTERNET REFERENCES

ICON Group International, Inc.

PRIMARY PULMONARY HYPERTENSION

A Bibliography and Dictionary for Physicians, Patients, and Genome Researchers

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

ICON Health Publications
ICON Group International, Inc.
7404 Trade Street
San Diego, CA 92121 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.

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Cataloging-in-Publication Data

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

Primary Pulmonary Hypertension: A Bibliography and Dictionary for Physicians, Patients, and Genome Researchers/ James N. Parker and Philip M. Parker, editors
p. cm.
Includes bibliographical references, glossary, and index.
ISBN: 0-497-11280-9
1. Primary Pulmonary Hypertension-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 primary pulmonary hypertension. 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.

About the Editors

James N. Parker, M.D.

Dr. James N. Parker received his Bachelor of Science degree in Psychobiology from the University of California, Riverside and his M.D. from the University of California, San Diego. In addition to authoring numerous research publications, he has lectured at various academic institutions. Dr. Parker is the medical editor for health books by ICON Health Publications.

Philip M. Parker, Ph.D.

Philip M. Parker is the Chaired Professor of Management Science at INSEAD (Fontainebleau, France and Singapore). Dr. Parker has also been Professor at the University of California, San Diego and has taught courses at Harvard University, the Hong Kong University of Science and Technology, the Massachusetts Institute of Technology, Stanford University, and UCLA. Dr. Parker is the associate editor for ICON Health Publications.

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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 primary pulmonary hypertension 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 primary pulmonary hypertension, 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 primary pulmonary hypertension, from the essentials to the most advanced areas of research. Special attention has been paid to present the genetic basis and pattern of inheritance of primary pulmonary hypertension. 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 primary pulmonary hypertension. 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 primary pulmonary hypertension, 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. We hope these resources will prove useful to the widest possible audience seeking information on primary pulmonary hypertension.

The Editors

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/**.

CHAPTER 1. STUDIES ON PRIMARY PULMONARY HYPERTENSION

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on primary pulmonary hypertension. For those interested in basic information about primary pulmonary hypertension, we begin with a condition summary published by the National Library of Medicine.

Genetics Home Reference

Genetics Home Reference (GHR) is the National Library of Medicine's Web site for consumer information about genetic conditions and the genes or chromosomes responsible for those conditions. Here you can find a condition summary on primary pulmonary hypertension that describes the major features of the condition, provides information about the condition's genetic basis, and explains its pattern of inheritance. In addition, a summary of the gene or chromosome related to primary pulmonary hypertension is provided.[2]

The Genetics Home Reference has recently published the following summary for primary pulmonary hypertension:

What Is Pulmonary Arterial Hypertension?[3]

Pulmonary arterial hypertension is a progressive disorder characterized by abnormally high blood pressure (hypertension) in the pulmonary artery, the blood vessel that carries blood from the heart to the lungs. Hypertension occurs when most of the very small arteries throughout the lungs narrow in diameter, which increases the resistance to blood flow through the lungs. To overcome the increased resistance, pressure increases in the

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[2] This section has been adapted from the National Library of Medicine: **http://ghr.nlm.nih.gov/**.

[3] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/condition=primarypulmonaryhypertension**.

pulmonary artery and in the heart chamber that pumps blood into the pulmonary artery (the right ventricle).

Signs and symptoms of pulmonary arterial hypertension occur when increased pressure cannot fully overcome the elevated resistance and blood flow to the body is insufficient. Shortness of breath (dyspnea) during exertion and fainting spells are the most common symptoms of pulmonary arterial hypertension. People with this disorder may experience additional symptoms, particularly as the condition worsens. Other symptoms include dizziness, swelling (edema) of the ankles or legs, chest pain, and a racing pulse.

How Common Is Pulmonary Arterial Hypertension?

In the United States, about 1,000 new cases of pulmonary arterial hypertension are diagnosed each year. This disorder is twice as common in females as in males.

What Genes Are Related to Pulmonary Arterial Hypertension?

Mutations in the **BMPR2** (**http://ghr.nlm.nih.gov/gene=bmpr2**) gene cause pulmonary arterial hypertension.

The BMPR2 gene plays a role in regulating the number of cells in certain tissues. Researchers suggest that a mutation in this gene promotes cell division or prevents cell death, resulting in an overgrowth of cells in small arteries throughout the lungs. As a result, these arteries narrow in diameter, which increases the resistance to blood flow. Blood pressure in the pulmonary artery and the right ventricle of the heart increases to overcome the increased resistance to blood flow.

Other genes that have not yet been identified may also cause pulmonary arterial hypertension. In people with a BMPR2 mutation, other genes or environmental factors may contribute to the development of this disorder.

How Do People Inherit Pulmonary Arterial Hypertension?

This condition is inherited in an autosomal dominant pattern, which means each cell has one copy of an altered BMPR2 gene. In many cases, however, people with an altered BMPR2 gene never develop symptoms of pulmonary arterial hypertension.

Inherited cases of this disorder are known as familial pulmonary arterial hypertension. As the altered gene is passed down from one generation to the next, the disorder generally begins earlier in life. This phenomenon is called anticipation.

Most cases of pulmonary arterial hypertension, however, occur in individuals with no known family history of the disorder. These cases are known as idiopathic pulmonary arterial hypertension. Some idiopathic cases are due to mutations in the BMPR2 gene, but in most cases a gene mutation has not yet been identified.

Where Can I Find Additional Information about Pulmonary Arterial Hypertension?

You may find the following resources about pulmonary arterial hypertension helpful. These materials are written for the general public.

NIH Publications - National Institutes of Health

- **http://www.nhlbi.nih.gov/health/dci/Diseases/pah/pah_what.html**

MedlinePlus - Health Information

- Encyclopedia: Primary Pulmonary Hypertension:
  http://www.nlm.nih.gov/medlineplus/ency/article/000112.htm
- Health Topic: Pulmonary Hypertension:
  http://www.nlm.nih.gov/medlineplus/pulmonaryhypertension.html

Educational Resources - Information Pages

- Centers for Disease Control and Prevention (CDC):
  http://www.cdc.gov/dhdsp/library/fs_pulmonary_hypertension.htm
- Children's Hospital Boston:
  http://www.childrenshospital.org/az/Site510/mainpageS510P0.html
- Cincinnati Children's Hospital Medical Center:
  http://www.cincinnatichildrens.org/health/heart-encyclopedia/disease/pph.htm
- Cleveland Clinic Health Information Center:
  http://www.clevelandclinic.org/health/health-info/docs/0600/0622.asp?index=6530
- Madisons Foundation:
  http://www.madisonsfoundation.org/content/3/1/display.asp?did=561
- Mayo Clinic:
  http://www.mayoclinic.org/pulmonary-hypertension/index.html
- Merck Manual of Medical Information, Second Home Edition:
  http://www.merck.com/mmhe/sec04/ch054/ch054a.html
- New York Online Access to Health:
  http://www.noah-health.org/en/lung/conditions/pulmonaryhyper.html
- Ohio State University Medical Center:
  http://medicalcenter.osu.edu/patientcare/healthinformation/diseasesandconditions/respiratory/lung/hypertension/
- Orphanet:
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=422
- Vanderbilt University Medical Center:
  http://www.mc.vanderbilt.edu/root/vumc.php?site=vupphstudy

Patient Support - for Patients and Families

- American Heart Association:
  http://www.americanheart.org/presenter.jhtml?identifier=4752
- American Lung Association:
  http://www.lungusa.org/site/pp.asp?c=dvLUK9O0E&b=35699
- National Registry for Familial Primary Pulmonary Hypertension:
  http://www.mc.vanderbilt.edu/root/vumc.php?site=vupphstudy
- PH Central:
  http://www.phcentral.org/
- Pulmonary Hypertension Association:
  http://www.phassociation.org/Learn/What-is-PH/index.asp

Professional Resources

You may also be interested in these resources, which are designed for healthcare professionals and researchers.

- Gene Reviews - Clinical summary:
  http://www.genetests.org/query?dz=pph
- Gene Tests - DNA tests ordered by healthcare professionals:
  http://www.genetests.org/query?testid=2609
- ClinicalTrials.gov - Linking patients to medical research:
  http://clinicaltrials.gov/search/condition=%22primary+pulmonary+hypertension%22?recruiting=false
- OMIM - Genetic disorder catalog:
  http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=178600

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These sources were used to develop the Genetics Home Reference condition summary on pulmonary arterial hypertension.

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- Zhang S, Fantozzi I, Tigno DD, Yi ES, Platoshyn O, Thistlethwaite PA, Kriett JM, Yung G, Rubin LJ, Yuan JX. Bone morphogenetic proteins induce apoptosis in human pulmonary vascular smooth muscle cells. Am J Physiol Lung Cell Mol Physiol. 2003 Sep;285(3):L740-54. Epub 2003 May 09. PubMed citation

A summary of the gene related to pulmonary arterial hypertension is provided below:

What Is the Official Name of the BMPR2 Gene?[4]

The official name of this gene is "bone morphogenetic protein receptor, type II (serine/threonine kinase)."

BMPR2 is the gene's official symbol. The BMPR2 gene is also known by other names, listed below.

What Is the Normal Function of the BMPR2 Gene?

The BMPR2 gene provides instructions for making a protein called bone morphogenetic protein receptor, type II. The BMPR2 gene belongs to a family of genes originally identified for its role in regulating the growth and maturation (differentiation) of bone and cartilage. Recently, researchers have found that this gene family plays a broader role in regulating the growth and differentiation of numerous types of cells.

Bone morphogenetic protein receptor, type II spans the cell membrane, so that one end of the protein is on the outer surface of the cell and the other end remains inside the cell. This arrangement allows the protein to receive and transmit signals that help the cell respond to its environment by growing and dividing (cell proliferation) or by undergoing controlled cell death (apoptosis). This balance of cell proliferation and cell death regulates the number of cells in tissues.

What Conditions Are Related to the BMPR2 Gene?

Pulmonary Arterial Hypertension - Caused by Mutations in the BMPR2 Gene

Researchers have identified more than 140 BMPR2 mutations that cause pulmonary arterial hypertension. About half of these mutations disrupt the assembly of bone morphogenetic protein receptor, type II, reducing the amount of this protein in cells. Other mutations prevent bone morphogenetic protein receptor, type II from reaching the cell surface, or alter its structure so it cannot receive or transmit signals.

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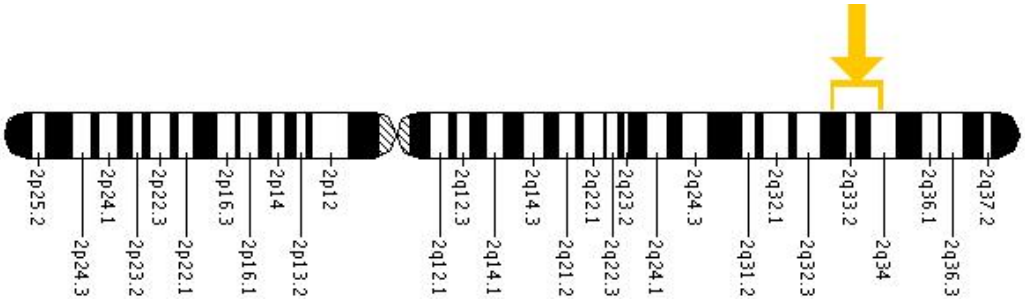
[4] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/gene=bmpr2**.

Where Is the BMPR2 Gene Located?

Cytogenetic Location: 2q33-q34

Molecular Location on chromosome 2: base pairs 202,949,915 to 203,140,718



The BMPR2 gene is located on the long (q) arm of chromosome 2 between positions 33 and 34.

More precisely, the BMPR2 gene is located from base pair 202,949,915 to base pair 203,140,718 on chromosome 2.

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These sources were used to develop the Genetics Home Reference gene summary on the BMPR2 gene.

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Federally Funded Research on Primary Pulmonary Hypertension

The U.S. Government supports a variety of research studies relating to primary pulmonary hypertension. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[5]

CRISP (Computerized Retrieval of Information on Scientific Projects)

CRISP 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 primary pulmonary hypertension.

[5] 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).

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

- **Project Title: ACE INHIBITION IN SINGLE VENTRICLE/PULMON. HYPERTENSION**

  Principal Investigator & Institution: Gersony, Welton M.; Director; Pediatrics; Columbia University Health Sciences Columbia University Medical Center New York, Ny 100323702

  Timing: Fiscal Year 2005; Project Start 05-SEP-2001; Project End 31-AUG-2006

  Summary: (provided by applicant) The overall goal of this application is to examine treatment modalities which may improve the clinical care of two groups of patients with congenital heart disease: infants born with a single ventricle supplying blood flow to the lungs and body and children with pulmonary hypertension associated with congenital heart disease. The primary hypothesis in infants with single ventricle is that chronic angiotensin converting enzyme (ACE) inhibition favorably modifies the ventricular remodeling response to volume overload and improves ventricular function over the first year of life. Serial changes in ventricular geometry will be assessed using magnetic resonance imaging and compared with measurements of systolic and diastolic function, including the pressure/volume relation and the Tei index, and clinical outcome measures including post-operative course and changes in the Ross? heart failure classification. The beneficial effect of ACE inhibition is expected to occur prior to and following volume unloading surgery with the bidirectional Glenn shunt or hemi-Fontan. The primary hypothesis of the study in congenital heart disease associated with pulmonary hypertension is that the effect of long-term treatment with an oral prostacyclin analogue or an oral endothelin receptor blocker has a salutory effect on exercise capacity, longevity, and quality of life. It will also be determined whether any of these patients carry a defect of the primary pulmonary hypertension-1 gene. Each of these studies could potentially lead to a significant improvement in prognosis: in the single ventricle group by preventing a long-term deterioration in ventricular function and in the pulmonary hypertension patients by improving quality of life and survival without transplantation.

- **Project Title: AMBULATORY ARTERIOVENOUS CARBON DIOXIDE REMOVAL**

  Principal Investigator & Institution: Zwischenberger, Joseph B.; Professor; Mc3, Inc. 3550 W Liberty Rd Ann Arbor, Mi 481038802

  Timing: Fiscal Year 2005; Project Start 30-SEP-2002; Project End 30-JUN-2007

  Summary: (provided by applicant): End-stage lung disease from COPD, cystic fibrosis, **primary pulmonary hypertension,** and ideopathic pulmonary fibrosis affects 15-17 million people in the United States and is the fourth leading cause of death in the U.S. With end-stage lung disease, carbon dioxide retention is a common and grave prognostic sign with limited treatment options. Long-term ventilator management is very restrictive. For emphysema, Lung Volume Reduction Surgery remains investigational as few patients are showing efficacy. Lung transplantation is available to only 900/year as the average wait for a donor is two years with a 30 percent wait-list mortality. An artificial lung is years away. We developed Arteriovenous Carbon Dioxide Removal (AVCO2R) with a low-resistance gas exchanger in a simple percutaneous arteriovenous shunt to achieve near-total extracorporeal removal of CO2

production with only 800-1000 ml/min blood flow. From our animal and patient safety trials, AVCO2 R decreases minute ventilation with an increase in PaO2/FiO2 and no significant change in WBC, platelets, or complement while maintaining CO2 and pH homeostasis. A prototype Ambulatory AVCO2R (A-AVCO2R) gas exchanger was designed and built by MC3 (Ann Arbor, Mt) for high gas exchange efficiency and very low blood flow resistance. The necessary prototype A-AVCO2R modifications in Phase I were achieved including: 1) optimization and downsizing of the oxygenator design for ambulatory arterio-venous CO2 removal (A-AVCO2R), and 2) implementation of a portable sweep gas control system. For Phase II we will complete the preclinical development of the A-AVCO2R system. Specifically, we will: 1) fabricate the preclinical A-AVCO2R device and vascular attachment cannulae; 2) complete the portable gas flow controller; 3) in vitro performance testing of the entire circuit, then 4a) short-term (1 day) studies to determine gas exchange performance of the entire circuit in normal sheep for final changes; 4b) long-term (1,4, 10 day) studies in ambulatory sheep for preclinical testing of the system and assessment of biocompatibility. Upon completion of this Phase II proposal, we will initiate FDA approval of A-AVCO2R using a simple brachial arteriovenous shunt as a long-term treatment for end-stage lung disease or as a bridge to lung transplantation.

- **Project Title: BIOLOGY OF MONOCROTALINE INDUCED PULMONARY HYPERTENSION**

  Principal Investigator & Institution: Wilson, Dennis W.; Professor and Chairman; Vet Molecular Biosciences; University of California Davis Office of Research - Sponsored Programs Davis, Ca 95618

  Timing: Fiscal Year 2005; Project Start 01-JAN-1993; Project End 31-MAR-2008

  Summary: Monocrotaline (MCT) induced pulmonary hypertension remains a principle model for the biology and development of intervention strategies for the human disease. Current concepts of pulmonary hypertension (PH) assign a primary pathogenetic role to the pulmonary endothelial cell in both human PH and that induced by MCT. Recently, a genetic lesion in the Bone Morphogenic Protein Receptor (BMPR) has been identified in humans with pulmonary hypertension The overall objective of this grant is to characterize the effects of MCT on the biology of the pulmonary endothelial cell and relate them to the initiating mechanisms of PH. Our previous work has demonstrated that several proteins with potential functional significance for endothelial cells have selective covalent interactions with the reactive intermediate of MCT metabolism, monocrotaline pyrrole (MCTP). This leads to our hypothesis that protein targets of MCT initiate vascular remodeling by altering endothelial cell function similar to endothelial dysfunction in persons with genetic susceptibility to **primary pulmonary hypertension.** Our specific aims are to further characterize the protein targets of MCT, to determine the functional significance of protein binding in endothelial cells, to evaluate proteins regulating endothelial cell barrier function as potential MCT targets and to determine whether the MCT model alters the BMPR signal pathway affected in humans with PH.

- **Project Title: BMPR2 AND THE PATHOGENESIS OF PULMONARY HYPERTENSION**

  Principal Investigator & Institution: Bloch, Kenneth D.; Associate Professor of Medcine; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2005; Project Start 01-JUL-2003; Project End 30-JUN-2008

  Summary: (provided by applicant): **Primary pulmonary hypertension** (PPH) is a disease characterized by elevated pulmonary artery blood pressure, remodeling of the

lung vasculature, and progressive right ventricular hypertrophy. Despite recent therapeutic advances, nearly 40% of PPH patients die within three years of diagnosis. The familial form of PPH is inherited as an autosomal dominant trait with incomplete penetrance and has been associated with mutations in the gene encoding the type II bone morphogenetic protein receptor (BMPR2). Moreover, about 25% of patients with sporadic PPH also have BMPR2 mutations. The principal investigator has assembled a multidisciplinary team of scientists with the objective of elucidating the role of BMPR2 in the pathogenesis of PPH. The investigators have already developed a series of genetically modified mice with mutations in the BMPR2 gene, as well as mice with a conditional BMPR2 mutation. BMPR2 mice were found to be normal at baseline but develop greater pulmonary hypertension than wild type mice after prolonged hypoxia. The proposed research is divided into four aims. First, the pulmonary vascular remodeling response to environmental and pharmacologic stimuli associated with the development of pulmonary hypertension in animal models will be compared in wild type and BMPR2 mice. Second, pulmonary vascular endothelial and smooth muscle cells will be isolated from genetically modified mice, and the ability of BMP to modulate cell proliferation, migration, and apoptosis will be assessed. Third, pulmonary vascular structure and function will be evaluated in mice with BMPR2 mutations that retain kinase activity. Finally, mice with a conditional BMPR2 mutation will be used to investigate the contribution of endothelial and smooth muscle cells to the pathogenesis of pulmonary hypertension. The results of the proposed studies will likely provide important insights into the pathogenesis of PPH including why only some patients with BMPR2 mutations develop the disease. Moreover, these studies may validate BMPR2 mice as a valuable model with which to screen new and old drugs with the goal of identifying agents that may cause PPH in individuals predisposed to the disease.

- **Project Title: CELLULAR DEFECTS IN FAMILIAL PULMONARY HYPERTENSION**

  Principal Investigator & Institution: De Caestecker, Mark P.; Assistant Professor; Medicine; Vanderbilt University Medical Center Nashville, Tn 372036869

  Timing: Fiscal Year 2005; Project Start 10-SEP-2005; Project End 31-AUG-2007

  Summary: (provided by applicant): **Primary pulmonary hypertension** (PPH) is a rare disease of unknown etiology characterized by severe, isolated **pulmonary arterial hypertension** leading to right ventricular failure and death. Genetic studies in patients with Familial PPH (FPPH) indicate that the majority carry mutations in the BMP Type II receptor (BMPR2) locus, while functional assays indicate that defects in BMP-signaling are also found in patients with sporadic PPH. For this reason, analysis of cellular dysfunction in FPPH patients carrying defined BMPR2 mutations provides an opportunity to explore pathological events underlying both sporadic and familial forms of PPH. Despite this, the cellular defects resulting from these mutations are essentially unknown, as direct approaches to evaluate alterations in cell function have been hindered by limited access to FPPH patient derived vascular cells. To address this we have developed a surrogate system using primary skin fibroblasts from patients with FPPH to study effects of diverse BMPR2 mutations on cellular function. These cells are easy to harvest and propagate, and share properties in common with vascular smooth muscle cells. Skin fibroblasts and pulmonary artery smooth muscle cells from patients with FPPH do not proliferate in response to BMPs, and show constitutive phosphorylation of the TGF-beta-activated Smads. These findings are the first evidence of a consistent abnormality associated with diverse BMPR2 mutations. In these studies we will validate this cell culture system by interrogating the functional impact of this defect in Smad-signaling using FPPH fibroblasts and pulmonary artery smooth muscle cells. We will then use these to evaluate an unbiased approach to identify changes in the

cellular proteome shared by FPPH cells carrying a range of different BMPR2 mutations. These studies will establish a technological platform to identify and evaluate cellular abnormalities in these patients and in patients with other forms of **pulmonary arterial hypertension.**

- **Project Title: CELLULAR MECHANISMS OF PPH: ROLE OF K+ CHANNELS**

  Principal Investigator & Institution: Yuan, Jason X-J.; Professor; Medicine; University of California San Diego 9500 Gilman Dr, Dept. 0934 La Jolla, Ca 920930934

  Timing: Fiscal Year 2005; Project Start 15-JUL-1999; Project End 30-JUN-2007

  Summary: (provided by applicant): Pulmonary vascular medial hypertrophy in patients with **primary pulmonary hypertension** (PPH) is mainly due to increased pulmonary artery smooth muscle cell (PASMC) growth and/or decreased PASMC apoptosis. The precise control of the balance between PASMC proliferation and apoptosis plays a critical role in maintaining the structural integrity of the pulmonary vasculature. Activation of apoptosis is implicated in the regression of pulmonary vascular medial hypertrophy, whereas inhibition of apoptosis leads to the progression of pulmonary vascular wall thickening. Cell volume decrease is an early hallmark of apoptosis. Maintenance of a high concentration of cytosolic K+ ([K+]cyt) is essential to the regulation of normal ion homeostasis and cell volume, and to the suppression of cytoplasmic caspases. Thus, activation of K+ channels induces apoptotic volume decrease (AVD) and apoptosis by enhancing K +loss, whereas inhibition of K+ channel activity attenuates AVD by maintaining sufficient [K+]cyt to inhibit apoptosis. In normal PASMC, our preliminary data demonstrate that apoptosis inducers, such as staurosporine (ST) and cytochrome c, increased K+ channel activity, whereas anti-apoptotic proteins (e.g., Bcl-2) decreased K+ channel activity. Pharmacological blockade of voltage-gated K+(Kv) channels attenuated ST-induced apoptosis. Furthermore, expression and function of Kv channels were markedly reduced in PASMC from PPH patients in comparison to PASMC from normal subjects and patients with secondary pulmonary hypertension (SPH). The ST-induced apoptosis was also significantly inhibited in PPH-PASMC in comparison to SPH-PASMC. Based on these data, we hypothesize that inhibition of apoptosis in PASMC as a result of down regulation and dysfunction of Kv channels plays an critical role in the development of pulmonary vascular medial hypertrophy in PPH. Three Specific Aims are addressed to test the hypothesis: 1) To investigate the role of Kv channels in the development of AVD and apoptosis and to identify Kv channel subtypes that are involved in regulating cell volume in normal human PASMC; 2) To determine the effects of pro-apoptotic and anti-apoptotic proteins on Kv channel expression and function in human PASMC; and 3) To determine whether apoptosis is inhibited in PPH-PASMC and if so, what cellular and molecular mechanisms are responsible for the inhibited apoptosis.

- **Project Title: CLONING OF FAMILIAL PRIMARY PULMONARY HYPERTENSION GENE**

  Principal Investigator & Institution: Nichols, William C.; Assistant Professor; Children's Hospital Med Ctr (Cincinnati) 3333 Burnet Ave Cincinnati, Oh 452293039

  Timing: Fiscal Year 2005; Project Start 01-JUL-1998; Project End 31-JUL-2007

  Summary: This abstract is not available.

- **Project Title: DNA MODIFICATIONS IN PRIMARY PULMONARY HYPERTENSION**

  Principal Investigator & Institution: Gillespie, Mark N.; Professor and Chairman; Pharmacology; University of South Alabama 307 N University Blvd. Ad200 Mobile, Al 366880002

  Timing: Fiscal Year 2006; Project Start 01-JUL-2006; Project End 30-JUN-2008

  Summary: (provided by applicant): The pathobiology of **primary pulmonary hypertension** (PPH) is associated with changes in expression of about 300 genes. Understanding the molecular events driving abnormal transcription in PPH is critical for improved diagnosis and design of new therapies, but the mechanism(s) is currently unknown. Several emerging lines of evidence support a new concept for transcriptional regulation in PPH. Chief among these is the finding that oxidative DNA damage is present in cells from PPH lung tissue. Recent studies in human cortical neurons show that age-related accumulation of oxidative DNA damage in selectively vulnerable promoters impairs transcription of genes involved in neuronal survival and plasticity. Conversely, experiments in cultured rat pulmonary vascular cells suggest that targeted nucleotide specific base modifications in promoter sequences, caused by growth stimuli found in PPH, facilitate induction of VEGF expression. Integrating these disparate lines of evidence leads to a new concept for the abnormal gene expression in PPH. We propose that the equilibrium density and nucleotide-specific patterns of oxidative modifications in promoter sequences govern increases and decreases in gene expression in PPH. Two aims will be addressed: Aim 1 will test the hypothesis that promoters of genes that are up- or down-regulated in PPH lung tissue display changes in the equilibrium density of oxidative promoter modifications that are predictive of the transcriptional state of the gene; and, Aim 2 will test the hypothesis that nucleotide-specific pattern of oxidative base modifications in the VEGF promoter in lung DNA from PPH patients with increased VEGF mRNA expression differs from that in lung DNA from patients with **pulmonary arterial hypertension** secondary to chronic obstructive lung disease wherein VEGF expression is decreased. These "translational" studies are significant and innovative because the concept that the position and density of oxidative "modifications" in promoters are determinants of gene expression is entirely new. If evidence for this regulatory mechanism extends to PPH, it will point to novel diagnostic strategies founded on detection of sequence-specific oxidative DNA modifications and to DNA damage and repair pathways as potential targets for intervention. Finally, if DNA is oxidatively threatened in an acquired disease like PPH, this will point to unappreciated mechanisms of somatic mutation, age-related vasculopathies and other disorders wherein genes targeted by ROS play a pivotal role.

- **Project Title: EFFECTS OF BMPRII MUTATIONS IN PULMONARY HYPERTENSION**

  Principal Investigator & Institution: West, James D.; Medicine; University of Colorado Denver/Hsc Aurora P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2005; Project Start 19-SEP-2003; Project End 31-JUL-2007

  Summary: (provided by applicant): **Primary pulmonary hypertension** (PPH) is a potentially lethal disorder characterized by pulmonary vasoconstriction and vascular remodeling involving abnormal proliferation of fibroblasts, smooth muscle and endothelial cells. In the year 2000, mutations in the type 2 bone morphogenic protein receptor (BMPR2) were identified as the genetic basis for familial PPH and about 30% of sporadic PPH. BMP signaling had not previously been connected to pulmonary hypertension, and the mechanistic linkage is unknown. We hypothesize that in normal

individuals the BMP pathway acts to down-regulate both inflammatory cytokine-mediated positive feedback loops and vascular smooth muscle cell proliferation. Insufficient BMP pathway activity in individuals with BMPR2 mutations leads to insufficient damping of these auto-regulatory loops, resulting in the PPH phenotype. We provide preliminary evidence in cell culture systems supporting this hypothesis and have constructed a unique series of transgenic mice to further test the hypothesis. These mice express a human dominant-negative BMPR2 (dnBMPR2) using the tetracycline gene switch system, allowing both spatial and temporal control of expression. We have successfully bred smooth muscle cell and epithelial cell specific dnBMPR2 expressing mice, and are constructing endothelial cell specific mice at this time. Using our in vitro and transgenic models we will test the following three specific aims: 1: Test the hypothesis that the BMP pathway is a negative modulator of the cytokine interleukin-6 (IL-6) in PA SMC, leading to reduced IL-6-mediated signaling and proliferation. 2: Test the hypothesis that loss of PA SMC BMPR2 function in SM22-dnBMPR2 transgenic mice leads to an exaggerated pulmonary hypertensive response in vivo. 3: Test the hypothesis that loss of BMPR2 function in lung cell types other than SMC also contributes to the development of pulmonary hypertension. Upon completion of our studies, we will have tested the hypothesis that the link between BMP signaling and pulmonary hypertension involves both regulation of the critical cytokine, IL-6, as well as modulation of smooth muscle cell proliferation. We will have also tested the role of four pulmonary cell types, smooth muscle, endothelium, airway epithelium and macrophages in the link between BMPR2 and pulmonary hypertension.

- **Project Title: GENE TRANSFER OF ADENYLYL CYCLASE TO PULMONARY SMOOTH MUSCLE CELLS**

  Principal Investigator & Institution: Insel, Paul A.; Professor of Pharmacology and Medicine; University of California San Diego 9500 Gilman Dr, Dept. 0934 La Jolla, Ca 920930934

  Timing: Fiscal Year 2005

  Summary: The overriding of this hypothesis is that gene transfer of isoforms of adenylyl cyclase (CA) can be used to increase cyclic AMP (cAMP) synthesis and action in pulmonary artery smooth muscle cells (PASMC). PASMC, whose function is altered in a variety of important clinical conditions associated with **pulmonary arterial hypertension,** will be used with adenoviral or other viral vectors to assess gene transfer of AC type 6 and 8, two AC isoforms with unique patterns of regulation. We will assess impact o increased AC expression on cAMP generation and on "downstream" responses including activation of cAMP-dependent protein kinase, metabolic, contractile and growth responses, and on ion channel activity and expression. Other studies will assess compartmentation of AC expression and function of PASMC cells derived from patients with **primary pulmonary hypertension.** Taken together, the proposed studies should provide new information regarding gene transfer of AC to PASMC and impact of increased AC expression of PASMC function. Successful completion of these studies would provide an experimental basis to initiate clinical studies in patients with abnormal PASMC function.

- **Project Title: GENETIC AND ENVIRONMENTAL PATHOGENESIS OF PPH**

  Principal Investigator & Institution: Loyd, James E.; Associate Professor; Medicine; Vanderbilt University Medical Center Nashville, Tn 372036869

  Timing: Fiscal Year 2005; Project Start 04-AUG-2003; Project End 31-JUL-2008

Summary: (provided by applicant): **Primary pulmonary hypertension** (PPH) is a progressive, fatal disease, which threatens the lives of thousands of patients across all age groups. In a recent important advance, mutations in bone morphogenetic protein receptor 2 (BMPR2) have been associated with both familial and sporadic PPH. Our hypothesis is that other genes and biologic events participate in the development of familial PPH, because only 20% of persons with a BMPR2 mutation ever develop PPH. Our target goals are to identify the modifying genes and environmental features that regulate the clinical expression of mutations in BMPR2; to develop understanding about how BMPR2 mutations result in disease; and to identify the undiscovered mutations which cause PPH. The program forms a structural basis to enhance existing collaborations among experienced investigators from six disciplines to optimize progress in the study of PPH. The program will utilize the unique resources of our database and specimen bank developed from 116 PPH families across the US. In families with mutations not yet identified, we will search for alterations in the BMPR2 gene, including promoter and intronic regions, and search for chance recombination events which could confirm another locus near 2q33. Experimental approaches for identifying modifier genes will include genome wide single nucleotide polymorphism and microsatellite scans in large families with known mutations, examination of mitochondrial DNA haplotypes and candidate genes as modifiers, including NOS-1, NOS-3, and the serotonin transporter. We will study the perceived risks and benefits of genetic testing and counseling in many individuals in families at high risk for PPH. We will also identify genetic modifiers of BMPR2 in mouse models of pulmonary hypertension. We will determine the functional mechanisms by which variations found in the BMPR2 alleles alter BMP signal transduction by defining the biochemical effects of the mutant proteins on signaling pathways. The proposal emphasizes that the common themes, complementary expertise and unique technologies assembled into a coordinated program will be more creative, more productive and more likely to advance understanding of the molecular pathogenesis of PPH.

- **Project Title: GENETIC ASPECTS OF PULMONARY HYPERTENSION**

  Principal Investigator & Institution: Morse, Jane H.; Associate Professor of Medicine; Medicine; Columbia University Health Sciences Columbia University Medical Center New York, Ny 100323702

  Timing: Fiscal Year 2005; Project Start 23-AUG-1999; Project End 30-NOV-2007

  Summary: (provided by applicant): The pathogenesis of primary **pulmonary arterial hypertension** (PAH) is unknown. The main goal of this project continues to be the identification of genes that cause PAH and how these genes contribute to the pathophysiology of the disease and its clinical subsets. The familial form of **primary pulmonary hypertension** (FPPH), inherited as an autosomal dominant disease with incomplete penetrance, was known to have a gene, PPH1 located on chromosome 2q32,33. After narrowing this large locus, our studies found mutations of bone morphogenetic protein receptor 2 (BMPR2) caused disease in 9 of 21 FPPH families. Others found BMPR2 mutations in 26% of sporadic PPH. BMPR2 mutations were also found 9% of fenfluramine appetite-associated PAH whereas no mutations were found in PAH patients with HIV-infection or with scleroderma spectrum of disease. BMPR2 mutations remain to be determined in large PAH cohorts of children and adults with anatomically large congenital pulmonary to systemic communications and with sporadic PPH. Our clinical resources include 100 FPPH families and 5 hereditary hemorrhagic telangiectasia (HHT1) families, four have mutations in activin-like receptor 1 (ALK-1), another gene associated with PPH. The identification of BMPR2 gene, a member of the TGF-B superfamly has focused the BMP/TGF-B signaling pathway for

new explorations into the pathogenesis of PPH. Our newer aims will investigate the mechanism by which BMPR2 mutations cause disease, identify genetic mutations that cause disease in the 50% of FPPH cases that do not contain mutations in the exons of BMPR2, and identify DNA variations that alter the penetrance of BMPR2 mutations. We are most interested in the long C-terminal tail of BMPR2, which is unique in the TGF-B superfamily. Hopefully, these aims and the large available clinical material should provide pathophysiological information on the functional relevance of BMPR2 mutations, provide an in vitro method of BMPR2 evaluation, and provide the identification of additional risk factors and genes required for disease penetrance. Longitudinal follow of the FPPH and sporadic cases and of the HHT families should give information on the natural history of disease. The results could also define further avenues for therapeutic interventions and potentially provide in vitro models for drug testing.

- **Project Title: MECHANISM OF APOPTOSIS IN LUNG VASCULAR SMOOTH MUSCLE**

  Principal Investigator & Institution: Suzuki, Yuichiro Justin.; Associate Professor; Pharmacology; Georgetown University 37Th and O Sts Nw Washington, Dc 20057

  Timing: Fiscal Year 2005; Project Start 01-APR-2003; Project End 31-MAR-2006

  Summary: (provided by applicant): **Primary pulmonary hypertension** (PPH) is rare, but often fatal, with increased incidence in users of appetite suppressants. It is characterized by increased lung vascular resistance due to thickening of pulmonary arterial walls. The cellular mechanisms that regulate smooth muscle cell number, however, have not been defined. Lack of such knowledge interferes with the development of new therapeutic strategies that are designed to prevent and/or treat this condition. My long-range goal is to identify the mechanisms for the regulation of apoptosis in human pulmonary artery smooth muscle cells (HPASMC). The objective of this application is to evaluate specifically the role of GATA transcription factors. The central hypothesis of the application is that GATA factors regulate apoptosis and survival. The hypothesis has been formulated on the basis of strong preliminary data, which suggest that i) GATA-4 and -6 are expressed in HPASMC, ii) apoptotic stimuli downregulate the GATA activity, and iii) serotonin and endothelin-1 exert anti-apoptotic signaling and enhance the GATA activity. The rationale for the proposed research is that, once knowledge of the mechanisms that regulate the lung vascular medial thickening has been obtained, it will lead to new strategies that can be used to prevent and/or treat PPH, thereby reducing the morbidity and mortality that are associated with this condition. I am uniquely prepared to undertake the proposed research because my lab has been studying GATA factors, and many of the techniques and reagents are already available. The central hypothesis will be tested and the objective of the application accomplished by pursuing two specific aims: 1) Identify the mechanisms of HPASMC apoptosis induced by nitric oxide and retinoic acid, and 2) Determine the mechanisms by which serotonin and endothelin-1 exert anti-apoptotic signaling. The proposed work is innovative, because it will investigate novel transcription factors in lung using an approach that has been used in the studies of cardiac muscle. It is my expectation that GATA factors are involved in the regulation of apoptosis of HPASMC. These results will be significant because they are expected to provide new agents for preventative and therapeutic interventions of PPH. In addition, it is expected that the results will fundamentally advance the field of lung cell biology.

- **Project Title: MODIFYING GENES IN PULMONARY HYPERTENSION**

  Principal Investigator & Institution: Zaiman, Ari L.; Medicine; Johns Hopkins University W400 Wyman Park Building Baltimore, Md 212182680

  Timing: Fiscal Year 2005; Project Start 01-JUL-2004; Project End 30-JUN-2009

  Summary: (provided by applicant): The goal of this K08 Mentored Career Development Award is to evaluate genetic influences in the development of pulmonary and arterial hypertension (PAH), a progressive disease characterized by an elevation in the mean pulmonary artery pressure, right heart failure, and death. This goal is based on the sobering observation that despite intensive investigation, the natural progression and the molecular mechanisms underlying the development of severe pulmonary hypertension are not well understood. Recently, genetic studies of **familial primary pulmonary hypertension** (FPPH) elucidated alterations in the bone morphogenetic protein receptor II (BMPRII) gene, a member of the transforming growth factor (TGF) super-family. However, although about 50% of patients with FPPH have this gene defect, only 20% of persons carrying a mutation in this gene develop PAH, clearly implicating additional host/environment interactions involving modifier genes that influence the development of PAH. In this K08 application, the PI will leverage the unique resources provided by the NHLBI-sponsored Programs in Genomic Applications (PhysGen, HopGene and TIGR) and apply contemporary genetic/genomic approaches in an established rat model of pulmonary hypertension in order to identify novel genes which are involved in the development of PAH. Specific Aim 1 will characterize PAH responses in two inbred rat strains (Brown Norway and SS Dahl) shown by the PI to differ in their susceptibility to hypoxia. Specific Aim 2 will utilize a consomic rat panel to identify chromosome-specific regulation of the rodent pulmonary hypertensive response. These consomic rats contain a single chromosome from the "resistant" parent strain introgressed into the "sensitive" strain background in order to allow the rapid isolation of the chromosome(s) containing genes that influence the development of PAH. Specific Aim 3 will next utilize congenic rats which have been rapidly generated in order to further localize the region(s) of interest. This approach, combined with extensive gene expression profiling, will allow the PI to identify quantitative trait loci (QTL)-specific candidate genes that modify the pulmonary hypertensive response. These data obtained in rats have the potential to identify relevant candidate genes which modify the susceptibility and severity of PAH in humans, utilizing highly translational approaches that can be implemented within the overarching HopGene PGA. We speculate that the elucidation of these molecular targets will lead to novel insights into the molecular mechanisms involved in human PAH and provide the rationale for novel therapies designed to improve the prognosis of patients with this devastating disease.

- **Project Title: NEUROHORMONAL ACTIVATION IN PULMONARY HYPERTENSION**

  Principal Investigator & Institution: Kawut, Steven M.; Assistant Professor; Medicine; Columbia University Health Sciences Columbia University Medical Center New York, Ny 100323702

  Timing: Fiscal Year 2005; Project Start 01-SEP-2001; Project End 31-AUG-2007

  Summary: Candidate's Plans/Training: The candidate plans a career as an independent clinical investigator focusing on patient-oriented research related to pulmonary vascular disease. Training will include formal epidemiological course work in clinical research and closely mentored completion of the research protocol. Environment: The Center for Clinical Epidemiology and Biostatistics (CCEB) will provide formal coursework and structured mentoring. The CCEB, Pulmonary Vascular Disease Program, and General

Clinical Research Center at the University of Pennsylvania Medical Center will provide research support. Research: **Primary pulmonary hypertension** (idiopathic) and secondary pulmonary hypertension (associated with portal hypertension, anorectic use, HIV, scleroderma, and other collagen vascular diseases) cause substantial morbidity and mortality. Although there are available therapies and interventions, they may be costly and risky in themselves. In addition, targeting therapy at the mechanism of morbidity and mortality and distinguishing highrisk patients have been suboptimal. There is evidence that certain vasoactive substances may play an important role in the disease process of **pulmonary arterial hypertension.** Studies have documented elevated levels of endothelin, natriuretic peptides, and norepinephine in patients with this disease. It is well known that these neurohormones play important mechanistic and predictive roles in left-sided heart failure. Similarly, there is much potential for these neurohormone levels in determining 1) the mechanism of disease and 2) the prognosis in **pulmonary arterial hypertension.** We propose an investigation of patients with **pulmonary arterial hypertension** to examine whether levels of these biomarkers at baseline and at six month follow-up are associated with right-sided heart failure and cardiovascular death. We will formulate prediction rules using neurohormone levels and clinical variables to improve prognostication and management in this disease.

- **Project Title: NITRIC OXIDE PRODUCTION AND REACTIONS IN THE LUNG**

  Principal Investigator & Institution: Erzurum, Serpil C.; Professor; Molecular Medicine; Cleveland Clinic Lerner Col/Med-Cwru 9500 Euclid Avenue Cleveland, Oh 44195

  Timing: Fiscal Year 2005; Project Start 01-APR-1999; Project End 30-JUN-2009

  Summary: (provided by applicant): **Primary pulmonary hypertension** (PPH) is a fatal disease of unknown etiology characterized by impaired regulation of both pulmonary hemodynamics and vascular growth. Our preliminary data show that primary pulmonary artery endothelial cells (PAEC) from PPH lung have enhanced proliferation, migration and abnormal tube formation in vitro. The signal transducer and activator of transcription (STAT) 3, recently identified as a critical regulator for angiogenesis, is persistently activated in PPH PAEC, but not in control cells. High-level expression of putative downstream target genes, arginase II and vascular endothelial growth factor (VEGF), are present only in PPH PAEC. Previously, we showed that diminished vasodilator nitric oxide (NO) is important in the pathophysiology of PPH, but NO synthases (NOS) expression are intact. Here, we propose a post-translational mechanism for low NO, i.e. arginase II, an enzyme that competes for the NOS substrate arginine, is increased. Thus, we hypothesize that the pathogenesis of PPH stems from abnormal endothelial cells, which have persistent STAT3 activation with consequent expression of VEGF and arginase II, that leads to increased proliferation, deregulated angiogenesis, and loss of NO. Initially, we will quantitate proliferation, migration and tube formation of PPH PAEC in comparison to healthy and disease controls. To identify mechanisms that account for the altered biology of PPH cells and low NO in PPH, we focus our investigations on arginase II using strategies of over-expression, RNA silencing or pharmacologic inhibition of arginase under conditions that assess enzyme substrate and product effects, and NO synthesis. To investigate mechanisms for high-level arginase expression in PPH, we plan to analyze STAT-mediated transcriptional activation of arginase II. Our studies also include evaluation for type II bone morphogenetic protein receptor (BMPR2) mutations and Human Herpesvirus 8 (HHV8) infection, both implicated in PPH pathogenesis, and use proteomic methods to discover novel differences between control and PPH. Our previous study showed an inverse correlation of NO to pulmonary artery pressure. Here, we propose a longitudinal study of PPH patients to test our hypothesis that determinants of NO synthesis, i.e. arginase

and arginine, predict outcomes in PPH. Taken together, these studies will conclusively reveal fundamental and inherent alterations in PPH endothelial cells, identify the causal mechanisms, and lead to novel therapies for treatment of PPH.

- **Project Title: NITRIC OXIDE/CARBON MONOXIDE IN PULMONARY HYPERTENTION**

  Principal Investigator & Institution: Dweik, Raed A.; Associate Professor of Medicine; Molecular Medicine; Cleveland Clinic Lerner Col/Med-Cwru 9500 Euclid Avenue Cleveland, Oh 44195

  Timing: Fiscal Year 2005; Project Start 10-JUL-2002; Project End 30-JUN-2007

  Summary: (provided by applicant): We have shown that patients with **primary pulmonary hypertension** (PPH) have low levels of nitric oxide (NO), a potent vasodilator, in exhaled breath suggesting a role for NO in the pathophysiology of pulmonary hypertension. The purpose of this proposed research is to determine the mechanism(s) for low NO in PPH. Potential mechanisms that will be addressedin the experiments are inhibition of NO production by CO and enzyme kinetic abnormalities affecting the sensitivity of NO synthase (NOS) to oxygen. We have previously shown that oxygen concentrations in the physiologic range determine the rate of NO synthesis in the lung. However, PPH individuals have low NO despite receiving supplemental oxygen therapy. This suggests that NO synthases in PPH may be less sensitive to oxygen and thus require higher than normal oxygen to produce NO. Furthermore, CO can directly affect endogenous NO synthesis. In preliminary data, CO in PPH is in the range that may lead to inhibition of NOS activity and NO generation. We hypothesize that NO is decreased in PPH perhaps as a consequence of high CO levels and/or impaired NO production in response to oxygen. As an extension of this hypothesis, we also propose that effective therapies such as epoprostenol, may act in part by increasing NO levels in PPH. To test this hypothesis, we propose the following specific aims: Aim 1. Determine the levels of Carbon monoxide (CO) in relationship to NO and severity of disease in PPH. Aim 2. Study the effect of oxygen and epoprostenol on NO levels in PPH in vivo. Aim 3. Study the effect of 02 and CO on NOS expression and activity in vitro. Formal course work and education are incorporated into the training component of this proposal. The candidate will have direction from leaders in the field of lung biology and pulmonary hypertension through a mentoring group. Through the 5 year award, the candidate will develop his skills in (i) hypotheses-driven design of studies, (ii) analyses and interpretation of data, and (iii) writing of manuscripts, abstracts and presenting data at meetings. The training component of this proposal will lead to the candidate's transition to a fully independent investigator.

- **Project Title: NONINVASIVE ASSESSMENT OF PRIMARY PULMONARY HYPERTENSION**

  Principal Investigator & Institution: Shandas, Robin; Professor; Pediatrics; University of Colorado Denver/Hsc Aurora P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2004; Project Start 01-JUL-2001; Project End 31-MAY-2007

  Summary: (Applicant's Abstract): This proposal addresses the problem of evaluating the efficacy of newly developed agents for the treatment of **primary pulmonary hypertension.** The use of catheter techniques to measure pulmonary vascular resistance severely limits routine evaluation of such treatments. We propose to develop, refine and test a non-invasive ultrasound based means of accurately evaluating pulmonary vascular resistance in children with **primary pulmonary hypertension.** The hypothesis

for this project is based on the relationship between changes in downstream impedance within a fluid system and the characteristics of the pressure pulse propagation wave that develops within the arterial walls. We propose to show that downstream impedance affects the pulse propagation wave traveling within the main pulmonary artery and that changes in downstream impedance, as would occur with treatments such as inhaled nitric oxide or infused prostaclyin, can be followed by measuring pulse propagation characteristics. Furthermore, we propose that the pressure pulse propagation in the main PA affects local velocities, and that such changes in local velocities can be quantified as a velocity propagation using non-invasive ultrasound color M-mode imaging. This should significantly aid in evaluating new treatments for **primary pulmonary hypertension** and thereby expand treatment options and improve quality of life for patients. The aims of this project, therefore, are: 1. Demonstrate analytically that a fundamentally rooted mathematical and physical foundation exists for using velocity data to extract pressure pulse propagation characteristics for pediatric **primary pulmonary hypertension.** 2. Develop and test a method for using color M-mode velocity data to predict downstream impedance using highly reproducible in vitro models. 3. Determine clinical utility of the color M-mode approach using existing clinical protocols studying the efficacy of nitric oxide and/or 100 percent 02 treatment in the catheterization laboratory to reduce pulmonary vascular resistance in children with **primary pulmonary hypertension.** 4. Determine whether color M-mode measured velocity propagation (Vel-prop) predicts pulmonary vascular resistance in the clinical situation.

- **Project Title: PATHOBIOLOGY OF HIV(SIV)-INDUCED ANGIOPROLIFERATIVE PUL***

  Principal Investigator & Institution: Flores, Sonia C.; Associate Professor; Medicine; University of Colorado Denver/Hsc Aurora P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2005; Project Start 29-SEP-2005; Project End 30-JUN-2010

  Summary: (provided by applicant): **Primary pulmonary hypertension** (PPH), a rapidly progressive and usually fatal disease, has an incidence rate among the HIV infected population many times higher than in the general population. Unfortunately, the pathogenesis of HIV-related pulmonary hypertension (HRPH) is not well understood. Nevertheless, the histological similarities are striking: uncontrolled endothelial cell (EC) proliferation and formation of plexogenic lesions obliterate the Lumina of the pulmonary arteries with subsequent right heart failure. The immune dysregulation, chronic exposure to viral products in the lung and altered chemokine/cytokine profile may contribute to the injury. In the lung, HIV-1 infects primarily macrophages providing a potential reservoir of virus and a source of localized viral proteins such as Nef, which can circulate and affect surrounding cells. Studies of HRPH have been hampered by lack of a suitable animal model. Since numerous primate models of HIV-1 recapitulate the immune deficiencies and complications seen in humans, we undertook a study of lungs from macaques infected with an SIV/HIV chimeric virus containing HIV-1 Nef (SHIVnefSF33A) and found plexogenic lesions in the lungs of SHIV-nef but not in SIV Nef-infected macaques, suggesting that there are functional differences between the nef alleles in their ability to promote pulmonary vascular remodeling. We propose to study the natural history and progression of HRPH in SHIVnef infected monkeys. Our specific hypothesis is that immune dysregulation of SHIVnef-infected monkeys, triggers a phenotypic switch in EC that allows selection of a highly proliferative, growth-dysregulated EC population that obliterates the Lumina of pulmonary arteries through plexiform lesion formation. To study this, we will address

the following question: What is the natural history of PH in macaques infected with SHIVnef, and in a background of gammaherpesvirus infection? We will infect the monkeys, track PH development post-infection, and will correlate immunological parameters with lesion formation. Does HIV nef lead to the acquisition of a proliferative phenotype in lung microvascular EC? We will examine the in vitro proliferative properties of pulmonary endothelial cells after exposure to various nef alleles/mutants or to conditioned media from macrophages exposed to these as well. Using a primate model system that is phylogenetically very close to humans allows us to study both the initiation and progression phases of HRPH.

- **Project Title: PHARMACOGENOMICS IN PULMONARY ARTERIAL HYPERTENSION**

  Principal Investigator & Institution: Benza, Raymond L.; Medicine; University of Alabama at Birmingham 1530 3Rd Avenue South Birmingham, Al 35294

  Timing: Fiscal Year 2005; Project Start 01-SEP-2005; Project End 31-JUL-2009

  Summary: (provided by applicant): Our goal is to determine clinically in PAH patients if associations exist between the efficacy and toxicity of sitaxsentan and bosentan and several gene polymorphisms in several key disease-specific and therapy specific genes. We will also characterize the relationship between these polymorphisms and PAH severity using either baseline hemodynamic or clinical surrogates for disease severity. Hypothesis: Polymorphisms influence the efficacy and toxicity of specific PAH therapy as well as development/severity of PAH via, their effect on PA remodeling, drug response or metabolism. This proposal will make use of a large population of well defined patients with PAH who were enrolled in several large clinical trials including Encysive protocols FPH02, 02x, 03 and 06 and a prospective cohort from four large PAH Centers. The sum total number of patients will be approximately 920, including 550 with PPH. This worldwide effort constitutes the largest clinical study of this deadly disease and in as such has great potential to alter clinical practice by revealing novel gene-drug interactions. We will test this hypothesis by executing the following Aims: Aim 1: Determine in PPH the relationship between known disease-specific polymorphisms (Serotorin transporter gene and PAI Hindlll) and variants in BMPR2 and SMAD4 with several well defined clinical efficacy endpoints of sitaxsentan and bosentan therapy. Aim 2: Determine in PAH the relationship between existing potentially "therapy-specific" polymorphism in the ET-1, ETAR, ETBR, NPR-c, prostacyclin receptor and prostacyclin synthase genes with several defined clinical efficacy endpoints of sitaxsentan and bosentan therapy. PAH = **pulmonary arterial hypertension** PA = pulmonary artery PPH = primary pulmonary hypertension

- **Project Title: PKC SIGNALING IN CAMP-INDUCED PULMONARY VASODILATION**

  Principal Investigator & Institution: Barman, Scott A.; Pharmacology and Toxicology; Medical College of Georgia (Mcg) 1120 15Th St Augusta, Ga 30912

  Timing: Fiscal Year 2004; Project Start 01-JUL-2001; Project End 31-MAR-2007

  Summary: (provided by applicant): **Primary Pulmonary Hypertension** (PPH) is a disease of unknown origin that results in narrowing Of the pulmonary vasculature causing high pulmonary blood pressure often leading to heart failure. Currently there is little knowledge on the cellular and molecular foundation of PPH. Normally, signaling mechanisms which elevate cAMP and cGMP in the pulmonary vasculature allow for the maintenance of a low pressure, high perfusion environment. It is well documented that the activation of the large-conductance, calcium-and voltage-activated potassium (BKca)

channel is of primary importance in the regulation of pulmonary arterial pressure and inhibition of the BKca channel has been implicated in the development of pulmonary hypertension. Preliminary data from patch-clamp studies in pulmonary arterial smooth muscle cells (PASM) of the fawn-hooded rat (FHR), a recognized animal model of pulmonary hypertension, suggests that cAMP, an activator of cAMP-dependent protein kinase (PKA), opens the BKca channel through "cross-activation" of the cGMP-dependent protein kinase (PKG). In contrast, protein kinase C (PKC) which causes pulmonary vasoconstriction, inhibits the BKca channel in FHR PASM, but activates the BKca channel in Sprague-Dawley (control) rats. Therefore, the hypothesis of the proposed studies is that cAMP-dependent vasodilators relax pulmonary arteries by opening BKca channels in pulmonary arterial smooth muscle by stimulating the activity of PKG, an effect inhibited by activation of PKC in FHR. This hypothesis will be tested by employing state-of-the-art techniques of electrophysiology, vascular contraction, and biochemistry/molecular biology to determine: 1) the effect of cAMP-dependent vasodilators on pulmonary arteries in vitro, 2) the effect of cAMP-elevating agents on whole-cell and single channel K+ currents from single myocytes isolated from pulmonary arteries, 3) cAMP-dependent "cross-activation" of PKG, and 4) the role of PKC on BKca channel activity and whether there is a direct interaction between PKG and PKC on BKca channel modulation. The long term goal of the proposed study is to understand how cAMP-elevating agents cause pulmonary arterial vasodilation by an endothelium-independent mechanism. It is believed that these studies will lead to the development of novel therapeutic agents that will help reduce the morbidity and mortality associated with PPH and other pulmonary vascular diseases.

- **Project Title: PROSTACYCLIN SYNTHASE AND PROSTACYCLIN RECEPTOR IN PH**

  Principal Investigator & Institution: Geraci, Mark W.; Professor and Division Head; University of Colorado Denver/Hsc Aurora P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2005

  Summary: (provided by applicant) Severe pulmonary hypertension, including **primary pulmonary hypertension** (PPH), is an important clinical problem with few clinical treatment options. The chronic, intravenous infusion of prostacyclin (PGI2) has been established as the treatment of choice for patients with PPH. It is now clear that long-term benefits occur which obviate the need for transplant in many cases. The physiological effects of prostacyclin on platelet behavior, vascular tone control, and cell proliferation are well established; however, we do not know whether prostacyclin effects the vascular remodeling in chronic pulmonary hypertension. Our overall hypothesis is that prostacyclin, through membrane-receptor dependent and independent mechanisms, is an important modulator of pulmonary vascular remodeling. We have demonstrated loss of the prostacyclin receptor (PGIR) protein in the smooth muscle cells of precapillary resistance arteries in patients with PPH. We postulate that impairment of the prostacyclin signal transduction contributes to pulmonary vascular remodeling. We have generated transgenic animals with selective pulmonary prostacyclin synthase (PGIS) overexpression. These animals are protected from the development of hypoxic pulmonary hypertension, and show no acute vasoconstriction or chronic vascular remodeling. In contrast, PGIR knockout (KO) mice, in response to hypoxia, develop rapid pulmonary hypertension accompanied by vascular remodeling. Microarray analysis of the lungs from the transgenic animals demonstrates a change in the global pattern of gene expression, which may be responsible for the "protected" phenotype, including changes in PPARs and COX-2. Our

underlying concept is that PGI2 exhibits both membrane-receptor mediated and nuclear-receptor-mediated actions. These alternative mechanisms could include direct effects on gene expression, signaling pathways not yet recognized, or changes in the level of other eicosanoids. Our goal is to examine, using both animal models and cell systems, the effects of PGIS and PGIR on vascular smooth muscle cell (VSMO) growth and differentiation. In Specific Aim 1, we will determine whether pulmonary vascular tone and remodeling are mediated through the PGI2 receptor using bitransgenic mice with PGIS overexpression, but lacking PGIR. Specific Aim 2 is designed to define the effect of PGIS and PGIR on the growth and remodeling of vascular smooth muscle cells. The results of this work are designed to elucidate new potential therapeutic targets for treating pulmonary hypertension, and broaden our understanding of vascular pathology in general.

- **Project Title: PULMONARY VASCULAR TREE DEVELOPMENT, GROWTH & REMODLING**

  Principal Investigator & Institution: Glenny, Robb W.; Associate Professor; Medicine; University of Washington Office of Sponsored Programs Seattle, Wa 98105

  Timing: Fiscal Year 2005; Project Start 20-AUG-1997; Project End 30-JUN-2007

  Summary: (provided by applicant): The pulmonary vascular tree has a unique design that optimizes the distribution of blood flow for gas exchange. Under normal conditions, its geometry is an end product of fetal development and postnatal growth. In disease, further restructuring occurs through vascular remodeling. Recent advances in molecular and cellular biology provide insights into how these three determinants influence vascular structure at the cellular level. The proposed work integrates physiologic studies with in situ cellular and molecular techniques to determine the functional significance of these factors in the whole living animal. Specific aim 1: Determine the degree of genetic control on pulmonary vascular tree growth during fetal development and how its geometry changes with postnatal growth. We will use armadillos, a unique animal that produces litters of identical offspring. By comparing the spatial distribution of blood flow within and across litters, we can quantify the genetic influence on vascular tree development and regional perfusion. We will also measure regional blood flow in growing pigs to identify patterns of blood flow redistribution. Patterns that are spatially clustered will provide evidence that postnatal growth of the pulmonary vascular tree may be locally regulated. Specific aim 2: Identify triggers of pulmonary vascular remodeling during chronic hypoxia. We will focus on the roles of mechanical wall stresses in promoting cellular proliferation and apoptosis in rat pulmonary arteries. Specific aim 3: Identify triggers of pulmonary vascular remodeling in pulmonary hypertension induced by vascular endothelial growth factor receptor-1 inhibition. We will focus on the roles of mechanical wall stresses in promoting plexiform lesions that are characteristic of **primary pulmonary hypertension.** The proposed work is designed to determine relationships between function, structure and genetic controls in the pulmonary circulation at the organ level. The most novel and significant aspect of the work is that cellular and molecular mechanisms will be explored in the intact animal. The findings will fill important gaps in our knowledge of pulmonary vascular development and triggers of remodeling.

- **Project Title: RAFT/CAVEOLAR MECHANISMS IN PULMONARY HYPERTENSION**

  Principal Investigator & Institution: Sehgal, Pravin B.; Professor; Cell Biology and Anatomy; New York Medical College Administration Building Valhalla, Ny 10595

Timing: Fiscal Year 2005; Project Start 01-APR-2003; Project End 31-MAR-2008

Summary: (provided by applicant): This translational research proposal seeks to apply recent novel insights into the mechanisms of cell signaling at the level of the plasma membrane (the caveola/raft signaling hypothesis and the interleukin-6-raft-STAT3 signaling model) to an understanding of the pathogenesis of PH. Caveolin-1-containing detergent-resistant plasma membrane rafts are now recognized as specialized signaling organelles, including cytokine signaling. There is now growing evidence for a role of cytokines in the pathogenesis of lung diseases. As examples, elevated serum levels of IL-6 have been observed in **primary pulmonary hypertension** (PH) and in PH associated with autoimmune diseases and AIDS. In a rat model, a single injection of the plant alkaloid monocrotaline (MCI) results within 48 hrs in endothelial cell damage, membrane leakage, upregulation of IL-6 mRNA and bioactivity but a marked downregulation of caveolin-1 in the lung, followed by development of PH 10-14 days later. The focus of the proposed studies is two-pronged: (a) to evaluate the hypothesis that pulmonary endothelial-cell raft/caveolar disruption by MCT is an initiating event in the pathogenesis of PH (Specific Aim I), and (b) to investigate the function of membrane rafts and of the newly discovered cytosolic caveolin-containing Palade complexes in IL-6-induced STAT3 signaling in lung-specific cells (Specific Aims II and III). Aim I will include investigations of the time-course, histologic location, and cellular and molecular mechanisms for the downregulation of caveolin proteins and gene expression, and of the integrity of caveolar/raft function in pulmonary vascular and parenehymal tissues of MCT-treated rats. Aim II includes molecular studies of the mechanisms of association of STAT3 with caveolin-1 and of STAT3 activation in plasma membrane rafts in pulmonary endothelial cells, alveolar type II-like epithelial cells and lung fibroblasts. Aim Ill includes studies of the protein components of STAT3-containing cytosolic Palade complexes and their function in ferrying signaling molecules from the plasma membrane rafts to the cell interior. Mechanistic insights derived from this project are likely to suggest novel therapeutic approaches in the management of pulmonary hypertension. Moreover, the proposed studies are of particularly broad significance in that insights into the molecular mechanisms involved in raft-STAT signaling are likely to be applicable to cytokine-mediated activation of STAT transcription factors in perhaps all cell types, as well as to other signaling pathways localized in raft microdomains (eNOS and angiotensin II signaling).

- **Project Title: REGULATION OF KV CHANNELS BY ANOREXIGENS**

  Principal Investigator & Institution: Takimoto, Koichi; Environ & Occupational Health; University of Pittsburgh at Pittsburgh 350 Thackeray Hall Pittsburgh, Pa 15260

  Timing: Fiscal Year 2005; Project Start 01-APR-2004; Project End 31-MAR-2008

  Summary: Voltage-gated K+ (Kv) channels in pulmonary arterial smooth muscle cells (PASMCs) have been implicated in the initiation of pulmonary hypertension: inhibition of these channels results in membrane depolarization and an increase in intracellular Ca2+ concentration, leading to vasoconstriction and cell growth / remodeling. The use of anorexic agents (phentermine, fenfluramine and their related drugs) is associated with an increased incidence of pulmonary hypertension. These drugs also decrease the activity and expression of Kv channels in PASMCs. Thus, understanding the mechanisms by which these identified stimuli produce alterations in the function and level of these channels may provide clues for prevention and treatment of **primary pulmonary hypertension.** The anorexic agents reduce Kv channel activity at multiple steps. They acutely inhibit 4-aminopyridine (4-AP)-sensitive Kv current in PASMCs. Furthermore, long-term treatment of PASMCs with fenfluramine leads to decreases in

Kv current density and the expression of Kv1.5 mRNA. Lung tissues from patients with primary, but not secondary, pulmonary hypertension also exhibit reduced expression of Kv1.5 mRNA. These findings suggest acute and long-term exposures to these drugs influence 4-AP-sensitive Kv channels at plasma membrane and transcription of Kv channel subunit genes, respectively. Using Xenopus oocyte expression system, we found that fenfluramine and phentermine inhibit Kv1.5, Kv2.1 and Kv4.2, but not Kv3.1b, current. Using cultured rat PASMCs and heterologous expression systems, we have analyzed molecular mechanisms underlying the anorexigen-induced changes in the activity and expression of Kv channels. First, exposure to fenfluramine decreased endogenous Kv2.1 proteins in PASMCs. The drug also reduced heterologously expressed Kv2.1, but not Kv1.5 or Kv4.3, proteins in a mammalian cell line. In addition, the non-selective kinase inhibitor staurosporin mimicked and occluded the fenfluramine-induced decrease in the channel protein level in PASMCs. Second, the anorexic drugs caused significant decreases in the level of endogenous Kv1.5 mRNA and reporter gene expression driven by the Kv1.5 promoter in PASMCs. Reductions in the channel promoter activity were also seen in A7r5 smooth muscle cells, but not in CHO or HEK293 cells. Finally, fenfluramine and phentermine rapidly and reversibly inhibited Kv1.5, Kv2.1 and Kv4.2, but not Kv3.1b, currents in Xenopus oocytes. Thus, the anorexigen-induced pulmonary hypertension may be mediated by their multitude of actions to produce acute and long-term inhibition of PASMC Kv channels. Hence, this proposal is to identify molecular mechanisms for anorexigen-induced inhibition of Kv channels at the three levels: a slow decrease in Kv2.1 proteins, inhibition of Kv1.5 gene transcription and blockade of Kv currents at plasma membrane.

- **Project Title: ROLE OF TGF-BETA FAMILY SIGNALING IN HHT AND PPH**

  Principal Investigator & Institution: Oh, S Paul.; Associate Professor; Physiology & Functional Genomics; University of Florida 219 Grinter Hall Gainesville, Fl 32611

  Timing: Fiscal Year 2005; Project Start 01-DEC-1999; Project End 30-JUN-2009

  Summary: (provided by applicant): The long-term goal of the proposal is to elucidate the role of transforming growth factor b family signals in the pathogenesis of 2 vascular diseases; hereditary hemorrhagic telangiectasia (HHT) and **primary pulmonary hypertension** (PPH). HHT is an autosomal dominant vascular disorder characterized by epistaxis, mucocutaneous telangiectases and arteriovenous malformations (AVM). Direct shunting of blood through cerebral AVMs may result in ischemic and/or hemorrhagic infarctions in the brain and lead to stroke. It has been shown that the reduced expression of either endoglin (ENG) or activin receptor-like kinase 1 (ALK1) causes HHT. Both genes are involved in the transforming growth factor b signaling pathways. However, the precise role of these genes in the pathogenesis of HHT remains elusive. PPH is a rare lung disorder (2-3 per million per year), in which the pulmonary artery pressure rises far above normal levels (25 mmHg at rest and 30mmHg during exercise) without an apparent reason. PPH is a fatal disease with mean survival from diagnosis of 2.8 years without proper treatment. Familial form of PPH are inherited in an autosomal dominant manner, and heterozygous mutations of bone morphogenic protein type II receptor (BMPR2) were found in a half of familial PPH cases. Furthermore, 26% of apparently sporadic PPH cases also contain germline BMPR2 mutations. In addition to BMPR2, recent studies have shown that HHT patients with ALK1 mutations also develop PPH. However, cellular and pathogenetic mechanisms underlying PPH have yet to be elucidated. Identification of signaling pathway of ALK1 is fundamental in understanding the pathogenic mechanism of HHT and PPH. We have previously hypothesized that both ALK1 and ALK5 (Tgfbrl) are type I receptor for TGF-B signal in endothelial cells, and TGF-B signal mediated by each type I receptor form an

opposing balance which controls the property of endothelial cells during angiogenesis. This hypothesis was challenged by several other groups, and became evolved into a more complicated form. The immediate goals of this proposal are to dissolve the intertwined signaling mechanisms surrounding ALK1 in endothelium, and to develop animal models for PPH. Results from the proposed studies would provide novel insights and perspectives on the role of TGF-B signaling on endothelial functions and smooth muscle cell growth and differentiation, and also shed light on the understanding the pathologic mechanisms underlying HHT, PPH, atherosclerosis, and restenosis.

- **Project Title: TARGETING ACTIVE ADAPTORS TO CONTROL ENDOTHELIAL DAMAGE**

  Principal Investigator & Institution: Wei, Sheng; H. Lee Moffitt Cancer Ctr & Research Ins 12902 Magnolia Dr Tampa, Fl 336129497

  Timing: Fiscal Year 2005; Project Start 01-MAY-2004; Project End 30-APR-2009

  Summary: (provided by applicant): Upon cell-cell contact, one of the mechanisms of immune cells to cause tissue damage is by delivery of lytic granules containing preformed effector molecules--perforin proteins and granzyme proteases. The presence of granzymes and perforin in the extracellular milieu not only reflects the presence of activated CTL and NK cells but also significantly contribute to inflammatory reaction. These protein enzymes can cause circular pore-like lesions on the membrane surface of endothelial cells and induce target cell death leading to local tissue damage and chronic vascular cell damage. Increased granzyme level is closely correlated with the inflammatory activity in autoimmune diseases (e.g. rheumatoid arthritis) and virally-infected lung and heart diseases. A clear understanding of the pathophysiology of inflammation mediated tissue damage would greatly facilitate management of this disease. The signal transduction pathways in effector lymphocytes, which trigger the redistribution of the lytic granules towards the target endothelial cells, are not well defined. Identification of key signaling molecules which specifically control this lytic process could enable pharmaceutical disruption of this process, thereby reducing the tissue damage mediated by activated lymphocytes. In this proposal, we will use a human primary pulmonary endothelial cell line, CRL- 2598, as the trigger to activate the lytic signal cascade in NK cells. Using biochemical and gene delivery approaches, we will directly test the hypothesis that the early signals via NK activation receptors and their associated adaptor proteins, DAP12 and DAP10, will play a specific role in control of granule movement in NK cells. Blocking of this initial step, at the level of the adaptor proteins, will inhibit granule exocytosis. More importantly, we will test our hypothesis on LGL leukemic patients with **primary pulmonary hypertension** (PPH) and determine if DAP10 and/or DAP12 critically control NK cell- mediated endothelial cell damage and death. A better understanding of the signaling pathways that control granule movement and exocytosis will offer new opportunities, e.g. design of DAP10 and DAP12 antagonists, for therapeutic intervention to specifically control lymphocyte-mediated tissue damage.

- **Project Title: THE ROLE OF THE BMP TYPE II RECEPTOR IN VASCULAR FUNCTION**

  Principal Investigator & Institution: Yu, Paul B.; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2006; Project Start 01-APR-2006; Project End 31-MAR-2011

  Summary: (provided by applicant): The proposed research examines the function of bone morphogenetic protein (BMP) signaling in the vasculature. Previous work in the

field has demonstrated the impact of BMP signals upon the function of vascular endothelial and smooth muscle cells, indicating that BMP signals are important regulators of vessel brmation and remodeling. Loss-of-function mutations in the principal receptor for BMP signals, the BMP type II receptor (BMPR2) are implicated in the vasculopathic disease **primary pulmonary hypertension,** further supporting an essential role in vascular function. However, the mechanisms by which BMP signals modify the function of vascular tissues are incompletely defined. Use of the Cre-lox system and genetically modified mice has permitted tissue-specific disruption of the BMPR2 gene in vivo and in vitro. The impact of BMPR2 signaling upon vascular cell functions and transcriptional activity will be investigated, as well as the potential mechanisms of effect. Cell physiology will be correlated with the impact of disrupting BMPR2 in vivo, using the endpoints of pulmonary vascular hemodynamic function, structure and development. These studies will help define the role of BMPR2 and BMP signaling in normal and pathologic vascular function and may provide an animal model of pulmonary hypertension. Completion of the research program and the acquisition of the required skills and experience will provide a solid foundation for the development of a career as a physician-scientist specializing in cardiac and pulmonary vascular biology. The principal investigator is transitioning from fellowship training to faculty in the Division of Cardiology at Massachusetts General Hospital and proposes to expand upon his scientific skills in molecular genetics, cell biology, and animal physiology to facilitate the transition to independence as an investigator skilled in integrating molecular and physiologic aspects of disease. The career development plan includes scientific and career mentorship from an advisory committee of accomplished scientists; participation in relevant seminars, courses, and national meetings; and the provision of protected research time. The proposal will take advantage of extensive local technical expertise and the highly collaborative environment present at Massachusetts General Hospital. Health Relevance: Bone morphogenetic proteins are used by cells to coordinate growth of new tissues and maintain existing tissues, and are especially important in developing and maintaining normal blood vessels. This study examines in mice how a receptor for bone morphogenetic proteins (BMPR2) coordinates the function of blood vessel cells, and how abnormal function of BMPR2 may lead to disorders of the circulation. (End of Abstract)

- **Project Title: THROMBOXANE SYNTHASES-ENZYMOLOGY AND GENE REGULATION**

  Principal Investigator & Institution: Wang, Lee-Ho; Internal Medicine; University of Texas Hlth Sci Ctr Houston Box 20036 Houston, Tx 77225

  Timing: Fiscal Year 2005; Project Start 01-JUL-1998; Project End 30-NOV-2007

  Summary: (provided by applicant): Thromboxane synthase (TXAS) is a "non-classical" cytochrome P450 that converts prostaglandin H2 to thromboxane A2 (TXA2), a potent inducer of vasoconstriction and platelet aggregation. TXA2 is believed to be a crucial factor contributing to a variety of cardiovascular and pulmonary diseases such as atherosclerosis, myocardial infarction and **primary pulmonary hypertension.** To understand how the biosynthesis of TXA2 is controlled, it is essential to have an integrated knowledge of TXAS structure/function relationship and its gene regulation. We showed that TXAS shared similar spectral features with other P450s but, unlike other P450s, had a very high turnover number and catalyzed a "peroxidase-like" reaction with a rate-limiting step at the substrate binding. To continue our efforts in understanding this important enzyme, our specific aims are to (1) evaluate the mono-oxygenase potential of TXAS by determining the redox potential of TXAS heme-iron, characterizing the interaction of TXAS with P450 reductase and investigating the

hydroxylase reaction using oxene-donating reagent, (2) determine the structure/function relationship of the active site residues in TXAS catalysis by site-directed mutagenesis and self-inactivation analysis, and (3) solve crystallographic structures of TXAS and its complexes with substrate analog. Regulation of TXAS expression occurs at the transcriptional level. TXAS expression level is cell-type preferential; high in hematopoietic cells and low in non-hematopoietic cells. The binding site for NF-E2 is the most important cis-element for TXAS expression in vivo. The transcription factors p45 NF-E2 and mafG form a heterodimer which activates TXAS transcription in hematopoietic cells. In the non-hematopoietic A549 cells, Nrf2 activated TXAS expression through the NF-E2 site. Thus, TXAS gene utilizes a single cis-acting element but different trans-acting factors to achieve cell-preferential expression. Our results also demonstrated that chromatin structure plays a critical role in TXAS expression. We showed that binding of NF-E2 is associated with the disruption of nucleosomal structure of TXAS promoter. This disruption is likely via CBP/p300. We hypothesize that the differential abilities of NF-E2 proteins in NF-E2 binding, recruiting CBP/p300, disrupting the nucleosomal structure and exerting their trans-activation potency from the TXAS promoter context account for the cell-preferential expression. To test this hypothesis, we propose to: (4) characterize the role of the NF-E2 in altering the nucleosomal structure of TXAS gene and to delineate the TXAS cell-preferential expression using an in vitro chromatin system.

- **Project Title: TREATMENT OF HEART DISEASE WITH AN INTRAVENTRICULAR SAC**

  Principal Investigator & Institution: Chambers, Sean D.; Research Engineer; Mc3, Inc. 3550 W Liberty Rd Ann Arbor, Mi 481038802

  Timing: Fiscal Year 2005; Project Start 30-SEP-2004; Project End 31-MAY-2007

  Summary: (provided by applicant): The purpose of this project is to develop a diastolic volume limiting apparatus (divola) for treatment of advanced heart disease in humans. This technology is an entirely new method of treatment of heart disease, and may be used in both dilated and ischemic cardiomyopathy. The device is simply a plastic sac that is placed inside the left ventricle of a diseased heart, and functions by limiting filling of the ventricle during diastole. The divola protects the left ventricle from the harmful effects of high ventricular pressure during diastole, allowing for reverse remodelling (shrinkage) of a pathologically jenlarged ventricle. The device may be used in patients who would otherwise require a heart transplant or a mechanical circulatory assist device. The device may also be applied to other forms of heart disease, including left ventricular aneurysms, ischemic ventricular septal defects, and (with modification) **primary pulmonary hypertension.** Initial research efforts in phase I are directed to designing and testing advanced prototypes of the divola for implantation into animals. Geometric measurements will be taken from sheep echocardiograms to establish the parameters for construction of the divola. The process of fabrication of divolas will be established and refined. High speed video analysis will be used to determine ideal folding patterns and pumping action in order to minimize thrombogenicity and maximize durability. Flow visualization studies will be performed to determine the ideal shape and dimensions of the divola. The divola will be tested on a benchtop apparatus to determine durability and hemolysis. Successful Phase I research will lead to an advance design of the divola suitable for implantation and testing in large animal models of heart failiure in Phase II research. Successful development of this techology would provide a practical and inexpensive method for treatment of advance heart disease as an alternative to heart transplantation or mechanical circulatory assist devices.

- **Project Title: VIRAL INFECTION AND PRIMARY PULMONARY HYPERTENSION**

  Principal Investigator & Institution: Damania, Blossom A.; Assistant Professor; Microbiology and Immunology; University of North Carolina Chapel Hill Office of Sponsored Research Chapel Hill, Nc 27599

  Timing: Fiscal Year 2005; Project Start 29-SEP-2005; Project End 30-JUN-2010

  Summary: (provided by applicant): This proposal is aimed at exploring the roles of viral infection with Human Immunodeficiency virus (HIV) and Kaposi's sarcoma-associated herpes virus (KSHV) in the pathogenesis of HIV-associated pulmonary hypertension. We will examine the effect of HIV and KSHV viral infection on activation of the bone morphogenetic protein receptor (BMPR) pathway and abnormal cytokine, vasoconstrictor and vasodilator production in endothelial cells. **Primary Pulmonary Hypertension** (PPH) is a disease that causes narrowing of the pulmonary vasculature leading to a high pulmonary blood pressure that often results in heart failure. The development of PPH is thought to occur through multiple events involving genetic and cellular environment factors. The primary dysfunction lies in the pulmonary endothelial cells which exhibit enhanced synthesis of vasoconstrictors, reduced synthesis of vasodilator production, and enhanced thrombogenesis. Endothelial cells are the predominant component of the plexiform. It has been estimated that the incidence of pulmonary hypertension among HIV-positive persons is several thousand times greater than among the general population. In both PPH and AIDS-associated PPH, the plexiform lesions contain proliferating endothelial cells. HIV might play either a direct or indirect role in endothelial cell dysfunction seen in PPH. The inability to identify HIV protein or RNA in pulmonary arteries of patients with HIV-associated pulmonary hypertension suggests that HIV does not directly infect the endothelial cells in the lesion. Thus, HIV may play an indirect role in the endothelial cell dysfunction seen in PPH. This could occur through the up regulation of paracrine factors such as proinflammatory cytokines or growth factors, leading to endothelial dysfunction and PPH. KSHV has also been recently linked to the development of PPH. Cool et al. reported that 62% of PPH patients displayed KSHV antigen within and around the plexiform lesions and the lesions themselves resembled Kaposi's sarcoma (KS) cutaneous lesionslt is very well established that KSHV can infect endothelial cells both in vitro and in vivo. Our hypothesis is that KSHV infection of endothelial cells predisposes the endothelial cells to aberrant signaling and proliferation, and this dysfunction is enhanced with HIV co infection.

NTIS (National Technical Information Service)

The NTIS (**www.ntis.gov**), a service of the U.S. Department of Commerce, has published the following information on sponsored studies related to primary pulmonary hypertension:

- **"Effect of Inhaled Nitric Oxide on Pulmonary Function After Sepsis in a Swine Model,"** published in August 1994.

  Sponsored by: Army Inst. of Surgical Research, Fort Sam Houston, TX.

  Written by: H. Ogura, W. G. Cioffi, P. J. Offner, B. S. Jordan and A. A. Johnson.

  Abstract: SEPSIS, A CONDITION that significantly affects the out come of severely injured patients, is characterized by a systemic inflammatory response that is mediated by various cytokines and activated leukocytes.' Pulmonary dysfunction as indexed by pulmonary arterial hyper- tension, decreasing compliance, and VA/Q mismatching leading to hypoxemia is a common sequeis of sepsis. The exact mechanism by which

sepsis affects the pulmonary system is unknown. Activation of both leukocytes and endothelial cells in concert with the release of various compounds results in pulmonary vasoconstriction and increased vascular permeability leading to pulmonary failure, which often necessitates ventilatory support. 3 Inhaled nitric oxide (NO) has been reported to act as a selective pulmonary vasodilator without causing systemic vasodilation. This effect has been shown in various animal models of **pulmonary arterial hypertension** including those induced by thromboxane analogues, hypoxemia, and endotoxemia.The hypoxemia that accompanies endotoxemia has also been improved by NO.5 These beneficial effects of NO have been documented in patients with chronic obstructive pulmonary disease, adult respiratory distress syndrome (ARDS), congenital heart failure, and **pulmonary arterial hypertension**. JMD.

- **"Pulmonary Effect of Nitric Oxide Synthase Inhibition Following Endotoxemia in a Swine Model,"** published in December 1994.

  Sponsored by: Army Inst. of Surgical Research, Fort Sam Houston, TX.

  Written by: H. Ogura, P. J. Offner, D. Saitoh, B. S. Jordan and A. A. Johnson.

  Abstract: Sepsis results in a systemic inflammatory response that is mediated by various cytokines and activated leukocytes. Systemic vasodilation and hypotension characteristic of sepsis have been hypothesized to occur secondarily to endogenous overproduction of nitric oxide (NO). In contrast to the systemic vasodilatory response, pulmonary vasoconstriction and **pulmonary arterial hypertension** caused by the release of potent vasoconstrictors usually occurs. Despite this pulmonary vasoconstrictive response, we and others have found that hypoxic pulmonary vasoconstriction (HPv) is blunted and blood flow to poorly and unventilated lung areas is maintained. This loss of the hypoxic vasoconstrictive response adversely affects pulmonary oxygenation by increasing the ventilation perfusion ratio (VA/Q) mismatching. Because respiratory failure following sepsis is a significant comorbid factor, therapy aimed at attenuating this deleterious process may exert a beneficial effect on outcome.

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 primary pulmonary hypertension, simply go to the PubMed Web site at **http://www.ncbi.nlm.nih.gov/pubmed**. Type **primary pulmonary hypertension** (or synonyms) into the search box, and click **Go**. The following is the type of output you can expect from PubMed for primary pulmonary hypertension (hyperlinks lead to article summaries):

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

- **A case series of six children with primary pulmonary hypertension.**
  Author(s): Quek SC, Yip CL, Wong ML, Chan KY, Wong CL.
  Source: Ann Acad Med Singapore.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11379407&query_hl=14&itool=pubmed_docsum

- **A gene for primary pulmonary hypertension.**
  Author(s): Wilkins MR, Gibbs JS, Shovlin CL.
  Source: Lancet.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11072932&query_hl=14&itool=pubmed_docsum

- **A new era in the treatment of primary pulmonary hypertension.**
  Author(s): Bailey CL, Channick RN, Rubin LJ.
  Source: Heart (British Cardiac Society).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11179256&query_hl=14&itool=pubmed_docsum

- **A noninvasive assessment of pulmonary perfusion abnormality in patients with primary pulmonary hypertension.**
  Author(s): Ting H, Sun XG, Chuang ML, Lewis DA, Hansen JE, Wasserman K.
  Source: Chest.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11243964&query_hl=14&itool=pubmed_docsum

- **A study of clinical efficacy of sildenafil in patients with primary pulmonary hypertension.**
  Author(s): Sastry BK, Narasimhan C, Reddy NK, Anand B, Prakash GS, Raju PR, Kumar DN.
  Source: Indian Heart J.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12462670&query_hl=14&itool=pubmed_docsum

- **Abnormal pulmonary artery pressure response in asymptomatic carriers of primary pulmonary hypertension gene.**
  Author(s): Grunig E, Janssen B, Mereles D, Barth U, Borst MM, Vogt IR, Fischer C, Olschewski H, Kuecherer HF, Kubler W.
  Source: Circulation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10973844&query_hl=14&itool=pubmed_docsum

- **Absence of human herpesvirus 8 in lung tissues from Japanese patients with primary pulmonary hypertension.**
  Author(s): Daibata M, Miyoshi I, Taguchi H, Matsubara H, Date H, Shimizu N, Ohtsuki Y.
  Source: Respiratory Medicine.
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  Source: J Cardiol.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=3267719&query_hl=14&itool=pubmed_docsum

- **Sildenafil in the management of primary pulmonary hypertension.**
  Author(s): Singh B, Gupta R, Punj V, Ghose T, Sapra R, Grover DN, Kaul U.
  Source: Indian Heart J.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12216929&query_hl=14&itool=pubmed_docsum

- **Sildenafil treatment of primary pulmonary hypertension.**
  Author(s): Laupland KB, Helmersen D, Zygun DA, Viner SM.
  Source: Can Respir J.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12624621&query_hl=14&itool=pubmed_docsum

- **Successful palliation of primary pulmonary hypertension by atrial septostomy.**
  Author(s): Hausknecht MJ, Sims RE, Nihill MR, Cashion WR.
  Source: The American Journal of Cardiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1691586&query_hl=14&itool=pubmed_docsum

- **Survival in primary pulmonary hypertension: the impact of epoprostenol therapy.**
  Author(s): McLaughlin VV, Shillington A, Rich S.
  Source: Circulation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12234951&query_hl=14&itool=pubmed_docsum

- **Survival with first-line bosentan in patients with primary pulmonary hypertension.**
  Author(s): McLaughlin VV, Sitbon O, Badesch DB, Barst RJ, Black C, Galie N, Rainisio M, Simonneau G, Rubin LJ.
  Source: The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15684287&query_hl=14&itool=pubmed_docsum

- **Systemic collateral supply in patients with chronic thromboembolic and primary pulmonary hypertension: assessment with multi-detector row helical CT angiography.**
  Author(s): Remy-Jardin M, Duhamel A, Deken V, Bouaziz N, Dumont P, Remy J.
  Source: Radiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15703314&query_hl=14&itool=pubmed_docsum

- **The acute administration of vasodilators in primary pulmonary hypertension. Experience from the National Institutes of Health Registry on Primary Pulmonary Hypertension.**
  Author(s): Weir EK, Rubin LJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Elliott CG, Fishman AP, Goldring RM, Groves BM, et al.
  Source: Am Rev Respir Dis.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=2690706&query_hl=14&itool=pubmed_docsum

- **The acute effect of the synthetic prostacyclin analogue iloprost in primary pulmonary hypertension.**
  Author(s): Scott JP, Higenbottam T, Wallwork J.
  Source: Br J Clin Pract.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1698429&query_hl=14&itool=pubmed_docsum

- **The putative satiety hormone PYY is raised in cardiac cachexia associated with primary pulmonary hypertension.**
  Author(s): le Roux CW, Ghatei MA, Gibbs JS, Bloom SR.
  Source: Heart (British Cardiac Society).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15657252&query_hl=14&itool=pubmed_docsum

- **The United States experience with the acute and chronic treatment of primary pulmonary hypertension.**
  Author(s): Weir EK.
  Source: European Heart Journal.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=3053183&query_hl=14&itool=pubmed_docsum

- **Transcatheter embolization of pulmonary artery false aneurysm associated with primary pulmonary hypertension.**
  Author(s): Hiraki T, Kanazawa S, Mimura H, Yasui K, Okumura Y, Dendo S, Yoshimura K, Takahara M, Hiraki Y.
  Source: Cardiovascular and Interventional Radiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15259821&query_hl=14&itool=pubmed_docsum

- **Treatment for primary pulmonary hypertension. Back to the future.**
  Author(s): McManigle JE, Tenholder MF.
  Source: Chest.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=2676396&query_hl=14&itool=pubmed_docsum

- **Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial.**
  Author(s): Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, Williams WB, Diehl JH, Crow J, Long W.
  Source: Annals of Internal Medicine.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=2107780&query_hl=14&itool=pubmed_docsum

- **Treatment of primary pulmonary hypertension with oral sildenafil.**
  Author(s): Karatza AA, Narang I, Rosenthal M, Bush A, Magee AG.
  Source: Respiration; International Review of Thoracic Diseases.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15031578&query_hl=14&itool=pubmed_docsum

- **Two cases of familial primary pulmonary hypertension.**
  Author(s): Yamashita K, Tasaki H, Kubara T, Nakashima Y.
  Source: J Uoeh.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15624356&query_hl=14&itool=pubmed_docsum

- **Two-dimensional and Doppler-echocardiographic and cardiac catheterization correlates of survival in primary pulmonary hypertension.**
  Author(s): Eysmann SB, Palevsky HI, Reichek N, Hackney K, Douglas PS.
  Source: Circulation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=2752562&query_hl=14&itool=pubmed_docsum

- **Understanding primary pulmonary hypertension.**
  Author(s): Berkowitz DS, Coyne NG.
  Source: Critical Care Nursing Quarterly.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12669944&query_hl=14&itool=pubmed_docsum

- **Unilateral acheiria and fatal primary pulmonary hypertension in a girl with incontinentia pigmenti.**
  Author(s): Hayes IM, Varigos G, Upjohn EJ, Orchard DC, Penny DJ, Savarirayan R.
  Source: Am J Med Genet A.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15884011&query_hl=14&itool=pubmed_docsum

- **Unpredictable response to vasodilator therapy in primary pulmonary hypertension.**
  Author(s): Schmiedt MI, Shettigar UR, Siddique M, Barbier G, Bialow M, Carranza S.
  Source: Int J Clin Pharmacol Ther.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9726697&query_hl=14&itool=pubmed_docsum

- **Urinary cGMP concentrations in severe primary pulmonary hypertension.**
  Author(s): Bogdan M, Humbert M, Francoual J, Claise C, Duroux P, Simonneau G, Lindenbaum A.
  Source: Thorax.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10195079&query_hl=14&itool=pubmed_docsum

- **Use of assisted reproductive technologies and anesthesia in a patient with primary pulmonary hypertension.**
  Author(s): Metzler E, Ginsburg E, Tsen LC.
  Source: Fertility and Sterility.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15193496&query_hl=14&itool=pubmed_docsum

- **Use of epoprostenol (Flolan) in the management of primary pulmonary hypertension.**
  Author(s): Kayser SR.
  Source: Progress in Cardiovascular Nursing.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9950022&query_hl=14&itool=pubmed_docsum

- **Use of inhaled nitric oxide for emergency Cesarean section in a woman with unexpected primary pulmonary hypertension.**
  Author(s): Decoene C, Bourzoufi K, Moreau D, Narducci F, Crepin F, Krivosic-Horber R.
  Source: Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11444454&query_hl=14&itool=pubmed_docsum

- **Use of stellate ganglion blocks for chronic chest pain associated with primary pulmonary hypertension.**
  Author(s): Parris WC, Lin S, Frist W Jr.
  Source: Anesthesia and Analgesia.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=3421503&query_hl=14&itool=pubmed_docsum

- **Uveal effusion and angle-closure glaucoma in primary pulmonary hypertension.**
  Author(s): Krohn J, Bjune C.
  Source: American Journal of Ophthalmology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12719080&query_hl=14&itool=pubmed_docsum

- **Uveal effusion syndrome associated with primary pulmonary hypertension and vomiting.**
  Author(s): Akduman L, Del Priore LV, Kaplan HJ, Meredith T.
  Source: American Journal of Ophthalmology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8610808&query_hl=14&itool=pubmed_docsum

- **Value of a Doppler-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension.**
  Author(s): Yeo TC, Dujardin KS, Tei C, Mahoney DW, McGoon MD, Seward JB.
  Source: The American Journal of Cardiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9605059&query_hl=14&itool=pubmed_docsum

- **Vascular remodeling in primary pulmonary hypertension. Potential role for transforming growth factor-beta.**
  Author(s): Botney MD, Bahadori L, Gold LI.
  Source: American Journal of Pathology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8311113&query_hl=14&itool=pubmed_docsum

- **Vascular smooth muscle cell phenotypes in primary pulmonary hypertension.**
  Author(s): Mitani Y, Ueda M, Komatsu R, Maruyama K, Nagai R, Matsumura M, Sakurai M.
  Source: The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11334137&query_hl=14&itool=pubmed_docsum

- **Vasoactive intestinal peptide as a new drug for treatment of primary pulmonary hypertension.**
  Author(s): Petkov V, Mosgoeller W, Ziesche R, Raderer M, Stiebellehner L, Vonbank K, Funk GC, Hamilton G, Novotny C, Burian B, Block LH.
  Source: The Journal of Clinical Investigation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12727925&query_hl=14&itool=pubmed_docsum

- **Vasodilator therapy for primary pulmonary hypertension in children.**
  Author(s): Barst RJ, Maislin G, Fishman AP.
  Source: Circulation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10069788&query_hl=14&itool=pubmed_docsum

- **Vasodilator therapy in primary pulmonary hypertension.**
  Author(s): Elkayam U.
  Source: Chest.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7471853&query_hl=14&itool=pubmed_docsum

- **Vasodilators and primary pulmonary hypertension. Variability of long-term response.**
  Author(s): Dantzker DR, D'Alonzo GE, Gianotti L, Fuentes F, Nickeson D, Emerson M.
  Source: Chest.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=2721250&query_hl=14&itool=pubmed_docsum

- **Vasodilators in the treatment of primary pulmonary hypertension.**
  Author(s): Weir EK, Schremmer B.
  Source: The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9727771&query_hl=14&itool=pubmed_docsum

- **Vasopressin during spinal anesthesia in a patient with primary pulmonary hypertension treated with intravenous epoprostenol.**
  Author(s): Braun EB, Palin CA, Hogue CW.
  Source: Anesthesia and Analgesia.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15281498&query_hl=14&itool=pubmed_docsum

- **Ventricular arrhythmias and autonomic profile in patients with primary pulmonary hypertension.**
  Author(s): Folino AF, Bobbo F, Schiraldi C, Tona F, Romano S, Buja G, Bellotto F.
  Source: Lung.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14749936&query_hl=14&itool=pubmed_docsum

- **What role for echocardiography in primary pulmonary hypertension? New ultrasound methods accurately estimate pulmonary pressures.**
  Author(s): Liebson PR.
  Source: J Crit Illn.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10147919&query_hl=14&itool=pubmed_docsum

CHAPTER 2. ALTERNATIVE MEDICINE AND PRIMARY PULMONARY HYPERTENSION

Overview

In this chapter, we will begin by introducing you to official information sources on complementary and alternative medicine (CAM) relating to primary pulmonary hypertension. 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 primary pulmonary hypertension 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 **primary pulmonary hypertension** (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 primary pulmonary hypertension:

- **A pulmonary hypertension-producing plant from Tanzania.**
  Author(s): Heath D, Shaba J, Williams A, Smith P, Kombe A.
  Source: Thorax.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=126502&query_hl=1&itool=pubmed_docsum

- **Acute pulmonary hypertension following paclitaxel in a patient with AIDS-related primary effusion lymphoma.**
  Author(s): Cherifi S, Hermans P, De Wit S, Cantinieaux B, Clumeck N.
  Source: Clinical Microbiology and Infection : the Official Publication of the European Society of Clinical Microbiology and Infectious Diseases.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11422257&query_hl=1&itool=pubmed_docsum

- **Bosentan and warfarin interaction.**
  Author(s): Murphey LM, Hood EH.
  Source: The Annals of Pharmacotherapy.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12841813&query_hl=1&itool=pubmed_docsum

- **Drug therapy during pregnancy.**
  Author(s): Niebyl JR.
  Source: Current Opinion in Obstetrics & Gynecology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1543829&query_hl=1&itool=pubmed_docsum

- **Drug therapy of primary pulmonary hypertension.**
  Author(s): Nagaya N.
  Source: American Journal of Cardiovascular Drugs : Drugs, Devices, and Other Interventions.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15049720&query_hl=1&itool=pubmed_docsum

- **Genetically engineered stem cell therapy for tissue regeneration.**
  Author(s): Alessandri G, Emanueli C, Madeddu P.
  Source: Annals of the New York Academy of Sciences.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15201167&query_hl=1&itool=pubmed_docsum

- **High dose titration of calcium channel blocking agents for primary pulmonary hypertension: guidelines for short-term drug testing.**
  Author(s): Rich S, Kaufmann E.
  Source: Journal of the American College of Cardiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1918710&query_hl=1&itool=pubmed_docsum

- **High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy.**
  Author(s): Rich S, Brundage BH.
  Source: Circulation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=2954725&query_hl=1&itool=pubmed_docsum

- **Left ventricular assist devices: evolving devices and indications for use in ischemic heart disease.**
  Author(s): Lietz K, Miller LW.
  Source: Current Opinion in Cardiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15502508&query_hl=1&itool=pubmed_docsum

- **New therapies for sickle cell disease.**
  Author(s): Am Fam Physician. 2006 Jul 15;74(2):313-4
  Source: Hematology/Oncology Clinics of North America.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16883929&itool=pubmed_docsum

- **Opportunities to improve outcomes in sickle cell disease.**
  Author(s): Mehta SR, Afenyi-Annan A, Byrns PJ, Lottenberg R.
  Source: American Family Physician.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16883928&query_hl=1&itool=pubmed_docsum

- **Overview of treprostinil sodium for the treatment of pulmonary arterial hypertension.**
  Author(s): Budev MM, Minai OA, Arroliga AC.
  Source: Drugs Today (Barc).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15148531&query_hl=1&itool=pubmed_docsum

- **Reserpine for primary pulmonary hypertension.**
  Author(s): Kersh ES.
  Source: The New England Journal of Medicine.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=4106284&query_hl=1&itool=pubmed_docsum

- **Risks associated with herbal slimming remedies.**
  Author(s): Corns C, Metcalfe K.
  Source: J R Soc Health.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12557729&query_hl=1&itool=pubmed_docsum

- **The effect of the anorectic agent, d-fenfluramine, and its primary metabolite, d-norfenfluramine, on intact human platelet serotonin uptake and efflux.**
  Author(s): Johnson GJ, Leis LA, Dunlop PC, Weir EK.
  Source: Journal of Thrombosis and Haemostasis : Jth.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14675103&query_hl=1&itool=pubmed_docsum

- **The future potential of eicosanoids and their inhibitors in paediatric practice.**
  Author(s): Shimizu T.
  Source: Drugs.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9711442&query_hl=1&itool=pubmed_docsum

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://health.aol.com/healthyliving/althealth**
- Chinese Medicine: **http://www.newcenturynutrition.com/**
- drkoop.com®: **http://www.drkoop.com/naturalmedicine.html**
- Family Village: **http://www.familyvillage.wisc.edu/med_altn.htm**
- Google: **http://directory.google.com/Top/Health/Alternative/**
- Healthnotes: **http://www.healthnotes.com/**
- Open Directory Project: **http://dmoz.org/Health/Alternative/**
- Yahoo.com: **http://dir.yahoo.com/Health/Alternative_Medicine/**

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

- **General Overview**

  Pulmonary Hypertension
  Source: Integrative Medicine Communications; www.drkoop.com

  Raynaud's Phenomenon
  Source: Integrative Medicine Communications; www.drkoop.com

General References

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

CHAPTER 3. DISSERTATIONS ON PRIMARY PULMONARY HYPERTENSION

Overview

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

Dissertations on Primary Pulmonary Hypertension

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 primary pulmonary hypertension. 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:

- **Cognitive, emotional, and quality of life outcomes in patients with pulmonary arterial hypertension** Demanuele, Joanne G. from BRIGHAM YOUNG UNIVERSITY, 2006, 23 pages
  http://wwwlib.umi.com/dissertations/fullcit/3214145
- **The monocrotaline pyrrole model of pulmonary arterial hypertension: Characterization of the bone morphogenetic protein type II receptor (BMPrII) in the pulmonary vasculature and alterations in the TGFbeta superfamily of signal transduction molecules** Ferrell Ramos, Margaret Ann from UNIVERSITY of CALIFORNIA, DAVIS, 2006
  http://wwwlib.umi.com/dissertations/fullcit/3230626

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 4. PATENTS ON PRIMARY PULMONARY HYPERTENSION

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

Patent Applications on Primary Pulmonary Hypertension

As of December 2000, U.S. patent applications are open to public viewing.[8] 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 primary pulmonary hypertension:

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

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

- **BMPR2 mutations in pulmonary arterial hypertension related to congenital heart disease**

  Inventor(s): Barst; Robyn; (Scarsdale, NY), Knowles; James; (Norwalk, CT), Morse; Jane; (Bronx, NY)

  Correspondence: Cooper & Dunham, Llp; 1185 Avenue OF The Americas; New York; NY; 10036; US

  Patent Application Number: 20060121497

  Date filed: August 30, 2005

  Abstract: This invention provides a method of detecting whether a subject is predisposed to, or afflicted with, **pulmonary arterial hypertension** (PAH) which comprises (A) obtaining a suitable sample comprising a nucleic acid encoding bone morphogenetic protein receptor II from the subject; and (B) detecting in the nucleic acid encoding bone morphogenetic protein receptor II whether a mutation is present which is not present in a nucleic acid encoding wildtype bone morphogenetic protein receptor-II. This invention also provides a method of detecting whether a subject is predisposed to, or afflicted with, **pulmonary arterial hypertension** (PAH) which comprises (A) obtaining a suitable sample comprising bone morphogenetic protein receptor II from the subject; and (B) detecting in the bone morphogenetic protein receptor II whether a mutation is present which is not present in wildtype bone morphogenetic protein receptor-II.

  Excerpt(s): This application claims benefit of U.S. Provisional No. 60/605,901, filed Aug. 30, 2004, the contents of which are hereby incorporated by reference into this application. Throughout this application, certain publications are referenced. Full citations for these publications may be found immediately preceding the claims. The disclosures of these publications are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention relates. Pulmonary arterial hypertension (PAH) consists of a group of vascular abnormalities with elevated pulmonary arterial pressure and pulmonary vascular resistance. The clinical spectrum includes familial and sporadic idiopathic PAH (IPAH), previously referred to as **primary pulmonary hypertension,** as well as PAH related to congenital heart disease (CHD), portal hypertension, connective tissue diseases, HIV-infection, and appetite suppressant exposure. Germline mutations of bone morphogenetic protein receptor 2 (BMPR2), a member of the TGF-B superfamily, have been found in familial and sporadic forms of IPAH, and in appetite-suppressant PAH but not in PAH with HIV-infection or PAH with connective tissue diseases.

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

- **Iloprost in combination therapies for the treatment of pulmonary arterial hypertension**

  Inventor(s): Santel, Donald J.; (Palo Alto, CA)

  Correspondence: Knobbe Martens Olson & Bear Llp; 2040 Main Street; Fourteenth Floor; Irvine; CA; 92614; US

  Patent Application Number: 20050101608

  Date filed: September 20, 2004

Abstract: Preferred embodiments of the present invention are related to novel therapeutic drug combinations and methods for treating **pulmonary arterial hypertension.** More particularly, aspects of the present invention are related to using a combination of iloprost and at least one additional agent, selected from the group consisting of an endothelin receptor antagonist and a PDE inhibitor.

Excerpt(s): This application claims the benefit of U.S. Provisional Application No. 60/505,653 filed Sep. 24, 2003, the entire disclosure of which is hereby expressly incorporated by reference in its entirety. Embodiments of this invention are related to using iloprost in combination with one or more additional agents, preferably an endothelin receptor antagonist and/or a PDE inhibitor, for treating and/or preventing **pulmonary arterial hypertension.** Pulmonary arterial hypertension is a debilitating disease characterized by an increase in pulmonary vascular resistance leading to right ventricular failure and death. **Pulmonary arterial hypertension** (PAH) with no apparent cause is termed **primary pulmonary hypertension** (PPH). Recently, various pathophysiological changes associated with this disorder, including vasoconstriction, vascular remodeling (i.e. proliferation of both media and intima of the pulmonary resistance vessels), and in situ thrombosis have been characterized (e.g., D'Alonzo, G. E. et al. 1991 Ann Intern Med 115:343-349; Palevsky, H. I. et al. 1989 Circulation 80:1207-1221; Rubin, L. J. 1997 N Engl J Med 336:111-117; Wagenvoort, C. A. & Wagenvoort, N. 1970 Circulation 42:1163-1184; Wood, P. 1958 Br Heart J20:557-570). Impairment of vascular and endothelial homeostasis is evidenced from a reduced synthesis of prostacyclin (PGI.sub.2), increased thromboxane production, decreased formation of nitric oxide and increased synthesis of endothelin-1 (Giaid, A. & Saleh, D. 1995 N Engl J Med 333:214-221; Xue, C & Johns, R. A. 1995 N Engl J Med 333:1642-1644). The intracellular free calcium concentration of vascular smooth muscle cells of pulmonary arteries in PPH has been reported to be elevated.

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

- **Pharmaceutical composition for the treatment of pulmonary arterial hypertension**

  Inventor(s): Bodin, Frederic; (San Francisco, CA)

  Correspondence: Jones Day; 222 East 41st Street; New York; NY; 10017; US

  Patent Application Number: 20040102361

  Date filed: November 27, 2002

  Abstract: The invention relates to pharmaceutical compositions for the treatment of **pulmonary arterial hypertension** comprising a prostacyclin or a prostacyclin analogue, preferably epoprostenol, and an endothelin receptor antagonist, preferably bosentan. The invention further provides methods for treating a subject suffering from **pulmonary arterial hypertension** using the compositions of the invention. The concomitant administration of prostacyclin or a prostacyclin analogue and an endothelin receptor antagonist not only increases the efficacy compared to administration of each alone but also reduces the side effects associated with prostacyclin or prostacyclin analogues.

  Excerpt(s): The invention relates to pharmaceutical compositions for the treatment of **pulmonary arterial hypertension** comprising a prostacyclin or a prostacyclin analogue and an endothelin receptor antagonist, characterized in that the side effects of the prostacyclin or the prostacyclin analogue are greatly reduced by the concomitant administration of the prostacyclin or the prostacyclin analogue and the endothelin receptor antagonist. Pulmonary hypertension is a disease defined by a progressive

elevation of pulmonary artery pressure and pulmonary vascular resistance, leading to right ventricular failure and death. Pulmonary hypertension is associated with endothelial dysfunction, characterized by a decreased expression of the vasodilators nitric oxide and prostacyclin, and by an increased expression of the growth factor and vasoconstrictive substance endothelin-1 and its receptors. Prostacyclin and prostacyclin analogues such as epoprostenol, treprostinil, iloprost, beraprost significantly improve hemodynamic parameters and clinical symptoms in patients with **pulmonary arterial hypertension.** The major mechanism of action of prostacyclin and prostacyclin analogues is vasodilation, whereas improvement in pulmonary vascular hypertrophy and inhibition of platelet aggregation may also play a role. However, the use of prostacyclin or prostacyclin analogues is associated with a number of side effects such as jaw pain, headaches, flushing, tachycardia and systemic hypotension.

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 primary pulmonary hypertension, 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 **primary pulmonary hypertension** (or a synonym) 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 primary pulmonary hypertension.

You can also use this procedure to view pending patent applications concerning primary pulmonary hypertension. 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 5. BOOKS ON PRIMARY PULMONARY HYPERTENSION

Overview

This chapter provides bibliographic book references relating to primary pulmonary hypertension. In addition to online booksellers such as **www.amazon.com** and **www.bn.com**, the National Library of Medicine is an excellent source for book titles on primary pulmonary hypertension. Your local medical library also may have these titles available for loan.

Book Summaries: Online Booksellers

Commercial Internet-based booksellers, such as Amazon.com and Barnes&Noble.com, offer summaries which have been supplied by each title's publisher. Some summaries also include customer reviews. Your local bookseller may have access to in-house and commercial databases that index all published books (e.g. Books in Print®). **IMPORTANT NOTE:** Online booksellers typically produce search results for medical and non-medical books. When searching for **primary pulmonary hypertension** at online booksellers' Web sites, you may discover non-medical books that use the generic term "primary pulmonary hypertension" (or a synonym) in their titles. The following is indicative of the results you might find when searching for **primary pulmonary hypertension** (sorted alphabetically by title; follow the hyperlink to view more details at Amazon.com):

- **Big change in pulmonary arterial hypertension Tx. (New Agents Approach Market).: An article from: Family Practice News** Bruce Jancin (2005); ISBN: B0008F85D6; http://www.amazon.com/exec/obidos/ASIN/B0008F85D6/icongroupinterna
- **Primary Pulmonary Hypertension (Lung Biology in Health and Disease)** Lewis J. Rubin and Stuart Rich (1996); ISBN: 0824795059; http://www.amazon.com/exec/obidos/ASIN/0824795059/icongroupinterna
- **Primary pulmonary hypertension (SuDoc HE 20.3202:P 96/8)** U.S. Dept of Health and Human Services (1992); ISBN: B00010D23Q; http://www.amazon.com/exec/obidos/ASIN/B00010D23Q/icongroupinterna

- **Screen systemic sclerosis patients for early PAH.(Clinical Rounds)(pulmonary arterial hypertension) : An article from: Skin & Allergy News** Mitchel L. Zoler (2005); ISBN: B000AJPMIG;
  http://www.amazon.com/exec/obidos/ASIN/B000AJPMIG/icongroupinterna
- **Sitaxsentan proves effective in pulmonary arterial hypertension: the phase III trial found that the 100-mg dose improved WHO functional class vs. placebo.(Cardiovascular. : An article from: Family Practice News** Bruce Goldman (2005); ISBN: B000BGDW9O;
  http://www.amazon.com/exec/obidos/ASIN/B000BGDW9O/icongroupinterna
- **The Official Patient's Sourcebook on Primary Pulmonary Hypertension** Icon Health Publications (2002); ISBN: 0597831548;
  http://www.amazon.com/exec/obidos/ASIN/0597831548/icongroupinterna

The National Library of Medicine Book Index

The National Library of Medicine at the National Institutes of Health has a massive database of books published on healthcare and biomedicine. Go to the following Internet site, **http://locatorplus.gov/**, and then select **LocatorPlus**. Once you are in the search area, simply type **primary pulmonary hypertension** (or synonyms) into the search box, and select the Quick Limit Option for Keyword, Title, or Journal Title Search: **Books**. From there, results can be sorted by publication date, author, or relevance. The following was recently catalogued by the National Library of Medicine[9]:

- **Primary pulmonary hypertension** Author: Rubin, Lewis J.; Year: 1997; New York: M. Dekker, c1997; ISBN: 9780824795
  http://www.amazon.com/exec/obidos/ASIN/9780824795/icongroupinterna
- **Pulmonary arterial hypertension: a pocketbook guide** Author: Stewart, Simon,; Year: 2005; London; New York: Taylor & Francis, 2005; ISBN: 9781841843
  http://www.amazon.com/exec/obidos/ASIN/9781841843/icongroupinterna
- **Pulmonary arterial hypertension related to congenital heart disease** Author: Beghetti, Maurice.; Year: 2006; Munich: Elsevier, 2006; ISBN: 9780702028
  http://www.amazon.com/exec/obidos/ASIN/9780702028/icongroupinterna

[9] In addition to LocatorPlus, in collaboration with authors and publishers, the National Center for Biotechnology Information (NCBI) is currently adapting biomedical books for the Web. The books may be accessed in two ways: (1) by searching directly using any search term or phrase (in the same way as the bibliographic database PubMed), or (2) by following the links to PubMed abstracts. Each PubMed abstract has a **Books** button that displays a facsimile of the abstract in which some phrases are hypertext links. These phrases are also found in the books available at NCBI. Click on hyperlinked results in the list of books in which the phrase is found. Currently, the majority of the links are between the books and PubMed. In the future, more links will be created between the books and other types of information, such as gene and protein sequences and macromolecular structures. See **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Books**.

CHAPTER 6. MULTIMEDIA ON PRIMARY PULMONARY HYPERTENSION

Overview

In this chapter, we show you how to find bibliographic information related to multimedia sources of information on primary pulmonary hypertension.

Bibliography: Multimedia on Primary Pulmonary Hypertension

The National Library of Medicine is a rich source of information on healthcare-related multimedia productions including slides, computer software, and databases. To access the multimedia database, go to the following Web site: **http://locatorplus.gov/**. Select **LocatorPlus**. Once you are in the search area, simply type **primary pulmonary hypertension** (or synonyms) into the search box, and select the Quick Limit Option for Keyword, Title, or Journal Title Search: **Audiovisuals and Computer Files**. From there, you can choose to sort results by publication date, author, or relevance. The following multimedia has been indexed on primary pulmonary hypertension:

- **Primary pulmonary hypertension [videorecording]** Source: presented by the Department of Medicine, Emory University, School of Medicine [and] the Emory Medical Television Network; Year: 1988; Format: Videorecording; Atlanta, Ga.: The University, 1988
- **Primary pulmonary hypertension [videorecording]** Source: presented by Department of Medicine, Emory University, School of Medicine; Year: 1983; Format: Videorecording; Atlanta, Ga.: Emory Medical Television Network, 1983
- **Primary pulmonary hypertension [videorecording]: diagnosis and treatment** Source: Biomedical Media Production Unit, the University of Michigan Medical Center, Office of Educational Resources & Research; Year: 1982; Format: Videorecording; Ann Arbor, Mich.: The University, c1982

APPENDICES

APPENDIX A. HELP ME UNDERSTAND GENETICS

Overview

This appendix presents basic information about genetics in clear language and provides links to online resources.[10]

The Basics: Genes and How They Work

This section gives you information on the basics of cells, DNA, genes, chromosomes, and proteins.

What Is a Cell?

Cells are the basic building blocks of all living things. The human body is composed of trillions of cells. They provide structure for the body, take in nutrients from food, convert those nutrients into energy, and carry out specialized functions. Cells also contain the body's hereditary material and can make copies of themselves.

Cells have many parts, each with a different function. Some of these parts, called organelles, are specialized structures that perform certain tasks within the cell. Human cells contain the following major parts, listed in alphabetical order:

- **Cytoplasm:** The cytoplasm is fluid inside the cell that surrounds the organelles.
- **Endoplasmic reticulum (ER):** This organelle helps process molecules created by the cell and transport them to their specific destinations either inside or outside the cell.
- **Golgi apparatus**: The golgi apparatus packages molecules processed by the endoplasmic reticulum to be transported out of the cell.
- **Lysosomes and peroxisomes**: These organelles are the recycling center of the cell. They digest foreign bacteria that invade the cell, rid the cell of toxic substances, and recycle worn-out cell components.

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[10] This appendix is an excerpt from the National Library of Medicine's handbook, *Help Me Understand Genetics*. For the full text of the *Help Me Understand Genetics* handbook, see **http://ghr.nlm.nih.gov/handbook**.

- **Mitochondria**: Mitochondria are complex organelles that convert energy from food into a form that the cell can use. They have their own genetic material, separate from the DNA in the nucleus, and can make copies of themselves.
- **Nucleus**: The nucleus serves as the cell's command center, sending directions to the cell to grow, mature, divide, or die. It also houses DNA (deoxyribonucleic acid), the cell's hereditary material. The nucleus is surrounded by a membrane called the nuclear envelope, which protects the DNA and separates the nucleus from the rest of the cell.
- **Plasma membrane:** The plasma membrane is the outer lining of the cell. It separates the cell from its environment and allows materials to enter and leave the cell.
- **Ribosomes:** Ribosomes are organelles that process the cell's genetic instructions to create proteins. These organelles can float freely in the cytoplasm or be connected to the endoplasmic reticulum.

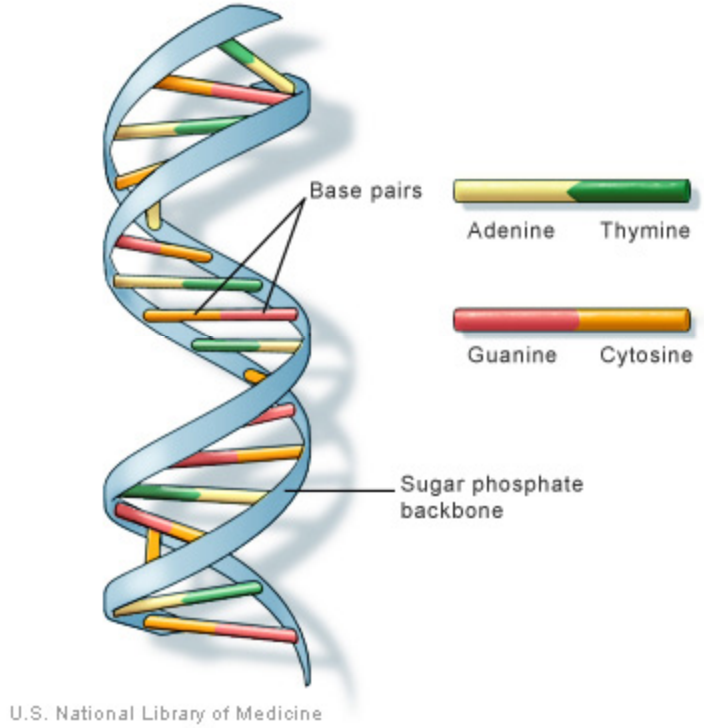
What Is DNA?

DNA, or deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms. Nearly every cell in a person's body has the same DNA. Most DNA is located in the cell nucleus (where it is called nuclear DNA), but a small amount of DNA can also be found in the mitochondria (where it is called mitochondrial DNA or mtDNA).

The information in DNA is stored as a code made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). Human DNA consists of about 3 billion bases, and more than 99 percent of those bases are the same in all people. The order, or sequence, of these bases determines the information available for building and maintaining an organism, similar to the way in which letters of the alphabet appear in a certain order to form words and sentences.

DNA bases pair up with each other, A with T and C with G, to form units called base pairs. Each base is also attached to a sugar molecule and a phosphate molecule. Together, a base, sugar, and phosphate are called a nucleotide. Nucleotides are arranged in two long strands that form a spiral called a double helix. The structure of the double helix is somewhat like a ladder, with the base pairs forming the ladder's rungs and the sugar and phosphate molecules forming the vertical sidepieces of the ladder.

An important property of DNA is that it can replicate, or make copies of itself. Each strand of DNA in the double helix can serve as a pattern for duplicating the sequence of bases. This is critical when cells divide because each new cell needs to have an exact copy of the DNA present in the old cell.



DNA is a double helix formed by base pairs attached to a sugar-phosphate backbone.

What Is Mitochondrial DNA?

Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA. This genetic material is known as mitochondrial DNA or mtDNA.

Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Each cell contains hundreds to thousands of mitochondria, which are located in the fluid that surrounds the nucleus (the cytoplasm).

Mitochondria produce energy through a process called oxidative phosphorylation. This process uses oxygen and simple sugars to create adenosine triphosphate (ATP), the cell's main energy source. A set of enzyme complexes, designated as complexes I-V, carry out oxidative phosphorylation within mitochondria.

In addition to energy production, mitochondria play a role in several other cellular activities. For example, mitochondria help regulate the self-destruction of cells (apoptosis). They are also necessary for the production of substances such as cholesterol and heme (a component of hemoglobin, the molecule that carries oxygen in the blood).

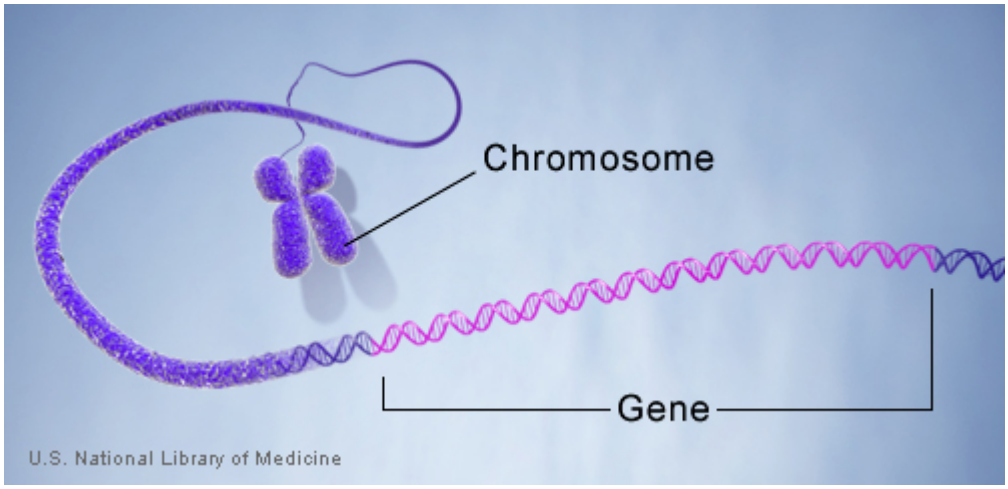
Mitochondrial DNA contains 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation. The remaining genes provide instructions for making molecules called transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), which are chemical cousins of

DNA. These types of RNA help assemble protein building blocks (amino acids) into functioning proteins.

What Is a Gene?

A gene is the basic physical and functional unit of heredity. Genes, which are made up of DNA, act as instructions to make molecules called proteins. In humans, genes vary in size from a few hundred DNA bases to more than 2 million bases. The Human Genome Project has estimated that humans have between 20,000 and 25,000 genes.

Every person has two copies of each gene, one inherited from each parent. Most genes are the same in all people, but a small number of genes (less than 1 percent of the total) are slightly different between people. Alleles are forms of the same gene with small differences in their sequence of DNA bases. These small differences contribute to each person's unique physical features.



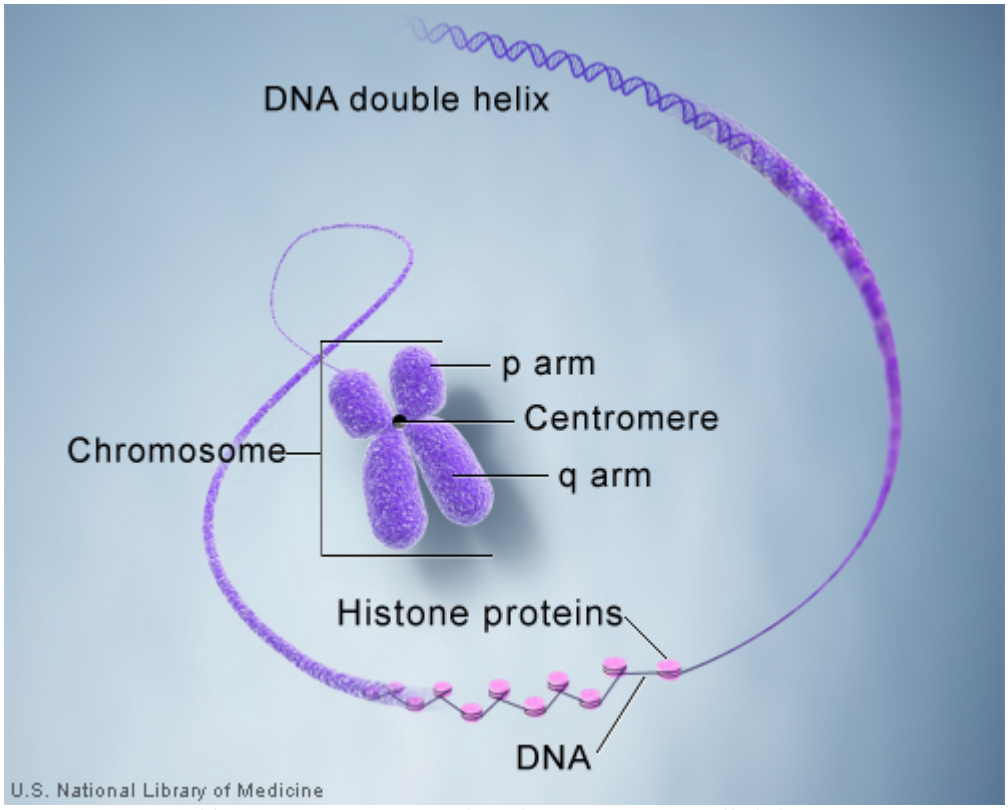
Genes are made up of DNA. Each chromosome contains many genes.

What Is a Chromosome?

In the nucleus of each cell, the DNA molecule is packaged into thread-like structures called chromosomes. Each chromosome is made up of DNA tightly coiled many times around proteins called histones that support its structure.

Chromosomes are not visible in the cell's nucleus—not even under a microscope—when the cell is not dividing. However, the DNA that makes up chromosomes becomes more tightly packed during cell division and is then visible under a microscope. Most of what researchers know about chromosomes was learned by observing chromosomes during cell division.

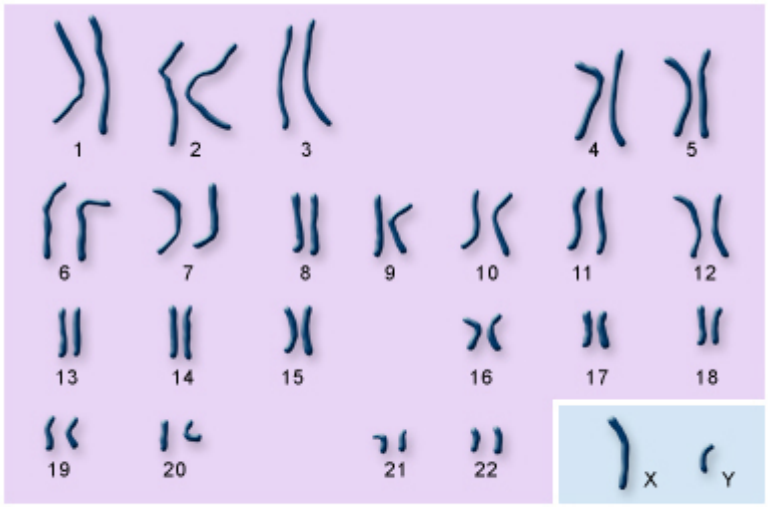
Each chromosome has a constriction point called the centromere, which divides the chromosome into two sections, or "arms." The short arm of the chromosome is labeled the "p arm." The long arm of the chromosome is labeled the "q arm." The location of the centromere on each chromosome gives the chromosome its characteristic shape, and can be used to help describe the location of specific genes.



DNA and histone proteins are packaged into structures called chromosomes.

How Many Chromosomes Do People Have?

In humans, each cell normally contains 23 pairs of chromosomes, for a total of 46. Twenty-two of these pairs, called autosomes, look the same in both males and females. The 23rd pair, the sex chromosomes, differ between males and females. Females have two copies of the X chromosome, while males have one X and one Y chromosome.



The 22 autosomes are numbered by size.
The other two chromosomes, X and Y, are the sex chromosomes.
This picture of the human chromosomes lined up in pairs is called a karyotype.

How Do Geneticists Indicate the Location of a Gene?

Geneticists use maps to describe the location of a particular gene on a chromosome. One type of map uses the cytogenetic location to describe a gene's position. The cytogenetic location is based on a distinctive pattern of bands created when chromosomes are stained with certain chemicals. Another type of map uses the molecular location, a precise description of a gene's position on a chromosome. The molecular location is based on the sequence of DNA building blocks (base pairs) that make up the chromosome.

Cytogenetic Location

Geneticists use a standardized way of describing a gene's cytogenetic location. In most cases, the location describes the position of a particular band on a stained chromosome:

17q12

It can also be written as a range of bands, if less is known about the exact location:

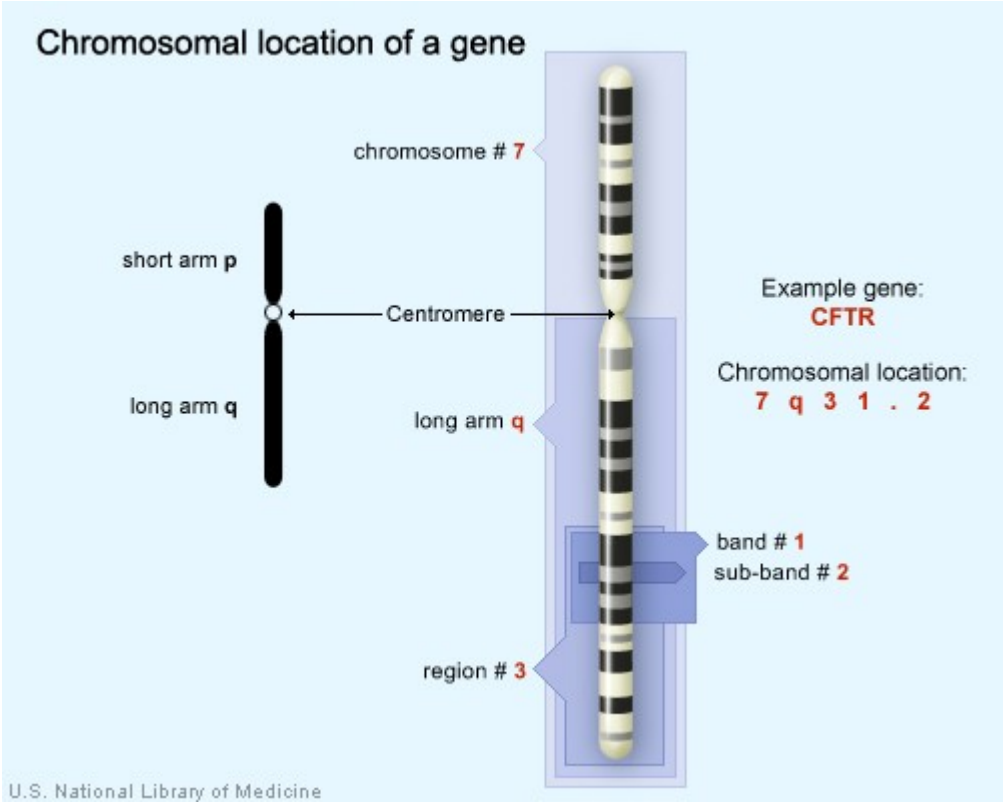
17q12-q21

The combination of numbers and letters provide a gene's "address" on a chromosome. This address is made up of several parts:

- The chromosome on which the gene can be found. The first number or letter used to describe a gene's location represents the chromosome. Chromosomes 1 through 22 (the autosomes) are designated by their chromosome number. The sex chromosomes are designated by X or Y.

- The arm of the chromosome. Each chromosome is divided into two sections (arms) based on the location of a narrowing (constriction) called the centromere. By convention, the shorter arm is called p, and the longer arm is called q. The chromosome arm is the second part of the gene's address. For example, 5q is the long arm of chromosome 5, and Xp is the short arm of the X chromosome.
- The position of the gene on the p or q arm. The position of a gene is based on a distinctive pattern of light and dark bands that appear when the chromosome is stained in a certain way. The position is usually designated by two digits (representing a region and a band), which are sometimes followed by a decimal point and one or more additional digits (representing sub-bands within a light or dark area). The number indicating the gene position increases with distance from the centromere. For example: 14q21 represents position 21 on the long arm of chromosome 14. 14q21 is closer to the centromere than 14q22.

Sometimes, the abbreviations "cen" or "ter" are also used to describe a gene's cytogenetic location. "Cen" indicates that the gene is very close to the centromere. For example, 16pcen refers to the short arm of chromosome 16 near the centromere. "Ter" stands for terminus, which indicates that the gene is very close to the end of the p or q arm. For example, 14qter refers to the tip of the long arm of chromosome 14. ("Tel" is also sometimes used to describe a gene's location. "Tel" stands for telomeres, which are at the ends of each chromosome. The abbreviations "tel" and "ter" refer to the same location.)



The CFTR gene is located on the long arm of chromosome 7 at position 7q31.2.

Molecular Location

The Human Genome Project, an international research effort completed in 2003, determined the sequence of base pairs for each human chromosome. This sequence information allows researchers to provide a more specific address than the cytogenetic location for many genes. A gene's molecular address pinpoints the location of that gene in terms of base pairs. For example, the molecular location of the APOE gene on chromosome 19 begins with base pair 50,100,901 and ends with base pair 50,104,488. This range describes the gene's precise position on chromosome 19 and indicates the size of the gene (3,588 base pairs). Knowing a gene's molecular location also allows researchers to determine exactly how far the gene is from other genes on the same chromosome.

Different groups of researchers often present slightly different values for a gene's molecular location. Researchers interpret the sequence of the human genome using a variety of methods, which can result in small differences in a gene's molecular address. For example, the National Center for Biotechnology Information (NCBI) identifies the molecular location of the APOE gene as base pair 50,100,901 to base pair 50,104,488 on chromosome 19. The Ensembl database identifies the location of this gene as base pair 50,100,879 to base pair 50,104,489 on chromosome 19. Neither of these addresses is incorrect; they represent different interpretations of the same data. For consistency, Genetics Home Reference presents data from NCBI for the molecular location of genes.

What Are Proteins and What Do They Do?

Proteins are large, complex molecules that play many critical roles in the body. They do most of the work in cells and are required for the structure, function, and regulation of the body's tissues and organs.

Proteins are made up of hundreds or thousands of smaller units called amino acids, which are attached to one another in long chains. There are 20 different types of amino acids that can be combined to make a protein. The sequence of amino acids determines each protein's unique 3-dimensional structure and its specific function.

Examples of Protein Functions

Proteins can be described according to their large range of functions in the body, listed in alphabetical order:

Function	Description	Example
Antibody	Antibodies bind to specific foreign particles, such as viruses and bacteria, to help protect the body.	Immunoglobulin G (IgG)
Enzyme	Enzymes carry out almost all of the thousands of chemical reactions that take place in cells. They also assist with the formation of new molecules by reading the genetic information stored in DNA.	Phenylalanine hydroxylase
Messenger	Messenger proteins, such as some types of hormones, transmit signals to coordinate biological processes between different cells, tissues, and organs.	Growth hormone
Structural component	These proteins provide structure and support for cells. On a larger scale, they also allow the body to move.	Actin
Transport/storage	These proteins bind and carry atoms and small molecules within cells and throughout the body.	Ferritin

How Does a Gene Make a Protein?

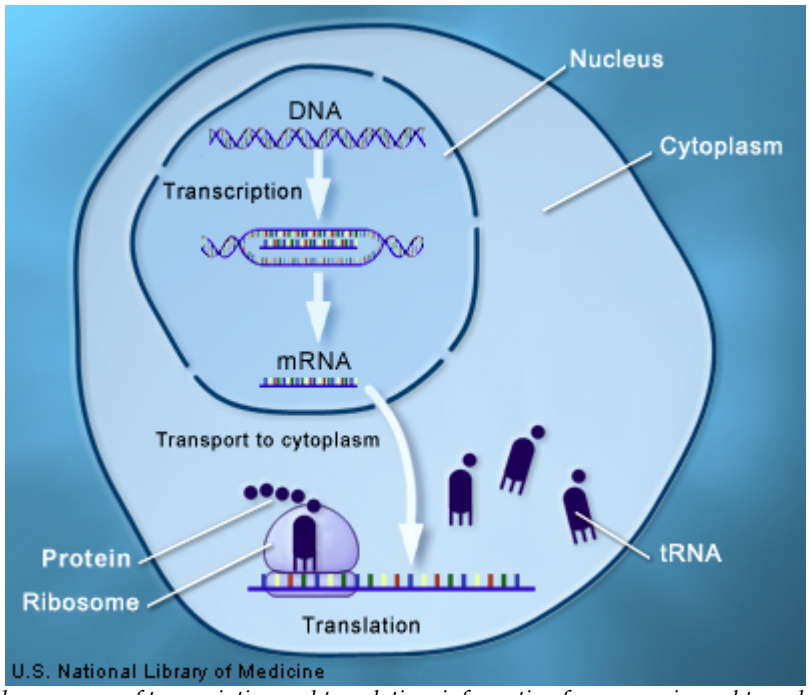
Most genes contain the information needed to make functional molecules called proteins. (A few genes produce other molecules that help the cell assemble proteins.) The journey from gene to protein is complex and tightly controlled within each cell. It consists of two major steps: transcription and translation. Together, transcription and translation are known as gene expression.

During the process of transcription, the information stored in a gene's DNA is transferred to a similar molecule called RNA (ribonucleic acid) in the cell nucleus. Both RNA and DNA are made up of a chain of nucleotide bases, but they have slightly different chemical properties. The type of RNA that contains the information for making a protein is called messenger RNA (mRNA) because it carries the information, or message, from the DNA out of the nucleus into the cytoplasm.

Translation, the second step in getting from a gene to a protein, takes place in the cytoplasm. The mRNA interacts with a specialized complex called a ribosome, which "reads" the sequence of mRNA bases. Each sequence of three bases, called a codon, usually codes for

one particular amino acid. (Amino acids are the building blocks of proteins.) A type of RNA called transfer RNA (tRNA) assembles the protein, one amino acid at a time. Protein assembly continues until the ribosome encounters a "stop" codon (a sequence of three bases that does not code for an amino acid).

The flow of information from DNA to RNA to proteins is one of the fundamental principles of molecular biology. It is so important that it is sometimes called the "central dogma."



Through the processes of transcription and translation, information from genes is used to make proteins.

Can Genes Be Turned On and Off in Cells?

Each cell expresses, or turns on, only a fraction of its genes. The rest of the genes are repressed, or turned off. The process of turning genes on and off is known as gene regulation. Gene regulation is an important part of normal development. Genes are turned on and off in different patterns during development to make a brain cell look and act different from a liver cell or a muscle cell, for example. Gene regulation also allows cells to react quickly to changes in their environments. Although we know that the regulation of genes is critical for life, this complex process is not yet fully understood.

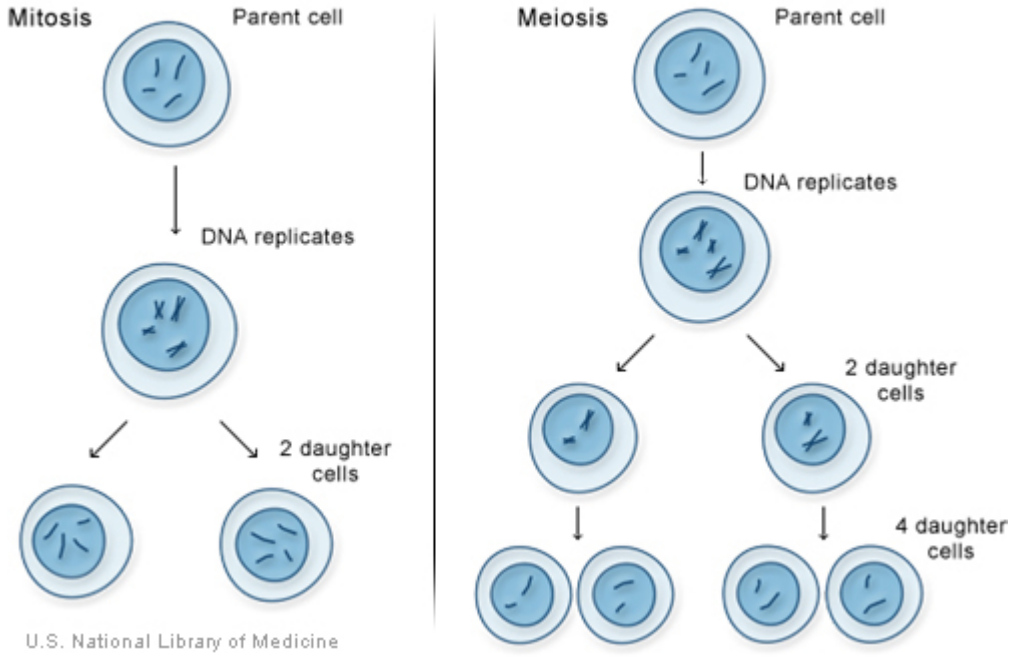
Gene regulation can occur at any point during gene expression, but most commonly occurs at the level of transcription (when the information in a gene's DNA is transferred to mRNA). Signals from the environment or from other cells activate proteins called transcription factors. These proteins bind to regulatory regions of a gene and increase or decrease the level of transcription. By controlling the level of transcription, this process can determine the amount of protein product that is made by a gene at any given time.

How Do Cells Divide?

There are two types of cell division: mitosis and meiosis. Most of the time when people refer to "cell division," they mean mitosis, the process of making new body cells. Meiosis is the type of cell division that creates egg and sperm cells.

Mitosis is a fundamental process for life. During mitosis, a cell duplicates all of its contents, including its chromosomes, and splits to form two identical daughter cells. Because this process is so critical, the steps of mitosis are carefully controlled by a number of genes. When mitosis is not regulated correctly, health problems such as cancer can result.

The other type of cell division, meiosis, ensures that humans have the same number of chromosomes in each generation. It is a two-step process that reduces the chromosome number by half—from 46 to 23—to form sperm and egg cells. When the sperm and egg cells unite at conception, each contributes 23 chromosomes so the resulting embryo will have the usual 46. Meiosis also allows genetic variation through a process of DNA shuffling while the cells are dividing.



Mitosis and meiosis, the two types of cell division.

How Do Genes Control the Growth and Division of Cells?

A variety of genes are involved in the control of cell growth and division. The cell cycle is the cell's way of replicating itself in an organized, step-by-step fashion. Tight regulation of this process ensures that a dividing cell's DNA is copied properly, any errors in the DNA are repaired, and each daughter cell receives a full set of chromosomes. The cycle has checkpoints (also called restriction points), which allow certain genes to check for mistakes and halt the cycle for repairs if something goes wrong.

If a cell has an error in its DNA that cannot be repaired, it may undergo programmed cell death (apoptosis). Apoptosis is a common process throughout life that helps the body get rid of cells it doesn't need. Cells that undergo apoptosis break apart and are recycled by a type of white blood cell called a macrophage. Apoptosis protects the body by removing genetically damaged cells that could lead to cancer, and it plays an important role in the development of the embryo and the maintenance of adult tissues.

Cancer results from a disruption of the normal regulation of the cell cycle. When the cycle proceeds without control, cells can divide without order and accumulate genetic defects that can lead to a cancerous tumor.

Genetic Mutations and Health

This section presents basic information about gene mutations, chromosomal changes, and conditions that run in families.[11]

What Is a Gene Mutation and How Do Mutations Occur?

A gene mutation is a permanent change in the DNA sequence that makes up a gene. Mutations range in size from a single DNA building block (DNA base) to a large segment of a chromosome.

Gene mutations occur in two ways: they can be inherited from a parent or acquired during a person's lifetime. Mutations that are passed from parent to child are called hereditary mutations or germline mutations (because they are present in the egg and sperm cells, which are also called germ cells). This type of mutation is present throughout a person's life in virtually every cell in the body.

Mutations that occur only in an egg or sperm cell, or those that occur just after fertilization, are called new (de novo) mutations. De novo mutations may explain genetic disorders in which an affected child has a mutation in every cell, but has no family history of the disorder.

Acquired (or somatic) mutations occur in the DNA of individual cells at some time during a person's life. These changes can be caused by environmental factors such as ultraviolet radiation from the sun, or can occur if a mistake is made as DNA copies itself during cell division. Acquired mutations in somatic cells (cells other than sperm and egg cells) cannot be passed on to the next generation.

Mutations may also occur in a single cell within an early embryo. As all the cells divide during growth and development, the individual will have some cells with the mutation and some cells without the genetic change. This situation is called mosaicism.

Some genetic changes are very rare; others are common in the population. Genetic changes that occur in more than 1 percent of the population are called polymorphisms. They are common enough to be considered a normal variation in the DNA. Polymorphisms are

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[11] This section has been adapted from the National Library of Medicine's handbook, *Help Me Understand Genetics*, which presents basic information about genetics in clear language and provides links to online resources: **http://ghr.nlm.nih.gov/handbook**.

responsible for many of the normal differences between people such as eye color, hair color, and blood type. Although many polymorphisms have no negative effects on a person's health, some of these variations may influence the risk of developing certain disorders.

How Can Gene Mutations Affect Health and Development?

To function correctly, each cell depends on thousands of proteins to do their jobs in the right places at the right times. Sometimes, gene mutations prevent one or more of these proteins from working properly. By changing a gene's instructions for making a protein, a mutation can cause the protein to malfunction or to be missing entirely. When a mutation alters a protein that plays a critical role in the body, it can disrupt normal development or cause a medical condition. A condition caused by mutations in one or more genes is called a genetic disorder.

In some cases, gene mutations are so severe that they prevent an embryo from surviving until birth. These changes occur in genes that are essential for development, and often disrupt the development of an embryo in its earliest stages. Because these mutations have very serious effects, they are incompatible with life.

It is important to note that genes themselves do not cause disease—genetic disorders are caused by mutations that make a gene function improperly. For example, when people say that someone has "the cystic fibrosis gene," they are usually referring to a mutated version of the CFTR gene, which causes the disease. All people, including those without cystic fibrosis, have a version of the CFTR gene.

Do All Gene Mutations Affect Health and Development?

No, only a small percentage of mutations cause genetic disorders—most have no impact on health or development. For example, some mutations alter a gene's DNA base sequence but do not change the function of the protein made by the gene.

Often, gene mutations that could cause a genetic disorder are repaired by certain enzymes before the gene is expressed (makes a protein). Each cell has a number of pathways through which enzymes recognize and repair mistakes in DNA. Because DNA can be damaged or mutated in many ways, DNA repair is an important process by which the body protects itself from disease.

A very small percentage of all mutations actually have a positive effect. These mutations lead to new versions of proteins that help an organism and its future generations better adapt to changes in their environment. For example, a beneficial mutation could result in a protein that protects the organism from a new strain of bacteria.

For More Information about DNA Repair and the Health Effects of Gene Mutations

- The University of Utah Genetic Science Learning Center provides information about genetic disorders that explains why some mutations cause disorders but others do not. (Refer to the questions in the far right column.)
  See **http://learn.genetics.utah.edu/units/disorders/whataregd/**.

- Additional information about DNA repair is available from the NCBI Science Primer. In the chapter called "What Is A Cell?", scroll down to the heading "DNA Repair Mechanisms." See **http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html**.

What Kinds of Gene Mutations Are Possible?

The DNA sequence of a gene can be altered in a number of ways. Gene mutations have varying effects on health, depending on where they occur and whether they alter the function of essential proteins. The types of mutations include:

- **Missense mutation**: This type of mutation is a change in one DNA base pair that results in the substitution of one amino acid for another in the protein made by a gene.
- **Nonsense mutation**: A nonsense mutation is also a change in one DNA base pair. Instead of substituting one amino acid for another, however, the altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all.
- **Insertion**: An insertion changes the number of DNA bases in a gene by adding a piece of DNA. As a result, the protein made by the gene may not function properly.
- **Deletion**: A deletion changes the number of DNA bases by removing a piece of DNA. Small deletions may remove one or a few base pairs within a gene, while larger deletions can remove an entire gene or several neighboring genes. The deleted DNA may alter the function of the resulting protein(s).
- **Duplication**: A duplication consists of a piece of DNA that is abnormally copied one or more times. This type of mutation may alter the function of the resulting protein.
- **Frameshift mutation**: This type of mutation occurs when the addition or loss of DNA bases changes a gene's reading frame. A reading frame consists of groups of 3 bases that each code for one amino acid. A frameshift mutation shifts the grouping of these bases and changes the code for amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift mutations.
- **Repeat expansion**: Nucleotide repeats are short DNA sequences that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of 3-base-pair sequences, and a tetranucleotide repeat is made up of 4-base-pair sequences. A repeat expansion is a mutation that increases the number of times that the short DNA sequence is repeated. This type of mutation can cause the resulting protein to function improperly.

Can Changes in Chromosomes Affect Health and Development?

Changes that affect entire chromosomes or segments of chromosomes can cause problems with growth, development, and function of the body's systems. These changes can affect many genes along the chromosome and alter the proteins made by those genes. Conditions caused by a change in the number or structure of chromosomes are known as chromosomal disorders.

Human cells normally contain 23 pairs of chromosomes, for a total of 46 chromosomes in each cell. A change in the number of chromosomes leads to a chromosomal disorder. These

changes can occur during the formation of reproductive cells (eggs and sperm) or in early fetal development. A gain or loss of chromosomes from the normal 46 is called aneuploidy. The most common form of aneuploidy is trisomy, or the presence of an extra chromosome in each cell. "Tri-" is Greek for "three"; people with trisomy have three copies of a particular chromosome in each cell instead of the normal two copies. Down syndrome is an example of a condition caused by trisomy—people with Down syndrome typically have three copies of chromosome 21 in each cell, for a total of 47 chromosomes per cell.

Monosomy, or the loss of one chromosome from each cell, is another kind of aneuploidy. "Mono-" is Greek for "one"; people with monosomy have one copy of a particular chromosome in each cell instead of the normal two copies. Turner syndrome is a condition caused by monosomy. Women with Turner syndrome are often missing one copy of the X chromosome in every cell, for a total of 45 chromosomes per cell.

Chromosomal disorders can also be caused by changes in chromosome structure. These changes are caused by the breakage and reunion of chromosome segments when an egg or sperm cell is formed or in early fetal development. Pieces of DNA can be rearranged within one chromosome, or transferred between two or more chromosomes. The effects of structural changes depend on their size and location. Many different structural changes are possible; some cause medical problems, while others may have no effect on a person's health.

Many cancer cells also have changes in their chromosome number or structure. These changes most often occur in somatic cells (cells other than eggs and sperm) during a person's lifetime.

Can Changes in Mitochondrial DNA Affect Health and Development?

Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA (known as mitochondrial DNA or mtDNA). In some cases, inherited changes in mitochondrial DNA can cause problems with growth, development, and function of the body's systems. These mutations disrupt the mitochondria's ability to generate energy efficiently for the cell.

Conditions caused by mutations in mitochondrial DNA often involve multiple organ systems. The effects of these conditions are most pronounced in organs and tissues that require a lot of energy (such as the heart, brain, and muscles). Although the health consequences of inherited mitochondrial DNA mutations vary widely, frequently observed features include muscle weakness and wasting, problems with movement, diabetes, kidney failure, heart disease, loss of intellectual functions (dementia), hearing loss, and abnormalities involving the eyes and vision.

Mitochondrial DNA is also prone to noninherited (somatic) mutations. Somatic mutations occur in the DNA of certain cells during a person's lifetime, and typically are not passed to future generations. Because mitochondrial DNA has a limited ability to repair itself when it is damaged, these mutations tend to build up over time. A buildup of somatic mutations in mitochondrial DNA has been associated with some forms of cancer and an increased risk of certain age-related disorders such as heart disease, Alzheimer disease, and Parkinson disease. Additionally, research suggests that the progressive accumulation of these mutations over a person's lifetime may play a role in the normal process of aging.

What Are Complex or Multifactorial Disorders?

Researchers are learning that nearly all conditions and diseases have a genetic component. Some disorders, such as sickle cell anemia and cystic fibrosis, are caused by mutations in a single gene. The causes of many other disorders, however, are much more complex. Common medical problems such as heart disease, diabetes, and obesity do not have a single genetic cause—they are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors. Conditions caused by many contributing factors are called complex or multifactorial disorders.

Although complex disorders often cluster in families, they do not have a clear-cut pattern of inheritance. This makes it difficult to determine a person's risk of inheriting or passing on these disorders. Complex disorders are also difficult to study and treat because the specific factors that cause most of these disorders have not yet been identified. By 2010, however, researchers predict they will have found the major contributing genes for many common complex disorders.

What Information about a Genetic Condition Can Statistics Provide?

Statistical data can provide general information about how common a condition is, how many people have the condition, or how likely it is that a person will develop the condition. Statistics are not personalized, however—they offer estimates based on groups of people. By taking into account a person's family history, medical history, and other factors, a genetics professional can help interpret what statistics mean for a particular patient.

Common Statistical Terms

Some statistical terms are commonly used when describing genetic conditions and other disorders. These terms include:

Statistical Term	Description	Examples
Incidence	The incidence of a gene mutation or a genetic disorder is the number of people who are born with the mutation or disorder in a specified group per year. Incidence is often written in the form "1 in [a number]" or as a total number of live births.	About 1 in 200,000 people in the United States are born with syndrome A each year. An estimated 15,000 infants with syndrome B were born last year worldwide.

Prevalence	The prevalence of a gene mutation or a genetic disorder is the total number of people in a specified group at a given time who have the mutation or disorder. This term includes both newly diagnosed and pre-existing cases in people of any age. Prevalence is often written in the form "1 in [a number]" or as a total number of people who have a condition.	Approximately 1 in 100,000 people in the United States have syndrome A at the present time. About 100,000 children worldwide currently have syndrome B.
Mortality	Mortality is the number of deaths from a particular disorder occurring in a specified group per year. Mortality is usually expressed as a total number of deaths.	An estimated 12,000 people worldwide died from syndrome C in 2002.
Lifetime risk	Lifetime risk is the average risk of developing a particular disorder at some point during a lifetime. Lifetime risk is often written as a percentage or as "1 in [a number]." It is important to remember that the risk per year or per decade is much lower than the lifetime risk. In addition, other factors may increase or decrease a person's risk as compared with the average.	Approximately 1 percent of people in the United States develop disorder D during their lifetimes. The lifetime risk of developing disorder D is 1 in 100.

Naming Genetic Conditions

Genetic conditions are not named in one standard way (unlike genes, which are given an official name and symbol by a formal committee). Doctors who treat families with a particular disorder are often the first to propose a name for the condition. Expert working groups may later revise the name to improve its usefulness. Naming is important because it allows accurate and effective communication about particular conditions, which will ultimately help researchers find new approaches to treatment.

Disorder names are often derived from one or a combination of sources:

- The basic genetic or biochemical defect that causes the condition (for example, alpha-1 antitrypsin deficiency)
- One or more major signs or symptoms of the disorder (for example, sickle cell anemia)
- The parts of the body affected by the condition (for example, retinoblastoma)
- The name of a physician or researcher, often the first person to describe the disorder (for example, Marfan syndrome, which was named after Dr. Antoine Bernard-Jean Marfan)

- A geographic area (for example, familial Mediterranean fever, which occurs mainly in populations bordering the Mediterranean Sea)
- The name of a patient or family with the condition (for example, amyotrophic lateral sclerosis, which is also called Lou Gehrig disease after a famous baseball player who had the condition).

Disorders named after a specific person or place are called eponyms. There is debate as to whether the possessive form (e.g., Alzheimer's disease) or the nonpossessive form (Alzheimer disease) of eponyms is preferred. As a rule, medical geneticists use the nonpossessive form, and this form may become the standard for doctors in all fields of medicine. Genetics Home Reference uses the nonpossessive form of eponyms.

Genetics Home Reference consults with experts in the field of medical genetics to provide the current, most accurate name for each disorder. Alternate names are included as synonyms.
Naming genes

The HUGO Gene Nomenclature Committee (HGNC) designates an official name and symbol (an abbreviation of the name) for each known human gene. Some official gene names include additional information in parentheses, such as related genetic conditions, subtypes of a condition, or inheritance pattern. The HGNC is a non-profit organization funded by the U.K. Medical Research Council and the U.S. National Institutes of Health. The Committee has named more than 13,000 of the estimated 20,000 to 25,000 genes in the human genome.

During the research process, genes often acquire several alternate names and symbols. Different researchers investigating the same gene may each give the gene a different name, which can cause confusion. The HGNC assigns a unique name and symbol to each human gene, which allows effective organization of genes in large databanks, aiding the advancement of research. For specific information about how genes are named, refer to the HGNC's Guidelines for Human Gene Nomenclature.

Genetics Home Reference describes genes using the HGNC's official gene names and gene symbols. Genetics Home Reference frequently presents the symbol and name separated with a colon (for example, FGFR4: Fibroblast growth factor receptor 4).

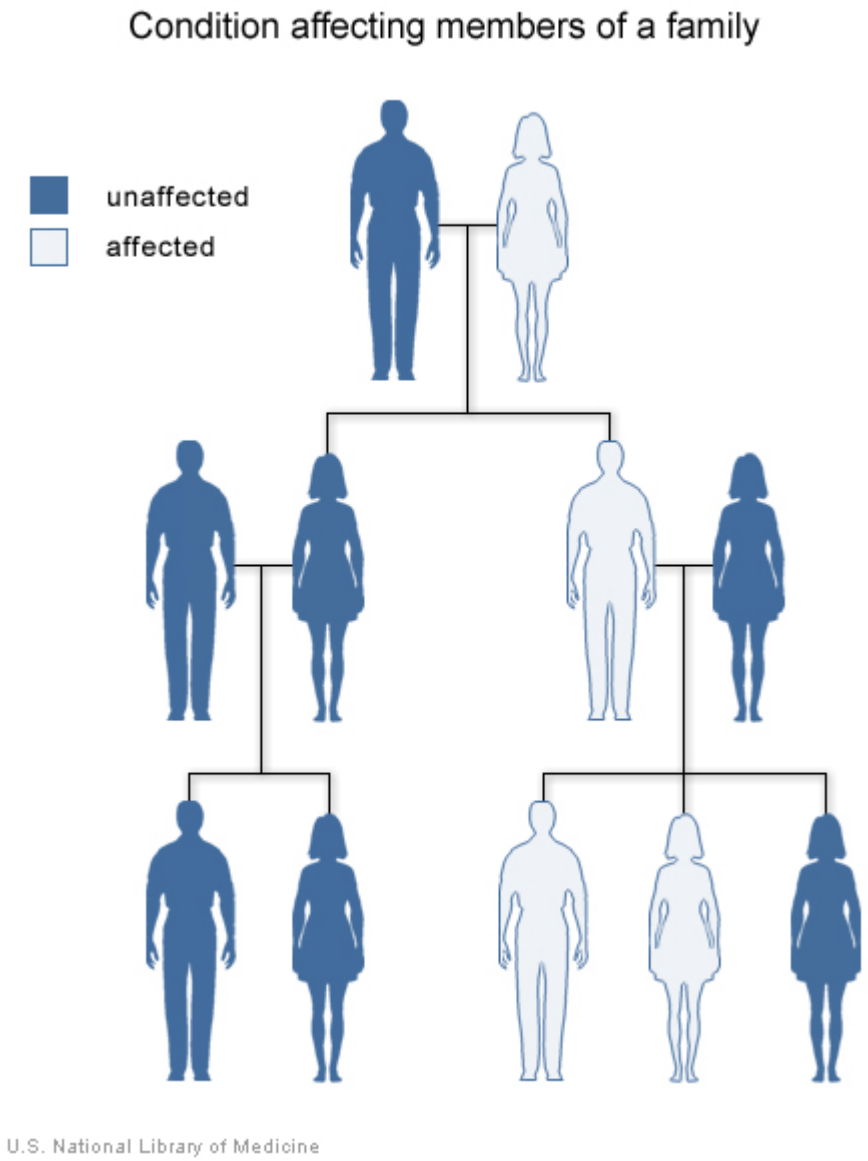
Inheriting Genetic Conditions

This section gives you information on inheritance patterns and understanding risk.

What Does It Mean If a Disorder Seems to Run in My Family?

A particular disorder might be described as "running in a family" if more than one person in the family has the condition. Some disorders that affect multiple family members are caused by gene mutations, which can be inherited (passed down from parent to child). Other conditions that appear to run in families are not inherited. Instead, environmental factors such as dietary habits or a combination of genetic and environmental factors are responsible for these disorders.

It is not always easy to determine whether a condition in a family is inherited. A genetics professional can use a person's family history (a record of health information about a person's immediate and extended family) to help determine whether a disorder has a genetic component.



Some disorders are seen in more than one generation of a family.

Why Is It Important to Know My Family Medical History?

A family medical history is a record of health information about a person and his or her close relatives. A complete record includes information from three generations of relatives, including children, brothers and sisters, parents, aunts and uncles, nieces and nephews, grandparents, and cousins.

Families have many factors in common, including their genes, environment, and lifestyle. Together, these factors can give clues to medical conditions that may run in a family. By noticing patterns of disorders among relatives, healthcare professionals can determine whether an individual, other family members, or future generations may be at an increased risk of developing a particular condition.

A family medical history can identify people with a higher-than-usual chance of having common disorders, such as heart disease, high blood pressure, stroke, certain cancers, and diabetes. These complex disorders are influenced by a combination of genetic factors, environmental conditions, and lifestyle choices. A family history also can provide information about the risk of rarer conditions caused by mutations in a single gene, such as cystic fibrosis and sickle cell anemia.

While a family medical history provides information about the risk of specific health concerns, having relatives with a medical condition does not mean that an individual will definitely develop that condition. On the other hand, a person with no family history of a disorder may still be at risk of developing that disorder.

Knowing one's family medical history allows a person to take steps to reduce his or her risk. For people at an increased risk of certain cancers, healthcare professionals may recommend more frequent screening (such as mammography or colonoscopy) starting at an earlier age. Healthcare providers may also encourage regular checkups or testing for people with a medical condition that runs in their family. Additionally, lifestyle changes such as adopting a healthier diet, getting regular exercise, and quitting smoking help many people lower their chances of developing heart disease and other common illnesses.

The easiest way to get information about family medical history is to talk to relatives about their health. Have they had any medical problems, and when did they occur? A family gathering could be a good time to discuss these issues. Additionally, obtaining medical records and other documents (such as obituaries and death certificates) can help complete a family medical history. It is important to keep this information up-to-date and to share it with a healthcare professional regularly.

What Are the Different Ways in which a Genetic Condition Can Be Inherited?

Some genetic conditions are caused by mutations in a single gene. These conditions are usually inherited in one of several straightforward patterns, depending on the gene involved:

Inheritance Pattern	Description	Examples
Autosomal dominant	One mutated copy of the gene in each cell is sufficient for a person to be affected by an autosomal dominant disorder. Each affected person usually has one affected parent. Autosomal dominant disorders tend to occur in every generation of an affected family.	Huntington disease, neurofibromatosis type 1

Autosomal recessive	Two mutated copies of the gene are present in each cell when a person has an autosomal recessive disorder. An affected person usually has unaffected parents who each carry a single copy of the mutated gene (and are referred to as carriers). Autosomal recessive disorders are typically not seen in every generation of an affected family.	cystic fibrosis, sickle cell anemia
X-linked dominant	X-linked dominant disorders are caused by mutations in genes on the X chromosome. Females are more frequently affected than males, and the chance of passing on an X-linked dominant disorder differs between men and women. Families with an X-linked dominant disorder often have both affected males and affected females in each generation. A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).	fragile X syndrome
X-linked recessive	X-linked recessive disorders are also caused by mutations in genes on the X chromosome. Males are more frequently affected than females, and the chance of passing on the disorder differs between men and women. Families with an X-linked recessive disorder often have affected males, but rarely affected females, in each generation. A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).	hemophilia, Fabry disease
Codominant	In codominant inheritance, two different versions (alleles) of a gene can be expressed, and each version makes a slightly different protein. Both alleles influence the genetic trait or determine the characteristics of the genetic condition.	ABO blood group, alpha-1 antitrypsin deficiency
Mitochondrial	This type of inheritance, also known as maternal inheritance, applies to genes in mitochondrial DNA. Mitochondria, which are structures in each cell that convert molecules into energy, each contain a small amount of DNA. Because only egg cells contribute mitochondria to the developing embryo, only females can pass on mitochondrial conditions to their children. Mitochondrial disorders can appear in every generation of a family and can affect both males and females, but fathers do not pass mitochondrial traits to their children.	Leber hereditary optic neuropathy (LHON)

Many other disorders are caused by a combination of the effects of multiple genes or by interactions between genes and the environment. Such disorders are more difficult to analyze because their genetic causes are often unclear, and they do not follow the patterns of inheritance described above. Examples of conditions caused by multiple genes or gene/environment interactions include heart disease, diabetes, schizophrenia, and certain types of cancer. Disorders caused by changes in the number or structure of chromosomes do not follow the straightforward patterns of inheritance listed above. Other genetic factors can also influence how a disorder is inherited.

If a Genetic Disorder Runs in My Family, What Are the Chances That My Children Will Have the Condition?

When a genetic disorder is diagnosed in a family, family members often want to know the likelihood that they or their children will develop the condition. This can be difficult to predict in some cases because many factors influence a person's chances of developing a genetic condition. One important factor is how the condition is inherited. For example:

- **Autosomal dominant inheritance**: A person affected by an autosomal dominant disorder has a 50 percent chance of passing the mutated gene to each child. The chance that a child will not inherit the mutated gene is also 50 percent.
- **Autosomal recessive inheritance**: Two unaffected people who each carry one copy of the mutated gene for an autosomal recessive disorder (carriers) have a 25 percent chance with each pregnancy of having a child affected by the disorder. The chance with each pregnancy of having an unaffected child who is a carrier of the disorder is 50 percent, and the chance that a child will not have the disorder and will not be a carrier is 25 percent.
- **X-linked dominant inheritance**: The chance of passing on an X-linked dominant condition differs between men and women because men have one X chromosome and one Y chromosome, while women have two X chromosomes. A man passes on his Y chromosome to all of his sons and his X chromosome to all of his daughters. Therefore, the sons of a man with an X-linked dominant disorder will not be affected, but all of his daughters will inherit the condition. A woman passes on one or the other of her X chromosomes to each child. Therefore, a woman with an X-linked dominant disorder has a 50 percent chance of having an affected daughter or son with each pregnancy.
- **X-linked recessive inheritance**: Because of the difference in sex chromosomes, the probability of passing on an X-linked recessive disorder also differs between men and women. The sons of a man with an X-linked recessive disorder will not be affected, and his daughters will carry one copy of the mutated gene. With each pregnancy, a woman who carries an X-linked recessive disorder has a 50 percent chance of having sons who are affected and a 50 percent chance of having daughters who carry one copy of the mutated gene.
- **Codominant inheritance**: In codominant inheritance, each parent contributes a different version of a particular gene, and both versions influence the resulting genetic trait. The chance of developing a genetic condition with codominant inheritance, and the characteristic features of that condition, depend on which versions of the gene are passed from parents to their child.
- **Mitochondrial inheritance**: Mitochondria, which are the energy-producing centers inside cells, each contain a small amount of DNA. Disorders with mitochondrial inheritance result from mutations in mitochondrial DNA. Although mitochondrial

disorders can affect both males and females, only females can pass mutations in mitochondrial DNA to their children. A woman with a disorder caused by changes in mitochondrial DNA will pass the mutation to all of her daughters and sons, but the children of a man with such a disorder will not inherit the mutation.

It is important to note that the chance of passing on a genetic condition applies equally to each pregnancy. For example, if a couple has a child with an autosomal recessive disorder, the chance of having another child with the disorder is still 25 percent (or 1 in 4). Having one child with a disorder does not "protect" future children from inheriting the condition. Conversely, having a child without the condition does not mean that future children will definitely be affected.

Although the chances of inheriting a genetic condition appear straightforward, factors such as a person's family history and the results of genetic testing can sometimes modify those chances. In addition, some people with a disease-causing mutation never develop any health problems or may experience only mild symptoms of the disorder. If a disease that runs in a family does not have a clear-cut inheritance pattern, predicting the likelihood that a person will develop the condition can be particularly difficult.

Estimating the chance of developing or passing on a genetic disorder can be complex. Genetics professionals can help people understand these chances and help them make informed decisions about their health.

Factors that Influence the Effects of Particular Genetic Changes

Reduced penetrance and variable expressivity are factors that influence the effects of particular genetic changes. These factors usually affect disorders that have an autosomal dominant pattern of inheritance, although they are occasionally seen in disorders with an autosomal recessive inheritance pattern.

Reduced Penetrance

Penetrance refers to the proportion of people with a particular genetic change (such as a mutation in a specific gene) who exhibit signs and symptoms of a genetic disorder. If some people with the mutation do not develop features of the disorder, the condition is said to have reduced (or incomplete) penetrance. Reduced penetrance often occurs with familial cancer syndromes. For example, many people with a mutation in the BRCA1 or BRCA2 gene will develop cancer during their lifetime, but some people will not. Doctors cannot predict which people with these mutations will develop cancer or when the tumors will develop.

Reduced penetrance probably results from a combination of genetic, environmental, and lifestyle factors, many of which are unknown. This phenomenon can make it challenging for genetics professionals to interpret a person's family medical history and predict the risk of passing a genetic condition to future generations.

Variable Expressivity

Although some genetic disorders exhibit little variation, most have signs and symptoms that differ among affected individuals. Variable expressivity refers to the range of signs and

symptoms that can occur in different people with the same genetic condition. For example, the features of Marfan syndrome vary widely— some people have only mild symptoms (such as being tall and thin with long, slender fingers), while others also experience life-threatening complications involving the heart and blood vessels. Although the features are highly variable, most people with this disorder have a mutation in the same gene (FBN1).

As with reduced penetrance, variable expressivity is probably caused by a combination of genetic, environmental, and lifestyle factors, most of which have not been identified. If a genetic condition has highly variable signs and symptoms, it may be challenging to diagnose.

What Do Geneticists Mean by Anticipation?

The signs and symptoms of some genetic conditions tend to become more severe and appear at an earlier age as the disorder is passed from one generation to the next. This phenomenon is called anticipation. Anticipation is most often seen with certain genetic disorders of the nervous system, such as Huntington disease, myotonic dystrophy, and fragile X syndrome.

Anticipation typically occurs with disorders that are caused by an unusual type of mutation called a trinucleotide repeat expansion. A trinucleotide repeat is a sequence of three DNA building blocks (nucleotides) that is repeated a number of times in a row. DNA segments with an abnormal number of these repeats are unstable and prone to errors during cell division. The number of repeats can change as the gene is passed from parent to child. If the number of repeats increases, it is known as a trinucleotide repeat expansion. In some cases, the trinucleotide repeat may expand until the gene stops functioning normally. This expansion causes the features of some disorders to become more severe with each successive generation.

Most genetic disorders have signs and symptoms that differ among affected individuals, including affected people in the same family. Not all of these differences can be explained by anticipation. A combination of genetic, environmental, and lifestyle factors is probably responsible for the variability, although many of these factors have not been identified. Researchers study multiple generations of affected family members and consider the genetic cause of a disorder before determining that it shows anticipation.

What Is Genomic Imprinting?

Genomic imprinting is a factor that influences how some genetic conditions are inherited.

People inherit two copies of their genes—one from their mother and one from their father. Usually both copies of each gene are active, or "turned on," in cells. In some cases, however, only one of the two copies is normally turned on. Which copy is active depends on the parent of origin: some genes are normally active only when they are inherited from a person's father; others are active only when inherited from a person's mother. This phenomenon is known as genomic imprinting.

In genes that undergo genomic imprinting, the parent of origin is often marked, or "stamped," on the gene during the formation of egg and sperm cells. This stamping process, called methylation, is a chemical reaction that attaches small molecules called methyl groups to certain segments of DNA. These molecules identify which copy of a gene was inherited

from the mother and which was inherited from the father. The addition and removal of methyl groups can be used to control the activity of genes.

Only a small percentage of all human genes undergo genomic imprinting. Researchers are not yet certain why some genes are imprinted and others are not. They do know that imprinted genes tend to cluster together in the same regions of chromosomes. Two major clusters of imprinted genes have been identified in humans, one on the short (p) arm of chromosome 11 (at position 11p15) and another on the long (q) arm of chromosome 15 (in the region 15q11 to 15q13).

What Is Uniparental Disomy?

Uniparental disomy is a factor that influences how some genetic conditions are inherited.

Uniparental disomy (UPD) occurs when a person receives two copies of a chromosome, or part of a chromosome, from one parent and no copies from the other parent. UPD can occur as a random event during the formation of egg or sperm cells or may happen in early fetal development.

In many cases, UPD likely has no effect on health or development. Because most genes are not imprinted, it doesn't matter if a person inherits both copies from one parent instead of one copy from each parent. In some cases, however, it does make a difference whether a gene is inherited from a person's mother or father. A person with UPD may lack any active copies of essential genes that undergo genomic imprinting. This loss of gene function can lead to delayed development, mental retardation, or other medical problems.

Several genetic disorders can result from UPD or a disruption of normal genomic imprinting. The most well-known conditions include Prader-Willi syndrome, which is characterized by uncontrolled eating and obesity, and Angelman syndrome, which causes mental retardation and impaired speech. Both of these disorders can be caused by UPD or other errors in imprinting involving genes on the long arm of chromosome 15. Other conditions, such as Beckwith-Wiedemann syndrome (a disorder characterized by accelerated growth and an increased risk of cancerous tumors), are associated with abnormalities of imprinted genes on the short arm of chromosome 11.

Are Chromosomal Disorders Inherited?

Although it is possible to inherit some types of chromosomal abnormalities, most chromosomal disorders (such as Down syndrome and Turner syndrome) are not passed from one generation to the next.

Some chromosomal conditions are caused by changes in the number of chromosomes. These changes are not inherited, but occur as random events during the formation of reproductive cells (eggs and sperm). An error in cell division called nondisjunction results in reproductive cells with an abnormal number of chromosomes. For example, a reproductive cell may accidentally gain or lose one copy of a chromosome. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have an extra or missing chromosome in each of the body's cells.

Changes in chromosome structure can also cause chromosomal disorders. Some changes in chromosome structure can be inherited, while others occur as random accidents during the formation of reproductive cells or in early fetal development. Because the inheritance of these changes can be complex, people concerned about this type of chromosomal abnormality may want to talk with a genetics professional.

Some cancer cells also have changes in the number or structure of their chromosomes. Because these changes occur in somatic cells (cells other than eggs and sperm), they cannot be passed from one generation to the next.

Why Are Some Genetic Conditions More Common in Particular Ethnic Groups?

Some genetic disorders are more likely to occur among people who trace their ancestry to a particular geographic area. People in an ethnic group often share certain versions of their genes, which have been passed down from common ancestors. If one of these shared genes contains a disease-causing mutation, a particular genetic disorder may be more frequently seen in the group.

Examples of genetic conditions that are more common in particular ethnic groups are sickle cell anemia, which is more common in people of African, African-American, or Mediterranean heritage; and Tay-Sachs disease, which is more likely to occur among people of Ashkenazi (eastern and central European) Jewish or French Canadian ancestry. It is important to note, however, that these disorders can occur in any ethnic group.

Genetic Consultation

This section presents information on finding and visiting a genetic counselor or other genetics professional.

What Is a Genetic Consultation?

A genetic consultation is a health service that provides information and support to people who have, or may be at risk for, genetic disorders. During a consultation, a genetics professional meets with an individual or family to discuss genetic risks or to diagnose, confirm, or rule out a genetic condition.

Genetics professionals include medical geneticists (doctors who specialize in genetics) and genetic counselors (certified healthcare workers with experience in medical genetics and counseling). Other healthcare professionals such as nurses, psychologists, and social workers trained in genetics can also provide genetic consultations.

Consultations usually take place in a doctor's office, hospital, genetics center, or other type of medical center. These meetings are most often in-person visits with individuals or families, but they are occasionally conducted in a group or over the telephone.

Why Might Someone Have a Genetic Consultation?

Individuals or families who are concerned about an inherited condition may benefit from a genetic consultation. The reasons that a person might be referred to a genetic counselor, medical geneticist, or other genetics professional include:

- A personal or family history of a genetic condition, birth defect, chromosomal disorder, or hereditary cancer.
- Two or more pregnancy losses (miscarriages), a stillbirth, or a baby who died.
- A child with a known inherited disorder, a birth defect, mental retardation, or developmental delay.
- A woman who is pregnant or plans to become pregnant at or after age 35. (Some chromosomal disorders occur more frequently in children born to older women.)
- Abnormal test results that suggest a genetic or chromosomal condition.
- An increased risk of developing or passing on a particular genetic disorder on the basis of a person's ethnic background.
- People related by blood (for example, cousins) who plan to have children together. (A child whose parents are related may be at an increased risk of inheriting certain genetic disorders.)

A genetic consultation is also an important part of the decision-making process for genetic testing. A visit with a genetics professional may be helpful even if testing is not available for a specific condition, however.

What Happens during a Genetic Consultation?

A genetic consultation provides information, offers support, and addresses a patient's specific questions and concerns. To help determine whether a condition has a genetic component, a genetics professional asks about a person's medical history and takes a detailed family history (a record of health information about a person's immediate and extended family). The genetics professional may also perform a physical examination and recommend appropriate tests.

If a person is diagnosed with a genetic condition, the genetics professional provides information about the diagnosis, how the condition is inherited, the chance of passing the condition to future generations, and the options for testing and treatment.

During a consultation, a genetics professional will:

- Interpret and communicate complex medical information.
- Help each person make informed, independent decisions about their health care and reproductive options.
- Respect each person's individual beliefs, traditions, and feelings.

A genetics professional will NOT:

- Tell a person which decision to make.
- Advise a couple not to have children.

- Recommend that a woman continue or end a pregnancy.
- Tell someone whether to undergo testing for a genetic disorder.

How Can I Find a Genetics Professional in My Area?

To find a genetics professional in your community, you may wish to ask your doctor for a referral. If you have health insurance, you can also contact your insurance company to find a medical geneticist or genetic counselor in your area who participates in your plan.

Several resources for locating a genetics professional in your community are available online:

- GeneTests from the University of Washington provides a list of genetics clinics around the United States and international genetics clinics. You can also access the list by clicking on "Clinic Directory" at the top of the GeneTests home page. Clinics can be chosen by state or country, by service, and/or by specialty. State maps can help you locate a clinic in your area. See **http://www.genetests.org/**.
- The National Society of Genetic Counselors offers a searchable directory of genetic counselors in the United States. You can search by location, name, area of practice/specialization, and/or ZIP Code. See **http://www.nsgc.org/resourcelink.cfm**.
- The National Cancer Institute provides a Cancer Genetics Services Directory, which lists professionals who provide services related to cancer genetics. You can search by type of cancer or syndrome, location, and/or provider name at the following Web site: **http://cancer.gov/search/genetics_services/**.

Genetic Testing

This section presents information on the benefits, costs, risks, and limitations of genetic testing.

What Is Genetic Testing?

Genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins. Most of the time, testing is used to find changes that are associated with inherited disorders. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder. Several hundred genetic tests are currently in use, and more are being developed.

Genetic testing is voluntary. Because testing has both benefits and limitations, the decision about whether to be tested is a personal and complex one. A genetic counselor can help by providing information about the pros and cons of the test and discussing the social and emotional aspects of testing.

What Are the Types of Genetic Tests?

Genetic testing can provide information about a person's genes and chromosomes. Available types of testing include:

- **Newborn screening** is used just after birth to identify genetic disorders that can be treated early in life. Millions of babies are tested each year in the United States. All states currently test infants for phenylketonuria (a genetic disorder that causes mental retardation if left untreated) and congenital hypothyroidism (a disorder of the thyroid gland). Most states also test for other genetic disorders.
- **Diagnostic testing** is used to identify or rule out a specific genetic or chromosomal condition. In many cases, genetic testing is used to confirm a diagnosis when a particular condition is suspected based on physical signs and symptoms. Diagnostic testing can be performed before birth or at any time during a person's life, but is not available for all genes or all genetic conditions. The results of a diagnostic test can influence a person's choices about health care and the management of the disorder.
- **Carrier testing** is used to identify people who carry one copy of a gene mutation that, when present in two copies, causes a genetic disorder. This type of testing is offered to individuals who have a family history of a genetic disorder and to people in certain ethnic groups with an increased risk of specific genetic conditions. If both parents are tested, the test can provide information about a couple's risk of having a child with a genetic condition.
- **Prenatal testing** is used to detect changes in a fetus's genes or chromosomes before birth. This type of testing is offered during pregnancy if there is an increased risk that the baby will have a genetic or chromosomal disorder. In some cases, prenatal testing can lessen a couple's uncertainty or help them make decisions about a pregnancy. It cannot identify all possible inherited disorders and birth defects, however.
- **Preimplantation testing**, also called preimplantation genetic diagnosis (PGD), is a specialized technique that can reduce the risk of having a child with a particular genetic or chromosomal disorder. It is used to detect genetic changes in embryos that were created using assisted reproductive techniques such as in-vitro fertilization. In-vitro fertilization involves removing egg cells from a woman's ovaries and fertilizing them with sperm cells outside the body. To perform preimplantation testing, a small number of cells are taken from these embryos and tested for certain genetic changes. Only embryos without these changes are implanted in the uterus to initiate a pregnancy.
- **Predictive and presymptomatic types of testing** are used to detect gene mutations associated with disorders that appear after birth, often later in life. These tests can be helpful to people who have a family member with a genetic disorder, but who have no features of the disorder themselves at the time of testing. Predictive testing can identify mutations that increase a person's risk of developing disorders with a genetic basis, such as certain types of cancer. Presymptomatic testing can determine whether a person will develop a genetic disorder, such as hemochromatosis (an iron overload disorder), before any signs or symptoms appear. The results of predictive and presymptomatic testing can provide information about a person's risk of developing a specific disorder and help with making decisions about medical care.
- **Forensic testing** uses DNA sequences to identify an individual for legal purposes. Unlike the tests described above, forensic testing is not used to detect gene mutations associated with disease. This type of testing can identify crime or catastrophe victims, rule out or implicate a crime suspect, or establish biological relationships between people (for example, paternity).

How Is Genetic Testing Done?

Once a person decides to proceed with genetic testing, a medical geneticist, primary care doctor, specialist, or nurse practitioner can order the test. Genetic testing is often done as part of a genetic consultation.

Genetic tests are performed on a sample of blood, hair, skin, amniotic fluid (the fluid that surrounds a fetus during pregnancy), or other tissue. For example, a procedure called a buccal smear uses a small brush or cotton swab to collect a sample of cells from the inside surface of the cheek. The sample is sent to a laboratory where technicians look for specific changes in chromosomes, DNA, or proteins, depending on the suspected disorder. The laboratory reports the test results in writing to a person's doctor or genetic counselor.

Newborn screening tests are done on a small blood sample, which is taken by pricking the baby's heel. Unlike other types of genetic testing, a parent will usually only receive the result if it is positive. If the test result is positive, additional testing is needed to determine whether the baby has a genetic disorder.

Before a person has a genetic test, it is important that he or she understands the testing procedure, the benefits and limitations of the test, and the possible consequences of the test results. The process of educating a person about the test and obtaining permission is called informed consent.

What Is Direct-to-Consumer Genetic Testing?

Traditionally, genetic tests have been available only through healthcare providers such as physicians, nurse practitioners, and genetic counselors. Healthcare providers order the appropriate test from a laboratory, collect and send the samples, and interpret the test results. Direct-to-consumer genetic testing refers to genetic tests that are marketed directly to consumers via television, print advertisements, or the Internet. This form of testing, which is also known as at-home genetic testing, provides access to a person's genetic information without necessarily involving a doctor or insurance company in the process.

If a consumer chooses to purchase a genetic test directly, the test kit is mailed to the consumer instead of being ordered through a doctor's office. The test typically involves collecting a DNA sample at home, often by swabbing the inside of the cheek, and mailing the sample back to the laboratory. In some cases, the person must visit a health clinic to have blood drawn. Consumers are notified of their results by mail or over the telephone, or the results are posted online. In some cases, a genetic counselor or other healthcare provider is available to explain the results and answer questions. The price for this type of at-home genetic testing ranges from several hundred dollars to more than a thousand dollars.

The growing market for direct-to-consumer genetic testing may promote awareness of genetic diseases, allow consumers to take a more proactive role in their health care, and offer a means for people to learn about their ancestral origins. At-home genetic tests, however, have significant risks and limitations. Consumers are vulnerable to being misled by the results of unproven or invalid tests. Without guidance from a healthcare provider, they may make important decisions about treatment or prevention based on inaccurate, incomplete, or misunderstood information about their health. Consumers may also experience an invasion of genetic privacy if testing companies use their genetic information in an unauthorized way.

Genetic testing provides only one piece of information about a person's health—other genetic and environmental factors, lifestyle choices, and family medical history also affect a person's risk of developing many disorders. These factors are discussed during a consultation with a doctor or genetic counselor, but in many cases are not addressed by at-home genetic tests. More research is needed to fully understand the benefits and limitations of direct-to-consumer genetic testing.

What Do the Results of Genetic Tests Mean?

The results of genetic tests are not always straightforward, which often makes them challenging to interpret and explain. Therefore, it is important for patients and their families to ask questions about the potential meaning of genetic test results both before and after the test is performed. When interpreting test results, healthcare professionals consider a person's medical history, family history, and the type of genetic test that was done.

A positive test result means that the laboratory found a change in a particular gene, chromosome, or protein of interest. Depending on the purpose of the test, this result may confirm a diagnosis, indicate that a person is a carrier of a particular genetic mutation, identify an increased risk of developing a disease (such as cancer) in the future, or suggest a need for further testing. Because family members have some genetic material in common, a positive test result may also have implications for certain blood relatives of the person undergoing testing. It is important to note that a positive result of a predictive or presymptomatic genetic test usually cannot establish the exact risk of developing a disorder. Also, health professionals typically cannot use a positive test result to predict the course or severity of a condition.

A negative test result means that the laboratory did not find a change in the gene, chromosome, or protein under consideration. This result can indicate that a person is not affected by a particular disorder, is not a carrier of a specific genetic mutation, or does not have an increased risk of developing a certain disease. It is possible, however, that the test missed a disease-causing genetic alteration because many tests cannot detect all genetic changes that can cause a particular disorder. Further testing may be required to confirm a negative result.

In some cases, a negative result might not give any useful information. This type of result is called uninformative, indeterminate, inconclusive, or ambiguous. Uninformative test results sometimes occur because everyone has common, natural variations in their DNA, called polymorphisms, that do not affect health. If a genetic test finds a change in DNA that has not been associated with a disorder in other people, it can be difficult to tell whether it is a natural polymorphism or a disease-causing mutation. An uninformative result cannot confirm or rule out a specific diagnosis, and it cannot indicate whether a person has an increased risk of developing a disorder. In some cases, testing other affected and unaffected family members can help clarify this type of result.

What Is the Cost of Genetic Testing, and How Long Does It Take to Get the Results?

The cost of genetic testing can range from under $100 to more than $2,000, depending on the nature and complexity of the test. The cost increases if more than one test is necessary or if multiple family members must be tested to obtain a meaningful result. For newborn

screening, costs vary by state. Some states cover part of the total cost, but most charge a fee of $15 to $60 per infant.

From the date that a sample is taken, it may take a few weeks to several months to receive the test results. Results for prenatal testing are usually available more quickly because time is an important consideration in making decisions about a pregnancy. The doctor or genetic counselor who orders a particular test can provide specific information about the cost and time frame associated with that test.

Will Health Insurance Cover the Costs of Genetic Testing?

In many cases, health insurance plans will cover the costs of genetic testing when it is recommended by a person's doctor. Health insurance providers have different policies about which tests are covered, however. A person interested in submitting the costs of testing may wish to contact his or her insurance company beforehand to ask about coverage.

Some people may choose not to use their insurance to pay for testing because the results of a genetic test can affect a person's health insurance coverage. Instead, they may opt to pay out-of-pocket for the test. People considering genetic testing may want to find out more about their state's privacy protection laws before they ask their insurance company to cover the costs.

What Are the Benefits of Genetic Testing?

Genetic testing has potential benefits whether the results are positive or negative for a gene mutation. Test results can provide a sense of relief from uncertainty and help people make informed decisions about managing their health care. For example, a negative result can eliminate the need for unnecessary checkups and screening tests in some cases. A positive result can direct a person toward available prevention, monitoring, and treatment options. Some test results can also help people make decisions about having children. Newborn screening can identify genetic disorders early in life so treatment can be started as early as possible.

What Are the Risks and Limitations of Genetic Testing?

The physical risks associated with most genetic tests are very small, particularly for those tests that require only a blood sample or buccal smear (a procedure that samples cells from the inside surface of the cheek). The procedures used for prenatal testing carry a small but real risk of losing the pregnancy (miscarriage) because they require a sample of amniotic fluid or tissue from around the fetus.

Many of the risks associated with genetic testing involve the emotional, social, or financial consequences of the test results. People may feel angry, depressed, anxious, or guilty about their results. In some cases, genetic testing creates tension within a family because the results can reveal information about other family members in addition to the person who is tested. The possibility of genetic discrimination in employment or insurance is also a concern.

Genetic testing can provide only limited information about an inherited condition. The test often can't determine if a person will show symptoms of a disorder, how severe the symptoms will be, or whether the disorder will progress over time. Another major limitation is the lack of treatment strategies for many genetic disorders once they are diagnosed.

A genetics professional can explain in detail the benefits, risks, and limitations of a particular test. It is important that any person who is considering genetic testing understand and weigh these factors before making a decision.

What Is Genetic Discrimination?

Genetic discrimination occurs when people are treated differently by their employer or insurance company because they have a gene mutation that causes or increases the risk of an inherited disorder. People who undergo genetic testing may be at risk for genetic discrimination.

The results of a genetic test are normally included in a person's medical records. When a person applies for life, disability, or health insurance, the insurance company may ask to look at these records before making a decision about coverage. An employer may also have the right to look at an employee's medical records. As a result, genetic test results could affect a person's insurance coverage or employment. People making decisions about genetic testing should be aware that when test results are placed in their medical records, the results might not be kept private.

Fear of discrimination is a common concern among people considering genetic testing. Several laws at the federal and state levels help protect people against genetic discrimination; however, genetic testing is a fast-growing field and these laws don't cover every situation.

How Does Genetic Testing in a Research Setting Differ from Clinical Genetic Testing?

The main differences between clinical genetic testing and research testing are the purpose of the test and who receives the results. The goals of research testing include finding unknown genes, learning how genes work, and advancing our understanding of genetic conditions. The results of testing done as part of a research study are usually not available to patients or their healthcare providers. Clinical testing, on the other hand, is done to find out about an inherited disorder in an individual patient or family. People receive the results of a clinical test and can use them to help them make decisions about medical care or reproductive issues.

It is important for people considering genetic testing to know whether the test is available on a clinical or research basis. Clinical and research testing both involve a process of informed consent in which patients learn about the testing procedure, the risks and benefits of the test, and the potential consequences of testing.

Gene Therapy

This section presents information on experimental techniques, safety, ethics, and availability of gene therapy.

What Is Gene Therapy?

Gene therapy is an experimental technique that uses genes to treat or prevent disease. In the future, this technique may allow doctors to treat a disorder by inserting a gene into a patient's cells instead of using drugs or surgery. Researchers are testing several approaches to gene therapy, including:

- Replacing a mutated gene that causes disease with a healthy copy of the gene.
- Inactivating, or "knocking out," a mutated gene that is functioning improperly.
- Introducing a new gene into the body to help fight a disease.

Although gene therapy is a promising treatment option for a number of diseases (including inherited disorders, some types of cancer, and certain viral infections), the technique remains risky and is still under study to make sure that it will be safe and effective. Gene therapy is currently only being tested for the treatment of diseases that have no other cures.

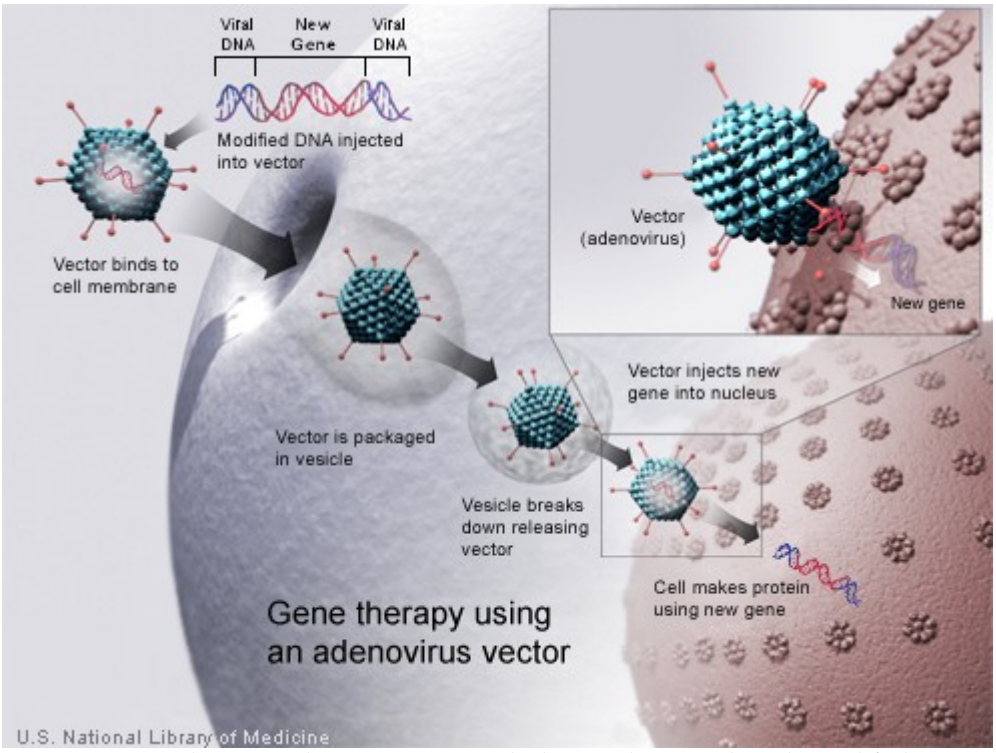
How Does Gene Therapy Work?

Gene therapy is designed to introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein. If a mutated gene causes a necessary protein to be faulty or missing, gene therapy may be able to introduce a normal copy of the gene to restore the function of the protein.

A gene that is inserted directly into a cell usually does not function. Instead, a carrier called a vector is genetically engineered to deliver the gene. Certain viruses are often used as vectors because they can deliver the new gene by infecting the cell. The viruses are modified so they can't cause disease when used in people. Some types of virus, such as retroviruses, integrate their genetic material (including the new gene) into a chromosome in the human cell. Other viruses, such as adenoviruses, introduce their DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome.

The vector can be injected or given intravenously (by IV) directly into a specific tissue in the body, where it is taken up by individual cells. Alternately, a sample of the patient's cells can be removed and exposed to the vector in a laboratory setting. The cells containing the vector are then returned to the patient. If the treatment is successful, the new gene delivered by the vector will make a functioning protein.

Researchers must overcome many technical challenges before gene therapy will be a practical approach to treating disease. For example, scientists must find better ways to deliver genes and target them to particular cells. They must also ensure that new genes are precisely controlled by the body.



A new gene is injected into an adenovirus vector, which is used to introduce the modified DNA into a human cell. If the treatment is successful, the new gene will make a functional protein.

Is Gene Therapy Safe?

Gene therapy is under study to determine whether it could be used to treat disease. Current research is evaluating the safety of gene therapy; future studies will test whether it is an effective treatment option. Several studies have already shown that this approach can have very serious health risks, such as toxicity, inflammation, and cancer. Because the techniques are relatively new, some of the risks may be unpredictable; however, medical researchers, institutions, and regulatory agencies are working to ensure that gene therapy research is as safe as possible.

Comprehensive federal laws, regulations, and guidelines help protect people who participate in research studies (called clinical trials). The U.S. Food and Drug Administration (FDA) regulates all gene therapy products in the United States and oversees research in this area. Researchers who wish to test an approach in a clinical trial must first obtain permission from the FDA. The FDA has the authority to reject or suspend clinical trials that are suspected of being unsafe for participants.

The National Institutes of Health (NIH) also plays an important role in ensuring the safety of gene therapy research. NIH provides guidelines for investigators and institutions (such as universities and hospitals) to follow when conducting clinical trials with gene therapy. These guidelines state that clinical trials at institutions receiving NIH funding for this type of research must be registered with the NIH Office of Biotechnology Activities. The protocol, or plan, for each clinical trial is then reviewed by the NIH Recombinant DNA Advisory Committee (RAC) to determine whether it raises medical, ethical, or safety issues that warrant further discussion at one of the RAC's public meetings.

An Institutional Review Board (IRB) and an Institutional Biosafety Committee (IBC) must approve each gene therapy clinical trial before it can be carried out. An IRB is a committee of scientific and medical advisors and consumers that reviews all research within an institution. An IBC is a group that reviews and approves an institution's potentially hazardous research studies. Multiple levels of evaluation and oversight ensure that safety concerns are a top priority in the planning and carrying out of gene therapy research.

What Are the Ethical Issues surrounding Gene Therapy?

Because gene therapy involves making changes to the body's set of basic instructions, it raises many unique ethical concerns. The ethical questions surrounding gene therapy include:

- How can "good" and "bad" uses of gene therapy be distinguished?
- Who decides which traits are normal and which constitute a disability or disorder?
- Will the high costs of gene therapy make it available only to the wealthy?
- Could the widespread use of gene therapy make society less accepting of people who are different?
- Should people be allowed to use gene therapy to enhance basic human traits such as height, intelligence, or athletic ability?

Current gene therapy research has focused on treating individuals by targeting the therapy to body cells such as bone marrow or blood cells. This type of gene therapy cannot be passed on to a person's children. Gene therapy could be targeted to egg and sperm cells (germ cells), however, which would allow the inserted gene to be passed on to future generations. This approach is known as germline gene therapy.

The idea of germline gene therapy is controversial. While it could spare future generations in a family from having a particular genetic disorder, it might affect the development of a fetus in unexpected ways or have long-term side effects that are not yet known. Because people who would be affected by germline gene therapy are not yet born, they can't choose whether to have the treatment. Because of these ethical concerns, the U.S. Government does not allow federal funds to be used for research on germline gene therapy in people.

Is Gene Therapy Available to Treat My Disorder?

Gene therapy is currently available only in a research setting. The U.S. Food and Drug Administration (FDA) has not yet approved any gene therapy products for sale in the United States.

Hundreds of research studies (clinical trials) are under way to test gene therapy as a treatment for genetic conditions, cancer, and HIV/AIDS. If you are interested in participating in a clinical trial, talk with your doctor or a genetics professional about how to participate.

You can also search for clinical trials online. ClinicalTrials.gov, a service of the National Institutes of Health, provides easy access to information on clinical trials. You can search for

specific trials or browse by condition or trial sponsor. You may wish to refer to a list of gene therapy trials that are accepting (or will accept) patients.

The Human Genome Project and Genomic Research

This section presents information on the goals, accomplishments, and next steps in understanding the human genome.

What Is a Genome?

A genome is an organism's complete set of DNA, including all of its genes. Each genome contains all of the information needed to build and maintain that organism. In humans, a copy of the entire genome—more than 3 billion DNA base pairs—is contained in all cells that have a nucleus.

What Was the Human Genome Project and Why Has It Been Important?

The Human Genome Project was an international research effort to determine the sequence of the human genome and identify the genes that it contains. The Project was coordinated by the National Institutes of Health and the U.S. Department of Energy. Additional contributors included universities across the United States and international partners in the United Kingdom, France, Germany, Japan, and China. The Human Genome Project formally began in 1990 and was completed in 2003, 2 years ahead of its original schedule.

The work of the Human Genome Project has allowed researchers to begin to understand the blueprint for building a person. As researchers learn more about the functions of genes and proteins, this knowledge will have a major impact in the fields of medicine, biotechnology, and the life sciences.

What Were the Goals of the Human Genome Project?

The main goals of the Human Genome Project were to provide a complete and accurate sequence of the 3 billion DNA base pairs that make up the human genome and to find all of the estimated 20,000 to 25,000 human genes. The Project also aimed to sequence the genomes of several other organisms that are important to medical research, such as the mouse and the fruit fly.

In addition to sequencing DNA, the Human Genome Project sought to develop new tools to obtain and analyze the data and to make this information widely available. Also, because advances in genetics have consequences for individuals and society, the Human Genome Project committed to exploring the consequences of genomic research through its Ethical, Legal, and Social Implications (ELSI) program.

What Did the Human Genome Project Accomplish?

In April 2003, researchers announced that the Human Genome Project had completed a high-quality sequence of essentially the entire human genome. This sequence closed the

gaps from a working draft of the genome, which was published in 2001. It also identified the locations of many human genes and provided information about their structure and organization. The Project made the sequence of the human genome and tools to analyze the data freely available via the Internet.

In addition to the human genome, the Human Genome Project sequenced the genomes of several other organisms, including brewers' yeast, the roundworm, and the fruit fly. In 2002, researchers announced that they had also completed a working draft of the mouse genome. By studying the similarities and differences between human genes and those of other organisms, researchers can discover the functions of particular genes and identify which genes are critical for life.

The Project's Ethical, Legal, and Social Implications (ELSI) program became the world's largest bioethics program and a model for other ELSI programs worldwide.

What Were Some of the Ethical, Legal, and Social Implications Addressed by the Human Genome Project?

The Ethical, Legal, and Social Implications (ELSI) program was founded in 1990 as an integral part of the Human Genome Project. The mission of the ELSI program was to identify and address issues raised by genomic research that would affect individuals, families, and society. A percentage of the Human Genome Project budget at the National Institutes of Health and the U.S. Department of Energy was devoted to ELSI research.

The ELSI program focused on the possible consequences of genomic research in four main areas:

- Privacy and fairness in the use of genetic information, including the potential for genetic discrimination in employment and insurance.
- The integration of new genetic technologies, such as genetic testing, into the practice of clinical medicine.
- Ethical issues surrounding the design and conduct of genetic research with people, including the process of informed consent.
- The education of healthcare professionals, policy makers, students, and the public about genetics and the complex issues that result from genomic research.

What Are the Next Steps in Genomic Research?

Discovering the sequence of the human genome was only the first step in understanding how the instructions coded in DNA lead to a functioning human being. The next stage of genomic research will begin to derive meaningful knowledge from the DNA sequence. Research studies that build on the work of the Human Genome Project are under way worldwide.

The objectives of continued genomic research include the following:

- Determine the function of genes and the elements that regulate genes throughout the genome.

- Find variations in the DNA sequence among people and determine their significance. These variations may one day provide information about a person's disease risk and response to certain medications.
- Discover the 3-dimensional structures of proteins and identify their functions.
- Explore how DNA and proteins interact with one another and with the environment to create complex living systems.
- Develop and apply genome-based strategies for the early detection, diagnosis, and treatment of disease.
- Sequence the genomes of other organisms, such as the rat, cow, and chimpanzee, in order to compare similar genes between species.
- Develop new technologies to study genes and DNA on a large scale and store genomic data efficiently.
- Continue to explore the ethical, legal, and social issues raised by genomic research.

What Is Pharmacogenomics?

Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.

Many drugs that are currently available are "one size fits all," but they don't work the same way for everyone. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience negative side effects (called adverse drug reactions). Adverse drug reactions are a significant cause of hospitalizations and deaths in the United States. With the knowledge gained from the Human Genome Project, researchers are learning how inherited differences in genes affect the body's response to medications. These genetic differences will be used to predict whether a medication will be effective for a particular person and to help prevent adverse drug reactions.

The field of pharmacogenomics is still in its infancy. Its use is currently quite limited, but new approaches are under study in clinical trials. In the future, pharmacogenomics will allow the development of tailored drugs to treat a wide range of health problems, including cardiovascular disease, Alzheimer disease, cancer, HIV/AIDS, and asthma.

APPENDIX B. 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[12]:

- National Institutes of Health (NIH); guidelines consolidated across agencies available at **http://health.nih.gov/**
- National Institute of General Medical Sciences (NIGMS); fact sheets available at **http://www.nigms.nih.gov/Publications/FactSheets.htm**
- 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/cancertopics/pdq**
- National Eye Institute (NEI); guidelines available at **http://www.nei.nih.gov/health/**
- 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/HealthInformation/Publications/**
- National Institute on Alcohol Abuse and Alcoholism (NIAAA); guidelines available at **http://www.niaaa.nih.gov/Publications/**

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[12] These publications are typically written by one or more of the various NIH Institutes.

- 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.nidcr.nih.gov/HealthInformation/**
- 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/healthinformation/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 Biomedical Imaging and Bioengineering; general information at **http://www.nibib.nih.gov/HealthEdu**
- 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.[13] 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

[13] 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**).

citations, full-text articles (when available), archival collections, and images are all available. The following are referenced by the National Library of Medicine[14]:

- **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/index.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**
- **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**

[14] See **http://www.nlm.nih.gov/databases/index.html**.

The NLM Gateway[15]

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.[16] To use the NLM Gateway, simply go to the search site at **http://gateway.nlm.nih.gov/gw/Cmd**. Type **primary pulmonary hypertension** (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	3258
Books / Periodicals / Audio Visual	18
Consumer Health	73
Meeting Abstracts	9
Other Collections	0
Total	3358

HSTAT[17]

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.[18] 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.[19] Simply search by **primary pulmonary hypertension** (or synonyms) at the following Web site: **http://text.nlm.nih.gov**.

Coffee Break: Tutorials for Biologists[20]

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.

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

[16] 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).

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

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

[19] 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.

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

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.[21] 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.[22] 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:

- **MD Consult:** Access to electronic clinical resources, see **http://www.mdconsult.com/**.
- **Medical Matrix:** Lists over 6000 medical Web sites and links to over 1.5 million documents with clinical content, see **http://www.medmatrix.org/**.
- **Medical World Search:** Searches full text from thousands of selected medical sites on the Internet; see **http://www.mwsearch.com/**.

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[21] 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.

[22] 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 C. 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 primary pulmonary hypertension 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

This section directs you to sources which either publish fact sheets or can help you find additional guidelines on topics related to primary pulmonary hypertension. 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 primary pulmonary hypertension. 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 **primary pulmonary hypertension**:

Cardiomyopathy
http://www.nlm.nih.gov/medlineplus/cardiomyopathy.html

Congenital Heart Defects
http://www.nlm.nih.gov/medlineplus/congenitalheartdefects.html

Creutzfeldt-Jakob Disease
http://www.nlm.nih.gov/medlineplus/creutzfeldtjakobdisease.html

Health Occupations
http://www.nlm.nih.gov/medlineplus/healthoccupations.html

Immune System and Disorders
http://www.nlm.nih.gov/medlineplus/immunesystemanddisorders.html

Lung Diseases
http://www.nlm.nih.gov/medlineplus/lungdiseases.html

Metabolic Disorders
http://www.nlm.nih.gov/medlineplus/metabolicdisorders.html

Neurologic Diseases
http://www.nlm.nih.gov/medlineplus/neurologicdiseases.html

Organ Transplantation
http://www.nlm.nih.gov/medlineplus/organtransplantation.html

Pulmonary Fibrosis
http://www.nlm.nih.gov/medlineplus/pulmonaryfibrosis.html

Pulmonary Hypertension
http://www.nlm.nih.gov/medlineplus/pulmonaryhypertension.html

Scleroderma
http://www.nlm.nih.gov/medlineplus/scleroderma.html

Vascular Diseases
http://www.nlm.nih.gov/medlineplus/vasculardiseases.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 National Guideline Clearinghouse™

The National Guideline Clearinghouse™ offers hundreds of evidence-based clinical practice guidelines published in the United States and other countries. You can search this site located at **http://www.guideline.gov/** by using the keyword **primary pulmonary hypertension** (or synonyms). The following was recently posted:

- **Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology**

  Source: European Society of Cardiology - Medical Specialty Society; 2004; 36 pages

  http://www.guideline.gov/summary/summary.aspx?doc_id=6467&nbr=004058&string=Primary+AND+pulmonary+AND+hypertension

- **Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines**

  Source: American College of Chest Physicians - Medical Specialty Society; 2004; 28 pages

  http://www.guideline.gov/summary/summary.aspx?doc_id=5460&nbr=003737&string=Primary+AND+pulmonary+AND+hypertension

- **Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines**

  Source: American College of Chest Physicians - Medical Specialty Society; 2004; 15 pages

  http://www.guideline.gov/summary/summary.aspx?doc_id=5463&nbr=003740&string=Primary+AND+pulmonary+AND+hypertension

- **Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines.**

  Source: American College of Chest Physicians - Medical Specialty Society; 2004; 21 pages

  http://www.guideline.gov/summary/summary.aspx?doc_id=5459&nbr=003736&string=Primary+AND+pulmonary+AND+hypertension

- **Surgical treatments/interventions for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines**

  Source: American College of Chest Physicians - Medical Specialty Society; 2004; 9 pages

  http://www.guideline.gov/summary/summary.aspx?doc_id=5461&nbr=003738&string=Primary+AND+pulmonary+AND+hypertension

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:

- **Division for Heart Disease and Stroke Prevention - Pulmonary.**

  Source: www.cdc.gov

  http://www.cdc.gov/dhdsp/library/fs_pulmonary_hypertension.htm

- **FCIC: Handout on Health: Scleroderma**

  Source: www.pueblo.gsa.gov

  http://www.pueblo.gsa.gov/cic_text/health/scleroderma/scleroderma.htm

- **geneticalliance.org**

  Source: www.geneticalliance.org

  http://www.geneticalliance.org/ws_display.asp?filter=diseases_what_is&char=P&s_Diseases=

- **Lung Information for Patients and the General Public, NHLBI**

  Source: www.nhlbi.nih.gov

  http://www.nhlbi.nih.gov/health/public/lung/

- **PHA Website**

  Source: www.phassociation.org

  http://www.phassociation.org/Learn/What-is-PH/glossary.asp

- **PHCentral - PAH: The Complete Resource: Medical**

  Source: phcentral.org

  http://phcentral.org/medical/whatisph.html

- **Pulmonary Hypertension Association**

  Source: www.phassociation.org

  http://www.phassociation.org/Learn/FAQs/General_FAQ.asp

- **Thyroid.org: Notes - March 2003**

  Source: www.thyroid.org

  http://www.thyroid.org/patients/notes/march03/03_03_18.html

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 primary pulmonary hypertension. 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://health.nih.gov/index.asp**. Under **Search Health Topics**, type **primary pulmonary hypertension** (or synonyms) into the search box, and click **Search**.

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:

- 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://www.webmd.com/diseases_and_conditions/default.htm**

Finding Associations

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

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 primary pulmonary hypertension. 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://sis.nlm.nih.gov/dirline.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. Simply type in **primary pulmonary hypertension** (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://healthhotlines.nlm.nih.gov/**. 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 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 **primary pulmonary hypertension** (or a synonym) into the search box, and click **Submit Query**.

Resources for Patients and Families

The following are organizations that provide support and advocacy for patient with genetic conditions and their families[23]:

- Genetic Alliance: **http://geneticalliance.org**
- Genetic and Rare Diseases Information Center: **http://rarediseases.info.nih.gov/html/resources/info_cntr.html**
- Madisons Foundation: **http://www.madisonsfoundation.org/**
- March of Dimes: **http://www.marchofdimes.com**
- National Organization for Rare Disorders (NORD): **http://www.rarediseases.org/**

For More Information on Genetics

The following publications offer detailed information for patients about the science of genetics:

- What Is a Genome?: **http://www.ncbi.nlm.nih.gov/About/primer/genetics_genome.html**
- A Science Called Genetics: **http://publications.nigms.nih.gov/genetics/science.html**

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[23] Adapted from the National Library of Medicine: **http://ghr.nlm.nih.gov/ghr/resource/patients**.

- Genetic Mapping: **http://www.genome.gov/10000715**

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/archive//20040831/nichsr/ta101/ta10108.html**

Beyond these, MEDLINEplus contains a very patient-friendly encyclopedia covering every aspect of medicine (licensed from A.D.A.M., Inc.). The ADAM Medical Encyclopedia can be accessed at **http://www.nlm.nih.gov/medlineplus/encyclopedia.html**. ADAM is also available on commercial Web sites such as drkoop.com (**http://www.drkoop.com/**) and Web MD (**http://my.webmd.com/adam/asset/adam_disease_articles/a_to_z/a**). The NIH suggests the following Web sites in the ADAM Medical Encyclopedia when searching for information on primary pulmonary hypertension:

- **Basic Guidelines for Primary Pulmonary Hypertension**

  Primary pulmonary hypertension
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000112.htm

  Pulmonary hypertension
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000112.htm

- **Signs & Symptoms for Primary Pulmonary Hypertension**

  Chest pain
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003079.htm

  Coughing up blood
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003073.htm

  Dizziness
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003093.htm

Edema
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003103.htm

Fainting
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003092.htm

Fatigue
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003088.htm

Hyperactivity
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003256.htm

Hyperventilation
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003071.htm

Lightheadedness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003092.htm

Shortness of breath
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003075.htm

Swelling
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003103.htm

Weakness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003174.htm

- **Diagnostics and Tests for Primary Pulmonary Hypertension**

ANA
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003535.htm

Angiogram
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003327.htm

Angiography
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003327.htm

Arteriogram
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003327.htm

Biopsy
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003416.htm

Blood gases
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003855.htm

Blood pressure
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003398.htm

Cardiac catheterization
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003419.htm

Chest X-ray
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003804.htm

CT
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003330.htm

ECG
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003868.htm

Echocardiogram
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003869.htm

Heart catheterization
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003419.htm

Lung scan
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003824.htm

Pulmonary arteriogram
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003813.htm

Pulmonary function
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003443.htm

Pulmonary function tests
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003853.htm

Pulse
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003399.htm

Right heart catheterization
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003870.htm

V/Q scan
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003828.htm

X-ray
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003337.htm

- **Surgery and Procedures for Primary Pulmonary Hypertension**

Heart-lung transplantation
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003004.htm

Lung transplant
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003010.htm

- **Background Topics for Primary Pulmonary Hypertension**

Incidence
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002387.htm

Physical examination
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002274.htm

Respiratory
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002290.htm

Online Dictionary Directories

The following are additional online directories compiled by the National Library of Medicine, including a number of specialized medical dictionaries:

- Medical Dictionaries: Medical & Biological (World Health Organization): **http://www.who.int/hlt/virtuallibrary/English/diction.htm#Medical**
- 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**

PRIMARY PULMONARY HYPERTENSION 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]

Aberrant: Wandering or deviating from the usual or normal course. [EU]

Abscess: A localized, circumscribed collection of pus. [NIH]

Acetylcholine: A neurotransmitter. Acetylcholine in vertebrates is the major transmitter at neuromuscular junctions, autonomic ganglia, parasympathetic effector junctions, a subset of sympathetic effector junctions, and at many sites in the central nervous system. It is generally not used as an administered drug because it is broken down very rapidly by cholinesterases, but it is useful in some ophthalmological applications. [NIH]

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

Adaptation: 1. The adjustment of an organism to its environment, or the process by which it enhances such fitness. 2. The normal ability of the eye to adjust itself to variations in the intensity of light; the adjustment to such variations. 3. The decline in the frequency of firing of a neuron, particularly of a receptor, under conditions of constant stimulation. 4. In dentistry, (a) the proper fitting of a denture, (b) the degree of proximity and interlocking of restorative material to a tooth preparation, (c) the exact adjustment of bands to teeth. 5. In microbiology, the adjustment of bacterial physiology to a new environment. [EU]

Adenine: A purine base and a fundamental unit of adenine nucleotides. [NIH]

Adenosine: A nucleoside that is composed of adenine and d-ribose. Adenosine or adenosine derivatives play many important biological roles in addition to being components of DNA and RNA. Adenosine itself is a neurotransmitter. [NIH]

Adenosine Triphosphate: Adenosine 5'-(tetrahydrogen triphosphate). An adenine nucleotide containing three phosphate groups esterified to the sugar moiety. In addition to its crucial roles in metabolism adenosine triphosphate is a neurotransmitter. [NIH]

Adenovirus: A group of viruses that cause respiratory tract and eye infections. Adenoviruses used in gene therapy are altered to carry a specific tumor-fighting gene. [NIH]

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

Aerobic: In biochemistry, reactions that need oxygen to happen or happen when oxygen is present. [NIH]

Affinity: 1. Inherent likeness or relationship. 2. A special attraction for a specific element, organ, or structure. 3. Chemical affinity; the force that binds atoms in molecules; the

tendency of substances to combine by chemical reaction. 4. The strength of noncovalent chemical binding between two substances as measured by the dissociation constant of the complex. 5. In immunology, a thermodynamic expression of the strength of interaction between a single antigen-binding site and a single antigenic determinant (and thus of the stereochemical compatibility between them), most accurately applied to interactions among simple, uniform antigenic determinants such as haptens. Expressed as the association constant (K litres mole -1), which, owing to the heterogeneity of affinities in a population of antibody molecules of a given specificity, actually represents an average value (mean intrinsic association constant). 6. The reciprocal of the dissociation constant. [EU]

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

Aged, 80 and Over: A person 80 years of age and older. [NIH]

Agenesis: Lack of complete or normal development; congenital absence of an organ or part. [NIH]

Agonist: In anatomy, a prime mover. In pharmacology, a drug that has affinity for and stimulates physiologic activity at cell receptors normally stimulated by naturally occurring substances. [EU]

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

Airway Obstruction: Any hindrance to the passage of air into and out of the lungs. [NIH]

Algorithms: A procedure consisting of a sequence of algebraic formulas and/or logical steps to calculate or determine a given task. [NIH]

Alkaline: Having the reactions of an alkali. [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]

Alleles: Mutually exclusive forms of the same gene, occupying the same locus on homologous chromosomes, and governing the same biochemical and developmental process. [NIH]

Alpha-1: A protein with the property of inactivating proteolytic enzymes such as leucocyte collagenase and elastase. [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]

Alveoli: Tiny air sacs at the end of the bronchioles in the lungs. [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]

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Amnion: The extraembryonic membrane which contains the embryo and amniotic fluid. [NIH]

Amniotic Fluid: Amniotic cavity fluid which is produced by the amnion and fetal lungs and kidneys. [NIH]

Ampulla: A sac-like enlargement of a canal or duct. [NIH]

Anaesthesia: Loss of feeling or sensation. Although the term is used for loss of tactile sensibility, or of any of the other senses, it is applied especially to loss of the sensation of pain, as it is induced to permit performance of surgery or other painful procedures. [EU]

Anal: Having to do with the anus, which is the posterior opening of the large bowel. [NIH]

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

Anatomical: Pertaining to anatomy, or to the structure of the organism. [EU]

Anemia: A reduction in the number of circulating erythrocytes or in the quantity of hemoglobin. [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]

Aneuploidy: The chromosomal constitution of cells which deviate from the normal by the addition or subtraction of chromosomes or chromosome pairs. In a normally diploid cell the loss of a chromosome pair is termed nullisomy (symbol: 2N-2), the loss of a single chromosome is monosomy (symbol: 2N-1), the addition of a chromosome pair is tetrasomy (symbol: 2N+2), the addition of a single chromosome is trisomy (symbol: 2N+1). [NIH]

Aneurysm: A sac formed by the dilatation of the wall of an artery, a vein, or the heart. [NIH]

Anginal: Pertaining to or characteristic of angina. [EU]

Angiography: Radiography of blood vessels after injection of a contrast medium. [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]

Antagonism: Interference with, or inhibition of, the growth of a living organism by another living organism, due either to creation of unfavorable conditions (e. g. exhaustion of food supplies) or to production of a specific antibiotic substance (e. g. penicillin). [NIH]

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]

Antihypertensive: An agent that reduces high blood pressure. [EU]

Anuria: Inability to form or excrete urine. [NIH]

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

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

Aortic Valve: The valve between the left ventricle and the ascending aorta which prevents backflow into the left ventricle. [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]

Aqueous: Having to do with water. [NIH]

Arachidonic Acid: An unsaturated, essential fatty acid. It is found in animal and human fat as well as in the liver, brain, and glandular organs, and is a constituent of animal phosphatides. It is formed by the synthesis from dietary linoleic acid and is a precursor in the biosynthesis of prostaglandins, thromboxanes, and leukotrienes. [NIH]

Arginase: A ureahydrolase that catalyzes the hydrolysis of arginine or canavanine to yield L-ORNITHINE and urea. Deficiency of this enzyme causes hyperargininemia. EC 3.5.3.1. [NIH]

Arginine: An essential amino acid that is physiologically active in the L-form. [NIH]

Armadillos: Burrowing, chiefly nocturnal mammals of the family Dasypodidae having bodies and heads encased in small bony plates. They are widely distributed in the warmer parts of the Americas. [NIH]

Arterial: Pertaining to an artery or to the arteries. [EU]

Arteries: The vessels carrying blood away from the heart. [NIH]

Arteriogram: An x-ray of arteries; the person receives an injection of a dye that outlines the vessels on an x-ray. [NIH]

Arterioles: The smallest divisions of the arteries located between the muscular arteries and the capillaries. [NIH]

Arteriosclerosis: Thickening and loss of elasticity of arterial walls. Atherosclerosis is the most common form of arteriosclerosis and involves lipid deposition and thickening of the intimal cell layers within arteries. Additional forms of arteriosclerosis involve calcification of

the media of muscular arteries (Monkeberg medial calcific sclerosis) and thickening of the walls of small arteries or arterioles due to cell proliferation or hyaline deposition (arteriolosclerosis). [NIH]

Arteriosus: Circle composed of anastomosing arteries derived from two long posterior ciliary and seven anterior ciliary arteries, located in the ciliary body about the root of the iris. [NIH]

Arteriovenous: Both arterial and venous; pertaining to or affecting an artery and a vein. [EU]

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

Aspartic Acid: One of the non-essential amino acids commonly occurring in the L-form. It is found in animals and plants, especially in sugar cane and sugar beets. It may be a neurotransmitter. [NIH]

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

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

Atrial: Pertaining to an atrium. [EU]

Atrial Fibrillation: Disorder of cardiac rhythm characterized by rapid, irregular atrial impulses and ineffective atrial contractions. [NIH]

Atrium: A chamber; used in anatomical nomenclature to designate a chamber affording entrance to another structure or organ. Usually used alone to designate an atrium of the heart. [EU]

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

Attenuation: Reduction of transmitted sound energy or its electrical equivalent. [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]

Autopsy: Postmortem examination of the body. [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]

Balloon dilation: A treatment for benign prostatic hyperplasia or prostate enlargement. A tiny balloon is inflated inside the urethra to make it wider so urine can flow more freely from the bladder. [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 Sequence: The sequence of purines and pyrimidines in nucleic acids and polynucleotides. It is also called nucleotide or nucleoside sequence. [NIH]

Benign: Not cancerous; does not invade nearby tissue or spread to other parts of the body. [NIH]

Benign prostatic hyperplasia: A benign (noncancerous) condition in which an overgrowth of prostate tissue pushes against the urethra and the bladder, blocking the flow of urine. Also called benign prostatic hypertrophy or BPH. [NIH]

Bewilderment: Impairment or loss of will power. [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]

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

Biological therapy: Treatment to stimulate or restore the ability of the immune system to fight infection and disease. Also used to lessen side effects that may be caused by some cancer treatments. Also known as immunotherapy, biotherapy, or biological response modifier (BRM) therapy. [NIH]

Biological Transport: The movement of materials (including biochemical substances and drugs) across cell membranes and epithelial layers, usually by passive diffusion. [NIH]

Biomarkers: Substances sometimes found in an increased amount in the blood, other body fluids, or tissues and that may suggest the presence of some types of cancer. Biomarkers include CA 125 (ovarian cancer), CA 15-3 (breast cancer), CEA (ovarian, lung, breast, pancreas, and GI tract cancers), and PSA (prostate cancer). Also called tumor markers. [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]

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 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 vessel: A tube in the body through which blood circulates. Blood vessels include a network of arteries, arterioles, capillaries, venules, and veins. [NIH]

Body Fluids: Liquid components of living organisms. [NIH]

Bone Marrow: The soft tissue filling the cavities of bones. Bone marrow exists in two types, yellow and red. Yellow marrow is found in the large cavities of large bones and consists mostly of fat cells and a few primitive blood cells. Red marrow is a hematopoietic tissue and is the site of production of erythrocytes and granular leukocytes. Bone marrow is made up of a framework of connective tissue containing branching fibers with the frame being filled with marrow cells. [NIH]

Bone Morphogenetic Proteins: Bone-growth regulatory factors that are members of the transforming growth factor-beta superfamily of proteins. They are synthesized as large precursor molecules which are cleaved by proteolytic enzymes. The active form can consist of a dimer of two identical proteins or a heterodimer of two related bone morphogenetic proteins. [NIH]

Bone scan: A technique to create images of bones on a computer screen or on film. A small amount of radioactive material is injected into a blood vessel and travels through the bloodstream; it collects in the bones and is detected by a scanner. [NIH]

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

Bradykinin: A nonapeptide messenger that is enzymatically produced from kallidin in the blood where it is a potent but short-lived agent of arteriolar dilation and increased capillary permeability. Bradykinin is also released from mast cells during asthma attacks, from gut walls as a gastrointestinal vasodilator, from damaged tissues as a pain signal, and may be a neurotransmitter. [NIH]

Bronchi: The larger air passages of the lungs arising from the terminal bifurcation of the trachea. [NIH]

Bronchial: Pertaining to one or more bronchi. [EU]

Bronchitis: Inflammation (swelling and reddening) of the bronchi. [NIH]

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

Cachexia: General ill health, malnutrition, and weight loss, usually associated with chronic disease. [NIH]

Caesarean section: A surgical incision through the abdominal and uterine walls in order to deliver a baby. [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]

Capnography: Continuous recording of the carbon dioxide content of expired air. [NIH]

Carbohydrates: The largest class of organic compounds, including starches, glycogens, cellulose, gums, and simple sugars. Carbohydrates are composed of carbon, hydrogen, and oxygen in a ratio of Cn(H2O)n. [NIH]

Carbon Dioxide: A colorless, odorless gas that can be formed by the body and is necessary

for the respiration cycle of plants and animals. [NIH]

Carcinogenic: Producing carcinoma. [EU]

Cardiac: Having to do with the heart. [NIH]

Cardiac catheterization: A procedure in which a thin, hollow tube is inserted into a blood vessel. The tube is then advanced through the vessel into the heart, enabling a physician to study the heart and its pumping activity. [NIH]

Cardiac Output: The volume of blood passing through the heart per unit of time. It is usually expressed as liters (volume) per minute so as not to be confused with stroke volume (volume per beat). [NIH]

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

Cardiopulmonary: Having to do with the heart and lungs. [NIH]

Cardiovascular: Having to do with the heart and blood vessels. [NIH]

Cardiovascular disease: Any abnormal condition characterized by dysfunction of the heart and blood vessels. CVD includes atherosclerosis (especially coronary heart disease, which can lead to heart attacks), cerebrovascular disease (e.g., stroke), and hypertension (high blood pressure). [NIH]

Carotene: The general name for a group of pigments found in green, yellow, and leafy vegetables, and yellow fruits. The pigments are fat-soluble, unsaturated aliphatic hydrocarbons functioning as provitamins and are converted to vitamin A through enzymatic processes in the intestinal wall. [NIH]

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]

Caspases: A family of intracellular cysteine endopeptidases. They play a key role in inflammation and mammalian apoptosis. They are specific for aspartic acid at the P1 position. They are divided into two classes based on the lengths of their N-terminal prodomains. Caspases-1,-2,-4,-5,-8, and -10 have long prodomains and -3,-6,-7,-9 have short prodomains. EC 3.4.22.-. [NIH]

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

Catheter: A flexible tube used to deliver fluids into or withdraw fluids from the body. [NIH]

Catheterization: Use or insertion of a tubular device into a duct, blood vessel, hollow organ, or body cavity for injecting or withdrawing fluids for diagnostic or therapeutic purposes. It differs from intubation in that the tube here is used to restore or maintain patency in obstructions. [NIH]

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]

Cavernous Sinus: An irregularly shaped venous space in the dura mater at either side of the sphenoid bone. [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 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 Respiration: The metabolic process of all living cells (animal and plant) in which oxygen is used to provide a source of energy for the cell. [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]

Central Nervous System: The main information-processing organs of the nervous system, consisting of the brain, spinal cord, and meninges. [NIH]

Centromere: The clear constricted portion of the chromosome at which the chromatids are joined and by which the chromosome is attached to the spindle during cell division. [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]

Cervical: Relating to the neck, or to the neck of any organ or structure. Cervical lymph nodes are located in the neck; cervical cancer refers to cancer of the uterine cervix, which is the lower, narrow end (the "neck") of the uterus. [NIH]

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]

Chest Pain: Pressure, burning, or numbness in the chest. [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]

Cholestasis: Impairment of biliary flow at any level from the hepatocyte to Vater's ampulla. [NIH]

Cholesterol: The principal sterol of all higher animals, distributed in body tissues, especially the brain and spinal cord, and in animal fats and oils. [NIH]

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 Fragility: Susceptibility of chromosomes to breakage and translocation or other aberrations. Chromosome fragile sites are regions that show up in karyotypes as a gap (uncondensed stretch) on the chromatid arm. They are associated with chromosome break sites and other aberrations. A fragile site on the X chromosome is associated with fragile X syndrome. Fragile sites are designated by the letters "FRA" followed by the designation for the specific chromosome and a letter which refers to the different fragile sites on a chromosome (e.g. FRAXA). [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 Obstructive Pulmonary Disease: Collective term for chronic bronchitis and emphysema. [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]

Clamp: A u-shaped steel rod used with a pin or wire for skeletal traction in the treatment of certain fractures. [NIH]

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

Clinical Protocols: Precise and detailed plans for the study of a medical or biomedical problem and/or plans for a regimen of therapy. [NIH]

Clinical study: A research study in which patients receive treatment in a clinic or other medical facility. Reports of clinical studies can contain results for single patients (case reports) or many patients (case series or clinical trials). [NIH]

Clinical trial: A research study that tests how well new medical treatments or other interventions work in people. Each study is designed to test new methods of screening, prevention, diagnosis, or treatment of a disease. [NIH]

Cloning: The production of a number of genetically identical individuals; in genetic engineering, a process for the efficient replication of a great number of identical DNA molecules. [NIH]

Clot Retraction: Retraction of a clot resulting from contraction of platelet pseudopods attached to fibrin strands that is dependent on the contractile protein thrombosthenin. Used as a measure of platelet function. [NIH]

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]

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]

Collagen: A polypeptide substance comprising about one third of the total protein in mammalian organisms. It is the main constituent of skin, connective tissue, and the organic substance of bones and teeth. Different forms of collagen are produced in the body but all consist of three alpha-polypeptide chains arranged in a triple helix. Collagen is differentiated from other fibrous proteins, such as elastin, by the content of proline, hydroxyproline, and hydroxylysine; by the absence of tryptophan; and particularly by the high content of polar groups which are responsible for its swelling properties. [NIH]

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]

Colonoscopy: Endoscopic examination, therapy or surgery of the luminal surface of the colon. [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]

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]

Computed tomography: CT scan. A series of detailed pictures of areas inside the body, taken from different angles; the pictures are created by a computer linked to an x-ray machine. Also called computerized tomography and computerized axial tomography (CAT) scan. [NIH]

Computerized axial tomography: A series of detailed pictures of areas inside the body, taken from different angles; the pictures are created by a computer linked to an x-ray machine. Also called CAT scan, computed tomography (CT scan), or computerized tomography. [NIH]

Computerized tomography: A series of detailed pictures of areas inside the body, taken from different angles; the pictures are created by a computer linked to an x-ray machine. Also called computerized axial tomography (CAT) scan and computed tomography (CT scan). [NIH]

Concentric: Having a common center of curvature or symmetry. [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]

Cones: One type of specialized light-sensitive cells (photoreceptors) in the retina that provide sharp central vision and color vision. [NIH]

Confusion: A mental state characterized by bewilderment, emotional disturbance, lack of clear thinking, and perceptual disorientation. [NIH]

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

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Connective Tissue Cells: A group of cells that includes fibroblasts, cartilage cells, adipocytes, smooth muscle cells, and bone cells. [NIH]

Connective Tissue Diseases: A heterogeneous group of disorders, some hereditary, others acquired, characterized by abnormal structure or function of one or more of the elements of connective tissue, i.e., collagen, elastin, or the mucopolysaccharides. [NIH]

Consciousness: Sense of awareness of self and of the environment. [NIH]

Constriction: The act of constricting. [NIH]

Constriction, Pathologic: The condition of an anatomical structure's being constricted beyond normal dimensions. [NIH]

Consultation: A deliberation between two or more physicians concerning the diagnosis and the proper method of treatment in a case. [NIH]

Continuous infusion: The administration of a fluid into a blood vessel, usually over a prolonged period of time. [NIH]

Contraindications: Any factor or sign that it is unwise to pursue a certain kind of action or treatment, e. g. giving a general anesthetic to a person with pneumonia. [NIH]

Contrast medium: A substance that is introduced into or around a structure and, because of the difference in absorption of x-rays by the contrast medium and the surrounding tissues, allows radiographic visualization of the structure. [EU]

Conus: A large, circular, white patch around the optic disk due to the exposing of the sclera as a result of degenerative change or congenital abnormality in the choroid and retina. [NIH]

Coronary: Encircling in the manner of a crown; a term applied to vessels; nerves, ligaments, etc. The term usually denotes the arteries that supply the heart muscle and, by extension, a pathologic involvement of them. [EU]

Coronary heart disease: A type of heart disease caused by narrowing of the coronary arteries that feed the heart, which needs a constant supply of oxygen and nutrients carried by the blood in the coronary arteries. When the coronary arteries become narrowed or clogged by fat and cholesterol deposits and cannot supply enough blood to the heart, CHD results. [NIH]

Coronary Thrombosis: Presence of a thrombus in a coronary artery, often causing a myocardial infarction. [NIH]

Cortex: The outer layer of an organ or other body structure, as distinguished from the internal substance. [EU]

Cortical: Pertaining to or of the nature of a cortex or bark. [EU]

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

Cutaneous: Having to do with the skin. [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]

Cystathionine beta-Synthase: A multifunctional pyridoxal phosphate enzyme. In the second stage of cysteine biosynthesis it catalyzes the reaction of homocysteine with serine to form cystathionine with the elimination of water. Deficiency of this enzyme leads to hyperhomocysteinemia and homocystinuria. EC 4.2.1.22. [NIH]

Cysteine: A thiol-containing non-essential amino acid that is oxidized to form cystine. [NIH]

Cysteine Endopeptidases: Endopeptidases which have a cysteine involved in the catalytic process. This group of enzymes is inactivated by sulfhydryl reagents. EC 3.4.22. [NIH]

Cytochrome: Any electron transfer hemoprotein having a mode of action in which the transfer of a single electron is effected by a reversible valence change of the central iron atom of the heme prosthetic group between the +2 and +3 oxidation states; classified as cytochromes a in which the heme contains a formyl side chain, cytochromes b, which contain protoheme or a closely similar heme that is not covalently bound to the protein, cytochromes c in which protoheme or other heme is covalently bound to the protein, and cytochromes d in which the iron-tetrapyrrole has fewer conjugated double bonds than the hemes have. Well-known cytochromes have been numbered consecutively within groups and are designated by subscripts (beginning with no subscript), e.g. cytochromes c, c1, C2, . New cytochromes are named according to the wavelength in nanometres of the absorption

maximum of the a-band of the iron (II) form in pyridine, e.g., c-555. [EU]

Cytokine: Small but highly potent protein that modulates the activity of many cell types, including T and B 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]

Cytosine: A pyrimidine base that is a fundamental unit of nucleic acids. [NIH]

Cytotoxic: Cell-killing. [NIH]

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

Death Certificates: Official records of individual deaths including the cause of death certified by a physician, and any other required identifying information. [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]

Dendrites: Extensions of the nerve cell body. They are short and branched and receive stimuli from other neurons. [NIH]

Deoxyribonucleic: A polymer of subunits called deoxyribonucleotides which is the primary genetic material of a cell, the material equivalent to genetic information. [NIH]

Deoxyribonucleic acid: A polymer of subunits called deoxyribonucleotides which is the primary genetic material of a cell, the material equivalent to genetic information. [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]

Dexfenfluramine: The S-isomer of fenfluramine. It is a serotonin agonist and is used as an anorectic. Unlike fenfluramine, it does not possess any catecholamine agonist activity. [NIH]

Dextroamphetamine: The d-form of amphetamine. It is a central nervous system stimulant and a sympathomimetic. It has also been used in the treatment of narcolepsy and of attention deficit disorders and hyperactivity in children. Dextroamphetamine has multiple mechanisms of action including blocking uptake of adrenergics and dopamine, stimulating release of monamines, and inhibiting monoamine oxidase. It is also a drug of abuse and a psychotomimetic. [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]

Diastole: Period of relaxation of the heart, especially the ventricles. [NIH]

Diastolic: Of or pertaining to the diastole. [EU]

Diffusion: The tendency of a gas or solute to pass from a point of higher pressure or

concentration to a point of lower pressure or concentration and to distribute itself throughout the available space; a major mechanism of biological transport. [NIH]

Digestion: The process of breakdown of food for metabolism and use by the body. [NIH]

Dihydrotestosterone: Anabolic agent. [NIH]

Dilatation, Pathologic: The condition of an anatomical structure's being dilated beyond normal dimensions. [NIH]

Dilation: A process by which the pupil is temporarily enlarged with special eye drops (mydriatic); allows the eye care specialist to better view the inside of the eye. [NIH]

Diltiazem: A benzothiazepine derivative with vasodilating action due to its antagonism of the actions of the calcium ion in membrane functions. It is also teratogenic. [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]

Discrimination: The act of qualitative and/or quantitative differentiation between two or more stimuli. [NIH]

Disorientation: The loss of proper bearings, or a state of mental confusion as to time, place, or identity. [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]

Dizziness: An imprecise term which may refer to a sense of spatial disorientation, motion of the environment, or lightheadedness. [NIH]

Double-blind: Pertaining to a clinical trial or other experiment in which neither the subject nor the person administering treatment knows which treatment any particular subject is receiving. [EU]

Drug Combinations: Single preparations containing two or more active agents, for the purpose of their concurrent administration as a fixed dose mixture. It is differentiated from combination drug therapy in which two or more drugs are administered separately for a combined effect. [NIH]

Drug Interactions: The action of a drug that may affect the activity, metabolism, or toxicity of another drug. [NIH]

Duct: A tube through which body fluids pass. [NIH]

Dyspnea: Difficult or labored breathing. [NIH]

Echocardiography: Ultrasonic recording of the size, motion, and composition of the heart and surrounding tissues. The standard approach is transthoracic. [NIH]

Edema: Excessive amount of watery fluid accumulated in the intercellular spaces, most commonly present in subcutaneous tissue. [NIH]

Effector: It is often an enzyme that converts an inactive precursor molecule into an active

second messenger. [NIH]

Efficacy: The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions. Ideally, the determination of efficacy is based on the results of a randomized control trial. [NIH]

Effusion: The escape of fluid into a part or tissue, as an exudation or a transudation. [EU]

Eicosanoids: A class of oxygenated, endogenous, unsaturated fatty acids derived from arachidonic acid. They include prostaglandins, leukotrienes, thromboxanes, and hydroxyeicosatetraenoic acid compounds (HETE). They are hormone-like substances that act near the site of synthesis without altering functions throughout the body. [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]

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]

Emboli: Bit of foreign matter which enters the blood stream at one point and is carried until it is lodged or impacted in an artery and obstructs it. It may be a blood clot, an air bubble, fat or other tissue, or clumps of bacteria. [NIH]

Embolism: Blocking of a blood vessel by a blood clot or foreign matter that has been transported from a distant site by the blood stream. [NIH]

Embolization: The blocking of an artery by a clot or foreign material. Embolization can be done as treatment to block the flow of blood to a tumor. [NIH]

Embryo: The prenatal stage of mammalian development characterized by rapid morphological changes and the differentiation of basic structures. [NIH]

Emphysema: A pathological accumulation of air in tissues or organs. [NIH]

Endemic: Present or usually prevalent in a population or geographical area at all times; said of a disease or agent. Called also endemial. [EU]

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]

Endothelium: A layer of epithelium that lines the heart, blood vessels (endothelium, vascular), lymph vessels (endothelium, lymphatic), and the serous cavities of the body. [NIH]

Endothelium, Lymphatic: Unbroken cellular lining (intima) of the lymph vessels (e.g., the high endothelial lymphatic venules). It is more permeable than vascular endothelium, lacking selective absorption and functioning mainly to remove plasma proteins that have filtered through the capillaries into the tissue spaces. [NIH]

Endothelium, Vascular: Single pavement layer of cells which line the luminal surface of the entire vascular system and regulate the transport of macromolecules and blood components from interstitium to lumen; this function has been most intensively studied in the blood capillaries. [NIH]

Endothelium-derived: Small molecule that diffuses to the adjacent muscle layer and relaxes

it. [NIH]

Endotoxemia: A condition characterized by the presence of endotoxins in the blood. If endotoxemia is the result of gram-negative rod-shaped bacteria, shock may occur. [NIH]

Endotoxins: Toxins closely associated with the living cytoplasm or cell wall of certain microorganisms, which do not readily diffuse into the culture medium, but are released upon lysis of the cells. [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]

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]

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]

Epistaxis: Bleeding from the nose. [NIH]

Epithelial: Refers to the cells that line the internal and external surfaces of the body. [NIH]

Epithelial Cells: Cells that line the inner and outer surfaces of the body. [NIH]

Epithelium: One or more layers of epithelial cells, supported by the basal lamina, which covers the inner or outer surfaces of the body. [NIH]

Epoprostenol: A prostaglandin that is biosynthesized enzymatically from prostaglandin endoperoxides in human vascular tissue. It is a potent inhibitor of platelet aggregation. The sodium salt has been also used to treat primary pulmonary hypertension. [NIH]

Ergometer: An instrument for measuring the force of muscular contraction. [NIH]

Ergometry: Any method of measuring the amount of work done by an organism, usually during exertion. Ergometry also includes measures of power. Some instruments used in these determinations include the hand crank and the bicycle ergometer. [NIH]

Erythrocytes: Red blood cells. Mature erythrocytes are non-nucleated, biconcave disks containing hemoglobin whose function is to transport oxygen. [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]

Ethnic Groups: A group of people with a common cultural heritage that sets them apart from others in a variety of social relationships. [NIH]

Eukaryotic Cells: Cells of the higher organisms, containing a true nucleus bounded by a nuclear membrane. [NIH]

Evacuation: An emptying, as of the bowels. [EU]

Excrete: To get rid of waste from the body. [NIH]

Exercise Test: Controlled physical activity, more strenuous than at rest, which is performed in order to allow assessment of physiological functions, particularly cardiovascular and pulmonary, but also aerobic capacity. Maximal (most intense) exercise is usually required but submaximal exercise is also used. The intensity of exercise is often graded, using criteria

such as rate of work done, oxygen consumption, and heart rate. Physiological data obtained from an exercise test may be used for diagnosis, prognosis, and evaluation of disease severity, and to evaluate therapy. Data may also be used in prescribing exercise by determining a person's exercise capacity. [NIH]

Exocytosis: Cellular release of material within membrane-limited vesicles by fusion of the vesicles with the cell membrane. [NIH]

Exogenous: Developed or originating outside the organism, as exogenous disease. [EU]

Exons: Coding regions of messenger RNA included in the genetic transcript which survive the processing of RNA in cell nuclei to become part of a spliced messenger of structural RNA in the cytoplasm. They include joining and diversity exons of immunoglobulin genes. [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]

Extracorporeal: Situated or occurring outside the body. [EU]

Eye Color: Color of the iris. [NIH]

Eye Infections: Infection, moderate to severe, caused by bacteria, fungi, or viruses, which occurs either on the external surface of the eye or intraocularly with probable inflammation, visual impairment, or blindness. [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]

Fathers: Male parents, human or animal. [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]

Fenfluramine: A centrally active drug that apparently both blocks serotonin uptake and provokes transport-mediated serotonin release. [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]

Fibroblasts: Connective tissue cells which secrete an extracellular matrix rich in collagen and other macromolecules. [NIH]

Fibrosis: Any pathological condition where fibrous connective tissue invades any organ, usually as a consequence of inflammation or other injury. [NIH]

Flatus: Gas passed through the rectum. [NIH]

Flushing: A transient reddening of the face that may be due to fever, certain drugs, exertion, stress, or a disease process. [NIH]

Foramen: A natural hole of perforation, especially one in a bone. [NIH]

Forearm: The part between the elbow and the wrist. [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]

Ganglia: Clusters of multipolar neurons surrounded by a capsule of loosely organized connective tissue located outside the central nervous system. [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]

Gas: Air that comes from normal breakdown of food. The gases are passed out of the body through the rectum (flatus) or the mouth (burp). [NIH]

Gas exchange: Primary function of the lungs; transfer of oxygen from inhaled air into the blood and of carbon dioxide from the blood into the lungs. [NIH]

Gastrin: A hormone released after eating. Gastrin causes the stomach to produce more acid. [NIH]

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 Expression: The phenotypic manifestation of a gene or genes by the processes of gene action. [NIH]

Gene Expression Profiling: The determination of the pattern of genes expressed i.e., transcribed, under specific circumstances or in a specific cell. [NIH]

Gene Products, rev: Trans-acting nuclear proteins whose functional expression are required for HIV viral replication. Specifically, the rev gene products are required for processing and translation of the HIV gag and env mRNAs, and thus rev regulates the expression of the viral structural proteins. rev can also regulate viral regulatory proteins. A cis-acting antirepression sequence (CAR) in env, also known as the rev-responsive element (RRE), is responsive to the rev gene product. rev is short for regulator of virion. [NIH]

Gene Rearrangement: The ordered rearrangement of gene regions by DNA recombination such as that which occurs normally during development. [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]

Genes, env: DNA sequences that form the coding region for the viral envelope (env) proteins in retroviruses. The env genes contain a cis-acting RNA target sequence for the rev

protein (= gene products, rev), termed the rev-responsive element (RRE). [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 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]

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]

Germline mutation: A gene change in the body's reproductive cells (egg or sperm) that becomes incorporated into the DNA of every cell in the body of offspring; germline mutations are passed on from parents to offspring. Also called hereditary mutation. [NIH]

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]

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]

Glucuronic Acid: Derivatives of uronic acid found throughout the plant and animal kingdoms. They detoxify drugs and toxins by conjugating with them to form glucuronides in the liver which are more water-soluble metabolites that can be easily eliminated from the body. [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]

Governing Board: The group in which legal authority is vested for the control of health-related institutions and organizations. [NIH]

Grafting: The operation of transfer of tissue from one site to another. [NIH]

Gram-negative: Losing the stain or decolorized by alcohol in Gram's method of staining, a primary characteristic of bacteria having a cell wall composed of a thin layer of peptidoglycan covered by an outer membrane of lipoprotein and lipopolysaccharide. [EU]

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]

Growth factors: Substances made by the body that function to regulate cell division and cell survival. Some growth factors are also produced in the laboratory and used in biological therapy. [NIH]

Guanine: One of the four DNA bases. [NIH]

Guanylate Cyclase: An enzyme that catalyzes the conversion of GTP to 3',5'-cyclic GMP and pyrophosphate. It also acts on ITP and dGTP. (From Enzyme Nomenclature, 1992) EC 4.6.1.2. [NIH]

Hair Color: Color of hair or fur. [NIH]

Half-Life: The time it takes for a substance (drug, radioactive nuclide, or other) to lose half of its pharmacologic, physiologic, or radiologic activity. [NIH]

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 Catheterization: Procedure which includes placement of catheter, recording of intracardiac and intravascular pressure, obtaining blood samples for chemical analysis, and cardiac output measurement, etc. Specific angiographic injection techniques are also involved. [NIH]

Heart failure: Loss of pumping ability by the heart, often accompanied by fatigue, breathlessness, and excess fluid accumulation in body tissues. [NIH]

Heart Transplantation: The transference of a heart from one human or animal to another. [NIH]

Heartbeat: One complete contraction of the heart. [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]

Hemodynamics: The movements of the blood and the forces involved in systemic or regional blood circulation. [NIH]

Hemoglobin: One of the fractions of glycosylated hemoglobin A1c. Glycosylated hemoglobin is formed when linkages of glucose and related monosaccharides bind to hemoglobin A and its concentration represents the average blood glucose level over the previous several weeks. HbA1c levels are used as a measure of long-term control of plasma glucose (normal, 4 to 6 percent). In controlled diabetes mellitus, the concentration of glycosylated hemoglobin A is within the normal range, but in uncontrolled cases the level may be 3 to 4 times the normal conentration. Generally, complications are substantially lower among patients with Hb levels of 7 percent or less than in patients with HbA1c levels of 9 percent or more. [NIH]

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]

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]

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]

Heparin: Heparinic acid. A highly acidic mucopolysaccharide formed of equal parts of

sulfated D-glucosamine and D-glucuronic acid with sulfaminic bridges. The molecular weight ranges from six to twenty thousand. Heparin occurs in and is obtained from liver, lung, mast cells, etc., of vertebrates. Its function is unknown, but it is used to prevent blood clotting in vivo and vitro, in the form of many different salts. [NIH]

Hepatocyte: A liver cell. [NIH]

Hereditary: Of, relating to, or denoting factors that can be transmitted genetically from one generation to another. [NIH]

Hereditary mutation: A gene change in the body's reproductive cells (egg or sperm) that becomes incorporated into the DNA of every cell in the body of offspring; hereditary mutations are passed on from parents to offspring. Also called germline mutation. [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]

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]

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]

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]

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]

Hydralazine: A direct-acting vasodilator that is used as an antihypertensive agent. [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]

Hydrolysis: The process of cleaving a chemical compound by the addition of a molecule of water. [NIH]

Hydroxylysine: A hydroxylated derivative of the amino acid lysine that is present in certain collagens. [NIH]

Hydroxyproline: A hydroxylated form of the imino acid proline. A deficiency in ascorbic acid can result in impaired hydroxyproline formation. [NIH]

Hyperhomocysteinemia: An inborn error of methionone metabolism which produces an excess of homocysteine in the blood. It is often caused by a deficiency of cystathionine beta-synthase and is a risk factor for coronary vascular disease. [NIH]

Hyperplasia: An increase in the number of cells in a tissue or organ, not due to tumor formation. It differs from hypertrophy, which is an increase in bulk without an increase in the number of cells. [NIH]

Hypersensitivity: Altered reactivity to an antigen, which can result in pathologic reactions upon subsequent exposure to that particular antigen. [NIH]

Hypertension: Persistently high arterial blood pressure. Currently accepted threshold levels are 140 mm Hg systolic and 90 mm Hg diastolic pressure. [NIH]

Hypertrophy: General increase in bulk of a part or organ, not due to tumor formation, nor to an increase in the number of cells. [NIH]

Hypotension: Abnormally low blood pressure. [NIH]

Hypoxemia: Deficient oxygenation of the blood; hypoxia. [EU]

Hypoxia: Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood. [EU]

Hypoxic: Having too little oxygen. [NIH]

Idiopathic: Describes a disease of unknown cause. [NIH]

Iloprost: An eicosanoid, derived from the cyclooxygenase pathway of arachidonic acid metabolism. It is a stable and synthetic analog of epoprostenol, but with a longer half-life than the parent compound. Its actions are similar to prostacyclin. Iloprost produces vasodilation and inhibits platelet aggregation. [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]

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]

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]

Impairment: In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [NIH]

Implantation: The insertion or grafting into the body of biological, living, inert, or radioactive material. [EU]

In situ: In the natural or normal place; confined to the site of origin without invasion of neighbouring tissues. [EU]

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]

Incontinentia Pigmenti: A genodermatosis occurring mostly in females and characterized by skin changes in three phases - vesiculobullous, verrucous papillomatous, and macular melanodermic. Hyperpigmentation is bizarre and irregular. Sixty percent of patients have abnormalities of eyes, teeth, central nervous system, and skin appendages. [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]

Infant, Newborn: An infant during the first month after birth. [NIH]

Infantile: Pertaining to an infant or to infancy. [EU]

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]

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]

Infusion: A method of putting fluids, including drugs, into the bloodstream. Also called intravenous infusion. [NIH]

Ingestion: Taking into the body by mouth [NIH]

Inhalation: The drawing of air or other substances into the lungs. [EU]

Initiation: Mutation induced by a chemical reactive substance causing cell changes; being a step in a carcinogenic process. [NIH]

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]

Interleukin-6: Factor that stimulates the growth and differentiation of human B-cells and is also a growth factor for hybridomas and plasmacytomas. It is produced by many different cells including T-cells, monocytes, and fibroblasts. [NIH]

Interstitial: Pertaining to or situated between parts or in the interspaces of a tissue. [EU]

Intestinal: Having to do with the intestines. [NIH]

Intestines: The section of the alimentary canal from the stomach to the anus. It includes the large intestine and small intestine. [NIH]

Intracellular: Inside a cell. [NIH]

Intrahepatic: Within the liver. [NIH]

Intravascular: Within a vessel or vessels. [EU]

Intravenous: IV. Into a vein. [NIH]

Intrinsic: Situated entirely within or pertaining exclusively to a part. [EU]

Intubation: Introduction of a tube into a hollow organ to restore or maintain patency if obstructed. It is differentiated from catheterization in that the insertion of a catheter is usually performed for the introducing or withdrawing of fluids from the body. [NIH]

Invasive: 1. Having the quality of invasiveness. 2. Involving puncture or incision of the skin or insertion of an instrument or foreign material into the body; said of diagnostic techniques. [EU]

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]

Iris: The most anterior portion of the uveal layer, separating the anterior chamber from the posterior. It consists of two layers - the stroma and the pigmented epithelium. Color of the iris depends on the amount of melanin in the stroma on reflection from the pigmented epithelium. [NIH]

Ischemia: Deficiency of blood in a part, due to functional constriction or actual obstruction of a blood vessel. [EU]

Karyotype: The characteristic chromosome complement of an individual, race, or species as defined by their number, size, shape, etc. [NIH]

Keto: It consists of 8 carbon atoms and within the endotoxins, it connects poysaccharide and lipid A. [NIH]

Kidney Failure: The inability of a kidney to excrete metabolites at normal plasma levels under conditions of normal loading, or the inability to retain electrolytes under conditions of normal intake. In the acute form (kidney failure, acute), it is marked by uremia and usually by oliguria or anuria, with hyperkalemia and pulmonary edema. The chronic form (kidney failure, chronic) is irreversible and requires hemodialysis. [NIH]

Kidney Failure, Acute: A clinical syndrome characterized by a sudden decrease in glomerular filtration rate, often to values of less than 1 to 2 ml per minute. It is usually associated with oliguria (urine volumes of less than 400 ml per day) and is always associated with biochemical consequences of the reduction in glomerular filtration rate such as a rise in blood urea nitrogen (BUN) and serum creatinine concentrations. [NIH]

Kidney Failure, Chronic: An irreversible and usually progressive reduction in renal function in which both kidneys have been damaged by a variety of diseases to the extent that they are unable to adequately remove the metabolic products from the blood and regulate the body's electrolyte composition and acid-base balance. Chronic kidney failure requires hemodialysis or surgery, usually kidney transplantation. [NIH]

Kinetic: Pertaining to or producing motion. [EU]

Labile: 1. Gliding; moving from point to point over the surface; unstable; fluctuating. 2. Chemically unstable. [EU]

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]

Leukemia: Cancer of blood-forming tissue. [NIH]

Leukotrienes: A family of biologically active compounds derived from arachidonic acid by oxidative metabolism through the 5-lipoxygenase pathway. They participate in host defense reactions and pathophysiological conditions such as immediate hypersensitivity and inflammation. They have potent actions on many essential organs and systems, including the cardiovascular, pulmonary, and central nervous system as well as the gastrointestinal tract and the immune system. [NIH]

Ligaments: Shiny, flexible bands of fibrous tissue connecting together articular extremities of bones. They are pliant, tough, and inextensile. [NIH]

Ligation: Application of a ligature to tie a vessel or strangulate a part. [NIH]

Linkage: The tendency of two or more genes in the same chromosome to remain together from one generation to the next more frequently than expected according to the law of independent assortment. [NIH]

Lipid: Fat. [NIH]

Liver: A large, glandular organ located in the upper abdomen. The liver cleanses the blood and aids in digestion by secreting bile. [NIH]

Liver scan: An image of the liver created on a computer screen or on film. A radioactive substance is injected into a blood vessel and travels through the bloodstream. It collects in the liver, especially in abnormal areas, and can be detected by the scanner. [NIH]

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]

Localized: Cancer which has not metastasized yet. [NIH]

Longitudinal study: Also referred to as a "cohort study" or "prospective study"; the analytic method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of this type of study is to observe large numbers of subjects over an extended time, with comparisons of incidence rates in groups that differ in exposure levels. [NIH]

Lung Transplantation: The transference of either one or both of the lungs from one human or animal to another. [NIH]

Lymph: The almost colorless fluid that travels through the lymphatic system and carries cells that help fight infection and disease. [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]

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]

Lymphokines: Soluble protein factors generated by activated lymphocytes that affect other cells, primarily those involved in cellular immunity. [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]

Lytic: 1. Pertaining to lysis or to a lysin. 2. Producing lysis. [EU]

Macrophage: A type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells. [NIH]

Macrophage Activation: The process of altering the morphology and functional activity of macrophages so that they become avidly phagocytic. It is initiated by lymphokines, such as the macrophage activation factor (MAF) and the macrophage migration-inhibitory factor (MMIF), immune complexes, C3b, and various peptides, polysaccharides, and immunologic adjuvants. [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]

Malformation: A morphologic defect resulting from an intrinsically abnormal developmental process. [EU]

Malignant: Cancerous; a growth with a tendency to invade and destroy nearby tissue and spread to other parts of the body. [NIH]

Malnutrition: A condition caused by not eating enough food or not eating a balanced diet. [NIH]

Mammography: Radiographic examination of the breast. [NIH]

Medial: Lying near the midsaggital plane of the body; opposed to lateral. [NIH]

Mediator: An object or substance by which something is mediated, such as (1) a structure of the nervous system that transmits impulses eliciting a specific response; (2) a chemical substance (transmitter substance) that induces activity in an excitable tissue, such as nerve or muscle; or (3) a substance released from cells as the result of the interaction of antigen with antibody or by the action of antigen with a sensitized lymphocyte. [EU]

Medical Records: Recording of pertinent information concerning patient's illness or illnesses. [NIH]

MEDLINE: An online database of MEDLARS, the computerized bibliographic Medical Literature Analysis and Retrieval System of the National Library of Medicine. [NIH]

Meiosis: A special method of cell division, occurring in maturation of the germ cells, by means of which each daughter nucleus receives half the number of chromosomes characteristic of the somatic cells of the species. [NIH]

Melanoma: A form of skin cancer that arises in melanocytes, the cells that produce pigment. Melanoma usually begins in a mole. [NIH]

Membrane: A very thin layer of tissue that covers a surface. [NIH]

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]

Mental: Pertaining to the mind; psychic. 2. (L. mentum chin) pertaining to the chin. [EU]

Mental Retardation: Refers to sub-average general intellectual functioning which originated during the developmental period and is associated with impairment in adaptive behavior. [NIH]

Metabolite: Any substance produced by metabolism or by a metabolic process. [EU]

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]

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]

Microtubules: Slender, cylindrical filaments found in the cytoskeleton of plant and animal cells. They are composed of the protein tubulin. [NIH]

Migration: The systematic movement of genes between populations of the same species, geographic race, or variety. [NIH]

Miscarriage: Spontaneous expulsion of the products of pregnancy before the middle of the second trimester. [NIH]

Mitochondria: Parts of a cell where aerobic production (also known as cell respiration) takes place. [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]

Mitotic: Cell resulting from mitosis. [NIH]

Mitral Valve: The valve between the left atrium and left ventricle of the heart. [NIH]

Modification: A change in an organism, or in a process in an organism, that is acquired from its own activity or environment. [NIH]

Modulator: A specific inductor that brings out characteristics peculiar to a definite region. [EU]

Molecular: Of, pertaining to, or composed of molecules : a very small mass of matter. [EU]

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]

Monocrotaline: A pyrrolizidine alkaloid and a toxic plant constituent that poisons livestock and humans through the ingestion of contaminated grains and other foods. The alkaloid causes pulmonary artery hypertension, right ventricular hypertrophy, and pathological changes in the pulmonary vasculature. Significant attenuation of the cardiopulmonary changes are noted after oral magnesium treatment. [NIH]

Monocyte: A type of white blood cell. [NIH]

Monocyte Chemoattractant Protein-1: A chemokine that is a chemoattractant for human monocytes and may also cause cellular activation of specific functions related to host defense. It is produced by leukocytes of both monocyte and lymphocyte lineage and by

fibroblasts during tissue injury. [NIH]

Monosomy: The condition in which one chromosome of a pair is missing. In a normally diploid cell it is represented symbolically as 2N-1. [NIH]

Morphological: Relating to the configuration or the structure of live organs. [NIH]

Morphology: The science of the form and structure of organisms (plants, animals, and other forms of life). [NIH]

Mosaicism: The occurrence in an individual of two or more cell populations of different chromosomal constitutions, derived from a single zygote, as opposed to chimerism in which the different cell populations are derived from more than one zygote. [NIH]

Motility: The ability to move spontaneously. [EU]

Mucocutaneous: Pertaining to or affecting the mucous membrane and the skin. [EU]

Mutagenesis: Process of generating genetic mutations. It may occur spontaneously or be induced by mutagens. [NIH]

Mutagens: Chemical agents that increase the rate of genetic mutation by interfering with the function of nucleic acids. A clastogen is a specific mutagen that causes breaks in chromosomes. [NIH]

Myelofibrosis: A disorder in which the bone marrow is replaced by fibrous tissue. [NIH]

Myocardial infarction: Gross necrosis of the myocardium as a result of interruption of the blood supply to the area; it is almost always caused by atherosclerosis of the coronary arteries, upon which coronary thrombosis is usually superimposed. [NIH]

Myocardium: The muscle tissue of the heart composed of striated, involuntary muscle known as cardiac muscle. [NIH]

Myotonic Dystrophy: A condition presenting muscle weakness and wasting which may be progressive. [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]

Neoplasm: A new growth of benign or malignant tissue. [NIH]

Nervous System: The entire nerve apparatus composed of the brain, spinal cord, nerves and ganglia. [NIH]

Neuronal: Pertaining to a neuron or neurons (= conducting cells of the nervous system). [EU]

Neurons: The basic cellular units of nervous tissue. Each neuron consists of a body, an axon, and dendrites. Their purpose is to receive, conduct, and transmit impulses in the nervous system. [NIH]

Neuropathy: A problem in any part of the nervous system except the brain and spinal cord. Neuropathies can be caused by infection, toxic substances, or disease. [NIH]

Neurophysiology: The scientific discipline concerned with the physiology of the nervous system. [NIH]

Neurotoxicity: The tendency of some treatments to cause damage to the nervous system. [NIH]

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]

Nifedipine: A potent vasodilator agent with calcium antagonistic action. It is a useful anti-anginal agent that also lowers blood pressure. The use of nifedipine as a tocolytic is being investigated. [NIH]

Nitric Oxide: A free radical gas produced endogenously by a variety of mammalian cells. It is synthesized from arginine by a complex reaction, catalyzed by nitric oxide synthase. Nitric oxide is endothelium-derived relaxing factor. It is released by the vascular endothelium and mediates the relaxation induced by some vasodilators such as acetylcholine and bradykinin. It also inhibits platelet aggregation, induces disaggregation of aggregated platelets, and inhibits platelet adhesion to the vascular endothelium. Nitric oxide activates cytosolic guanylate cyclase and thus elevates intracellular levels of cyclic GMP. [NIH]

Nitrogen: An element with the atomic symbol N, atomic number 7, and atomic weight 14. Nitrogen exists as a diatomic gas and makes up about 78% of the earth's atmosphere by volume. It is a constituent of proteins and nucleic acids and found in all living cells. [NIH]

Norfenfluramine: A fenfluramine analog that inhibits serotonin uptake and may provoke release of serotonin. It is used as an appetite depressant and an experimental tool in animal studies. [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]

Nuclear Envelope: The membrane system of the cell nucleus that surrounds the nucleoplasm. It consists of two concentric membranes separated by the perinuclear space. The structures of the envelope where it opens to the cytoplasm are called the nuclear pores (nuclear pore). [NIH]

Nuclear magnetic resonance imaging: NMRI. A procedure in which a magnet linked to a computer is used to create detailed pictures of areas inside the body. Also called magnetic resonance imaging (MRI). [NIH]

Nuclear Pore: An opening through the nuclear envelope formed by the nuclear pore complex which transports nuclear proteins or RNA into or out of the cell nucleus and which, under some conditions, acts as an ion channel. [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]

Nucleus: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Nurse Practitioners: Nurses who are specially trained to assume an expanded role in providing medical care under the supervision of a physician. [NIH]

Ocular: 1. Of, pertaining to, or affecting the eye. 2. Eyepiece. [EU]

Oliguria: Clinical manifestation of the urinary system consisting of a decrease in the amount of urine secreted. [NIH]

Oocytes: Female germ cells in stages between the prophase of the first maturation division and the completion of the second maturation division. [NIH]

Ophthalmic: Pertaining to the eye. [EU]

Opsin: A protein formed, together with retinene, by the chemical breakdown of meta-rhodopsin. [NIH]

Optic Nerve: The 2nd cranial nerve. The optic nerve conveys visual information from the retina to the brain. The nerve carries the axons of the retinal ganglion cells which sort at the optic chiasm and continue via the optic tracts to the brain. The largest projection is to the lateral geniculate nuclei; other important targets include the superior colliculi and the suprachiasmatic nuclei. Though known as the second cranial nerve, it is considered part of the central nervous system. [NIH]

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]

Osteopetrosis: Excessive formation of dense trabecular bone leading to pathological fractures, osteitis, splenomegaly with infarct, anemia, and extramedullary hemopoiesis. [NIH]

Ovaries: The pair of female reproductive glands in which the ova, or eggs, are formed. The ovaries are located in the pelvis, one on each side of the uterus. [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 Phosphorylation: Electron transfer through the cytochrome system liberating free energy which is transformed into high-energy phosphate bonds. [NIH]

Oxygen Consumption: The oxygen consumption is determined by calculating the difference between the amount of oxygen inhaled and exhaled. [NIH]

Oxygenase: Enzyme which breaks down heme, the iron-containing oxygen-carrying constituent of the red blood cells. [NIH]

Oxygenation: The process of supplying, treating, or mixing with oxygen. No:1245 - oxygenation the process of supplying, treating, or mixing with oxygen. [EU]

Oxygenator: An apparatus by which oxygen is introduced into the blood during circulation outside the body, as during open heart surgery. [NIH]

Paclitaxel: Antineoplastic agent isolated from the bark of the Pacific yew tree, Taxus brevifolia. Paclitaxel stabilizes microtubules in their polymerized form and thus mimics the action of the proto-oncogene proteins c-mos. [NIH]

Paediatric: Of or relating to the care and medical treatment of children; belonging to or concerned with paediatrics. [EU]

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]

Patch: A piece of material used to cover or protect a wound, an injured part, etc.: a patch

over the eye. [NIH]

Paternity: Establishing the father relationship of a man and a child. [NIH]

Pathologic: 1. Indicative of or caused by a morbid condition. 2. Pertaining to pathology (= branch of medicine that treats the essential nature of the disease, especially the structural and functional changes in tissues and organs of the body caused by the disease). [EU]

Pathologic Processes: The abnormal mechanisms and forms involved in the dysfunctions of tissues and organs. [NIH]

Pathophysiology: Altered functions in an individual or an organ due to disease. [NIH]

PDQ: Physician Data Query. PDQ is an online database developed and maintained by the National Cancer Institute. Designed to make the most current, credible, and accurate cancer information available to health professionals and the public, PDQ contains peer-reviewed summaries on cancer treatment, screening, prevention, genetics, and supportive care; a registry of cancer clinical trials from around the world; and directories of physicians, professionals who provide genetics services, and organizations that provide cancer care. Most of this information is available on the CancerNet Web site, and more specific information about PDQ can be found at http://cancernet.nci.nih.gov/pdq.html. [NIH]

Pelvis: The lower part of the abdomen, located between the hip bones. [NIH]

Peptide: Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [NIH]

Perceived risk: Estimate or evaluation of risk as observed through personal experience or personal study, and personal evaluation of consequences. [NIH]

Percutaneous: Performed through the skin, as injection of radiopacque material in radiological examination, or the removal of tissue for biopsy accomplished by a needle. [EU]

Perforation: 1. The act of boring or piercing through a part. 2. A hole made through a part or substance. [EU]

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]

Pericardial Effusion: Presence of fluid within the pericardium. [NIH]

Pericardium: The fibroserous sac surrounding the heart and the roots of the great vessels. [NIH]

Peroxidase: A hemeprotein from leukocytes. Deficiency of this enzyme leads to a hereditary disorder coupled with disseminated moniliasis. It catalyzes the conversion of a donor and peroxide to an oxidized donor and water. EC 1.11.1.7. [NIH]

Peroxide: Chemical compound which contains an atom group with two oxygen atoms tied to each other. [NIH]

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]

Phentermine: A central nervous system stimulant and sympathomimetic with actions and uses similar to those of dextroamphetamine. It has been used most frequently in the treatment of obesity. [NIH]

Phospholipases: A class of enzymes that catalyze the hydrolysis of phosphoglycerides or glycerophosphatidates. EC 3.1.-. [NIH]

Phosphorus: A non-metallic element that is found in the blood, muscles, nevers, bones, and teeth, and is a component of adenosine triphosphate (ATP; the primary energy source for the body's cells.) [NIH]

Phosphorylation: The introduction of a phosphoryl group into a compound through the formation of an ester bond between the compound and a phosphorus moiety. [NIH]

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]

Pigments: Any normal or abnormal coloring matter in plants, animals, or micro-organisms. [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]

Plasmin: A product of the lysis of plasminogen (profibrinolysin) by plasminogen activators. It is composed of two polypeptide chains, light (B) and heavy (A), with a molecular weight of 75,000. It is the major proteolytic enzyme involved in blood clot retraction or the lysis of fibrin and quickly inactivated by antiplasmins. EC 3.4.21.7. [NIH]

Plasminogen Activators: A heterogeneous group of proteolytic enzymes that convert plasminogen to plasmin. They are concentrated in the lysosomes of most cells and in the vascular endothelium, particularly in the vessels of the microcirculation. EC 3.4.21.-. [NIH]

Plasticity: In an individual or a population, the capacity for adaptation: a) through gene changes (genetic plasticity) or b) through internal physiological modifications in response to changes of environment (physiological plasticity). [NIH]

Plastids: Self-replicating cytoplasmic organelles of plant and algal cells that contain pigments and may synthesize and accumulate various substances. Plastids are used in phylogenetic studies. [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]

Platelet Aggregation: The attachment of platelets to one another. This clumping together can be induced by a number of agents (e.g., thrombin, collagen) and is part of the mechanism leading to the formation of a thrombus. [NIH]

Platelets: A type of blood cell that helps prevent bleeding by causing blood clots to form. Also called thrombocytes. [NIH]

Pneumonia: Inflammation of the lungs. [NIH]

Pneumonitis: A disease caused by inhaling a wide variety of substances such as dusts and molds. Also called "farmer's disease". [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]

Portal Hypertension: High blood pressure in the portal vein. This vein carries blood into the liver. Portal hypertension is caused by a blood clot. This is a common complication of cirrhosis. [NIH]

Portal Vein: A short thick vein formed by union of the superior mesenteric vein and the splenic vein. [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]

Preclinical: Before a disease becomes clinically recognizable. [EU]

Precursor: Something that precedes. In biological processes, a substance from which another, usually more active or mature substance is formed. In clinical medicine, a sign or symptom that heralds another. [EU]

Prenatal: Existing or occurring before birth, with reference to the fetus. [EU]

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]

Prognostic factor: A situation or condition, or a characteristic of a patient, that can be used to estimate the chance of recovery from a disease, or the chance of the disease recurring (coming back). [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]

Progressive disease: Cancer that is increasing in scope or severity. [NIH]

Proline: A non-essential amino acid that is synthesized from glutamic acid. It is an essential component of collagen and is important for proper functioning of joints and tendons. [NIH]

Promoter: A chemical substance that increases the activity of a carcinogenic process. [NIH]

Prone: Having the front portion of the body downwards. [NIH]

Prophase: The first phase of cell division, in which the chromosomes become visible, the nucleus starts to lose its identity, the spindle appears, and the centrioles migrate toward opposite poles. [NIH]

Prophylaxis: An attempt to prevent disease. [NIH]

Prospective study: An epidemiologic study in which a group of individuals (a cohort), all free of a particular disease and varying in their exposure to a possible risk factor, is followed over a specific amount of time to determine the incidence rates of the disease in the exposed and unexposed groups. [NIH]

Prostaglandin: Any of a group of components derived from unsaturated 20-carbon fatty acids, primarily arachidonic acid, via the cyclooxygenase pathway that are extremely potent mediators of a diverse group of physiologic processes. The abbreviation for prostaglandin is PG; specific compounds are designated by adding one of the letters A through I to indicate the type of substituents found on the hydrocarbon skeleton and a subscript (1, 2 or 3) to indicate the number of double bonds in the hydrocarbon skeleton e.g., PGE2. The predominant naturally occurring prostaglandins all have two double bonds and are synthesized from arachidonic acid (5,8,11,14-eicosatetraenoic acid) by the pathway shown in the illustration. The 1 series and 3 series are produced by the same pathway with fatty acids having one fewer double bond (8,11,14-eicosatrienoic acid or one more double bond (5,8,11,14,17-eicosapentaenoic acid) than arachidonic acid. The subscript a or ß indicates the configuration at C-9 (a denotes a substituent below the plane of the ring, ß, above the plane). The naturally occurring PGF's have the a configuration, e.g., PGF2a. All of the prostaglandins act by binding to specific cell-surface receptors causing an increase in the level of the intracellular second messenger cyclic AMP (and in some cases cyclic GMP also). The effect produced by the cyclic AMP increase depends on the specific cell type. In some cases there is also a positive feedback effect. Increased cyclic AMP increases prostaglandin synthesis leading to further increases in cyclic AMP. [EU]

Prostaglandin Endoperoxides: Precursors in the biosynthesis of prostaglandins and thromboxanes from arachidonic acid. They are physiologically active compounds, having effect on vascular and airway smooth muscles, platelet aggregation, etc. [NIH]

Prostaglandins A: (13E,15S)-15-Hydroxy-9-oxoprosta-10,13-dien-1-oic acid (PGA(1)); (5Z,13E,15S)-15-hydroxy-9-oxoprosta-5,10,13-trien-1-oic acid (PGA(2)); (5Z,13E,15S,17Z)-15-hydroxy-9-oxoprosta-5,10,13,17-tetraen-1-oic acid (PGA(3)). A group of naturally occurring secondary prostaglandins derived from PGE. PGA(1) and PGA(2) as well as their 19-hydroxy derivatives are found in many organs and tissues. [NIH]

Prostate: A gland in males that surrounds the neck of the bladder and the urethra. It secretes a substance that liquifies coagulated semen. It is situated in the pelvic cavity behind the lower part of the pubic symphysis, above the deep layer of the triangular ligament, and rests upon the rectum. [NIH]

Protein Binding: The process in which substances, either endogenous or exogenous, bind to proteins, peptides, enzymes, protein precursors, or allied compounds. Specific protein-binding measures are often used as assays in diagnostic assessments. [NIH]

Protein C: A vitamin-K dependent zymogen present in the blood, which, upon activation by thrombin and thrombomodulin exerts anticoagulant properties by inactivating factors Va and VIIIa at the rate-limiting steps of thrombin formation. [NIH]

Protein S: The vitamin K-dependent cofactor of activated protein C. Together with protein C, it inhibits the action of factors VIIIa and Va. A deficiency in protein S can lead to recurrent venous and arterial thrombosis. [NIH]

Proteins: Polymers of amino acids linked by peptide bonds. The specific sequence of amino

acids determines the shape and function of the protein. [NIH]

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]

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]

Proto-Oncogene Proteins: Products of proto-oncogenes. Normally they do not have oncogenic or transforming properties, but are involved in the regulation or differentiation of cell growth. They often have protein kinase activity. [NIH]

Proto-Oncogene Proteins c-mos: Cellular proteins encoded by the c-mos genes. They function in the cell cycle to maintain maturation promoting factor in the active state and have protein-serine/threonine kinase activity. Oncogenic transformation can take place when c-mos proteins are expressed at the wrong time. [NIH]

Proximal: Nearest; closer to any point of reference; opposed to distal. [EU]

Psychiatry: The medical science that deals with the origin, diagnosis, prevention, and treatment of mental disorders. [NIH]

Psychic: Pertaining to the psyche or to the mind; mental. [EU]

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]

Pulmonary: Relating to the lungs. [NIH]

Pulmonary Artery: The short wide vessel arising from the conus arteriosus of the right ventricle and conveying unaerated blood to the lungs. [NIH]

Pulmonary Circulation: The circulation of blood through the lungs. [NIH]

Pulmonary Edema: An accumulation of an excessive amount of watery fluid in the lungs, may be caused by acute exposure to dangerous concentrations of irritant gasses. [NIH]

Pulmonary Embolism: Embolism in the pulmonary artery or one of its branches. [NIH]

Pulmonary Fibrosis: Chronic inflammation and progressive fibrosis of the pulmonary alveolar walls, with steadily progressive dyspnea, resulting finally in death from oxygen lack or right heart failure. [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]

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]

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]

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]

Radiological: Pertaining to radiodiagnostic and radiotherapeutic procedures, and interventional radiology or other planning and guiding medical radiology. [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]

Reagent: A substance employed to produce a chemical reaction so as to detect, measure, produce, etc., other substances. [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]

Receptors, Serotonin: Cell-surface proteins that bind serotonin and trigger intracellular changes which influence the behavior of cells. Several types of serotonin receptors have been recognized which differ in their pharmacology, molecular biology, and mode of action. [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]

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]

Regurgitation: A backward flowing, as the casting up of undigested food, or the backward flowing of blood into the heart, or between the chambers of the heart when a valve is incompetent. [EU]

Reproductive cells: Egg and sperm cells. Each mature reproductive cell carries a single set of 23 chromosomes. [NIH]

Research Support: Financial support of research activities. [NIH]

Respiration: The act of breathing with the lungs, consisting of inspiration, or the taking into the lungs of the ambient air, and of expiration, or the expelling of the modified air which contains more carbon dioxide than the air taken in (Blakiston's Gould Medical Dictionary, 4th ed.). This does not include tissue respiration (= oxygen consumption) or cell respiration (= cell respiration). [NIH]

Respiratory distress syndrome: A lung disease that occurs primarily in premature infants; the newborn must struggle for each breath and blueing of its skin reflects the baby's inability to get enough oxygen. [NIH]

Respiratory failure: Inability of the lungs to conduct gas exchange. [NIH]

Respiratory Physiology: Functions and activities of the respiratory tract as a whole or of any of its parts. [NIH]

Retina: The ten-layered nervous tissue membrane of the eye. It is continuous with the optic nerve and receives images of external objects and transmits visual impulses to the brain. Its outer surface is in contact with the choroid and the inner surface with the vitreous body. The outer-most layer is pigmented, whereas the inner nine layers are transparent. [NIH]

Retinal: 1. Pertaining to the retina. 2. The aldehyde of retinol, derived by the oxidative enzymatic splitting of absorbed dietary carotene, and having vitamin A activity. In the retina, retinal combines with opsins to form visual pigments. One isomer, 11-cis retinal combines with opsin in the rods (scotopsin) to form rhodopsin, or visual purple. Another, all-trans retinal (trans-r.); visual yellow; xanthopsin) results from the bleaching of rhodopsin by light, in which the 11-cis form is converted to the all-trans form. Retinal also combines with opsins in the cones (photopsins) to form the three pigments responsible for colour vision. Called also retinal, and retinene1. [EU]

Retinal Vein: Central retinal vein and its tributaries. It runs a short course within the optic nerve and then leaves and empties into the superior ophthalmic vein or cavernous sinus. [NIH]

Retinal Vein Occlusion: Occlusion of the retinal vein. Those at high risk for this condition include patients with hypertension, diabetes mellitus, arteriosclerosis, and other cardiovascular diseases. [NIH]

Retinoblastoma: An eye cancer that most often occurs in children younger than 5 years. It occurs in hereditary and nonhereditary (sporadic) forms. [NIH]

Retinol: Vitamin A. It is essential for proper vision and healthy skin and mucous membranes. Retinol is being studied for cancer prevention; it belongs to the family of drugs called retinoids. [NIH]

Retinopathy: 1. Retinitis (= inflammation of the retina). 2. Retinosis (= degenerative, noninflammatory condition of the retina). [EU]

Retroviral vector: RNA from a virus that is used to insert genetic material into cells. [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]

Rhodopsin: A photoreceptor protein found in retinal rods. It is a complex formed by the binding of retinal, the oxidized form of retinol, to the protein opsin and undergoes a series of complex reactions in response to visible light resulting in the transmission of nerve impulses to the brain. [NIH]

Ribonucleic acid: RNA. One of the two nucleic acids found in all cells. The other is

deoxyribonucleic acid (DNA). Ribonucleic acid transfers genetic information from DNA to proteins produced by the cell. [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]

Sarcoma: A connective tissue neoplasm formed by proliferation of mesodermal cells; it is usually highly malignant. [NIH]

Scans: Pictures of structures inside the body. Scans often used in diagnosing, staging, and monitoring disease include liver scans, bone scans, and computed tomography (CT) or computerized axial tomography (CAT) scans and magnetic resonance imaging (MRI) scans. In liver scanning and bone scanning, radioactive substances that are injected into the bloodstream collect in these organs. A scanner that detects the radiation is used to create pictures. In CT scanning, an x-ray machine linked to a computer is used to produce detailed pictures of organs inside the body. MRI scans use a large magnet connected to a computer to create pictures of areas inside the body. [NIH]

Scatter: The extent to which relative success and failure are divergently manifested in qualitatively different tests. [NIH]

Schizophrenia: A mental disorder characterized by a special type of disintegration of the personality. [NIH]

Scleroderma: A chronic disorder marked by hardening and thickening of the skin. Scleroderma can be localized or it can affect the entire body (systemic). [NIH]

Sclerosis: A pathological process consisting of hardening or fibrosis of an anatomical structure, often a vessel or a nerve. [NIH]

Screening: Checking for disease when there are no symptoms. [NIH]

Segregation: The separation in meiotic cell division of homologous chromosome pairs and their contained allelomorphic gene pairs. [NIH]

Sensibility: The ability to receive, feel and appreciate sensations and impressions; the quality of being sensitive; the extend to which a method gives results that are free from false negatives. [NIH]

Sepsis: The presence of bacteria in the bloodstream. [NIH]

Septal: An abscess occurring at the root of the tooth on the proximal surface. [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]

Serotonin: A biochemical messenger and regulator, synthesized from the essential amino acid L-tryptophan. In humans it is found primarily in the central nervous system, gastrointestinal tract, and blood platelets. Serotonin mediates several important physiological functions including neurotransmission, gastrointestinal motility, hemostasis, and cardiovascular integrity. Multiple receptor families (receptors, serotonin) explain the broad physiological actions and distribution of this biochemical mediator. [NIH]

Serous: Having to do with serum, the clear liquid part of blood. [NIH]

Serum: The clear liquid part of the blood that remains after blood cells and clotting proteins have been removed. [NIH]

Shock: The general bodily disturbance following a severe injury; an emotional or moral upset occasioned by some disturbing or unexpected experience; disruption of the circulation, which can upset all body functions: sometimes referred to as circulatory shock. [NIH]

Shunt: A surgically created diversion of fluid (e.g., blood or cerebrospinal fluid) from one area of the body to another area of the body. [NIH]

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]

Social Work: The use of community resources, individual case work, or group work to promote the adaptive capacities of individuals in relation to their social and economic environments. It includes social service agencies. [NIH]

Sodium: An element that is a member of the alkali group of metals. It has the atomic symbol Na, atomic number 11, and atomic weight 23. With a valence of 1, it has a strong affinity for oxygen and other nonmetallic elements. Sodium provides the chief cation of the extracellular body fluids. Its salts are the most widely used in medicine. (From Dorland, 27th ed) Physiologically the sodium ion plays a major role in blood pressure regulation, maintenance of fluid volume, and electrolyte balance. [NIH]

Soft tissue: Refers to muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body. [NIH]

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 cells: All the body cells except the reproductive (germ) cells. [NIH]

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]

Spatial disorientation: Loss of orientation in space where person does not know which way is up. [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]

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]

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]

Splenomegaly: Enlargement of the spleen. [NIH]

Sporadic: Neither endemic nor epidemic; occurring occasionally in a random or isolated manner. [EU]

Staging: Performing exams and tests to learn the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. [NIH]

Stasis: A word termination indicating the maintenance of (or maintaining) a constant level; preventing increase or multiplication. [EU]

Staurosporine: A drug that belongs to the family of drugs called alkaloids. It is being studied in the treatment of cancer. [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]

Stellate: Star shaped. [NIH]

Stellate Ganglion: A paravertebral sympathetic ganglion formed by the fusion of the inferior cervical and first thoracic ganglia. [NIH]

Stillbirth: The birth of a dead fetus or baby. [NIH]

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]

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]

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]

Sudden death: Cardiac arrest caused by an irregular heartbeat. The term "death" is somewhat misleading, because some patients survive. [NIH]

Supportive care: Treatment given to prevent, control, or relieve complications and side effects and to improve the comfort and quality of life of people who have cancer. [NIH]

Suppression: A conscious exclusion of disapproved desire contrary with repression, in which the process of exclusion is not conscious. [NIH]

Sympathomimetic: 1. Mimicking the effects of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. 2. An agent that produces effects similar to those of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. Called also adrenergic. [EU]

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]

Systolic pressure: The highest pressure to which blood pressure rises with the contraction of

the ventricles. [NIH]

Tachycardia: Excessive rapidity in the action of the heart, usually with a heart rate above 100 beats per minute. [NIH]

Telangiectasia: The permanent enlargement of blood vessels, causing redness in the skin or mucous membranes. [NIH]

Temporal: One of the two irregular bones forming part of the lateral surfaces and base of the skull, and containing the organs of hearing. [NIH]

Teratogenic: Tending to produce anomalies of formation, or teratism (= anomaly of formation or development : condition of a monster). [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]

Tetracycline: An antibiotic originally produced by Streptomyces viridifaciens, but used mostly in synthetic form. It is an inhibitor of aminoacyl-tRNA binding during protein synthesis. [NIH]

Thoracic: Having to do with the chest. [NIH]

Threonine: An essential amino acid occurring naturally in the L-form, which is the active form. It is found in eggs, milk, gelatin, and other proteins. [NIH]

Threshold: For a specified sensory modality (e. g. light, sound, vibration), the lowest level (absolute threshold) or smallest difference (difference threshold, difference limen) or intensity of the stimulus discernible in prescribed conditions of stimulation. [NIH]

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]

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]

Thrombosis: The formation or presence of a blood clot inside a blood vessel. [NIH]

Thromboxanes: Physiologically active compounds found in many organs of the body. They are formed in vivo from the prostaglandin endoperoxides and cause platelet aggregation, contraction of arteries, and other biological effects. Thromboxanes are important mediators of the actions of polyunsaturated fatty acids transformed by cyclooxygenase. [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]

Thyroid Hormones: Hormones secreted by the thyroid gland. [NIH]

Tissue: A group or layer of cells that are alike in type and work together to perform a specific function. [NIH]

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]

Tone: 1. The normal degree of vigour and tension; in muscle, the resistance to passive elongation or stretch; tonus. 2. A particular quality of sound or of voice. 3. To make permanent, or to change, the colour of silver stain by chemical treatment, usually with a heavy metal. [EU]

Tonicity: The normal state of muscular tension. [NIH]

Tonus: A state of slight tension usually present in muscles even when they are not undergoing active contraction. [NIH]

Topical: On the surface of the body. [NIH]

Toxic: Having to do with poison or something harmful to the body. Toxic substances usually cause unwanted side effects. [NIH]

Toxicity: The quality of being poisonous, especially the degree of virulence of a toxic microbe or of a poison. [EU]

Toxicology: The science concerned with the detection, chemical composition, and pharmacologic action of toxic substances or poisons and the treatment and prevention of toxic manifestations. [NIH]

Toxins: Specific, characterizable, poisonous chemicals, often proteins, with specific biological properties, including immunogenicity, produced by microbes, higher plants, or animals. [NIH]

Trachea: The cartilaginous and membranous tube descending from the larynx and branching into the right and left main bronchi. [NIH]

Traction: The act of pulling. [NIH]

Transcription Factors: Endogenous substances, usually proteins, which are effective in the initiation, stimulation, or termination of the genetic transcription process. [NIH]

Transduction: The transfer of genes from one cell to another by means of a viral (in the case of bacteria, a bacteriophage) vector or a vector which is similar to a virus particle (pseudovirion). [NIH]

Transfection: The uptake of naked or purified DNA into cells, usually eukaryotic. It is analogous to bacterial transformation. [NIH]

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]

Trinucleotide Repeat Expansion: DNA region comprised of a variable number of repetitive, contiguous trinucleotide sequences. The presence of these regions is associated with diseases such as Fragile X Syndrome and myotonic dystrophy. Many chromosome fragile sites (chromosome fragility) contain expanded trinucleotide repeats. [NIH]

Trinucleotide Repeats: Microsatellite repeats consisting of three nucleotides dispersed in the euchromatic arms of chromosomes. [NIH]

Trisomy: The possession of a third chromosome of any one type in an otherwise diploid cell.

[NIH]

Tryptophan: An essential amino acid that is necessary for normal growth in infants and for nitrogen balance in adults. It is a precursor serotonin and niacin. [NIH]

Tumor marker: A substance sometimes found in an increased amount in the blood, other body fluids, or tissues and which may mean that a certain type of cancer is in the body. Examples of tumor markers include CA 125 (ovarian cancer), CA 15-3 (breast cancer), CEA (ovarian, lung, breast, pancreas, and gastrointestinal tract cancers), and PSA (prostate cancer). Also called biomarker. [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]

Ultraviolet radiation: Invisible rays that are part of the energy that comes from the sun. UV radiation can damage the skin and cause melanoma and other types of skin cancer. UV radiation that reaches the earth's surface is made up of two types of rays, called UVA and UVB rays. UVB rays are more likely than UVA rays to cause sunburn, but UVA rays pass deeper into the skin. Scientists have long thought that UVB radiation can cause melanoma and other types of skin cancer. They now think that UVA radiation also may add to skin damage that can lead to skin cancer and cause premature aging. For this reason, skin specialists recommend that people use sunscreens that reflect, absorb, or scatter both kinds of UV radiation. [NIH]

Urea: A compound (CO(NH2)2), formed in the liver from ammonia produced by the deamination of amino acids. It is the principal end product of protein catabolism and constitutes about one half of the total urinary solids. [NIH]

Uremia: The illness associated with the buildup of urea in the blood because the kidneys are not working effectively. Symptoms include nausea, vomiting, loss of appetite, weakness, and mental confusion. [NIH]

Urethra: The tube through which urine leaves the body. It empties urine from the bladder. [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]

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]

Vacuoles: Any spaces or cavities within a cell. They may function in digestion, storage, secretion, or excretion. [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]

Vasoactive: Exerting an effect upon the calibre of blood vessels. [EU]

Vasoconstriction: Narrowing of the blood vessels without anatomic change, for which constriction, pathologic is used. [NIH]

Vasodilation: Physiological dilation of the blood vessels without anatomic change. For dilation with anatomic change, dilatation, pathologic or aneurysm (or specific aneurysm) is

used. [NIH]

Vasodilator: An agent that widens blood vessels. [NIH]

Vasodilator Agents: Drugs used to cause dilation of the blood vessels. [NIH]

Vector: Plasmid or other self-replicating DNA molecule that transfers DNA between cells in nature or in recombinant DNA technology. [NIH]

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

Venous: Of or pertaining to the veins. [EU]

Venous Thrombosis: The formation or presence of a thrombus within a vein. [NIH]

Ventilation: 1. In respiratory physiology, the process of exchange of air between the lungs and the ambient air. Pulmonary ventilation (usually measured in litres per minute) refers to the total exchange, whereas alveolar ventilation refers to the effective ventilation of the alveoli, in which gas exchange with the blood takes place. 2. In psychiatry, verbalization of one's emotional problems. [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 Pressure: The pressure within a cardiac ventricle. Ventricular pressure waveforms can be measured in the beating heart by catheterization or estimated using imaging techniques (e.g., Doppler echocardiography). The information is useful in evaluating the function of the myocardium, cardiac valves, and pericardium, particularly with simultaneous measurement of other (e.g., aortic or atrial) pressures. [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]

Veterinary Medicine: The medical science concerned with the prevention, diagnosis, and treatment of diseases in animals. [NIH]

Viral: Pertaining to, caused by, or of the nature of virus. [EU]

Viral Proteins: Proteins found in any species of virus. [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]

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]

Voltage-gated: It is opened by the altered charge distribution across the cell membrane. [NIH]

Warfarin: An anticoagulant that acts by inhibiting the synthesis of vitamin K-dependent coagulation factors. Warfarin is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, pulmonary embolism, and atrial fibrillation with embolization. It is also used as an adjunct in the prophylaxis of systemic embolism after myocardial infarction. Warfarin is also used as a rodenticide. [NIH]

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]

Womb: A hollow, thick-walled, muscular organ in which the impregnated ovum is developed into a child. [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]

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]

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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