PRION DISEASE

A 3-in-1 Medical Reference

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

TO INTERNET REFERENCES

ICON Group International, Inc.

Prion Disease

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

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

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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with prion disease 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 prion disease, 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 prion disease, 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 prion disease. 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 prion disease. 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 prion disease, 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 prion disease.

The Editors

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

CHAPTER 1. STUDIES ON PRION DISEASE

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on prion disease. For those interested in basic information about prion disease, 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 prion disease 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 prion disease is provided.[2]

The Genetics Home Reference has recently published the following summary for prion disease:

What Is Prion Disease?[3]

Prion disease is a group of progressive conditions that affect the brain and nervous system of humans and animals. In people, these disorders impair brain function, causing memory changes, personality changes, and problems with movement that worsen over time. The signs and symptoms of prion disease typically begin in adulthood, and the course of these disorders ranges from a few months to several years.

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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=priondisease**.

Familial prion diseases of humans include classic Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, and fatal insomnia. These conditions form a spectrum of diseases with overlapping signs and symptoms.

How Common Is Prion Disease?

These disorders are very rare. They affect about one person per million worldwide each year. Approximately 300 cases occur annually in the United States.

What Genes Are Related to Prion Disease?

Mutations in the **PRNP** (**http://ghr.nlm.nih.gov/gene=prnp**) gene cause prion disease.

Familial forms of prion disease are caused by inherited mutations in the PRNP gene; however, only a small percentage of cases run in families. Most cases are sporadic, which means they occur in people without any known risk factors or gene mutations. Rarely, prion diseases can be transmitted by exposure to prion-contaminated tissues or other biological materials from affected individuals. This type of prion disease is described as iatrogenic.

One type of prion disease in humans, variant Creutzfeldt-Jakob disease (vCJD), is acquired by eating beef products obtained from affected cattle. (In cows, this form of prion disease is known as bovine spongiform encephalopathy, BSE, or, more commonly, "mad cow" disease). Another example of an acquired prion disease is kuru, which was identified in the South Fore tribe in Papua New Guinea. The disorder was transmitted when tribe members ate the tissue of affected people during cannibalistic funeral rituals.

The PRNP gene provides instructions for making a protein called a prion protein (PrP). Normally, this protein seems to be involved in transporting copper into cells. It may also play a role in protecting brain cells and helping them communicate. In familial cases of prion disease, mutations in the PRNP gene cause cells to produce an abnormal form of the prion protein known as PrP^{Sc}. In iatrogenic and acquired cases, an affected person develops prion disease from exposure to this abnormal protein.

In a process that is not fully understood, PrP^{Sc} has the ability to convert the normal prion protein, PrP^C, into PrP^{Sc}. This abnormal protein builds up in the brain, forming clumps that damage or destroy nerve cells. The loss of these cells creates microscopic sponge-like holes in the brain, which leads to the signs and symptoms of prion disease.

How Do People Inherit Prion Disease?

Familial forms of prion disease are inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person inherits the altered gene from one affected parent. In some people, familial forms of prion disease are caused by a new mutation in the PRNP gene. Although such people most likely do not have an affected parent, they can pass the genetic change to their children.

The sporadic, iatrogenic, and acquired forms of prion disease, including kuru and variant Creutzfeldt-Jakob disease, are not inherited.

Where Can I Find Additional Information about Prion Disease?

You may find the following resources about prion disease helpful. These materials are written for the general public.

NIH Publications - National Institutes of Health

- National Institute of Allergy and Infectious Diseases: NIAID Research on Prion Diseases:
  http://www.niaid.nih.gov/factsheets/priondis.htm
- National Institute of Neurological Disorders and Stroke: Creutzfeldt-Jakob Disease Fact Sheet:
  http://www.ninds.nih.gov/disorders/cjd/detail_cjd.htm
- National Institute of Neurological Disorders and Stroke: Kuru Information Page:
  http://www.ninds.nih.gov/disorders/kuru/kuru.htm
- National Institute of Neurological Disorders and Stroke: Transmissible Spongiform Encephalopathies Information Page:
  http://www.ninds.nih.gov/disorders/tse/tse.htm
- Test Could Improve Detection of Prion Disease in Humans (NIH News Release, February 14, 2005):
  http://www.nih.gov/news/pr/feb2005/nia-14.htm

MedlinePlus - Health Information

- Encyclopedia: Creutzfeldt-Jakob disease:
  http://www.nlm.nih.gov/medlineplus/ency/article/000788.htm
- Encyclopedia: Kuru:
  http://www.nlm.nih.gov/medlineplus/ency/article/001379.htm
- Health Topic: Creutzfeldt-Jakob Disease:
  http://www.nlm.nih.gov/medlineplus/creutzfeldtjakobdisease.html
- Health Topic: Degenerative Nerve Diseases:
  http://www.nlm.nih.gov/medlineplus/degenerativenervediseases.html
- Health Topic: Genetic Brain Disorders:
  http://www.nlm.nih.gov/medlineplus/geneticbraindisorders.html

Educational Resources - Information Pages

- Alzheimer's Association: Chronic Wasting Disease:
  http://www.alz.org/documents/national/fschronicwastingdisease.pdf
- Centers for Disease Control and Prevention: About Prion Diseases:
  http://www.cdc.gov/ncidod/dvrd/prions/

- Genome Affects Human Forms of "Mad Cow" Disease (Genome News Network, January 23, 2004):
  http://www.genomenewsnetwork.org/articles/2004/01/23/mad_cow.php
- Merck Manual of Medical Information, Second Home Edition:
  http://www.merck.com/mmhe/sec06/ch090/ch090a.html
- New York Online Access to Health: Creutzfeldt-Jakob Disease:
  http://www.noah-health.org/en/bns/disorders/creutz/index.html
- Orphanet: Creutzfeldt-Jakob disease:
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=204
- Orphanet: Gerstmann-Straussler-Scheinker syndrome:
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=356
- Orphanet: Insomnia, Familial Fatal:
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=466
- Orphanet: Transmissible Spongiform Encephalopathies:
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=56970
- World Health Organization: Variant Creutzfeldt-Jakob Disease:
  http://www.who.int/mediacentre/factsheets/fs180/en/

Patient Support - for Patients and Families

- CJD Insight:
  http://www.cjdinsight.org/
- National Organization for Rare Disorders:
  http://www.rarediseases.org/search/rdbdetail_abstract.html?disname=Creutzfeldt+Jakob+Disease
- National Prion Disease Pathology Surveillance Center:
  http://www.cjdsurveillance.com/
- The UK Creutzfeldt-Jakob Disease Surveillance Unit:
  http://www.cjd.ed.ac.uk/

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=prion
- Gene Tests - DNA tests ordered by healthcare professionals:
  http://www.genetests.org/query?testid=92189
- ClinicalTrials.gov - Linking patients to medical research:
  http://clinicaltrials.gov/search/condition=%22prion+disease%22+OR+%22Prion+Diseases%22?recruiting=false

- PubMed - Recent literature:
  http://ghr.nlm.nih.gov/condition=priondisease/show/PubMed;jsessionid=437B72F322A102996E76DF06404D2B96
- OMIM - Genetic disorder catalog:
  http://ghr.nlm.nih.gov/condition=priondisease/show/OMIM;jsessionid=437B72F322A102996E76DF06404D2B96

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- Collins S, McLean CA, Masters CL. Gerstmann-Straussler-Scheinker syndrome,fatal familial insomnia, and kuru: a review of these less common human transmissible spongiform encephalopathies. J Clin Neurosci. 2001 Sep;8(5):387-97. Review. PubMed citation
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- Glatzel M, Stoeck K, Seeger H, Luhrs T, Aguzzi A. Human prion diseases: molecular and clinical aspects. Arch Neurol. 2005 Apr;62(4):545-52. Review. PubMed citation
- Johnson RT. Prion diseases. Lancet Neurol. 2005 Oct;4(10):635-42. Review. PubMed citation
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- Scriver, Charles R; The metabolic & molecular bases of inherited disease; 8th ed.; New York : McGraw-Hill, c2001. p5703-5728. NLM Catalog
- Weissmann C. The state of the prion. Nat Rev Microbiol. 2004 Nov;2(11):861-71. Review. PubMed citation

A summary of the gene related to prion disease is provided below:

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

The official name of this gene is "prion protein (p27-30) (Creutzfeldt-Jakob disease, Gerstmann-Strausler-Scheinker syndrome, fatal familial insomnia)."

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

What Is the Normal Function of the PRNP Gene?

The PRNP gene provides instructions for making a protein called the prion protein (PrP), which is active in the brain and several other tissues. Although the precise function of PrP is unknown, it is probably involved in the transport of charged atoms (ions) of copper into cells from their surrounding environment. Researchers have also proposed roles for PrP in cell signaling and in the formation of gaps (synapses) between nerve cells, where cell-to-cell communication occurs.

Different forms of PrP have been identified in the nervous system. The usual cellular form is called PrP^{C}.

What Conditions Are Related to the PRNP Gene?

Prion Disease - Caused by Mutations in the PRNP Gene

More than 50 mutations in the PRNP gene have been identified in people with familial prion diseases, including classic Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, and fatal insomnia. Some PRNP mutations change single protein building blocks (amino acids) in PrP. Other mutations insert additional amino acids into the protein or lead to the production of an atypically short version of the protein. These changes alter the structure of PrP, resulting in an abnormal protein known as PrPSc. In a process that is not fully understood, PrPSc can promote the transformation of the normal prion protein, PrPC, into PrPSc. The abnormal protein builds up in the brain, forming clumps that damage or destroy nerve cells. The loss of these cells creates microscopic sponge-like holes in the brain, which leads to the mental and behavioral features of prion diseases.

Wilson Disease - Course of Condition Modified by Normal Variations in the PRNP Gene

More than 50 mutations in the PRNP gene have been identified in people with familial prion diseases, including classic Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, and fatal insomnia. Some PRNP mutations change single protein building blocks (amino acids) in PrP. Other mutations insert additional amino acids into the protein or lead

[4] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/gene=prnp;jsessionid=437B72F322A102996E76DF06404D2B96**.

to the production of an atypically short version of the protein. These changes alter the structure of PrP, resulting in an abnormal protein known as PrPSc. In a process that is not fully understood, PrPSc can promote the transformation of the normal prion protein, PrPC, into PrPSc. The abnormal protein builds up in the brain, forming clumps that damage or destroy nerve cells. The loss of these cells creates microscopic sponge-like holes in the brain, which leads to the mental and behavioral features of prion diseases.

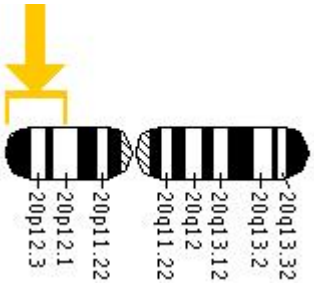
Other Disorders - Associated with the PRNP Gene

The Met129Val polymorphism appears to delay the onset of Wilson disease, an inherited disorder in which excessive amounts of copper accumulate in the body. Wilson disease is caused by mutations in the ATP7B gene, but research studies suggest that symptoms of Wilson disease begin several years later in people who have methionine (instead of valine) at position 129 in the PrP protein. Other research findings indicate that the Met129Val polymorphism may also affect the type of symptoms that develop in people with Wilson disease. Methionine, instead of valine, at PrP position 129 appears to be associated with an increased occurrence of symptoms that affect the nervous system, particularly tremors. Larger studies are needed, however, before the effects of the Met129Val polymorphism on Wilson disease can be established.

Where Is the PRNP Gene Located?

Cytogenetic Location: 20pter-p12

Molecular Location on chromosome 20: base pairs 4,615,068 to 4,630,233



The PRNP gene is located on the short (p) arm of chromosome 20 between the end (terminus) of the arm and position 12.

More precisely, the PRNP gene is located from base pair 4,615,068 to base pair 4,630,233 on chromosome 20.

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- Weissmann C. The state of the prion. Nat Rev Microbiol. 2004 Nov;2(11):861-71. Review. PubMed citation

Federally Funded Research on Prion Disease

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

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

- **Project Title: A CATALYTIC CONFORMATIONAL PRION SENSOR**

  Principal Investigator & Institution: Orser, Cindy S.; Adlyfe, Inc. 9430 Key West Ave, Ste 210 Rockville, Md 20850

  Timing: Fiscal Year 2005; Project Start 15-APR-2002; Project End 31-JAN-2007

  Summary: (provided by applicant): The major objective of the proposed project is to develop methodology that will allow fast and efficient detection of infectious prion proteins prior to the onset of clinical symptoms. This includes the detection of infectious prions in mortal products, early ante-mortem diagnostic of the prion diseases, and developing experimental approaches allowing delineation of the molecular mechanism of prion and prion-related diseases (folding disorders) in thermodynamic and kinetic terms. Preliminary studies successfully demonstrated that the specific detection of the pathologic prion protein could be approached by simple experimental means. The **prion disease** process involves a conformational change in the prion protein that in turn can serve as the basis for an early detection, diagnostic, prognostic and screening assay. The assay detects infectivity in a crude sample by identifying existing sub-picomolar levels of infectious prion protein through the use of specific, fluorescent target peptides. The labeled peptides undergo conformational change resulting in an amplified signal in a single step without protease pre-treatment, denaturants or washing. This methodology has three applications: first as a detection assay for infectious prion protein, second as a possible tool for similar diagnostics in other amyloid and/or mis-folded protein diseases; and, lastly as a tool for gaining a better understanding of the molecular mechanism of this group of diseases which can be used to optimize diagnostics and future therapeutics. The structural complexity of the target peptide sequence will be optimized and the thermodynamic and kinetic facets of peptide interaction with the infectious prion protein will be studied thoroughly at the quantitative level to highlight the prominent features that determine species specificity and to generate calibration

[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).

curves with binding constants for diagnostic development. To further assay improvement, a predictive model will be developed for the conformational diversity of the target peptides used as indicators and surrogates of conformational change upon interaction with the infectious prion protein. The universality of the target peptide concept as a detector for other amyloid diseases will also be evaluated.

- **Project Title: AN IMPROVED EXPRESSION VECTOR TO CREATE TRANSGENIC MICE FOR PRION RESEARCH.**

  Principal Investigator & Institution: Tamguney, Gultekin; Institute for Neurodegenerative Diseases (Ind); University of California San Francisco 3333 California St., Ste. 315 San Francisco, Ca 941430962

  Timing: Fiscal Year 2007; Project Start 19-JAN-2007; Project End 30-NOV-2008

  Summary: (provided by applicant): Prions are transmissible pathogenic agents responsible for fatal neurodegenerative diseases such as Creutzfeldt-Jakob disease (CJD) in humans, scrapie in sheep, and bovine spongiform encephalopathy (BSE) in cattle. These disorders are characterized by the conversion of the host-encoded cellular prion protein (PrPc) into an abnormally folded and infectious isoform (PrPSc) that accumulates in the brain and causes disease. Transgenic mice are important tools to study prion diseases. Due to the expression vectors in use, current transgenic mouse models are imperfect and show PrPc-expression profiles dissimilar from wild-type (wt) mice. Our long-term goal is to develop a transgenic mouse model in which the PrPc-expression profile is identical to wt PrPc expression. An authentic mouse model is a prerequisite to the development of accurate protocols that prevent the transmission of infectious prions and attenuate or cure the disease. Our specific hypothesis is that a transgenic expression vector based on a mouse bacterial artificial chromosome (BAG) clone will include all genetic regulatory elements necessary to drive a locus-independent expression of PrPc that is indistinguishable from wt mice. The specific aims are to: 1. Develop a new vector for PrPc expression in transgenic mice. Based on a fully sequenced mouse BAG clone, we will generate an array of truncated vectors that can drive PrPc expression in transgenic animals. We will introduce a cloning site into this vector that will allow replacing the open reading frame (ORF) of the prion protein gene (Prnp) with alternative sequences. 2. Create and identify transgenic mice that have a PrPc-expression profile identical to wt mice. We will use the expression vectors cloned in Specific Aim #1 to create transgenic mice through pronuclear microinjection into oozytes from Prnp-ablated mice. We will create and identify animals that have a PrPc-expression profile that is indistinguishable from wt mice. 3. Characterize the incubation time and PrPSc profile in transgenic mice after infection with prions. Once we have identified a vector that gives rise to transgenic animals that have a wt PrPc-expression profile, we will infect these animals with prions. We will determine the incubation time and the PrPSo profile generated in these mice and validate this new mouse model by comparison to wt mice.

- **Project Title: ANALYSIS OF CYTOPLASMIC PRION PROTEIN TOXICITY**

  Principal Investigator & Institution: Jackson, Walker S.; Whitehead Institute for Biomedical Res 9 Cambridge Ctr Cambridge, Ma 021421479

  Timing: Fiscal Year 2005; Project Start 01-SEP-2004; Project End 31-AUG-2007

  Summary: (provided by applicant): Evidence produced in the mid 1990's suggests that bovine spongiform encephalopathy (commonly known as mad cow disease) was probably transmitted to humans. The agents widely believed to be responsible for these diseases are abnormally shapened prion proteins. Along with an infectious route,

humans can also develop prion diseases either sporadically or by expressing a mutant prion protein (penetrance approximately 100%). Recent work points to the cytosol as being the site of toxicity of prion proteins. Mutant prion proteins may be highly toxic because they have an increased probability of misfolding and therefore mislocalizing to the cytosol. To study the mechanism of increased toxicity of the mutant prion proteins and how it relates to cytosolic prion toxicity, ES cells will be genetically altered to express mutant prion proteins directly into the cytosol. These cell lines will be differentiated into neurons, gila, or fibroblasts and used to study the effects these mutations have on subcellular traffciking, degradation, and toxicity of PrP. The gene-targeting approach will allow for a high probability of equivalent expression of these constructs at the mRNA level. The selection of ES cells as a model system will permit efficient transition of cell culture experiments into mice.

- **Project Title: ASSAY AND INSTRUMENT DEVELOPMENT FOR DIAGNOSIS OF PRION DISEASE**

  Principal Investigator & Institution: Zhu, Peizuan; Principal Investigato; Creatv Microtech, Inc. 11609 Lake Potomac Dr Potomac, Md 20854

  Timing: Fiscal Year 2006; Project Start 01-SEP-2006; Project End 31-AUG-2008

  Summary: (provided by applicant): Prion diseases are a family of fatal neurodegenerative diseases that are caused by infectious misfolded prion proteins (PrPSc) in both animals and humans. Prion diseases can occur spontaneously and can be contracted by multiple routes: consumption of contaminated foods, blood transfusion, organ and tissue transplant, and contamination of medical devices. Prion diseases have a years-, and even decades-long incubation period before onset of symptom. PrPSc are extraordinarily resistant to classic medical decontamination procedures. These factors raise major concerns about potential transmission of the diseases and the need for tools for timely diagnosis. Currently the diseases are diagnosed antemortem imperfectly based on clinical signs of neural disorders, and confirmed only postmortem by neuropathological and immunohistochemical analysis of brain tissue. A sensitive blood screening test is urgently needed for protecting against the risk of disease transmission. This Small Business Innovation Research proposes to apply a novel assay, coupled with sensitive biosensor technology, to develop a living test of **prion disease.** The assay will be able to quantify normal and variant prions. The initial goal for sensitivity in Phase I is 5 pg/ml in blood with further improvement to be made in Phase II.

- **Project Title: ASSESSING THE TRANSMISSIBILITY OF CWD TO HUMANS**

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

  Timing: Fiscal Year 2006; Project Start 01-JUN-2006; Project End 31-MAY-2011

  Summary: (provided by applicant): Chronic wasting disease (CWD), the **prion disease** in cervids (deer and elk), is widespread in North America. The cervid population is huge (approximately 22 million) and venison consumption very significant in USA. The fast spreading CWD is hard to contain, and it may pose a serious threat to human health if it is transmissible to humans, even at a low rate. This proposal will use transgenic (Tg) mouse models to answer three critical questions pertinent to the potential dangers posed by CWD to humans: Can CWD be transmitted to humans directly (Aim 1)? Can CWD be transmitted to humans after passage through secondary hosts (cattle or sheep) (Aim 2)? Has CWD transmission to humans already occurred (Aim 3)? The ultimate goals are to define the risks of direct and indirect CWD transmission to humans and to establish a surveillance program to monitor for human subjects infected by CWD prions.

Research Design: For Aims 1 and 2, humanized and cervidized Tg mice will be intracerebrally (i.e.) inoculated with brain homogenates either from human subjects with sporadic Creutzfeldt-Jakob disease (CJD) or from CWD-affected animals including: Rocky Mountain elk, mule deer, white-tail deer, cattle, and sheep; sheep scrapie will also be inoculated as a control. The inoculated animals will then be monitored and compared for the transmission rate, incubation time, neurological symptoms, accumulation and distribution of PrP-Sc, and the glycoforms and conformational stability of PrP-Sc before and after passage in the Tg mice. Secondary transmissions will be done to examine for asymptomatic carriers of prion infectivity. Oral transmissions will be performed for CWD isolates that demonstrated infectivity in humanized Tg mice after i.e. inoculation. For Aim 3, cervidized Tg mice will be i.e. inoculated with brain homogenates from CJD subjects who had consumed venison from CWD endemic areas as well as from sporadic CJD subjects not exposed to CWD. The prion infectivity liters in the brain homogenates will be determined for all involved CJD subjects, and the same infectivity dose will be used for inoculation. A statistically significant higher transmission efficiency of prions from "CWD-exposed" CJD subjects than that of the sporadic CJD subjects unexposed to CWD will suggest that the "CWD-exposed" subject likely acquired his CJD from CWD.

- **Project Title: BIOCHEMICAL DETECTION OF PRIONS IN BLOOD**

  Principal Investigator & Institution: Castilla, Joaquin; Neurology; University of Texas Medical Br Galveston 301 University Blvd Galveston, Tx 77555

  Timing: Fiscal Year 2005; Project Start 01-SEP-2004; Project End 31-JUL-2006

  Summary: (provided by applicant): This application is in response to the PAR-03-056 (NIA Pilot Research Grant Program) and focuses on the topic number four, **Transmissible Spongiform Encephalopathies. Transmissible spongiform encephalopathies,** also called prion diseases, are a group of fatal infectious neurodegenerative disorders affecting humans and animals. Although rare diseases, the recent outbreak of Bovine Spongiform Encephalopathy and Chronic Wasting disease and the transmission of the disease from cattle to humans have risen a great concern about a possible epidemic of Creutzfeldt-Jakob disease. This problem is aggravated by the lack of an early and sensitive diagnosis to identify individuals incubating the disease during the pre-symptomatic phase. The infectious agent (termed prion) is composed exclusively by a misfolded version of a normal protein and does not contain any nucleic acid. According to the prion hypothesis, the disease is transmitted by propagation of the misfolding from the disease associated isoform (termed PrPres) to the normal host protein (termed PrPc), which become converted into the pathological form. We have recently described a procedure to induce the conversion of PrPc into PrPres in vitro starting with minute quantities of brain PrPres. This procedure, named Protein Misfolding Cyclic Amplification (PMCA) mimics the process of prion replication in vivo, but at an accelerated speed resulting in an exponential amplification of the initial amount of PrPres. PMCA has tremendous promise to increase detection of prions in tissues and biological fluids during early stages of the disease and thus may be useful for pre-symptomatic diagnosis of **prion disease.** The major goal of this project is to take advantage of the PMCA technology to attempt developing a highly sensitive and non-invasive diagnosis of prion diseases in humans and animals. In specific aim 1 we will attempt the pre-symptomatic detection of PrPres in the brain of experimentally infected cattle sacrificed at different times after infection. In specific aim 2 we will attempt detection of PrPres in peripheral tissues of humans and animals. Specific aim 3 proposes the development of the conditions for amplification of PrPres from blood of experimental animals in order to reach reproducible detection of prions in blood. The results generated in this project may provide the basis for the development of a novel

highly-sensitive pre-mortem and pre-symptomatic diagnosis of **prion disease.** Such test will have tremendous applications in public health to minimize the risk of further propagation of prion to humans.

- **Project Title: BIOINORGANIC COPPER COORDINATION CHEMISTRY**

  Principal Investigator & Institution: Karlin, Kenneth D.; Professor; Chemistry; Johns Hopkins University W400 Wyman Park Building Baltimore, Md 212182680

  Timing: Fiscal Year 2005; Project Start 01-APR-1991; Project End 31-MAR-2007

  Summary: (provided by applicant): The goal of the proposed research is to further develop fundamental aspects of copper coordination chemistry relevant to its essential role in the biochemical processing of dioxygen (O2) and nitrogen oxides (NOx). Many questions remain concerning copper(I)/O2 interactions, formation of adducts, derived structures and their associated spectrocopy, O-O bond cleavage, and substrate oxidation chemistries. These may also be relevant to situations of oxidative stress, e.g., in neurological disorders such as Alzheimer's or prion diseases. Copper-NOx investigations are relevant to the active site chemistry in nitrous oxide reductase, and the possibly crucial role of copper ion in nitric oxide (.NO) biochemistry, including (cysteine) thiol nitrosylation chemistry, or mediation of nitroxyl (NO-) chemistry and peroxynitrite oxidative stress. The research methods break down into sub-projects, directed along various themes, questions or chemical systems. These include, (1) amplification of basic Cu/O2 chemistry: study sub-millisecond CuI/O2 interactions by Cu(I)/carbon monoxide photochemical triggering, and ligand electronic effects on Cu/O2 binding and hydroxylation, (2) study of Cu-superoxides, (3) mechanistic investigation of Cun/O2 mediated substrate oxidations, including probing dicopper side-on peroxo vs. bis-mu-oxo interconversion, and protonation-reduction of Cu(III)2(O)2 moieties, (4) generation of relevant chemistry with methionine (thioether) type ligands, and O-O cleavage chemistry with Cu(n)-OOR species, (5) modeling of amino-acid modified Cu-protein active-site cofactors, their biogenesis and chemistry, (6) elucidation of copper ion chemistry with.NO, NO-, peroxynitrite, their relationship to Cu/O2 derived species, and study of Cu mediated dentirosylation, i.e., Cu(I) + RSNO, (7) development of O2-chemistry with tricopper Cu3-cluster complexes relevant to copper oxidases, and (8) elaboration of new Cu-sulfide chemistry and N2O reactivity relevant to nitrous oxide reductase. The proposed studies contribute to a broader understanding of copper biochemistry, to protein activation/reduction of O2 and/or NOx, as applied to other metals (i.e., heme or non-heme iron) and disease states. Potential applications include development of enzyme inhibitors and relevant disease therapeutic strategies.

- **Project Title: BIOSENSOR FOR RAPID DETECTION OF PRION**

  Principal Investigator & Institution: Hazel, Thomas G.; Innovative Biosensors, Inc. 387 Technology Dr College Park, Md 20742

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

  Summary: (provided by applicant): Creutzfeldt-Jakob Disease and Bovine Spongiform Encephalopathy are transmissible, neurodegenerative and fatal prion diseases of humans and cattle, respectively. There are no commercially available, completely reliable diagnostic tests for use before the onset of symptoms. The only reliable tests in use are performed post mortem or via brain biopsy and involve histological examination. For these reasons, there is a great need for better diagnostics for these prion diseases. This application proposes to develop a rapid, extremely sensitive diagnostic test for prion based on the CANARY biosensor technology developed at MIT

and an antibody that specifically recognizes the scrapie form of the prion protein in cattle and humans. The CANARY technology is composed of B-lymphocytes that have been genetically engineered to express an antibody of interest on the cell surface and calcium sensitive protein in the cell's cytosol. The interaction of the antigen with the membrane bound antibody cause the engineered biosensors to emit light, which is detectable by a small, portable luminometer. This approach allows specific testing of analytes at previously unachievable levels of speed and sensitivity. The specific tasks for Phase I include: 1) Obtaining sequences of the light and heavy chains of the variable region of the anti-prion monoclonal antibody by RT-PCR. 2) Construction of these sequences into a well characterized two vector antibody expression system. 3) Generation of a stable cell line that expresses the recombinant antibody on its surface and a calcium sensitive bioluminescent protein in the cell's cytosol that responds to the prion antibody epitope.

- **Project Title: CELLULAR PATHOPHYSIOLOGY OF PRION DISEASE**

  Principal Investigator & Institution: Criado, Jose R.; Scripps Research Institute 10550 North Torrey Pines Road La Jolla, Ca 920371000

  Timing: Fiscal Year 2005

  Summary: (provided by applicant): Neurodegeneration associated with **transmissible spongiform encephalopathies** (TSE) requires post-translational modification of the cellular prion protein (PrPC) leading to the accumulation of an abnormal protease-resistant isoform (PrPSc or the scrapie isoform of PrPc). The proposed study is a detailed investigation on the roles of loss of PrPc expression and PrPsc aggregation on neurological deficits associated with TSE. Specific aims #1 and #2 will focus on determining whether loss of PrPc function alters hippocampal excitability, NMDA and non-NMDA receptor function, local circuit interactions and synaptic plasticity in the hippocampal dentate gyrus (DG) in vivo in mice devoid of PrPc (PrPNull mice). We will also determine in wild-type (WT) mice inoculated with mouse scrapie the relationship between hippocampal neurophysiology, cognitive function and hypothalamo pituitary-adrenal (HPA) axis regulation. After completion of these experiments, brains will be studied to determine the relationship between CNS function and the development of neuropathology. In collaboration with Dr. Oldstone (Project I), we will study in Specific aim 3 the consequences of deletion of the GPI anchor of PrPc on CNS function in PrP GPI-/- tg mice. We hypothesize the effects of deletion in the GPI anchor on CNS function will resemble our previous findings in PrP null mice. In collaboration with Dr. Williamson (Project II), specific aim 4 will determine the consequences of PrP-specific antibodies and small molecules interacting with regions of PrP on hippocampal DG neurophysiology in vivo. The proposed studies will provide critical information regarding the onset of several neurobehavioral symptoms that precede PrPsc accumulation and neuropathology. These findings will be essential for the development of a sensitive and specific neurobehavioral diagnostic test for the early detection of neurological deficits associated with TSE.

- **Project Title: CJD DIAGNOSIS BY IMMUNO-MULTI-SPECTRAL UV FLUORESCENCE**

  Principal Investigator & Institution: Rubenstein, Richard; Microbiology and Immunology; Suny Downstate Medical Center 450 Clarkson Ave Brooklyn, Ny 11203

  Timing: Fiscal Year 2002; Project Start 30-SEP-1999; Project End 31-AUG-2007

  Summary: Creutzfeldt-Jakob disease (CJD) is a progressive disorder of the central nervous system and belongs to a class of diseases known as **transmissible spongiform**

encephalopathies, or **prion disease.** The transmissibility and fatal nature of these diseases necessitates their rapid and accurate diagnosis. The hallmark of these diseases is the accumulation of PrP(Sc), a protease-resistant form of a host-coded glycoprotein. We propose to develop highly sensitive and specific PrP(Sc) detection methods by coupling state-of-the-art immuno-fluorescence techniques with novel fluorescence spectroscopic methods. We have evaluated the use of multi-spectral ultraviolet fluorescent spectroscopy (MUFS) as a means of detecting and distinguishing between different forms of PrP(Sc). Spectroscopic measurements of fluorescence from untreated and proteinase K (PK)-treated PrP(Sc), purified from 263K scrapie strain-infected hamster brains and ME7 scrapie strain-infected mouse brains, were performed. Spectra of untreated and PK-treated PrP(Sc) samples for 263K and ME7 appeared qualitatively different. The identification and discrimination of PrP(Sc) was possible based on these spectral signatures, calculations of their fluorescence cross sections and determination of the orthogonal differences. Furthermore, MUFS was successfully used within an optically dense medium spiked with sodium salicylate. These results indicate that it is possible to detect and discriminate between compounds or proteins in optically dense media, such as undiluted blood plasia, by this method. This technique has the potential not only for the detection of PrP(Sc) in optically dense media, but also for the ability to distinguish between different forms of the prion protein. Furthermore, in combination with multi-site directed, fluorophore-tagged monoclonal antibodies, this method will prove to be an extremely powerful tool for the analysis of PrP(Sc) and the diagnosis not only of CJD, but other prion diseases.

- **Project Title: CLINICAL STUDY FOR THE TREATMENT OF HUMAN PRION DISEASES**

  Principal Investigator & Institution: Miller, Bruce L.; Professor; University of California San Francisco 3333 California St., Ste. 315 San Francisco, Ca 941430962

  Timing: Fiscal Year 2005

  Summary: Creutzfeldt-Jakob disease (CJD) is a rapidly progressive, invariably fatal and untreatable neurodegenerative disease with a mean duration of about eight months. Beyond the debilitating cognitive and motor deficits that accompany CJD, the difficulty in treating behavioral and mood disturbances and the rapidity of its course compound its tragedy. Moreover, an epidemic of new variant CJD (nvCJD) in England has raised serious concerns regarding the safety of the world's beef supply; the possibility that prions might be passed through the blood has led to the banning of blood or tissue donations from individuals who have resided in England. The discovery of an effective therapy for prion diseases would have enormous human and economic implications. Recent results from experiments in Dr. Prusiner's laboratory show that, at physiological concentrations, the anti-malarial drug quinacrine permanently clears abnormal priori proteins from cell culture. The demonstrated efficacy of quinacrine in cell culture, its relative safety and well known side-effects in the clinical setting, and the universal fatality of CJD justify quinacrine as an immediate candidate for the treatment of CJD. We propose a treatment study for patients with sporadic CJD (sCJD) with racemic quinacrine. Over three years, 90 patients will be admitted to the University of California at San Francisco (UCSF) NIH-funded clinical research center where a diagnosis of sCJD will be determined and where patients will enter into a randomized, double-blinded, treatment study with quinacrine. Patients will be divided into two quinacrine arms, a high-dose titration (450 mg daily) and a low-dose titration (75 mg daily). They will be treated for one year and then be followed through to the end of the five-year study period. The dose of quinacrine may be increased or decreased in each patient depending on clinical deterioration or toxicity, respectively. Survival will be the primary outcome

measure of this clinical study. Also, additional outcome measures will be used that assess activities of daily living, cognition, MRI and EEG. We hypothesize that patients in the high-dose quinacrine arm will have increased survival and a slower rate of neurological progression compared with patients in the low dose arm. By year four of this program project grant (PPG), we hope to begin a clinical study with a new compound, developed in other Projects in this PPG, that shows even greater efficacy than racemic quinacrine.

- **Project Title: COMPUTER SIMULATIONS OF PROTEIN AGGREGATION**

  Principal Investigator & Institution: Hall, Carol K.; Alcoa Professor; Chemical Engineering; North Carolina State University Raleigh Sponsored Programs and Regulatory Compliance Raleigh, Nc 27695

  Timing: Fiscal Year 2005; Project Start 01-MAY-1999; Project End 28-FEB-2009

  Summary: (provided by applicant): The aberrant assembly of normally soluble proteins into ordered aggregates, called amyloid fibrils, is a cause or associated symptom of many different human disorders including Alzheimer's, Parkinson's and Huntington's diseases, the prion diseases and adult-onset diabetes. Known collectively as the amyloidoses, these diseases are characterized by the slow deposition of a specific protein into amyloid fibrils, which then accumulate into plaques, destroying the function of the affected tissue, usually with degenerative and ultimately fatal consequences. An understanding of the molecular-level mechanisms that result in the aggregation of proteins into amyloid is essential for the discovery of potential therapeutic strategies and diagnostics. As-part of our NIH-sponsored effort to uncover the general physical principles that govern protein aggregation, we developed an intermediate-resolution protein model that allowed the simulation using discontinuous molecular dynamics (DMD) of multi-protein systems within days on a fast workstation. A recent breakthrough enabled us to simulate assembly of 48 16-residue alanine peptides into a fibrillar structure starting from the random coil state. This suggests that the intermediate-resolution model could be used as a computational tool to explore fibril formation in short peptides. The project has three specific aims: (1) to learn the basic physical principles governing protein fibril formation by using DMD to simulate multi-protein systems containing polyalanine chains modeled using our intermediate-resolution model, (2) to shed light on the molecular-level mechanisms responsible for the aggregation of polyglutamine, the protein whose fibrillization is linked to Huntington's disease, by extending the intermediate-resolution model to the treatment of polyglutamine side chains and then performing DMD simulations, and (3) to investigate the aggregation and possible fibrillization of multi-protein systems containing specific amyloidogenic peptides, particularly the Alzheimer's peptides Abeta(1-40) and Abeta(1-42), by extending the intermediate-resolution model to a coarse-grained representation of all 20 residues, performing DMD simulations, and comparing our results with experiment. This work should culminate in a detailed molecular-level picture of the fibrillization process, thereby providing insights to guide medical research workers directly involved in developing therapeutic strategies or inhibitors to circumvent those steps in the fibrillization process that are most responsible for cell damage.

- **Project Title: CONFERENCE ON TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES**

  Principal Investigator & Institution: Aguzzi, Adriano; Keystone Symposia Drawer 1630, 221 Summit Pl #272 Silverthorne, Co 80498

Timing: Fiscal Year 2005; Project Start 01-JAN-2005; Project End 31-DEC-2005

Summary: Transmissible Spongiform Encephalopathies, or prion diseases, are known to affect humans and animals, and have been known to exist for centuries. The recent spread of Chronic Wasting Disease in North America and the discovery of the first case of Bovine Spongiform Encephalopathy in the US has once again demonstrated the impact of these diseases on society and industry. Although the exact nature of the infectious agent causing spongiform encephalopathies remains to be defined, circumstantial evidence indicates that the agent is devoid of nucleic acids and represents a new class of infectious agents. Progress in structural and molecular biology, genetics and epidemiology has improved our understanding of these diseases in the last years. These studies have advanced the pathophysiology of prion diseases and opened the possibility to assess therapeutical principles aimed at preventing these diseases. However, essential questions such as the true nature of the infectious agent and the molecular mechanisms leading to dementia await elucidation. The goal of the proposed meeting is to bring together (1) leading experts from different fields of **prion disease** research, (2) physicians, (3) postdocs, and (4) students in order to discuss recent advances, and in order to devise new approaches on solving problems posed by these enigmatic diseases.

- **Project Title: CORE--NEUROPATHOLOGY**

  Principal Investigator & Institution: De Armond, Stephen J.; Professor; Univ of California, San Fran

  Timing: Fiscal Year 2005

  Summary: The Neuropathology Cores (NP Core) during the past 17 years have performed the dual roles of providing thorough neuropathology expertise as a service function to the Program Projects and have also tested hypotheses regarding the etiology and pathogenesis of different forms of **prion protein diseases.** Project 4 proposes to make single, double and triple amino acid substitutions in the chimeric MHu2M PrP construct and similar changes in a mule deer (MuD)-mouse chimeric construct to more precisely define those portions of the PrP molecule that determine the host species barrier to different prion strains and incubation. Each of the resulting transgenic mouse lines will be inoculated with four different prion. Project 3 proposes new studies directed at understanding the structure of the transmembrane type of abnormal PrP, CtmPrP, which is found in both scrapie and Gerstmann-Straussler-Scheinker type **prion disease.** The NP Core is well suited to support both of these projects because the neuropathological phenotype is the most useful parameter defining the host's and prion strain's roles. Project 13 proposes a novel mutational approach to identify non-Prnp genes that alter scrapie incubation time or prevent scrapie infection. The NP Core will be asked to determine the subcellular location of the gene products and the pathological effects of knocking the genes. Project 7 proposes different techniques to learn more about the three dimensional structure of PrPSc. For the latter, the NP Core's role is largely indirect; however, it is no less important because the NP Core's goal is to determine which abnormal PrP form(s) play(s) the most critical pathogenic role in the different types of **prion disease.** Finally, previous NP Cores have focussed solely on detection and localization of protease-resistant rPrPSc; however, two other potentially pathogenic forms of PrP have been identified in scrapie: protease sensitive sPrPSc and CtmPrP. In contrast, large amounts of CtmPrP, but not rPrPSc, is characteristically formed by mutations of the Prnp gene in the region where mutations genetically linked to Gerstmann-Straussler-Scheinker disease occur. Therefore, this Program Project

provides a unique opportunity for the NP Core to better understand the roles played by the three abnormal forms of PrP in different PrP disorders.

- **Project Title: CYCLIC AMPLIFICATION OF PRION PROTEIN MISFOLDING**

  Principal Investigator & Institution: Soto, Claudio; Professor; Neurology; University of Texas Medical Br Galveston 301 University Blvd Galveston, Tx 77555

  Timing: Fiscal Year 2005; Project Start 21-APR-2005; Project End 28-FEB-2009

  Summary: (provided by applicant): Prion diseases are a group of infectious neurodegenerative disorders affecting humans and animals. Although rare diseases, the recent outbreak of Bovine Spongiform Encephalopathy and Chronic Wasting disease and the transmission of the disease from cattle to humans have risen a great concern about a possible epidemic of Creutzfeldt-Jakob disease. This problem is aggravated by many uncertainties surrounding the unprecedented nature of the infectious agent, its mechanism of propagation and the species barrier that seems to control prion transmission. The most accepted hypothesis proposes that the infectious agent (termed prion) is composed exclusively by a misfolded version of a normal protein and does not contain any nucleic acid. According to this hypothesis, the disease is transmitted by propagation of the misfolding from the disease associated isoform (termed PrPres) to the normal host protein (termed PrPc), which become converted into the pathological form. We have recently described a procedure to induce the conversion of PrPc into prPres in vitro starting with minute quantities of brain PrPres. This procedure, named Protein Misfolding Cyclic Amplification (PMCA) mimics the process of prion replication in vivo, but at an accelerated speed resulting in an exponential amplification of the initial amount of PrPres. The major goal of this project is to take advantage of the PMCA technology to attempt developing a highly sensitive and noninvasive diagnosis of prion diseases as well as to study diverse aspects related to the nature of the infection agent, other factors involved in prion conversion and the transmission between species. In specific aim 1 we will study the infectious and structural properties of prPres generated in vitro with the objective to attempt multiplying and producing infectivity in the test tube. This experiment is widely considered as the final pending proof for the prion hypothesis. In specific aim 2 we will attempt to identify cellular protein factors that seem to play a major role in prion replication in vivo. Specific aim 3 proposes to study the species barrier phenomenon and the influence of PrP polymorphisms in the efficiency of prion replication in vitro. In specific aim 4 we will develop a highly-sensitive diagnostic test to detect PrPres in blood of experimental animals, cattle and humans, based on amplifying minute quantities of the pathological protein present in blood to a level that enable reproducible detection. Therefore, this project offers a balanced combination between basic science studies aimed to understand the most relevant scientific problems in the prion field and applied studies to resolve the main practical problem associated to these diseases, which is the lack of a highly-sensitive pre-symptomatic blood diagnosis to limit the spreading of these incurable illnesses.

- **Project Title: DEFINING THE LINK BETWEEN THE PRION PROTEIN AND COPPER**

  Principal Investigator & Institution: Christensen, Heather M.; Cell Biology and Physiology; Washington University 1 Brookings Dr, Campus Box 1054 Saint Louis, Mo 631304899

  Timing: Fiscal Year 2005; Project Start 01-AUG-2003; Project End 31-JUL-2008

  Summary: (provided by applicant): Prion diseases, or **transmissible spongiform encephalopathies** (TSEs), are a class of fatal neurodegenerative disorders that have

acquired much public interest due to the epidemic of "mad cow disease" in Britain and recent cases of transmission of this disease to humans. Although much is known about the disease process associated with the pathogenic isoform (PrPsc), the normal physiological function of the cellular prion protein (PrPc) has remained elusive. Much evidence has accumulated supporting a role for PrPc in the trafficking and metabolism of copper. In this proposal, the link between copper and PrPc will be further dissected through a structure-function analysis and examination of the copper-induced endocytic response of PrPc in post-mitotic neurons. Copper binding properties of a mutant of PrPc, known as PG14, will be measured to gain an understanding of the molecular basis behind the PG14-associated heritable form of Creutzfeldt-Jakob disease. Finally, a mouse model of an inheritable disease of copper metabolism (Menkes disease) will be used to determine whether PrPc plays a role in the maintenance of copper homeostasis.

- **Project Title: DEFINING THE PRION DOMAIN OF PRP**

  Principal Investigator & Institution: Mastrianni, James A.; Associate Professor; Neurology; University of Chicago 5801 S Ellis Ave Chicago, Il 60637

  Timing: Fiscal Year 2005; Project Start 15-MAR-2003; Project End 28-FEB-2007

  Summary: (provided by applicant): The prion diseases are a family of transmissible neurodegenerative disorders that affect humans and animals. A large body of evidence argues that a post-translational, non-covalent modification of the prion protein (PrP) is the fundamental event in the mechanism underlying these diseases. The normal cellular isoform (PrPC) is misfolded to the beta-sheet rich pathogenic isoform (PrPSc). Once formed, PrPSc appears to act as a conformational template to convert additional PrPC to PrPSc. Considerable evidence supports sequence homology within the central region of PrP as a necessary feature in the association of PrPSc with PrPC as a prelude to conversion and propagation of PrPSc, but the exact segment(s) involved and the sequence determinants for this conversion are unknown. Studies targeted at understanding the site(s) of association of PrPC and PrPSc will no doubt define ways to inhibit their interaction and provide treatment for these currently untreatable diseases. The proposed studies are designed, therefore, to define the molecular determinants within PrP, and primarily within the putative priori domain, that are required for efficient self-association and conformational transfer. We will primarily utilize transgenic mice that express polymorphic PrP genes to act as hosts for a variety of sporadic and genetic human prion diseases to determine if and where homologous regions and residues are required for efficient transmission of prion strain. In addition a novel yeast-based model of **prion disease** will be extensively utilized to study the effect of specific substitutions or deletions at potentially critical association sites of PrP on the development of PrPSC-like protein. This powerful model is not only capable of generating prpSC-Iike protein, but can support the de novo generation of at least two strains of PrPSc so, and demonstrate conformational transference of PrPSc to PrPC. The information gained from these studies will then be applied to the development of novel peptide inhibitors that are designed to bind to critical sites within the defined "prion domain" and halt additional binding of PrP. With the continued threat of bovine spongiform encephalopathy in Europe, and the current spread of chronic wasting disease of deer and elk in the U.S., these studies are urgently needed.

- **Project Title: FUNCTIONAL GENETICS OF SUSCEPTIBILITY TO PRIONS**

  Principal Investigator & Institution: Carlson, George A.; Director; Mc Laughlin Research Institute 1520 23Rd Street South Great Falls, Mt 594054900

  Timing: Fiscal Year 2005; Project Start 30-SEP-2001; Project End 31-JUL-2007

Summary: (provided by applicant) Prion diseases are neurodegenerative disorders of humans and animals that involve misfolding of prion protein (PrP). These diseases can present as genetic, infectious or sporadic illnesses and each type is often transmissible to experimental animals. Diseases caused by prions include scrapie, bovine spongiform encephalopathy (BSE), and Creutzfeldt-Jakob disease (CJD) in humans. All prion diseases involve changes in the conformation of PrP from its benign cellular isoform, PrPC, to a disease-specific isoform, PrPsc. PrPsc is probably the sole functional component of the infectious particle and different conformations of PrPsc can encipher properties of prion strains. Originally thought to be diseases caused by an exogenous slow virus, convincing evidence now indicates that prion diseases are disorders of protein conformation. The discovery of a new principle of infection resulted from research involving many disciplines focused on PrP. The four senior investigators on this Program Project application propose to extend their collaborative prion research efforts in a new direction. Although PrP is central to infectivity, disease susceptibility and pathogenesis, other molecules also are involved. Recent discoveries provide the first opportunity to study mechanisms of prion replication and pathogenesis by focusing on genes other than that encoding PrP. Treating scrapie incubation time as a quantitative trait allowed the identification chromosomal regions harboring prion incubation time modifier genes. These genes will be identified using positional cloning and positional candidate approaches, aided by new technologies in DNA analysis, expression microarrays and BAC engineering for production of transgenic mice. Additional prion modifier genes will be identified by sampling natural polymorphisms in mouse strains using QTL analysis and by applying chemical mutagenesis to screen for novel prion incubation time genes. The first gene encoding a PrP-related protein, Dpl, was discovered downstream from the PrP gene. Although PrP and DpI exhibit only 25% sequence identity, they share a conserved three-helix bundle structure. This provides a unique opportunity to learn more about prion replication and disease pathogenesis through creation of chimeric PrP:Dpl molecules. DpI misexpression in brain causes cerebellar neurodegeneration that can be prevented by PrP expression, suggesting involvement of similar pathways which will be interrogated with cDNA arrays and by identification of modifier genes. In addition to providing a new perspective on **prion disease,** these studies may ultimately reveal pathways common to a variety of CNS degenerative disorders.

- **Project Title: GENETIC STUDY OF THE YEAST PRION-INTERACTING PROTEINS**

  Principal Investigator & Institution: Chernoff, Yury O.; Assistant Professor; School of Biology; Georgia Institute of Technology 505 10Th St Nw Atlanta, Ga 303320420

  Timing: Fiscal Year 2005; Project Start 01-JAN-1999; Project End 31-DEC-2007

  Summary: (provided by applicant): Incurable infectious neurodegenerative diseases, such as "mad cow" disease and human Creutzefeldt-Jacob disease, are postulated to be transmitted by an abnormal aggregation-prone protein isoform (prion). Prion aggregates are believed to be capable of seeding aggregation of the normal cellular protein, converting it into a prion. Pathology of prion diseases is reminiscent of other protein assembly disorders (such as Alzheimer?s disease) associated with amyloid-like aggregation. In yeast, prions control phenotypic traits inherited via cytoplasm. This provides a molecular basis for protein-based inheritance. As several unrelated proteins exhibit prion-forming potential, it is likely that protein-based inheritance may play an important biological role. The power of yeast genetic analysis makes yeast a useful model for studying general mechanisms of prion propagation. While many proteins can form amyloid-like aggregates in vitro, only some of them are capable of transmitting the aggregated state in vivo. This means that cells are normally able to prevent aggregate

propagation. However, prions are overcoming the cellular defense systems. Moreover, our research has proven that the cellular stress-defense machinery becomes an essential component of prion propagation in the yeast cell. The overall, goal of this proposal is to uncover mechanisms by which cellular systems control prion formation and propagation in the yeast cell. This will explain how environmental and physiological factors induce protein-based inheritable variations, and may provide a new tool for curing aggregation-based disorders by altering the cellular regulatory systems. Proteins affecting prion formation and propagation in yeast will be investigated: stress-related chaperones of the evolutionary conserved Hsp100 and Hsp70 groups; ubiquitin system, normally involved in targeting misfolded proteins for degradation; and cytoskeletal assembly proteins involved in formation of cortical actin patches and endocytic vesicles. Specific Aims of the proposal are as follows: 1) To study a mechanism of prion regulation by the heat shock protein balance. 2) To study the role of ubiquitin system in the cellular control of yeast prions. 3) To study interactions between prions and cytoskeleton-associated structures in yeast.

- **Project Title: IDENTIFICATION OF ANTI-SCRAPIE DRUGS**

  Principal Investigator & Institution: Burton, Dennis R.; Scripps Research Institute 10550 North Torrey Pines Road La Jolla, Ca 920371000

  Timing: Fiscal Year 2005

  Summary: (provided by applicant): **Transmissible spongiform encephalopathies** (TSEs) or prion diseases, are neurodegenerative diseases of conformation in which the cellular prion protein (PrPC) misassembles into an abnormal conformer (PrPSc). PrPSc is thought to be the sole constituent of infectious prion particles. Prion propagation proceeds via a highly-specific process of conformational rearrangement in which PrPSc imposes its own structure upon PrPC bound to it. The transmission of bovine spongiform encephalopathy prions to humans, manifesting clinically as variant Creutzfeldt-Jacob disease, and ongoing spread of chronic wasting disease in cervids in North America, have demonstrated the pressing need for effective prion therapeutics. In this proposal we have developed experimental strategies designed to yield small molecule inhibitors of prion propagation suitable for use in the prevention and/or therapy of prion infection and disease. Two distinct approaches have been taken. In the first, drawing upon our considerable experience using PrP-specific antibodies, we seek to identify small compounds binding specifically to key regions of either PrPC or PrPSc. We hypothesize that molecules preventing PrPC-PrPSc interactions will effectively inhibit assembly of the prion replicative complex, preventing generation of nascent prion infectivity. In a second approach, small molecules binding specifically to PrPC, increasing the intrinsic thermodynamic and kinetic stability of this molecule and thereby precluding the possibility of unwanted conformational changes that are intimately associated with prion pathogenesis and PrPSc formation will be identified. Molecules recovered via both of these strategies will be evaluated for their capacity to resolve prion infection in vitro and in vivo.

- **Project Title: IDENTIFYING GENES REQUIRED FOR PRION ACCUMULATION**

  Principal Investigator & Institution: Stanton, James B.; Vet Microbiology and Pathology; Washington State University 423 Neill Hall Pullman, Wa 99164

  Timing: Fiscal Year 2005; Project Start 15-JUL-2005; Project End 31-MAY-2008

  Summary: (provided by applicant): Research: A fundamental mechanism in the pathogenesis of animal and human prion diseases is the conformational conversion of a normal host-encoded protein (PrPc) from a non-infectious, soluble, protease sensitive

form to an infectious, aggregated, protease resistant, pathologic form termed PrPSc. The precise mechanism of prion conversion is not known and it is unknown if accessory molecules, in addition to prion protein, aid in the conversion process. However, there are data that do support the requirement for an accessory molecule. The goal of this project is to use a comparative transcriptomics approach on scrapie permissive sheep cell lines to identify possible accessory proteins necessary for PrP accumulation. The hypothesis to be tested is that PrPSc accumulation requires an accessory protein(s). Specific Aim 1 will determine if in vivo PrPSc permissive sheep cells maintain permissiveness in stable cell cultures. Specific Aim 2 will determine if unique gene expression patterns in permissive cells can be associated with PrPSc accumulation. Specific Aim 3 will determine if expression of a PrPSc-accumulation-associated gene(s) is required for PrPSc accumulation. The findings of the proposed study have applications to both human and veterinary medicine by defining the genetic response to prion accumulation and identifying co-factors required for the accumulation of PrPSc. Such co-factors would be putative targets for therapeutic intervention or potential surrogate markers for antemortem diagnosis. Candidate: The candidate is a veterinarian completing a residency in anatomic pathology and a Ph.D. degree. After fulfilling most of the requirements of his pathology training along with all didactic course work and his candidacy exam, the candidate is actively pursuing the research portion of his training. This research proposal constitutes his plan to investigate mechanisms of prion replication. Long-term goals of the candidate include investigation of infectious diseases of animals with zoonotic potential. Environment: The Department of Veterinary Microbiology and Pathology at Washington State University provides both modern research facilities for infectious disease research and a highly interactive training environment including intra- and interdisciplinary graduate education, residency programs, and extensive collaboration both within and outside the university. The sponsor collaborates closely in research and has successfully mentored graduate students to research independence.

- **Project Title: IMMUNO-BASED THERAPY FOR PRION DISEASE**

  Principal Investigator & Institution: Wuertzer, Charles; Neurology; University of Rochester 517 Hylan Bldg., Box 270140 Rochester, Ny 14627

  Timing: Fiscal Year 2005; Project Start 01-AUG-2003; Project End 31-JUL-2006

  Summary: This application proposes to isolate novel PrPc-specific single-chain variable fragment antibodies that will be utilized in a passive immuno-therapy on cell lines chronically infected with PrPsc and mobilized into herpes simplex virus amplicon and recombinant adeno-associated virus, serotype 2 platforms to be characterized for future utility in an in vivo therapy strategy. A combinatorial phage display library expressing linked human immunoglobin heavy and light chains variable regions has been used to enrich for scFv phage specific to recombinant mouse prion protein (recMoPrP). Identified sequences will be expressed, pudfied and assessed for functionality. Purified Prp-specific scFvs will be assessed for efficacy in positively effecting Prpsc-accumulation in established chronically infected cell-line models for murine **prion disease** by treatment with varying concentrations of purified PrP-specific scFvs. Treatment efficacy will be assessed via immuno blot analysis and sensitivity to proteinase K treatment. Isolated scFv sequences will be subcloned and packaged in-frame with a eukaryotic secretion signal and a c-myc epitope tag into HSV amplicon and rAAV2 vectors. An In vivo time course study in c57Bi/6 mice will assess expression levels, kinetics, and migration from intracerebral (IC) administration site via IHC.

- **Project Title: INTERCELLULAR TRANSFER OF PRION IN PRION DISEASE**

  Principal Investigator & Institution: Sy, Man-Sun; Professor; Pathology; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

  Timing: Fiscal Year 2005; Project Start 01-APR-2003; Project End 31-MAR-2007

  Summary: (provided by applicant): **Transmissible spongiform encephalopathies** (TSE) or prion diseases are a group of fatal neuro-degenerative disorders that affect both humans and animals. Most human TSE are sporadic, and about 10-15% of the cases are inherited as autosomal dominant traits. However, in several hundred cases, human TSE have been shown to be acquired by infection, which may be caused either by medical manipulations as in iatrogenic Creutzfeldt- Jakob Disease (CJD), or from the consumption of contaminated foods, as in kuru and variant CJD (vCJD). All prion diseases are believed to share the same pathogenic mechanism based on the conversion of the normal cellular prion (PrP c) into the infectious scrapie prion (prpSc). In animal TSE, such as scrapie in sheep and bovine spongiform encephalopathy (BSE) in cattle, it is believed that the PrP sc enters the host through the gastrointestinal tract, migrates to the spleen, and eventually causes disease in the CNS. However, in experimentally infected animals, PrP sc is first detected in the spleen even if the PrP Scis injected directly into the brain. The mechanism by which PrP sc moves in and out of the CNS is not known. Both PrP c and PrP sc are anchored to the membrane by glycosylphosphatidylinositol (GPI). Under some experimental conditions GPIanchored proteins can move from cell-to-cell. We hypothesize that inter-cellular transfer of PrP c or PrP sc facilitates the spread of infection. We developed a cell model to test whether PrP c is transfer from a human neuroblastoma cell line to a leukemia cell line, which lacks PrP c. We found that PrP c transfer requires cellular activation, cell-cell contact and is GPI anchor dependent. These findings strengthen the possibility that intercellular transfer of PrP c or PrP sc may play a role in the propagation of PrP L We propose: 1) to further characterize the intercellular transfer of prpC; 2) to investigate whether a similar transfer takes place for prpS; and 3) to explore whether intercellular transfer of PrP is important in the pathogenesis of **prion disease** in vivo using transgenic animals. The studies that we propose address very important and under studied aspects of prion diseases. The mechanisms that govern PrP sc propagation at the cellular level is one of the major remaining barriers to fully understanding the pathogenesis of prion diseases. New insights into this area will also lead to designs of more rational and effective treatment for prion diseases.

- **Project Title: INTRABODIES AS NOVEL NEUROLOGICAL THERAPEUTICS**

  Principal Investigator & Institution: Messer, Anne; Research Scientist/Professor; Wadsworth Center Health Research, Inc. Rensselaer, Ny 12144

  Timing: Fiscal Year 2006; Project Start 15-JAN-2006; Project End 31-DEC-2010

  Summary: (provided by applicant): The goal of this proposal is to optimize engineered intracellular antibodies (intrabodies) as novel clinical reagents and drug discovery tools for the treatment of Huntington's Disease (HD), with broad, long-term relevance to other neurodegenerative disorders caused by misfolded proteins. Intrabodies use the target specificity of antibodies to form complexes with intracellular proteins, and are already in clinical trials for treatment of cancers and AIDS. The research design starts with in vivo testing with a single-chain Fv anti-huntingtin (htt) intrabody (scFv C4) that has shown significant rescue of HD phenotypes in cell lines, organotypic slice cultures and a Drosophila HD model; plus a newer single domain intrabody (VL 12.3) that shows even stronger anti-htt aggregation properties in situ. Delivery of the intrabody genes will utilize a non-primate lentivirus, Equine Infectious Anemia Virus (EIAV), with either

a VSVG or Rabies-g envelope, as one gene therapy vector, with some experiments to compare with delivery using AAV vectors provided by a collaborator. Quantitative assays of abnormal nuclear htt accumulation and aggregation, DARPP- 32 levels, and open field activity behavior will be used to assess the efficacy of the intrabodies delivered to the brains of Exon 1 transgenic (R6/1) and Hdh knock-in (Q111) mouse models on the same inbred genetic background. Simultaneously, screening and testing of a small pool of newer intrabodies will be done using anti-aggregation, protection, and toxicity assays in neuronal cell lines. The most successful of the new intrabodies will then be tested as above. If correction is incomplete with individual intrabodies, combination therapies will be tested in cells and in vivo. At the end of these studies, we will have established the optimal characteristics of intrabodies for eventual HD therapeutics and further drug discovery. These approaches should also be generally applicable for other neurodegenerative diseases that result from abnormal protein folding and accumulation, including Alzheimer's, Parkinson's, and prion diseases.

- **Project Title: MECHANISMS OF PRION STRAIN SELECTION**

  Principal Investigator & Institution: Bartz, Jason C.; Assistant Professor; Medical Microbiol & Immunology; Creighton University 2500 California Plaza Omaha, Ne 68178

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

  Summary: (provided by applicant): Prion diseases are a group of emerging transmissible neurodegenerative diseases of humans and animals. Prion diseases of humans can be caused by interspecies transmission, for example, variant Creutzfeldt-Jacob disease is caused by transmission of bovine spongiform encephalopathy to humans. Following interspecies transmission, adaptation of prions to a new host species can involve competition between prion strains until one prion strain predominates. The long-term goal of this laboratory is to describe the mechanism(s) of prion adaptation to a new host species. In a step to achieve this goal, we plan to investigate the molecular basis of prion strain selection. We have developed a prion strain selection model where hamsters are first infected in the sciatic nerve (i.n.) with the drowsy (DY) strain of transmissible mink encephalopathy (TME), then i.n. superinfected with the hyper (HY) strain of TME. Using this model, we have localized the site of prion strain selection to the lumbar spinal cord, most likely within ventral motor neurons (VMNs). We hypothesize that alterations in prion agent transport and/or prion agent replication are responsible for prion strain selection within the central nervous system. To investigate this hypothesis we will i) establishing the degree to which DY TME infection alters axonal transport of a retrograde tracer or epitope or fluorescently labeled PrPSc from the sciatic nerve to VMNs in the lumbar spinal cord ii) determine the effect of DY TME replication in VMNs has on subsequent HY TME replication in VMNs by Western blot analysis and/or animal bioassay of microdissected VMNs and iii) assess the effect of DY TME infection on the viability of VMNs which are the first cell type infected by HY TME following sciatic nerve inoculation by quantifying VMN populations using unbiased stereology. Results from the aims in this proposal will define the mechanism(s) of prion selection, begin to address the factor(s) that prions compete for, and advance our understanding of how prions adapt to a new host species following interspecies transmission.

- **Project Title: MURINE TRANSGENIC MODELS OF PRION DISEASES**

  Principal Investigator & Institution: Harris, David A.; Associate Professor; Cell Biology and Physiology; Washington University 1 Brookings Dr, Campus Box 1054 Saint Louis, Mo 631304899

  Timing: Fiscal Year 2006; Project Start 15-JAN-2001; Project End 31-JAN-2011

Summary: (provided by applicant): The overall goal of this application is to investigate the pathogenesis of prion diseases using transgenic (Tg) mouse models. Our objective is to understand the molecular and cellular mechanisms by which prions kill neurons and damage the CNS. A major focus of our work has been on Tg mice that express a PrP molecule with a nine-octapeptide insertional mutation (PG14) associated with a familial form of Creutzfeldt- Jakob disease in humans. These mice model several essential features of inherited human prion diseases, including progressive ataxia, neuronal loss, astrocytosis, and accumulation of an abnormally folded form of mutant PrP. During the previous funding period, we created new lines of Tg mice which selectively express PG14 PrP in forebrain neurons under control of a tetracycline-regulated promoter; we investigated whether ER-associated degradation plays a role in the metabolism of the mutant protein; and we compared the molecular and biological properties of two forms of PG14 PrP that differ dramatically in their infectivity and oligomeric structure. In the present application, we propose to expand our search for PrP-related pathogenic processes. In each of the aims, we will explore one of three complementary mechanisms by which PrP might produce neurotoxic effects: gain of function, loss of function, and subversion of function. In the first aim, we will use Tg mice expressing a GFP-tagged version of PG14 PrP to explore the hypothesis that aggregates of PG14 PrP interfere with axonal transport and synaptic function, and that this toxic activity contributes to the disease phenotype in Tg(PG14) mice. In the second aim, we will determine whether loss of a normal neuroprotective activity of PrP contributes to neurodegeneration in Tg(PG14) mice. In the third aim, we will investigate the neurotoxic effects of a deleted form of PrP that may act by subverting the normal function of PrP, much like PrPSc is thought to do during prion infection. We anticipate that these studies will provide insights into the process of prion-induced neurodegeneration, and will identify molecular targets for therapeutic intervention in these and other neurodegenerative disorders.

- **Project Title: NEUROBIOLOGY OF DISEASE -- TEACHING WORKSHOP**

  Principal Investigator & Institution: Kriegstein, Arnold R.; Professor; Society for Neuroscience 11 Dupont Cir Nw, Ste 500 Washington, Dc 20036

  Timing: Fiscal Year 2005; Project Start 01-AUG-1983; Project End 31-OCT-2006

  Summary: The Society for Neuroscience (SFN) is the major professional organization for scientists who study the nervous system. An important goal of this organization is to encourage scientists in training to undertake research related to diseases of the nervous system. The objective of this grant application is to support teaching workshops that introduce young neuroscientists to current concepts about the etiology and pathogenesis of disorders of the nervous system. For each workshop, about 12 faculty are chosen by the Organizing Committee after eliciting proposals from the Society at large. Clinical presentations provide enrollees with an experience of the human dimension of particular diseases. Lectures cover both clinical research and relevant laboratory work. In addition to lectures, enrollees are given a choice of attending two of four small group workshops that emphasize either specific or methodological issues and encourage lively discussion. Since its inception, 20 workshops have been held, usually on the day prior to the start of the Society for Neuroscience meeting. Topics have included: Infections in the nervous system, epilepsy, Huntington's and Alzheimer's diseases, muscular dystrophy, multiple sclerosis, prion diseases, drug addiction, pain and affective disorders, stroke and excitotoxicity, neuromuscular diseases, amyotrophic lateral sclerosis, schizophrenia, migraine, mental retardation and developmental disorders, Tourette's syndrome and obsessive-compulsive disorder, and the neurobiology of brain tumors. Enrollment generally runs between 100 and 200 attendees. Most enrollees are graduate students or

postdoctoral fellows. Current plans are to cover the following topics in the near future: Genes, free radicals, mitochondria and apoptosis in Parkinson's disease, AIDS dementia, peripheral neuropathy, pain, language disorders, and affective disorders. Other topics will be chosen depending on their potential interest to young neuroscientists, their impact on society and the quality of recent research related to that disease area. We are especially interested in covering diseases of the nervous system which are important clinically but which are in need of enhanced basic cellular and molecular understanding. Society members are encouraged to suggest topics in the SFN Newsletter.

- **Project Title: NEUROIMAGING OF GENETICALLY-DEFINED INCIPIENT CJD**

  Principal Investigator & Institution: Prohovnik, Isak; Psychiatry; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 100296574

  Timing: Fiscal Year 2005; Project Start 01-JAN-2005; Project End 31-DEC-2007

  Summary: (provided by applicant): Creutzfeldt-Jakob Disease (CJD), the most notable of the human prion diseases, is invariably fatal. The rarity of CJD, difficulty of early diagnosis, virulent course, and variable modes of transmission, have made clinical studies exceedingly difficult. We here propose a unique method of addressing the difficulties of clinical research in this area. We will use advanced MRI methodology to elucidate early, and even premorbid, cerebral abnormalities of structure and function in such patients. We plan to capitalize on a singular cluster of high incidence occurring among Libyan Jews living in Israel, caused by familial transmission of a mutated prion protein (PrP) gene. Healthy carriers of the relevant mutation (E200K) will be identified (n=50), and will be studied before, as well as after, symptomatic expression. Family members lacking the mutation will serve as controls (n=50). In addition, we will recruit into the study all incident CJD cases in Israel that carry this mutation. We believe we will be able to examine these incident cases within 2 months of onset, and follow them for the duration of the disease. All subjects will have extensive neurological and neuropsychological examinations, as well as MRI, using both traditional structural imaging and newer neuroimaging methods: Diffusion- Weighted Imaging (DWI) and Chemical Shift Imaging (CSI). This project will be the largest neuroimaging study ever conducted in this disease, and the first to observe a genetically homogenous sample. Further, it will provide data on the earliest stages of the disease, including healthy mutation carriers before frank onset of symptomatology. The large sample sizes, availability of healthy mutation carriers, the noncarriers of similar environmental and cultural background, and rapid access to symptomatic patients, are all unprecedented features that should yield definitive data on the early stages of this devastating disease.

- **Project Title: NEW CLINICAL APPROACHES TO CREUTZFELDT-JAKOB DISEASE**

  Principal Investigator & Institution: Geschwind, Michael D.; Neurology; University of California San Francisco 3333 California St., Ste. 315 San Francisco, Ca 941430962

  Timing: Fiscal Year 2005; Project Start 15-SEP-2003; Project End 31-AUG-2008

  Summary: (provided by applicant): Creutzfeldt-Jakob disease (CJD)is a rapidly progressive, universally fatal, and transmissible neurodegenerative disease that imposes a terrible burden on patients and their families. The recent discovery that quinacrine may be a potential therapy for CJD could have enormous implications for patients. Unfortunately, patients are usually diagnosed in advanced stages of the disease - a time when available treatments may be ineffective. This delayed diagnosis is in part because current clinical criteria for sporadic CJD (sCJD) are based on a constellation of symptoms that often occur only late in a patient's course. Recently, neuroimaging has shown potential to improve the diagnosis of sCJD. Additionally, an elevated level of the

protein 14-3-3 in the cerebrospinal fluid (CSF) has been touted as a sensitive and specific biomarker for sCJD and has recently been added to the diagnostic criteria for sCJD. Yet, no systematic study has been undertaken to identify the sensitivity and specificity of these two types of biomarkers in pathologically proven sCJD versus non-prion rapidly progressive dementias. The research goals of this proposal focus on identifying better ways for early diagnosis of CJD through a systematic analysis of clinical and imaging findings. The specific aims of this research will be as follows: 1. To determine the sensitivity and specificity of diffusion-weighted imaging (DWI) sequence abnormalities in sporadic CJD, and 2. To determine the sensitivity and specificity of the CSF 14-3-3 protein as a marker for sporadic CJD. This research should provide new information on the early features of sCJD and thus facilitate diagnosis. In addition, this proposal will combine didactic teaching, mentoring, and clinical research experience to build upon Dr. Geschwind's training in behavioral neurology and neuroscience, thereby helping him to design and implement future clinical treatment studies for human **prion disease** and other dementias.

- **Project Title: NMR STUDIES OF PRION PROTEINS WITH POINT MUTATIONS**

  Principal Investigator & Institution: Wright, Peter E.; Professor and Chairman; University of California San Francisco 3333 California St., Ste. 315 San Francisco, Ca 941430962

  Timing: Fiscal Year 2003; Project Start 01-DEC-2002; Project End 30-NOV-2007

  Summary: Although a large amount of structural information is available on the cellular prion protein from a number of species, little beyond the bare knowledge of secondary structure content available from CD spectra is available for the disease-causing scrapie form of the protein. Given the multimeric and insoluble nature of this form of the protein, it appears unlikely that high-resolution structural information will be forthcoming on this form of the protein in the absence of breakthroughs in sample preparation or spectroscopic techniques. One approach to this problem is to examine the underlying structural basis for the enhanced disease susceptibility of mutant forms of the protein found in familial prion diseases, together with the reduced susceptibility found for certain dominant negative prion protein mutants. In order to address this question, this project will investigate the structure and dynamics of three mutant forms of the minimal infective domain (PrP90-231) of the mouse prion protein. In Specific Aim 1, the high-resolution NMR solution structures will be calculated and polypeptide chain dynamics will be analyzed for two mutant proteins that exhibit dominant negative phenotypes (that is, exhibit a lower propensity for **prion disease** than wild-type). These studies will have direct relevance and utility for the Program, providing detailed structural information that can be used for structure-based design of therapeutics. A control system, the P102L mutant protein frequently found in the inherited Gerstmann-Straussler-Scheinker disease, will be studied in Specific Aim 2. A high-resolution solution structure will be calculated for this protein, which shows increased propensity for prion formation. Polypeptide chain dynamics measured by NMR will also be an important component of this part of the project. Specific Aim 3 involves the direct visualization of the sites of binding of the therapeutic drugs developed in this Program using the technique of NMR chemical shift mapping. The studies in Specific Aims 1-3 should prove to be of direct use to other components of the Program Project, by providing information vital to the iterative design of novel, effective therapeutics. In addition, it is anticipated that important insights will be gained into the structural basis of the conversion of prion proteins to insoluble disease-causing forms.

- **Project Title: NOVEL THERAPEUTICS FOR PRION DISEASES**

  Principal Investigator & Institution: Prusiner, Stanley B.; Professor; Institute for Neurodegenerative Diseases (Ind); University of California San Francisco 3333 California St., Ste. 315 San Francisco, Ca 941430962

  Timing: Fiscal Year 2005; Project Start 01-JUN-2003; Project End 31-MAY-2008

  Summary: (provided by applicant): Prion diseases are neurodegenerative diseases of humans and animals, which are invariably fatal and lead to death within a year after the onset of clinical symptoms. As with most other neurodegenerative diseases, no effective therapy is known. Treatment of patients with sporadic (s) Creutzfeldt-Jakob disease (CJD), the most common human **prion disease,** employing quinacrine will be studied. CJD patients will initially receive a racemic mixture of quinacrine. Quinacrine has been shown to inhibit prion formation in cultured ScN2a cells at submicromolar concentrations. Additionally, experimental **prion disease** in mice will be treated with quinacrine. In studies with ScN2a cells, the (S)-quinacrine isomer was 2 to 3 times more potent with respect to inhibiting prion formation than (R)-quinacrine; these isomers will be compared to the racemic mixture in mice. Concurrently, murine models will be used to evaluate treatment of **prion disease** with new drugs produced through empirical and rational drug design. The empirical drug program will utilize a combinatorial chemistry approach with quinacrine as the lead compound. Quinacrine will be modified and tested in the ScN2a cell culture system. We plan to test about 2000 new quinacrine analogs per year. Only compounds that are 10 times more potent than quinacrine with respect to antiprion activity will be evaluated in mice. Initially, these new antiprion compounds will be screened for toxicity. Compounds that are determined to be sufficiently nontoxic will then be tested for their ability to block prion synthesis in transgenic (Tg) mice. Besides empirical drug discovery, we plan to expand a rational drug design program along two lines of investigation. Attempts will be made to increase the potency of quinacrine by further modifying the aliphatic side chain. Recent studies have shown that bis-quinacrine analogs are more potent than quinacrine by a factor of ten. We also plan to dissect the mode of quinacrine action through studies of PrP trafficking in cultured cells. A second line of rational drug design involves modifying compound 60, which was found by mimicking dominant negative inhibition of prion synthesis. In order to understand dominant negative inhibition of prion synthesis, the structures of dominant negative PrPs will be determined using NMR spectroscopy. The information obtained from these dominant negatives should facilitate improvements in the design of existing drugs or lead to the production of new drugs. PRINCIPAL INVESTIGATOR The PI of this PPG, Dr. Stanley Prusiner, is a professor of Biochemistry and the director of Neurodegenerative diseases at UCSF. He has extensive experience in the area of virology and neurology and in directing research projects of this magnitude. He is a leading authority in prion research for the last several years. He is the recipient of numerous national and international awards, including the nobel prize in 1998. He has published more than 200 articles in scientific journals of interanational repute. He has trained and supervised several researchers/clinicians and thus is well qualified to lead this group and the project. REVIEW OF INDIVIDUAL COMPONENTS PROJECT 1: Clinical Study of Quinacrine for Treatment of Human Prion Diseases; Dr. Richard Miller (PL) (provided by applicant): Creutzfeldt-Jakob disease (CJD)is a rapidly progressive, invariably fatal and untreatable neurodegenerative disease with a mean duration of about eight months. Beyond the debilitating cognitive and motor deficits that accompany CJD, the difficulty in treating behavioral and mood disturbances and the rapidity of its course compound its tragedy. Moreover, an epidemic of new variant CJD (nvCJD) in England has raised serious concerns regarding the safety of the world's beef supply; the possibility that prions might be passed through the blood has led to the

banning of blood or tissue donations from individuals who have resided in England. The discovery of an effective therapy for prion diseases would have enormous human and economic implications. Recent results from experiments in Dr. Prusiner's laboratory show that, at physiological concentrations, the anti-malarial drug quinacrine permanently clears abnormal prion proteins from cell culture. The demonstrated efficacy of quinacrine in cell culture, its relative safety and well known side-effects in the clinical setting, and the universal fatality of CJD justify quinacrine as an immediate candidate for the treatment of CJD. We propose a treatment study for patients with sporadic CJD (sCJD) with racemic quinacrine. Over three years, 90 patients will be admitted to the University of California at San Francisco (UCSF) NIH-funded clinical research center where a diagnosis of sCJD will be determined and where patients will enter into a randomized, double-blinded, treatment study with quinacrine. Patients will be divided into two quinacrine arms, a high-dose titration (450 mg daily) and a low-dose titration (75 mg daily). They will be treated for one year and then be followed through to the end of the five-year study period. The dose of quinacrine may be increased or decreased in each patient depending on clinical deterioration or toxicity, respectively. Survival will be the primary outcome measure of this clinical study. Also, additional outcome measures will be used that assess activities of daily living, cognition, MRI and EEG. We hypothesize that patients in the high-dose quinacrine arm will have increased survival and a slower rate of neurological progression compared with patients in the low dose arm. By year four of this program Project grant (PPG), we hope to begin a clinical study with a new compound, developed in other Projects in this PPG that shows even greater efficacy than racemic quinacrine.

- **Project Title: PATHOGENETIC MECHANISMS OF PRION DISEASES**

  Principal Investigator & Institution: Gambetti, Pierluigi; Professor and Director; Pathology; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

  Timing: Fiscal Year 2005; Project Start 15-JUN-1997; Project End 31-MAY-2007

  Summary: (provided by applicant): The present Program Project focuses on three major aspects of PrPsc: 1) mode of formation; 2) physical and chemical characteristics; 3) mechanisms of pathogenicity. Four Research Projects are proposed. Project by Surewicz addresses the critical issue of PrPsc conformation using the PrPsc-like recombinant PrP developed in our group. Mechanisms of amyloid fiber formation by the Yl45Stop mutant PrP, which generates an N-terminal PrP fragment, as well as the effect of other mutations on the conformation of PrPsc will also be examined. Project by Chen proposes a comparative study of PrPsc in human and animal prion diseases. Characteristics that will be analyzed include gel migration and pattern of glycosylation. In addition, N-terminal protease cleavage sites, beta-sheet structure and aggregation of distinct PrPsc species will be determined and correlated. Project by Gambetti deals with the regions of human PrPsc that carry the infectivity and with the role of glycans in PrPsc strain formation as well as disease phenotype determination. Furthermore, the mechanisms of PrP to PrPsc conversion likely to vary in different mutations will be examined in cell models of genetic prion diseases. Project by Singh iis dedicated to studying the important issue of intercellular spreading of PrPsc. It will be first assessed whether synthetic and naturally occurring short PrP peptides are transported through a monolayer of intestinal and endothelial cells. Then, similar studies will be carried out with PrPsc from brain homogenates and in intact animals. An Administrative Core, Animal Core and Tissue Core are also proposed. In addition to characterizing all tissues, the Tissue Core will continue to define classification and phenotypic spectrum of human prion diseases. This Program Project takes advantage of the close interactions and diverse expertise of several investigators to propose a multidisciplinary study of various

aspects of PrPsc. As PrPsc has emergedas the central player in prion diseases, the studies proposed will lead to a clearer understanding of the pathogenesis in these diseases.

- **Project Title: PREDOCTORAL FELLOWSHIP FOR STUDENTS WITH DISABILITIES**

  Principal Investigator & Institution: Click, Timothy H.; Chemistry and Biochemistry; University of Oklahoma Norman Office of Research Services Norman, Ok 73019

  Timing: Fiscal Year 2005; Project Start 22-AUG-2003; Project End 21-NOV-2007

  Summary: (provided by applicant): Scientists have used computational simulations to observe geometry optimization of molecules like proteins and to calculate the free energy differences between two molecules. Most simulations encounter large energy barriers that prevent the observation of a folded protein accurately or that prevent the calculation of absolute free energies. With methods developed in the lab of Dr. Ralph A. Wheeler, I will predict the correct folded structure of a protein and will calculate not only the relative free energy differences between molecules, but the absolute free energy of a molecule. First, I will test the geometry optimization method on dialanine, divaline, an a-helical polypeptide and a b-sheet polypeptide. I will extend the tests on prion proteins observing the folding of the mostly alpha-helical protein to the beta-sheet dominant protein. I will test the free energy calculation method with small organic molecules, dipeptides, and helix-forming and sheet-forming proteins. The tests will be extended to point mutations of the prion proteins calculating the propensities of the protein. Finally, calculations will be done to find the binding free energy differences between molecules bound to the prion protein. Through these simulations, drugs could be designed to combat the **prion disease.** Such possibilities include the stabilization of the a-helical form or the prevention of aggregation after the b-sheets are formed.

- **Project Title: PREVENTION OF RECOMBINANT PROTEIN AGGREGATION IN E.COLI**

  Principal Investigator & Institution: Chong, Shaorong; New England Biolabs, Inc. 240 County Road Ipswich, Ma 01938

  Timing: Fiscal Year 2005; Project Start 15-JUL-2005; Project End 30-JUN-2006

  Summary: (provided by applicant): The goal of the project is to use a novel approach to prevent recombinant protein misfolding and aggregation during overexpression in E. coli. The system used in this project consists of an aggregation-prone protein fused to a reporter protein (green fluorescent protein (GFP)) that reports solubility of the fusion protein in vivo. Co-expression of a third protein that binds and folds the aggregation-prone protein during protein synthesis prevents protein aggregation and results in a visible change in the signal of the reporter protein (GFP fluorescence). This system is used as a screening tool for two parallel efforts. The first is to engineer E. coli chaperones by random mutagenesis, followed by molecular evolution. The second is to construct expression libraries using yeast genomic DMA and mammalian cDNA libraries. By co-expressing libraries of chaperone mutants or eukaryotic ORFs in the E. coli cells containing the aggregation-prone protein-GFP fusion, chaperone variants, novel chaperones and folding partners that are efficient in preventing aggregation of a given recombinant protein or a family of recombinant proteins will be identified. Successful outcome of this project will help to solve one of the bottle-necks of structure genomics, lead to production of suitable amounts of proper folded proteins or protein complexes as commercial products or for structural studies, and reveal important protein-protein interactions. Structural studies of such interactions can lead to further

understanding of chaperone-assisted protein folding in particular and protein folding and aggregation in general. Several neurodegenerative diseases, such as Huntington's disease, Alzheimer's disease and prion diseases, are characterized by accumulation of specific protein aggregates. Molecular chaperones have been shown to modulate solubility states of these protein aggregates. As a long-term goal, this project aims to provide insights into the mechanism of the aggregation by these disease-related proteins and the means to prevent aggregation.

- **Project Title: PRION TRANSPORT ACROSS THE BLOOD-BRAIN BARRIER**

  Principal Investigator & Institution: Banks, William A.; Professor; Internal Medicine; Saint Louis University 221 N Grand Blvd Saint Louis, Mo 63103

  Timing: Fiscal Year 2006; Project Start 15-AUG-2006; Project End 31-JAN-2010

  Summary: (provided by applicant): Prion diseases represent a diverse group of infectious neurodegenerative disorders. The most accepted hypothesis is that the infectious agent (termed prion) is a misfolded version of a normal protein completely devoid of nucleic acids. Disease is propagated when the infectious form (PrPsc) converts the normal form (PrPc) to the infectious form by reversibly combining with it. In scrapie, the prion is a glycoprotein with about a 30,000 MW protein core. To produce central nervous system (CNS) disease, PrPsc must enter the brain, which requires it negotiate the blood-brain barrier (BBB). The major goal of this research is to determine how PrPsc crosses the BBB and ultimately to develop therapeutic strategies for blocking passage into the CNS and so preventing **prion disease.** Work by us and others have shown that other neurotoxic glycoproteins (such as wheatgerm agglutinin and gp120, the coat of the AIDS virus) cross the BBB by inducing absorptive endocytosis (AE). We hypothesize that PrPsc crosses the BBB through the mechanism of AE. This hypothesis provides a mechanism for passage across the BBB of cell-free PrPsc and of PrPsc- infected immune cells and explains how some regions of the CNS, such as the thoracic spinal cord, can be especially targeted. Although our working hypothesis is that cell-free PrPsc is the major mechanism, these experiments are designed to determine the extent to which the other possible mechanisms of entry into the CNS (immune cell transfer, retrograde splenic nerve transmission, transmembrane diffusion, saturable carrier/receptor mediated transport, leakage via extracellular pathways) are operational for PrPsc. We will use highly purified, radioactively labeled PrPsc to determine rates of transport and distribution into brain regions, spinal cord, and CSF, the role of splenic nerves and immune cells in neuroinvasion, and in vitro models to examine the cellular biology of passage across the brain endothelial cell. Lay Summary: Prions cause rare, but devastating, diseases such as mad cow disease. To cause disease, prions must cross the blood-brain barrier to enter the brain. We will determine how prions cross the BBB. Knowing how prions enter the brain should lead to strategies on how to prevent prion diseases.

- **Project Title: PRP-SCRAPIE TRANSPORT ACROSS INTESTINAL & BBB**

  Principal Investigator & Institution: Singh, Neena; Associate Professor; Pathology; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

  Timing: Fiscal Year 2005; Project Start 20-SEP-2004; Project End 30-JUN-2008

  Summary: (provided by applicant): The transmission of variant Creutzfeldt-Jakob disease (vCJD) to humans from bovine-spongiform encephalopathy (BSE)-contaminated meat, and the transmission of BSE by intra-venous inoculation of peripheral blood to experimental animals raises two important questions: 1) how are prions from food transported across the intestinal epithelial barrier, and 2) how do prions in the

peripheral blood cross the endothelial blood brain barrier (BBB). These questions have gained increasing importance with the realization that close to one million BSE infected cows may have entered the human food chain. An emerging concern is the spread of Chronic Wasting Disease (CWD), a **prion disease** of the deer and elk in certain parts of USA, and the uncertainties regarding its transmission to livestock and humans. Despite these concerns, surprisingly little is known about the mechanism(s) by which the infectious prion or PrP-scrapie (PrPsc), a protein of 27-30kDa, is transported from the intestine or peripheral blood to the central nervous system. Preliminary data from my laboratory demonstrate that PrPsc in sporadic CJD (sCJD) brain homogenates is transported across epithelial cells in association with ferritin. When considered in context with additional data indicating an upregulation of brain ferritin levels in response to redox active iron in the brain parenchyma of sCJD cases, this observation raises important questions. We hypothesize that the transport of PrPsc across epithelial and endothelial cell barriers is facilitated by proteins like ferritin that have a defined transcytotic route, and that imbalance of brain iron homeostasis contributes directly to the pathogenesis of certain prion disorders, and indirectly by promoting infectivity through ferritin. Thus, the central goal of this proposal is to investigate the role of PrPs-associated proteins including ferritin and transferrin in facilitating its transport across the intestinal epithelium and the BBB, and to evaluate the role of redox active iron in the pathogenesis of prion disorders. The proposed studies will be carried out in three specific aims. In aim 1, the role of ferritin, transferrin, and other PrPsc-associated proteins in the transport of PrPsc across in vitro models of human intestinal epithelial cell barrier and the BBB will be evaluated. In aim 2, the results obtained from in vitro models in aim 1 will be confirmed in vivo in transgenic mice expressing human PrP. In aim 3, the role of redox active iron in the pathogenesis of priori disorders will be investigated using ferritin over-expressing and H-ferritin deletion transgenic mice. These studies will help in evaluating the risk of human population to BSE, vCJD, and CWD infection, and help in understanding the mechanism of **prion disease** pathogenesis.

- **Project Title: QUALITY CONTROL: SELECTIVE DEGRADATION FROM THE ER/GOLGI**

  Principal Investigator & Institution: Cooper, Antony A.; Cell Biology and Biophysics; University of Missouri Kansas City 5100 Rockhill Road Kansas City, Mo 64110

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

  Summary: (provided by applicant): Soluble and membrane proteins of the secretory pathway enter the ER where they fold, are modified by carbohydrate addition and disulfide bond formation and assemble into complexes. Before exiting the ER, proteins must pass a quality control (ERQC) test. ERQC encompasses all those processes that ensure that only correctly folded/modified/assembled proteins exit the ER and includes retention in the ER, retrieval from downstream organelles and ER-associated degradation. ERQC contributes to the manifestation of disease either by depleting cells of essential proteins or by the toxic accumulation/aggregation of aberrant proteins. A progressive decline of ERQC in ageing highly differentiated neurons may play a major role in the neurodegenerative diseases such as Parkinson, Alzheimer's, Huntington's and prion diseases, all of which involve protein aggregation as the underlying pathology. The overall goal of this research is to understand the process of ERQC by defining the molecular components involved and determining how ERQC components function to recognize, retain, and retro-translocate misfolded substrates to be ubquitinated and degraded by the proteasome. The proposed project has four specific aims directed toward this goal. (1) The components of ERQC will be identified through

a characterization of previously isolated ERQC mutants obtained at the end of the last grant period and through a genome wide mutant screen, synthetic genetic array analysis, synthetic lethal screen and micro array analysis to identify new components. (2) The role of ER to Golgi trafficking in ERQC will be examined through the use of retrograde trafficking mutants, cross-linking to Erv29p (a cargo receptor for ER exit) and determining the impact that glycosylation in the Golgi has on the degradation of ERQC substrates. (3) The aggregation of misfolded ERQC substrates in the ER results in their accumulation and associated cytotoxic effects. This specific aim is designed to identify ERQC substrate proteins that misfold and aggregate in the ER for use as a disease model in examining how cells contend with these potentially lethal accumulations. (4) A model substrate will assist in determining how soluble and polytopic membrane protein is treated differently by the ERQC. Knowledge and insights gained from these aims will lead to an understanding of the process of ERQC to be used to interpret protein aggregation based diseases.

- **Project Title: REGULATION OF MAMMALIAN COPPER HOMEOTASIS**

  Principal Investigator & Institution: Petris, Michael J.; Assistant Professor; Nutritional Sciences; University of Missouri-Columbia 310 Jesse Hall Columbia, Mo 65211

  Timing: Fiscal Year 2005; Project Start 21-FEB-2004; Project End 30-NOV-2007

  Summary: (provided by applicant): Copper is an essential nutrient. However, despite its importance to human nutrition, little is known about the mechanisms regulating copper homeostasis in mammalian cells. Copper is required by several important enzymes, however, it is also toxic when present in excess concentrations. Thus, copper homeostasis mechanisms must supply sufficient copper to meet cellular needs, while preventing the over-accumulation of this nutrient. Copper uptake in mammalian cells occurs via the membrane-spanning protein, hCtr1. Currently, we have limited knowledge of whether hCtr1-mediated copper uptake is regulated in response to varying copper availability. In contrast, we have a more extensive knowledge of how copper export is regulated in mammalian cells. Two copper ATPases, ATP7A and ATP7B, which are normally located in the trans-Golgi network, are stimulated to relocate to cytoplasmic vesicles or the plasma membrane by elevated copper to facilitate copper efflux from the cytoplasm. In our preliminary studies, we show that the location of the hCtr1 protein is regulated by copper concentrations. Elevated copper stimulates the rapid endocytosis of hCtr1 from the plasma membrane, and this is associated with degradation of the transporter. We hypothesize that this process is likely to be the principle means by which high affinity copper uptake is regulated in mammalian cells. However, the underlying molecular mechanisms and signals involved have not yet been defined. Our long-term goal is to understand the molecular basis for regulating hCtr1-dependent copper uptake. To achieve this overall goal, we propose the following specific aims: 1.To define the intracellular pathway for copper-stimulated endocytosis and degradation of hCtr1. 2. To identify amino acids within hCtr1 important for copper uptake, copper-induced endocytosis and degradation. 3. To assess whether the localization, endocytosis and degradation of hCtr1 is responsive to intracellular copper levels. 4. To determine whether the hCtr1 protein undergoes copper-stimulated endocytosis and degradation in a range of cell types. Our research will contribute greatly to understanding how cells sense and respond to changes in copper availability. The implication of copper in Alzheimer's disease, prion diseases, and several genetic disorders, suggests the study of hCtr1 may have far-reaching implications for the improvement of human health.

- **Project Title: ROLE OF PRION PROTEIN IN NEURONAL SURVIVAL**

  Principal Investigator & Institution: Leblanc, Andrea C.; Professor; Mc Gill University 845 Sherbrooke Street West Montreal, Pq H3a 2T5

  Timing: Fiscal Year 2005; Project Start 15-FEB-2002; Project End 31-JAN-2007

  Summary: (Adapted from applicant's abstract): The long-term goal of this application is to identify the function of prion protein (PrP) in the central nervous system. Four octapeptide repeats in the N-terminus of PrP are homologous to the BH2 domain of Bcl2 family of proteins. Based on preliminary observations that PrP interacts with pro-apoptotic Bax proteins and protects yeast and primary human neurons against Bax-mediated cell death, the investigator proposes the hypothesis that interaction between PrP and Bax mediates neuronal survival, and that this mechanism may be implicated in **prion disease** associated neuronal loss. This hypothesis will be tested in the following Specific Aims. Aim 1 will determine if PrP interaction with Bax is necessary for the neuroprotective function of PrP. PrP mutants will be generated that prevent PrP-Bax interaction and determining if co-expression of these mutants abolishes PrP's ability to inhibit Bax-mediated cell death. The function of these mutants will be tested in yeast by using galactose inducible constructs and micro-injection of eukaryotic expression constructs in human neurons. Aim 2 will determine if human PrP mutations associated with prion diseases dysregulate PrP-Bax interaction and PrP neuroprotective function. Mutations of PrP that are known to cause disease will be tested for their ability to interact with Bax and protect yeast or neurons against Bax-mediated cell death. Aim 3 will determine the location of neuroprotective PrP. The functional location of PrP and Bax will be determined by using mutant PrP and protein trafficking blocks. Primary cultures of human neurons will be used to examine protein localization by subcellular fractionation, beta-galactosidase complementation, pulse-chase experiments, immunofluorescence and confocal microscopy, and immuno-EM. Aim 4 will determine the molecular mechanism of neuronal protection by PrP. Specific Aim 5 will determine if PrP interacts with other pro-apoptotic proteins. In Aim 6, the neuroprotective role of PrP and the possible elimination of this function in PrP mutations associated with familial prion diseases will be assessed in mice models of familial prion diseases. The result of these experiments will clearly define the neuroprotective role of PrP against Bax mediated cell death.

- **Project Title: SELF-PROPAGATING MECHANISM OF PRION DISEASES**

  Principal Investigator & Institution: Baskakov, Ilia V.; Associate Professor; None; University of Md Biotechnology Institute 701 E Pratt Street, Suite 200 Baltimore, Md 212023101

  Timing: Fiscal Year 2005; Project Start 30-SEP-2003; Project End 31-MAY-2007

  Summary: (provided by applicant): Prion protein (PrP) underlies a spectrum of diseases with no established treatment and devastating human and economic consequences. Several unique features separate prion diseases from other neurodegenerative maladies. (i) There is an infectious isoform of the prion protein, PrPSc, that propagates its abnormal conformation in an autocatalytic manner using the normal isoform, PrPC, as a substrate. (ii) The process of propagation requires the amino acid sequences of PrPC and PrPSc to be identical (or highly homologous). (iii) Within the same primary structure, PrP is capable of adopting conformationally distinct states when it is converted into pathological isoforms, which are known as "strains" of PrPSc. These features indicate that prion diseases have a unique molecular mechanism, distinct from other disorders related to protein aggregation. Our general strategy is to concentrate on these features of PrPSc propagation as a key for understanding the mechanism of **prion disease.** The

hypothesis to be tested is whether these distinguishing features are inherent properties of the prion protein. In particular, the PI will examine the extent to which the process of aggregation of non-glycosylated recombinant PrP mimics basic hallmarks of prion diseases outside of the cellular environment. Using state-of-the-art biochemical and biophysical methods, three aspects of the self-propagating process will be investigated: (1) the kinetic pathway of self-propagating aggregation, with special emphasis on the early events and the rate-limiting step of conversion; (2) the biophysical nature of the autocatalytic mechanism of aggregation; (3) the conformational diversity of self-propagating aggregates and fidelity of propagation. In the proposed work, an array of biophysical tools will be used: proteinase K digestion combined with mass spectrometry, immunoconformational assay, analytical size-exclusion chromatography with unique ultra sensitive detection, spectroscopic techniques, dynamic light scattering, and electron microscopy. The proposed research work will shed light on the mechanism of self-propagation, will reveal novel rules of protein folding that govern specific aggregations, and define the features that make PrP unique among proteins. Such knowledge should lay the foundation for novel molecular and pharmacological approaches for treating prion diseases.

- **Project Title: SPECIES SUSCEPTIBILITY ASSAY FOR CHRONIC WASTING DISEASE**

  Principal Investigator & Institution: Supattapone, Surachai; Assistant Professor; Biochemistry; Dartmouth College Office of Sponsored Projects Hanover, Nh 03755

  Timing: Fiscal Year 2005; Project Start 30-SEP-2004; Project End 31-AUG-2006

  Summary: (provided by applicant): Like rabies, chronic wasting disease (CWD) is a fatal infectious disease with a wildlife reservoir. Strategies to combat CWD and other wildlife prion diseases will require a combination of active surveillance and wildlife control measures. The identification of species susceptible to CWD is of particular importance because, while the mode of transmission in the wild remains unknown, it is not possible to predict the likely impact of the current epidemic. In the brains of humans and animals affected by prion diseases, a cellular glycoprotein termed PrPc converts into n protease-resistant pathogenic isoform called PrPsc. In our laboratory, we have focused on developing a novel method that can be conveniently used for susceptibility testing in a variety of prion diseases. This method amplifies PrPsc levels in prion-infected tissue homogenates biochemically in the presence of normal brain tissue containing PrPc. We have successfully amplified PrPsc>10-fold in brain membrane preparations biochemically without detergents or harsh physical disruption of cellular constituents. Consistent with the characteristics of PrPc conversion to PrPsc in vivo, our method of PrPsc amplification is prion-specific, and depends upon time, pH, and temperature. Significantly, the degree of PrPsc amplification in vitro correlates with the susceptibility of a specific animal species to prion infection in vivo. Furthermore, we have successfully amplified PrPsc from four different prion strains derived from two animal species. We now propose to test the hypothesis that non-cervid species might be susceptible to CWD infection or subclinical carriage. In partnership with the Dartmouth Hitchcock Medical Center, New Hampshire Fish and Game Authority, and New Hampshire State Veterinary Diagnostic Laboratory, we propose to use in vitro PrPsc amplification to measure the potential susceptibility of a range of potential host species to CWD as well as scrapie. Species to be tested include humans, cows, pigs, sheep, goats, chickens, dogs, cats, coyotes, foxes, raccoons, fisher cats, hares, and deer mice. The results of this work will efficiently identify species potentially susceptible to CWD and scrapie and help facilitate public health surveillance and control efforts for North American prion diseases.

- **Project Title: STRUCTURAL INVESTIGATIONS OF THE PRION PROTEIN HET-S**

  Principal Investigator & Institution: Riek, Roland P.; Associate Professor; Salk Institute for Biological Studies 10010 N Torrey Pines Rd La Jolla, Ca 920371099

  Timing: Fiscal Year 2005; Project Start 01-FEB-2003; Project End 31-JAN-2007

  Summary: (provided by applicant): The "protein-only hypothesis" states that prion diseases such as scrapie in sheep, bovine spongiform encephalopathy (BSE) and Creutzfeldt-Jakob disease in human are distinct from infectious diseases caused by bacteria, viruses, or viroids, in that the origin of the disease is related to conformational alterations of an ubiquitous protein and that nucleic acids are not essential for the propagation of the infectious agent. Thus, prions are infectious proteins which propagate by converting the normal form of the protein into an altered beta-sheet-rich conformation. Prion proteins have also been identified in lower eukaryotes, namely yeast and the filamentous fungus Podospora anserina. Totally, there are only four different proteins known so far which may adopt a prion state, and only for the het-s prion system in Podospora anserina has it been shown convincingly that the het-s prion protein is indeed the infectious agent. Furthermore, the het-s protein is the only known prion protein of which the prion state, pHET-s, is part of a normal cellular function, namely cell fusion incompatibility, a common feature in filamentous fungi. The aim of the project described in this proposal is to get structural insights into the components of the het-s prion system of the filamentous fungus Podospora anserina using solution-state nuclear magnetic resonance spectroscopy (NMR), other biophysical techniques, mutagenesis and in vivo studies. The three-dimensional structures of the non-prion form of the het-s protein and a prion-incompetent analog will be determined and accompanied with mutagnesis to elucidate the spatial regions and the residues important for the generation of infectivity. Furthermore, structural studies of the prion form of the het-s protein will be initiated to get insights into the conformational transition of the het-s protein which has been assoicated with infectivity. The structural knowledge of the individual components and detailed analysis of the conformational transition which is associated with the generation of a prion phenotype will therefore extend our understanding of the het-s system in particular, and also of the mechanism of prions and their origin of infectivity in general.

- **Project Title: STRUCTURE AND FUNCTION OF ALPHA-SYNUCLEIN**

  Principal Investigator & Institution: Eliezer, David; Assistant Professor; Biochemistry; Weill Medical College of Cornell Univ 1300 York Avenue New York, Ny 10021

  Timing: Fiscal Year 2005; Project Start 01-APR-2001; Project End 31-MAR-2010

  Summary: (provided by applicant): Aggregation of a-synuclein (aS) plays an important but still poorly understood role in the pathogenesis of Parkinson's disease (PD). The normal function of aS remains unknown, but the protein binds to phospholipid membranes and is believed to regulate synaptic vesicle pool size, vesicle recycling, neurotransmitter transport and release, and synaptic plasticity. Since the discovery of the link between aS and PD, there has been great interest in identifying aS interaction partners that influence either the pathogenic or normal roles of the protein. In the past few years, a growing number of proteins, polymers, and small molecules have been reported to bind to aS and alter its aggregation kinetics and/or its lipid-associated functions. Among these are two other members of the synuclein family, B-synuclein (BS) and y-synuclein (yS). Covalent modifications also affect aS aggregation and function. However, the mechanisms by which these various binding interactions and modifications influence aS behavior are not well understood. We have shown that residual structure in free aS may play an important role in mediating the intermolecular

interactions that precede amyloid fibril formation by this protein. We hypothesize that upon covalent modification or partner interactions, aS undergoes conformational changes that underlie the consequent effects on the aggregation or normal functions of the protein. We therefore propose to characterize, at high resolution, the structural changes that occur in aS as a function of its modifications and its interactions with different partners, with an initial focus on (BS, yS, histones, HSP70, PLD2, copper and other metals and polycations. We also propose to elucidate in detail the structure of (BS and yS in their free and lipid-bound states to clarify why aS exhibits different self-assembly behavior from these close relatives. Finally, we plan to test our conclusions regarding the role of structural changes in aS by introducing rationally designed mutants, collaboratively, into yeast and fly models of aS toxicity and function. The proposed studies are focused on improving our understanding of the molecular mechanisms underlying PD and may suggest strategies for developing new PD therapeutics. The results may have broader implications for understanding and treating other amyloid diseases, including Alzheimer's disease and the prion diseases.

- **Project Title: STRUCTURE AND FUNCTION OF HSP 100 PROTEINS**

  Principal Investigator & Institution: Zolkiewski, Michal; Biochemistry; Kansas State University 2 Fairchild Hall Manhattan, Ks 665061103

  Timing: Fiscal Year 2005; Project Start 01-MAY-2000; Project End 30-NOV-2006

  Summary: Failure of protein folding resulting in protein aggregation is a serious problem in molecular biology, biotechnology and medicine. Alzheimer's disease, prion diseases and inclusion-body myopathies are examples of pathological conditions arising from accumulation of misfolded and aggregated proteins in cells. Molecular chaperones, which belong to several heat-shock-protein (Hsp) families, inhibit protein aggregation and facilitate protein folding and assembly. Recently, novel multi-chaperone systems consisting of Hsp100, Hsp70, and Hsp40 proteins have been discovered in yeast and in Escherichia coli. Unlike previously studied chaperones, these multi-chaperone systems are capable of efficient reactivation of strongly aggregated proteins. In the E. coli system, ClpB, an Hsp100 protein with previously unknown function, cooperates with DnaK, DnaJ, and GrpE in reactivating aggregated luciferase. Our long-term goal is to understand the molecular mechanism of protein reactivation and disaggregation reactions involving Hsp100 proteins. In this proposal, we focus on ClpB as a member of the multi-chaperone system. ClpB is expressed in vivo as two gene products: 95-kDa ClpB95 and 80-kDa ClpB80. While both ClpB95 and ClpB80 exhibit ATPase activity, only the ATPase of ClpB95 is stimulated by other proteins. Our previous results show an ATP-induced self-association of ClpB, which is inhibited by ADP. We hypothesize that the mechanism of the ClpB chaperone function arises from allosteric couplings between ClpB-substrate of ClpB-co-chaperone interactions, ClpB self-association, and ATP binding and hydrolysis. We will test whether the observed differences in stimulation of the ATPase activities of ClpB95 and ClpB80 will be reflected in different protein-binding properties and chaperone activities of ClpB95 and ClkpB80. The proposed research will achieve the following aims: 1. Characterize nucleotide-dependent oligomerization of ClpB95 ClpB80. 2. Characterize interactions between ClpB95 or ClpB80 and the co-chaperones (DnaK, DnaJ, GrpE). 3. Characterize the role of ClpB95 or ClpB80 and the three co-chaperones in the disaggregation and reactivation of luciferase.

- **Project Title: SYNTHESIS OF NOVEL INHIBITORS OF AMYLOID FIBRILLOGENESIS**

  Principal Investigator & Institution: Torok, Bela; Chemical Engineering; Michigan Technological University 1400 Townsend Drive Houghton, Mi 499311295

  Timing: Fiscal Year 2005; Project Start 15-MAY-2005; Project End 15-AUG-2005

  Summary: (provided by applicant): Misfolded, amyIold-Iike protein deposits in cells and tissues are commonly associated with numerous human diseases, including Alzheimer's disease (AD), prion diseases (e.g. Creutzfeldt-Jakob disease), Parkinson's disease, Type-ll diabetes etc. representing tremendous medical, social and financial problems. The Alzheimer's disease involves the formation of extracellular amyloid-beta (Abeta) peptide into fibrillar deposits known as amyloid plaques (senile plaques). These fibrils (polymeric aggregates) or soluble oligomeric intermediates of Abeta peptide (or both) are associated with pathology. Accordingly, the inhibition of both seeding and fibril growing process in Abeta self-assembly is a promising therapeutic strategy. The goal of this proposal is to design and synthesize a new class of antifibrillogenic compounds. Based on literature data and encouraging preliminary results, we predict that a wide variety of our new compounds, such as CF3- containing indole-3-yl carboxylic acid derivatives and their higher analogs (peptidomimetics), will be able to inhibit the formation of amyloid oligomers and fibrils, and also might be able to reverse the oligomerization process. The inhibitors will be synthesized by our recently developed chiral organocatalytic process. The effect of inhibitors on fibrillogenesis will be tested in vitro by thioflavin-T fluorescence spectroscopy, Congo Red binding and high resolution transmission electron microscopy. A quantitative structure-activity relationship (QSAR) of the inhibitors will be determined. One series of experiments is designed to determine the inhibition, of Abeta fibrillogenesis, while another will describe whether these compounds are able to reverse the aggregation process, i.e. clear the already formed oligomers/fibrils. In the proposal, we will test our hypothesis with the fundamental goal of defining a new class of effective antifibrillogenic compounds, which, in turn, could lead to gain new insights into the mechanism of protein misfolding and amyloidogenesis and ultimately to the discovery of novel drug candidates against AD and related amyloid disorders.

- **Project Title: THE ROLE OF PRION PROTEIN CONFORMERS IN PRION DISEASE**

  Principal Investigator & Institution: Lingappa, Vishwanath R.; Professor; Physiology; University of California San Francisco 3333 California St., Ste. 315 San Francisco, Ca 941430962

  Timing: Fiscal Year 2005; Project Start 01-APR-1998; Project End 31-MAY-2005

  Summary: (provided by applicant): The prion protein (PrP) is a conserved glycoprotein of vertebrates that is involved in a group of spongiform neurodegenerative disorders, collectively termed prion diseases, some of which pose a substantial and currently unmet public health hazard around the globe. Hence a better understanding of PrP's role in **prion disease** pathogenesis is paramount. Prion diseases include overlapping sets of disorders that vary as to whether, and to what degree, they are inherited (genetic), infectious (transmissible), or seemingly spontaneous (sporadic) in etiology. These diverse manifestations suggest that important relationships between PrP and other genes involved in the development, maintenance, or function of the nervous system remain to be elucidated. Thus, the study of **prion disease** pathogenesis may be a powerful probe of otherwise currently intractable dimensions of neurobiology. PrP has also been of interest because of its remarkable biogenesis. Initially homogeneous nascent PrP chains are synthesized as distinctive forms, termed conformers that are identical in

primary amino acid sequence but different in both transmembrane topology and intrinsic folding. A complex machinery has been implicated in the genesis of two of the PrP conformers, termed SecPrP and CtmPrP, and a surprising role for signal sequences in directing this process has been identified. Independent lines of inquiry converged with the demonstration that the unusual features of PrP biogenesis are central to its role in genetic **prion disease.** From studies carried out over the past 4 years with support of the present grant, major progress has been made in understanding the conformer termed PrP, and its role in **prion disease** pathogenesis. In particular it has been established that CtmPrP also plays a crucial role in infectious as well as genetic **prion disease** and brings about neurodegeneration by triggering a pathway of apoptosis. Furthermore, powerful model systems, including cell culture and Tg mice that reproduce key features of prion disorders, have been developed and are beginning to be used for dissection of the disease-associated apoptotic pathway involving CtmPrP. In part as a result of the progress in the present grant period, important new questions regarding CtmPrP and other PrP conformers have emerged. In this renewal application we propose to build on our previous studies, utilizing the full range of tools and reagents that we have developed over the past four years, for the study of PrP conformers in disease. Based on our recent demonstration of their utility in detection of individual conformers, we will also generate conformer-specific mAbs optimized for immunocytochemistry. Using these tools we will: i) corroborate the Ctm index in other model systems of **prion disease** and explore the possibility of variations on this theme in triggering or suppressing apoptosis; ii) elucidate the precise interactions by which CtmPrP triggers apoptosis; iii) address the role of posttranslational modifications of PrP conformers in **prion disease,** including the putative role of cleavage of the signal peptide as a regulator of conformer production/export, iv) attempt to detect NtmPrP and explicate its role, if any, in **prion disease,** and v) identify the signaling pathway(s) by which PrPSc appears to trigger CtmPrP production. Through these studies, an ongoing fruitful line of investigation with regards to PrP-mediated neurodegeneration will be extended, providing a greater degree of clarity and precision with regards to the role of CtmPrP, SecPrP, and NtmPrP in **prion disease.** In addition, exciting new directions regarding the regulation of PrP conformers will be explored, setting the stage for the development of potential therapeutic modalities based on enhanced or suppressed production and maturation of PrP conformers.

- **Project Title: THERAPEUTIC APPROACHES FOR PRION DISEASE**

  Principal Investigator & Institution: Wisniewski, Thomas M.; Professor; Neurology; New York University School of Medicine 550 1St Ave New York, Ny 10016

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

  Summary: (provided by applicant): Currently, there is not effective form of treatment for **prion disease.** The pathogenesis of **prion disease** is related to a conformational change of the normal prion protein, PrPC, to a form with a high beta sheet content, PrPSc. The increased beta sheet content of the disease-associated protein provides both a therapeutic target and allows development of ligands for specific imaging of the diseased brain or organs. Recently vaccination has been shown to be an effective therapy in transgenic Alzheimer's disease (AD) model mice. We have developed an immunological approach making it potentially safer for human use. Recently, we have used a similar immunotherapeutic approach for the **prion disease** and found that both active and passive vaccination delays the disease onset. Our further preliminary data shows that mucosal immunization can prevent infection by the natural oral route. We propose that both active and passive immunization approaches will be effective at preventing prion infection. PrP is a copper binding protein and copper has been found

to be important in the conformational change to PrPSc. Our novel, preliminary data suggests that copper chelators also inhibit prion infection, suggesting this as an additional therapeutic approach which can be combined with the immunological therapies. A methodology to improve the diagnosis of **prion disease** is also needed. We have used ligands that are coupled to gadolinium which bind to the beta sheet rich amyloid deposits in AD transgenic mice. We show that similar techniques can be used to image prion related pathology. We also have preliminary data that non-toxic, Congo red analog ligands can be used to specifically image PrPSc amyloid deposits in vivo. In this proposal we will further develop our active and passive immunization, as well as metal chelation approaches utilizing peripherally infected prion model mice (using prion strains 139A and 87V), tissue culture models of prion infection and transgenic mice expressing either human or deer PrP. UMRI will be used to image T2 and gradient echo signal changes related to pre-symptomatic and symptomatic prion infection in model mice. We will also use non-toxic, PrP homologous peptides coupled to gadolinium which bind to PrPSc as ligands to visualize prion related amyloid deposits in vivo using uMRI. In vivo imaging will also be done with 2 photon microscopy and non-toxic, Congo red analogs. Our novel imaging techniques will be used to monitor our therapeutic experiments.

- **Project Title: TRANSGENETIC STUDIES OF PRION DISEASE IN CERVIDS**

  Principal Investigator & Institution: Telling, Glenn C.; Associate Professor; Microbiology, Immunology and Molecular Genetics; University of Kentucky 109 Kinkead Hall Lexington, Ky 405060057

  Timing: Fiscal Year 2005; Project Start 01-AUG-2000; Project End 30-JUN-2010

  Summary: (provided by applicant): Our broad long-term objective is to address the mechanisms by which species barriers and strain specificities control the pathogenesis and transmission of chronic wasting disease (CWD), a contagious disease of deer and elk belonging to a group of fatal, transmissible neurodegenerative disorders of animals and humans caused by prions. Our major objectives are to use proven transgenic (Tg) approaches to study the means by which primary structure elements of the prion protein (PrP) and prion strain properties influence CWD transmission barriers, to address the origins of CWD and the prevalence of CWD strains, and to determine the mechanism of prion transmission among cervids. Three Specific Aims are proposed: (1) To use Tg mice expressing cervid (Cer) PrP [Tg(CerPrP)] that simulate disease in deer and elk to study the mechanisms of CWD transmission among cervids and sub-clinical CWD replication in the absence of accumulation of conventional forms of pathogenic PrP; (2) To use Tg approaches to assess the influence of CWD strain variation and CerPrP polymorphisms on CWD pathogenesis and to address the disease-causing potential of CWD strains in other species; and, (3) To probe the molecular basis of species-dependent CWD transmission barriers using novel chimeric murine/CerPrP constructs and an innovative combination of Tg approaches and in vitro PrP amplification. Addressing the mechanism of CWD transmission will lead to better CWD control in cervid populations and allow more accurate assessments of the risks posed to humans and livestock from exposure to CWD. The proposed studies will also further our understanding of the general molecular events underlying prion propagation, species barriers and prion strains that will ultimately result in rational therapeutic and diagnostic approaches for human and animal prion diseases and will provide important information about the molecular nature of the infectious agent in the contexts of clinical and sub-clinical **prion disease.**

- **Project Title: TRANS-MONOLAYER COUPLING OF MEMBRANE DOMAINS**

  Principal Investigator & Institution: May, Sylvio E.; Physics; North Dakota State University 1735 Research Park Drive Fargo, Nd 581055756

  Timing: Fiscal Year 2006; Project Start 01-APR-2006; Project End 31-MAR-2009

  Summary: (provided by applicant): Membrane rafts represent small microdomains, evidenced most notably in the extracellular leaflet of the plasma membrane where they involve cholesterol, sphingolipids, and phospholipids with saturated acyl chains. A large number of biological functions have been identified to involve rafts, ranging from signal transduction and membrane traffic to viral coat assembly and toxin-induced pore formation. Seemingly unrelated diseases appear in the raft context: Alzheimer's disease, prion diseases, viral infections, and cholesterol biosynthesis disorders. In spite of accumulating needs to relate the raft concept to human diseases, even most basic aspects of membrane rafts are poorly understood; entirely unknown is how microdomain formation is coupled across the two membrane leaflets and, related, how protein-decorated lipid rafts convey information to the interior of the cell. A putative mechanism postulates structural coupling through conformational changes of trans-membrane proteins. We suggest an entirely different mechanism, namely a thermodynamic one, based on protein-induced lateral and trans-monolayer raft reorganization. That is, cooperative association of proteins with membrane rafts modifies the activity of cholesterol, leading besides lateral raft reorganization also to trans-monolayer coupling through cholesterol flip-flop. To test our hypothesis we construct a combined theoretical/experimental model system for protein-induced domain formation and cholesterol-mediated thermodynamic coupling of membrane domains across the bilayer. Specifically, we develop microscopic-level interaction models for cholesterol-containing membranes in the presence of associated proteins, we analyze the corresponding thermodynamic phase behavior, and we investigate the relation of thermodynamic and structural trans-monolayer coupling mechanisms. The modeling part employs microscopic-level and mean-field computational approaches such as Poisson- Boltzmann theory, chain packing theory, and membrane elasticity theory. In the experimental part, cholesterol activity will be deduced from binding isotherms of proteins onto mixed, cholesterol-containing membranes. Our proposed research is part of a new initiative in the Department of Physics at North Dakota State University to establish a focus in soft condensed matter and biophysical applications, and to expose graduate/undergraduate students to interdisciplinary research involving computational methods.

- **Project Title: YEAST MODEL FOR TWO NEURODEGENERATION-LINKED PROTEINS**

  Principal Investigator & Institution: Debburman, Shubhik Kumar.; Biology; Lake Forest College 555 N Sheridan Rd Lake Forest, Il 60045

  Timing: Fiscal Year 2004; Project Start 01-MAY-2004; Project End 30-APR-2007

  Summary: (provided by applicant): Budding Yeast (S. cerevisiae) has emerged as a powerful model system for understanding molecular aspects of many human diseases. Protein misfolding linked to certain neurodegenerative diseases (NDDs) like Huntington Disease, Lou Gehrig's disease, and prion diseases have been successfully recapitulated in S. cerevisiae and led to identification of therapeutically relevant regulators of misfolding. No S. cerevisiae models for Parkinson's Disease (PD) or dentatorubral pallidoluysian atrophy (DRPLA) have been reported. PD is one of the most common NDDs, while DRPLA is a rare inherited NDD of the triplet repeat disease family. In both diseases, misfolding of a specific protein (alpha-synuclein for PD and

atrophin for DRPLA) is thought to cause selective neuronal death. Unlike the well-characterized huntingtin protein in Huntington Disease (which shares many similarities to DRPLA), less is known about the misfolding of mutant atrophin in DRPLA. A S. cerevisiae expression system for studying alpha-synuclein has recently been developed in our lab. Preliminary evidence supports that both wildtype and disease-associated mutants are aggregating within yeast cells and upon purification. A similar effort to establish atrophin-1 expression in yeast is underway. To extend initial observations with alpha-synuclein in yeast and fully develop a yeast model for atrophin, three goals are proposed. 1) Misfolding properties between wildtype and mutant versions of both proteins will be investigated in vivo (immunofluorescence and GFP-based localization and assessment of protein half-life) and in vitro (by measuring protease sensitivity and differential solubility). 2) Influences of chaperones and ubiquitin-proteasomal pathway proteins on folding and degradation of these proteins will be assessed in strains compromised for chaperone/proteasomal function, or those that overexpress chaperones, and by co-immunoprecipitation assessment. 3) A fission yeast (S. pombe) expression model for alpha-synuclein and atrophin properties (as in Aim 1) will be developed and compared with the S. cerevisiae model; NDD models have not been reported in S. pombe. These studies may further clarify the molecular bases for misfolding and degradation of PD- and DRPLA-linked proteins and extend the usefulness of yeast models. Importantly, the scientific training of many undergraduates will be supported, strengthening their cell biology and molecular genetics skills and appreciation for model organisms.

- **Project Title: YEAST PRION AGGREGATES AND PROTEIN RECRUITMENT**

  Principal Investigator & Institution: Manogaran, Anita L.; Biological Sciences; University of Illinois at Chicago 310 Aob, M/C 672 Chicago, Il 60612

  Timing: Fiscal Year 2005; Project Start 01-SEP-2004; Project End 31-AUG-2007

  Summary: (provided by applicant): The presence of cellular aggregates is a hallmark of many neurodegenerative diseases like Alzheimer's Disease, Huntington's Disease and Prion diseases. Recent studies have revealed that the localization of glutamine-rich proteins into aggregates leads to a loss-of-function and is likely the reason for the observed cell toxicity. Cellular aggregates have been associated with the yeast prion [PSI+], a misfolded self-perpetuating form of the SUP35 protein. It appears that the presence of [PSI+] leads to slower growth in some SAGA mutants. Members of the SAGA complex, in conjunction with the Swi/Snf complex and the srb/mediator complex, are involved in chromatin remodeling and co-activation of transcription. Here, it is proposed that in the presence of [PSI+], glutamine rich proteins involved in chromatin remodeling are being recruited to aggregates, which leads to a loss of their function. The effects other yeast prions and variant strains of prions have on SAGA mutants will be tested. In addition, proteins found within cellular aggregates will be identified. The identification of proteins found within aggregate will provide insight to etiology of prion diseases.

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

- **"Strange things I have in head": evidence of prion disease in Shakespeare's Macbeth.**
  Author(s): Norton SA, Paris RM, Wonderlich KJ.
  Source: Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16355346&query_hl=19&itool=pubmed_docsum

- **A deadly prion disease: fatal familial insomnia.**
  Author(s): Sundstrom DG, Dreher HM.
  Source: The Journal of Neuroscience Nursing : Journal of the American Association of Neuroscience Nurses.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14713095&query_hl=19&itool=pubmed_docsum

- **A murine model of a familial prion disease.**
  Author(s): Harris DA, Chiesa R, Drisaldi B, Quaglio E, Migheli A, Piccardo P, Ghetti B.
  Source: Clin Lab Med.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12733431&query_hl=19&itool=pubmed_docsum

- **A new inherited prion disease (PrP-P105L mutation) showing spastic paraparesis.**
  Author(s): Kitamoto T, Amano N, Terao Y, Nakazato Y, Isshiki T, Mizutani T, Tateishi J.
  Source: Annals of Neurology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8250529&query_hl=19&itool=pubmed_docsum

[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 new variant of prion disease.**
  Author(s): Collinge J, Rossor M.
  Source: Lancet.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8598749&query_hl=19&itool=pubmed_docsum

- **A novel mutation (G114V) in the prion protein gene in a family with inherited prion disease.**
  Author(s): Rodriguez MM, Peoc'h K, Haik S, Bouchet C, Vernengo L, Manana G, Salamano R, Carrasco L, Lenne M, Beaudry P, Launay JM, Laplanche JL.
  Source: Neurology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15851745&query_hl=19&itool=pubmed_docsum

- **A prion disease with a novel 96-base pair insertional mutation in the prion protein gene.**
  Author(s): Campbell TA, Palmer MS, Will RG, Gibb WR, Luthert PJ, Collinge J.
  Source: Neurology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8618679&query_hl=19&itool=pubmed_docsum

- **A prion disease--possible Gerstmann-Straussler-Scheinker disease: a case report.**
  Author(s): Aralasmak A, Crain BJ, Zou WQ, Yousem DM.
  Source: Journal of Computer Assisted Tomography.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16365589&query_hl=19&itool=pubmed_docsum

- **A special report I. Prion protein (PrP)--amyloid plaques in the transmissible spongiform encephalopathies, or prion diseases revisited.**
  Author(s): Liberski PP, Bratosiewicz J, Walis A, Kordek R, Jeffrey M, Brown P.
  Source: Folia Neuropathol.
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  Author(s): Parchi P, Capellari S, Chin S, Schwarz HB, Schecter NP, Butts JD, Hudkins P, Burns DK, Powers JM, Gambetti P.
  Source: Neurology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10371520&query_hl=19&itool=pubmed_docsum

- **A transgenic model of a familial prion disease.**
  Author(s): Harris DA, Chiesa R, Drisaldi B, Quaglio E, Migheli A, Piccardo P, Ghetti B.
  Source: Arch Virol Suppl.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11214912&query_hl=19&itool=pubmed_docsum

- **A Yin-Yang role for metals in prion disease.**
  Author(s): Wong BS, Brown DR, Sy MS.
  Source: Panminerva Medica.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11677424&query_hl=19&itool=pubmed_docsum

- **Aberrant metal binding by prion protein in human prion disease.**
  Author(s): Wong BS, Chen SG, Colucci M, Xie Z, Pan T, Liu T, Li R, Gambetti P, Sy MS, Brown DR.
  Source: Journal of Neurochemistry.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11579148&query_hl=19&itool=pubmed_docsum

- **Academy calls for improved tests to beat prion disease.**
  Author(s): Knight J.
  Source: Nature.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14628008&query_hl=19&itool=pubmed_docsum

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  Author(s): Will RG.
  Source: British Medical Bulletin.
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  Author(s): Korth C, May BC, Cohen FE, Prusiner SB.
  Source: Proceedings of the National Academy of Sciences of the United States of America.
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  Author(s): Kovacs GG, Budka H.
  Source: Experimental Gerontology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11830364&query_hl=19&itool=pubmed_docsum

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  Author(s): Soto C.
  Source: Journal of Molecular Medicine (Berlin, Germany).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10426190&query_hl=19&itool=pubmed_docsum

- **Aminoacid polymorphism in human prion protein and age at death in inherited prion disease.**
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  Source: Curr Drug Targets Cns Neurol Disord.
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- **Amyloid plaques in transmissible spongiform encephalopathies (prion diseases).**
  Author(s): Liberski PP.
  Source: Folia Neuropathol.
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  Author(s): Yamada M, Itoh Y, Inaba A, Wada Y, Takashima M, Satoh S, Kamata T, Okeda R, Kayano T, Suematsu N, Kitamoto T, Otomo E, Matsushita M, Mizusawa H.
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  Source: The Journal of Clinical Investigation.
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  Author(s): Liberski PP, Brown P.
  Source: Folia Neuropathol.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16903143&query_hl=25&itool=pubmed_docsum

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  Author(s): Perry VH, Cunningham C, Boche D.
  Source: Current Opinion in Neurology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12045736&query_hl=19&itool=pubmed_docsum

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  Author(s): Bosque PJ.
  Source: Curr Neurol Neurosci Rep.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12359101&query_hl=19&itool=pubmed_docsum

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  Author(s): Kretzschmar HA, Giese A, Brown DR, Herms J, Keller B, Schmidt B, Groschup M.
  Source: Journal of Neural Transmission. Supplementum.
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  Author(s): Watanabe R, Duchen LW.
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  Source: Bmj (Clinical Research Ed.).
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  Source: Brain Research.
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CHAPTER 2. ALTERNATIVE MEDICINE AND PRION DISEASE

Overview

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

- **A case-control study of Creutzfeldt-Jakob disease in Japan: transplantation of cadaveric dura mater was a risk factor.**
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  Author(s): Stephen H.
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Author(s): Delichatsios H.
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Author(s): Glasse R.
Source: Trans N Y Acad Sci.
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Author(s): Schmerr MJ, Cutlip RC, Jenny A.
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  Source: Brain; a Journal of Neurology.
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  Source: Acupuncture in Medicine : Journal of the British Medical Acupuncture Society.
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  Source: Lancet.
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  Author(s): Roikhel VM, Fokina GI, Sobolev SG, Korolyev MB, Pogodina VV.
  Source: Acta Virol.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=6148854&query_hl=1&itool=pubmed_docsum

- **Effect of transition metals (Mn, Cu, Fe) and deoxycholic acid (DA) on the conversion of PrPC to PrPres.**
  Author(s): Kim NH, Choi JK, Jeong BH, Kim JI, Kwon MS, Carp RI, Kim YS.
  Source: The Faseb Journal : Official Publication of the Federation of American Societies for Experimental Biology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15758042&query_hl=1&itool=pubmed_docsum

- **Elevated silver, barium and strontium in antlers, vegetation and soils sourced from CWD cluster areas: do Ag/Ba/Sr piezoelectric crystals represent the transmissible pathogenic agent in TSEs?**
  Author(s): Purdey M.
  Source: Medical Hypotheses.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15236778&query_hl=1&itool=pubmed_docsum

- **Emotional and deliberative reactions to a public crisis: Mad Cow disease in France.**
  Author(s): Sinaceur M, Heath C, Cole S.
  Source: Psychological Science : a Journal of the American Psychological Society / Aps.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15733207&query_hl=1&itool=pubmed_docsum

- **Evaluation of new cell culture inhibitors of protease-resistant prion protein against scrapie infection in mice.**
  Author(s): Kocisko DA, Morrey JD, Race RE, Chen J, Caughey B.
  Source: The Journal of General Virology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15269390&query_hl=1&itool=pubmed_docsum

- **Fact vs. folklore: dealing with CJD.**
  Author(s): Uehling M.
  Source: Cap Today.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11317563&query_hl=1&itool=pubmed_docsum

- **Factors governing speed of societal responses to threats: precision of definition of the threat may be more important than its anticipated likely severity.**
  Author(s): Nusbaum NJ.
  Source: Medical Hypotheses.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12376075&query_hl=1&itool=pubmed_docsum

- **From sickness to health: an altered focus for health-care research.**
  Author(s): Brown VA.
  Source: Soc Sci Med [a].
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=6973200&query_hl=1&itool=pubmed_docsum

- **Genetic studies in relation of kuru. I. Cultural, historical, and demographic background.**
  Author(s): Gajdusek DC, Alpers M.
  Source: American Journal of Human Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=5081885&query_hl=1&itool=pubmed_docsum

- **Getting the message across.**
  Author(s): Galloway S.
  Source: Nursing Standard : Official Newspaper of the Royal College of Nursing.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8718228&query_hl=1&itool=pubmed_docsum

- **Ginkgolide B inhibits the neurotoxicity of prions or amyloid-beta1-42.**
  Author(s): Bate C, Salmona M, Williams A.
  Source: J Neuroinflammation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15285798&query_hl=1&itool=pubmed_docsum

- **Glycosyl transferase activity in normal and Scrapie-affected mouse brain.**
  Author(s): Suckling AJ, Hunter GD.
  Source: Journal of Neurochemistry.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=4212037&query_hl=1&itool=pubmed_docsum

- **High-dose exposure to systemic phosmet insecticide modifies the phosphatidylinositol anchor on the prion protein: the origins of new variant transmissible spongiform encephalopathies?**
  Author(s): Purdey M.
  Source: Medical Hypotheses.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9572563&query_hl=1&itool=pubmed_docsum

- **Hypersensitivity to central serotonin receptor activation in scrapie-infected hamsters and the effect of serotonergic drugs on scrapie symptoms.**
  Author(s): Goudsmit J, Rohwer RG, Silbergeld EK, Gajdusek DC.
  Source: Brain Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=6456788&query_hl=1&itool=pubmed_docsum

- **Immunoreactivity enhancement with chelators for increasing the detection sensitivity of human PrPSc by Western blotting.**
  Author(s): Kuczius T, Brinkmann B, Grassi J.
  Source: Neurochemistry International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16962685&query_hl=1&itool=pubmed_docsum

- **Industry self-regulation in the manufacture of dietary supplements and botanical medicines.**
  Author(s): Goldman EL.
  Source: Clinical Obstetrics and Gynecology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11600860&query_hl=1&itool=pubmed_docsum

- **Inhibition of protease-resistant prion protein accumulation in vitro by curcumin.**
  Author(s): Caughey B, Raymond LD, Raymond GJ, Maxson L, Silveira J, Baron GS.
  Source: Journal of Virology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12692251&query_hl=1&itool=pubmed_docsum

- **Inhibition of PrPSc formation by lentiviral gene transfer of PrP containing dominant negative mutations.**
  Author(s): Crozet C, Lin YL, Mettling C, Mourton-Gilles C, Corbeau P, Lehmann S, Perrier V.
  Source: Journal of Cell Science.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15494372&query_hl=1&itool=pubmed_docsum

- **Koro--its origin and nature as a disease entity.**
  Author(s): Leng GA.
  Source: Singapore Med J.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=5659892&query_hl=1&itool=pubmed_docsum

- **Kuru in the 21st century--an acquired human prion disease with very long incubation periods.**
  Author(s): Collinge J, Whitfield J, McKintosh E, Beck J, Mead S, Thomas DJ, Alpers MP.
  Source: Lancet.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16798390&query_hl=1&itool=pubmed_docsum

- **Life sciences update: environmental pollution; further fears on "new variant CJD"; attacking "superbugs".**
  Author(s): Rowbury R.
  Source: Sci Prog.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9449196&query_hl=1&itool=pubmed_docsum

- **New mad cow hideout: the medicine chest.**
  Author(s): Wadman M.
  Source: Fortune.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11272266&query_hl=1&itool=pubmed_docsum

- **Nutrition in the Kuru region. I. Gardening, food handling, and diet of the Fore people.**
  Author(s): Sorenson ER, Gajdusek C.
  Source: Acta Tropica.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=4391960&query_hl=1&itool=pubmed_docsum

- **Nutrition in the Kuru region. II. A nutritional evaluation of traditional Fore diet in Moke village in 1957.**
  Author(s): Reid LH, Gajdusek DC.
  Source: Acta Tropica.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=4391961&query_hl=1&itool=pubmed_docsum

- **Observations on the psychopharmacology of the aged.**
  Author(s): Eisdorfer C.
  Source: Journal of the American Geriatrics Society.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=237957&query_hl=1&itool=pubmed_docsum

- **PCR detection of bovine mitochondrial DNA derived from meat and bone meal in feed.**
  Author(s): Toyoda A, Nakajo M, Kawachi H, Matsui T, Yano H.
  Source: J Food Prot.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15633697&query_hl=1&itool=pubmed_docsum

- **Reusable acupuncture needles are a potential risk for transmitting Prion disease.**
  Author(s): Rosted P, Jorgensen VK.
  Source: Acupuncture in Medicine : Journal of the British Medical Acupuncture Society.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11471595&query_hl=1&itool=pubmed_docsum

- **The public health impact of prion diseases.**
  Author(s): Belay ED, Schonberger LB.
  Source: Annual Review of Public Health.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15760286&query_hl=1&itool=pubmed_docsum

- **The use of antioxidants in transmissible spongiform encephalopathies: a case report.**
  Author(s): Drisko JA.

Source: Journal of the American College of Nutrition.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11838883&query_hl=1&itool=pubmed_docsum

- **Uptake and efflux of quinacrine, a candidate for the treatment of prion diseases, at the blood-brain barrier.**
  Author(s): Dohgu S, Yamauchi A, Takata F, Sawada Y, Higuchi S, Naito M, Tsuruo T, Shirabe S, Niwa M, Katamine S, Kataoka Y.
  Source: Cellular and Molecular Neurobiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15176436&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/**

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. PATENTS ON PRION DISEASE

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

Patent Applications on Prion Disease

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 prion disease:

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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.

- **Test for transmissible spongiform encephalopathies**

  Inventor(s): O'Connor, Michael; (County Dublin, DE)

  Correspondence: B Todd Patterson; Moser Patterson & Sheridan; Suite 1500; 3040 Post Oak Boulevard; Houston; TX; 77056; US

  Patent Application Number: 20040115730

  Date filed: December 15, 2003

  Abstract: A method of detecting **transmissible spongiform encephalopathies** is described which involves (a) treating a sample of tissue, blood or a blood derivative from a test subject with alcohol and a detergent. (b) adding an agent which degrades normal prion protein (c) adding an agent which denatures abnormal prion protein. (d) adding a prion-specific antibody and (e) detecting binding of the antibody to the sample. Also described is a method of fixing abnormal prion protein to a substrate comprising (a) treating the protein or a sample suspected to contain the abnormal prion protein with alcohol and an anionic detergent ans (b) adding a protease in the presence of the substrate.

  Excerpt(s): The present invention relates to a method of detecting Transmissable Spongiform Encephalopathies, and in particular to a test which can be conducted on living or dead animals or humans to identify TSFs. Spongiform Encephalopathies are a group of degenerative neurological diseases. There are a number of examples of Spongiform Encephalopathies including BSE (Bovine Spongiform Encephalopathy), Scrapie, Creutzfeldt-Jacob Disease (CJD) Gerstmann-Straussler-Scheinker Syndrome, Kuru, Transmissible Mink Encephalopathy, Chronic Wasting Disease of Mule Deer, Feline Spongiform Encephalopathies and other Spongiform Encephalopathies found in animals such as elk, naya, greater kudu, gemsbok and tigers. It has also been reported that BSE can be transmitted under laboratory conditions to mice and pigs. This crossing of species barriers by the infective agent has led to increased concern that transfer to humans could occur. Bovine spongiform Encephalopathy (BSE) is a degenerative brain disorder of cattle which is popularly known as "mad cow disease". It has a slow incubation period, up to four or five years with symptoms of progressive degeneration of the mental state in cows include loss of coordination and staggering gait, lack of interest in their surroundings, disinterest in feed and water, or unpredictable behaviour, including aggressiveness. Affected cattle show symptoms when they are three to ten years old.

  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 prion disease, 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 **prion disease** (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 prion disease.

You can also use this procedure to view pending patent applications concerning prion disease. 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 4. BOOKS ON PRION DISEASE

Overview

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

- **A deadly prion disease: fatal familial insomnia.: An article from: Journal of Neuroscience Nursing** Dianne G. Sundstrom and H. Michael Dreher (2005); ISBN: B0008GCN6U; http://www.amazon.com/exec/obidos/ASIN/B0008GCN6U/icongroupinterna
- **Creutzfeldt-Jakob disease and other transmissible spongiform encephalopathies** (1991); ISBN: 0815105177; http://www.amazon.com/exec/obidos/ASIN/0815105177/icongroupinterna
- **Fatal Familial Insomnia: Inherited Prion Diseases, Sleep, and the Thalamus** Christian Guilleminault (1994); ISBN: 0781701147; http://www.amazon.com/exec/obidos/ASIN/0781701147/icongroupinterna
- **Fatal Protein: The Story of CJD, BSE, and Other Prion Diseases** Rosalind M. Ridley and Harry F. Baker (1998); ISBN: 0198524358; http://www.amazon.com/exec/obidos/ASIN/0198524358/icongroupinterna

- **FDA would like diagnostic test, but validation still key.(United States Food and Drug Administration on transmissible spongiform encephalopathies)(Brief Article): An article from: Validation Times** Howard Fields (2005); ISBN: B0008JCZH4; http://www.amazon.com/exec/obidos/ASIN/B0008JCZH4/icongroupinterna
- **Government Research into Transmissible Spongiform Encephalopathies and Intensive Farming (House of Commons Papers)** Agriculture Committee (2001); ISBN: 0102290016; http://www.amazon.com/exec/obidos/ASIN/0102290016/icongroupinterna
- **Human prion disease and relative risk associated with chronic wasting disease.: An article from: Emerging Infectious Diseases** Samantha MaWhinney, W. John Pape, Jeri E. Forster, and C. Alan Anderson (2006); ISBN: B000KC8S3Y; http://www.amazon.com/exec/obidos/ASIN/B000KC8S3Y/icongroupinterna
- **Mad Cows and Cannibals: A Guide to the Transmissible Spongiform Encephalopathies** Charlotte A. Spencer (2003); ISBN: 0131423398; http://www.amazon.com/exec/obidos/ASIN/0131423398/icongroupinterna
- **Neurodegeneration and Prion Disease** David R. Brown (2005); ISBN: 0387239227; http://www.amazon.com/exec/obidos/ASIN/0387239227/icongroupinterna
- **Precautions for Work with Human and Animal Transmissible Spongiform Encephalopathies (Advisory Committee on Dangerous Pathogens)** (1994); ISBN: 0113218052; http://www.amazon.com/exec/obidos/ASIN/0113218052/icongroupinterna
- **Prion disease called potential risk to humans: chronic wasting disease of deer.(Infectious Diseases): An article from: Internal Medicine News** Timothy F. Kirn (2005); ISBN: B000824UVU; http://www.amazon.com/exec/obidos/ASIN/B000824UVU/icongroupinterna
- **Prions and Prion Diseases (Neurological Disease and Therapy)** Neil Cashman (2008); ISBN: 0824729463; http://www.amazon.com/exec/obidos/ASIN/0824729463/icongroupinterna
- **Prions and Prion Diseases: Current Perspectives (Horizonbioscience)** Glenn Telling (2004); ISBN: 0954523261; http://www.amazon.com/exec/obidos/ASIN/0954523261/icongroupinterna
- **Reducing the risk of cross-contamination from transmissible spongiform encephalopathies. : An article from: AORN Journal** Timothy A. Brendle (2005); ISBN: B000BM89WI; http://www.amazon.com/exec/obidos/ASIN/B000BM89WI/icongroupinterna
- **Surveillance for Prion Disease in Cervids, Germany. : An article from: Emerging Infectious Diseases** Elvira Schettler, Falko Steinbach, Iris Eschenbacher-Kaps, and Kirsten Gerst (2006); ISBN: B000EWBG7A; http://www.amazon.com/exec/obidos/ASIN/B000EWBG7A/icongroupinterna
- **The Pathological Protein: Mad Cow, Chronic Wasting, and Other Deadly Prion Diseases** Philip Yam (2006); ISBN: 0387955089; http://www.amazon.com/exec/obidos/ASIN/0387955089/icongroupinterna
- **The Transmissible Spongiform Encephalopathies (Wales) Regulations 2006** (2006); ISBN: 0110913434; http://www.amazon.com/exec/obidos/ASIN/0110913434/icongroupinterna

- **Transmissible Subacute Spongiform Encephalopathies: Prion Diseases** L. Court and B. Bodet (1996); ISBN: 2906077917; http://www.amazon.com/exec/obidos/ASIN/2906077917/icongroupinterna
- **WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies** (2006); ISBN: 9241547014; http://www.amazon.com/exec/obidos/ASIN/9241547014/icongroupinterna

CHAPTER 5. MULTIMEDIA ON PRION DISEASE

Overview

In this chapter, we show you how to find bibliographic information related to multimedia sources of information on prion disease.

Bibliography: Multimedia on Prion Disease

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 **prion disease** (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 prion disease:

- **Immunobiology of prion diseases [videorecording]** Source: Office of Research Services, Medical Arts and Photography Branch; Year: 2002; Format: Videorecording; Bethesda, Md.: National Institutes of Health, 2002]
- **Report of a WHO consultation on medicinal and other products in relation to human and animal transmissible spongiform encephalopathies [electronic resource]: with the participation of the Office International des Epizooties (OIE), Geneva, Switzerland, 24-26 March 1997.** Year: 1997; Format: Electronic resource; Geneva]: World Health Organization, 1997
- **WHO infection control guidelines for transmissible spongiform encephalopathies: report of a WHO consultation, Geneva, Switzerland, 23-26 March 1999.** Year: 2000; Surveillance and Response, c2000

APPENDICES

APPENDIX A. HELP ME UNDERSTAND GENETICS

Overview

This appendix presents basic information about genetics in clear language and provides links to online resources.[9]

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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[9] 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.

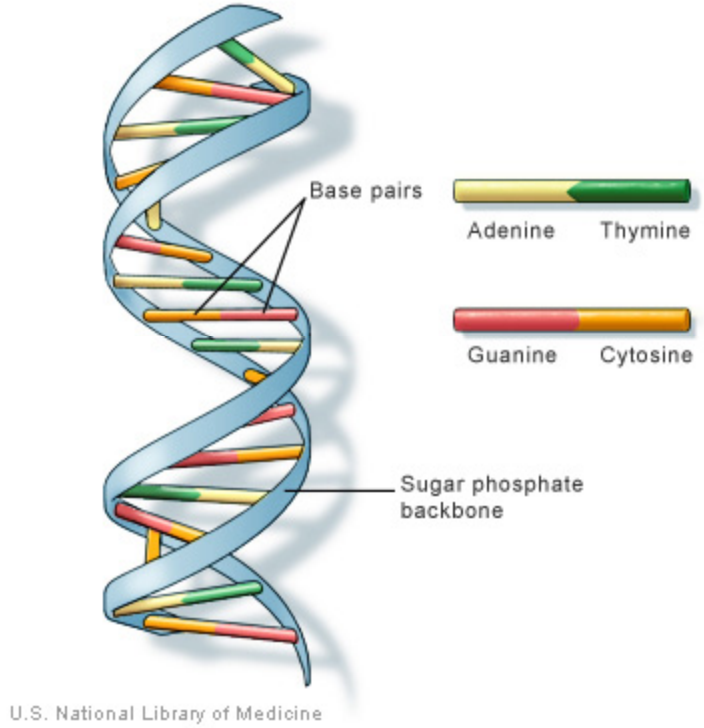
What Is DNA?

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).

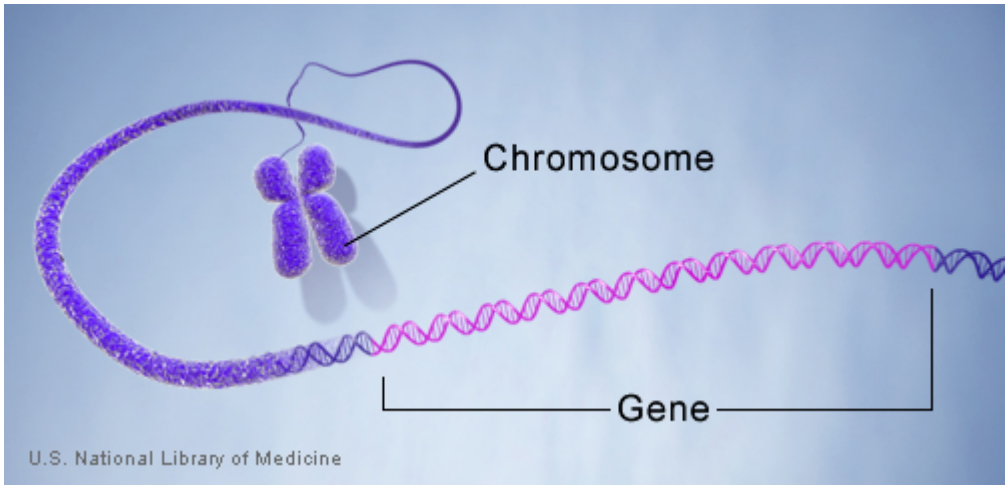
Mitochondrial DNA contains 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation. The remaining genes provide instructions for making molecules called transfer RNAs (tRNAs) and ribosomal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



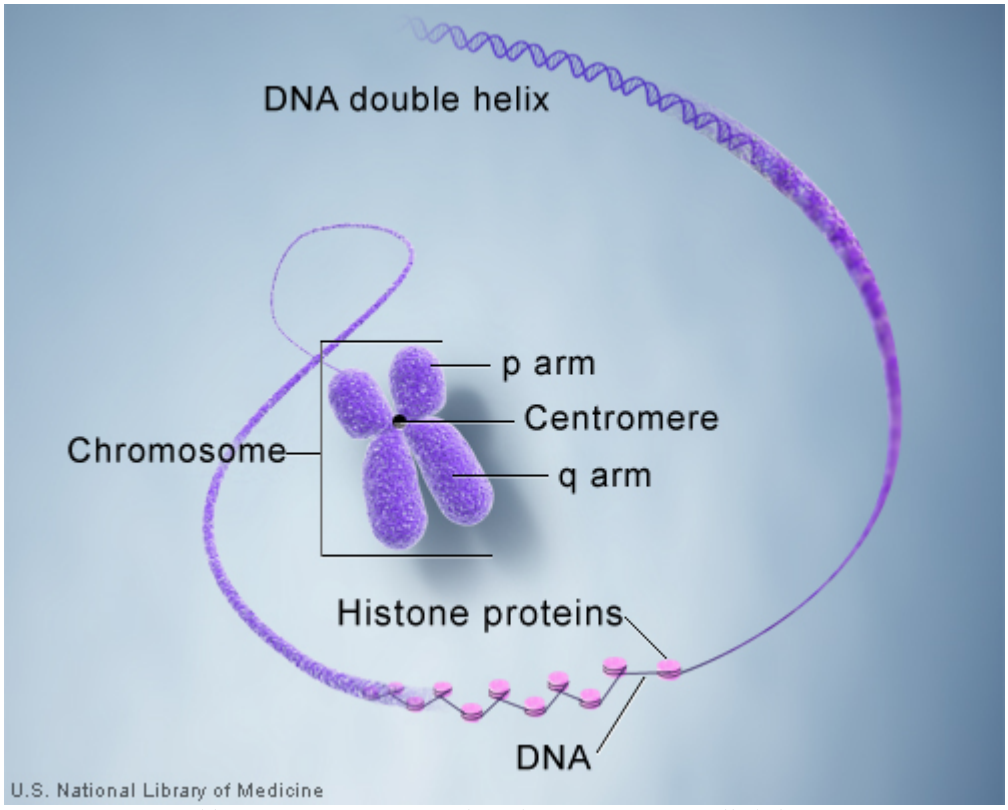
Genes are made up of DNA. Each chromosome contains many genes.

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.

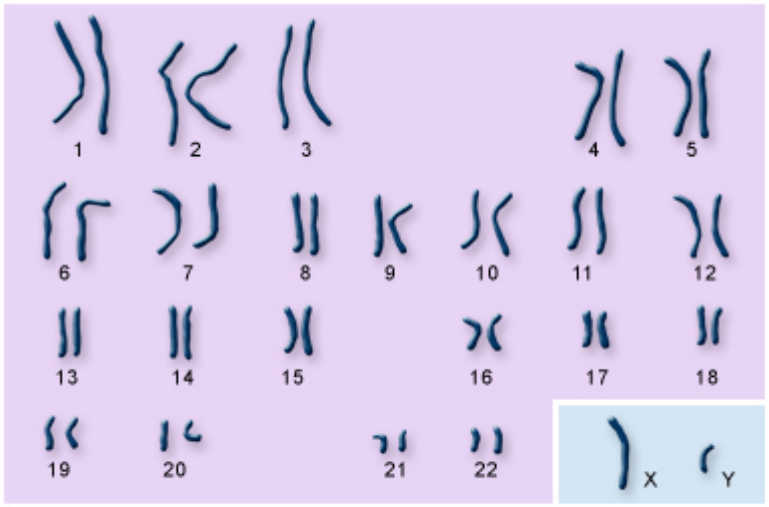
Each chromosome has a constriction point called the centromere, which divides the chromosome into two sections, or "arms." The short arm of the chromosome is labeled the "p arm." The long arm of the chromosome is labeled the "q arm." The location of the centromere on each chromosome gives the chromosome 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:

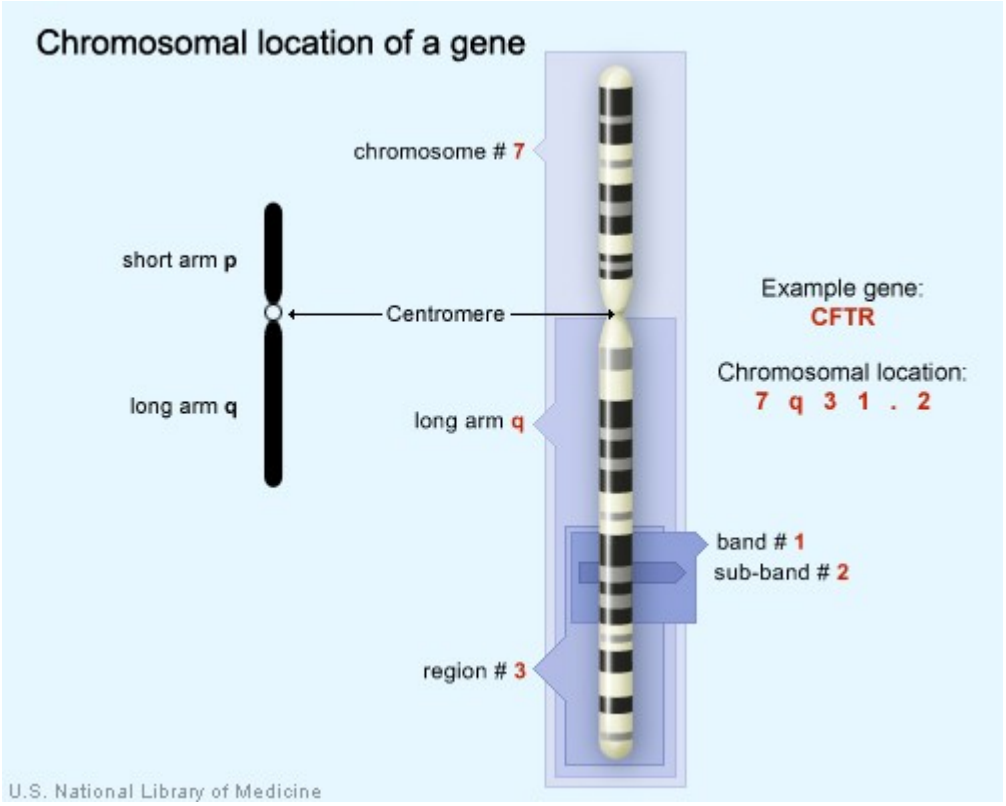
17q12-q21

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?

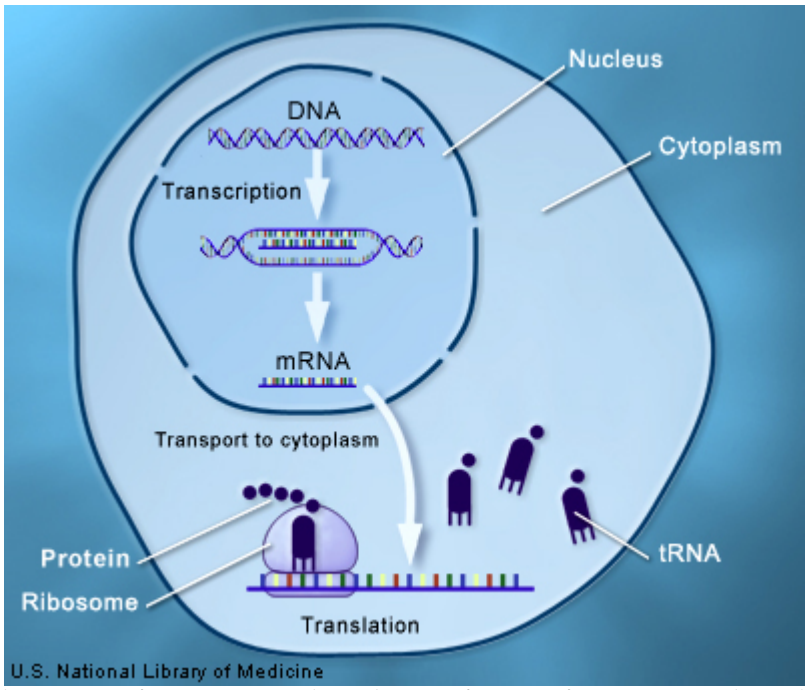
Most genes contain the information needed to make functional molecules called proteins. (A few genes produce other molecules that help the cell assemble proteins.) The journey from gene to protein is complex and tightly controlled within each cell. It consists of two major steps: transcription and translation.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

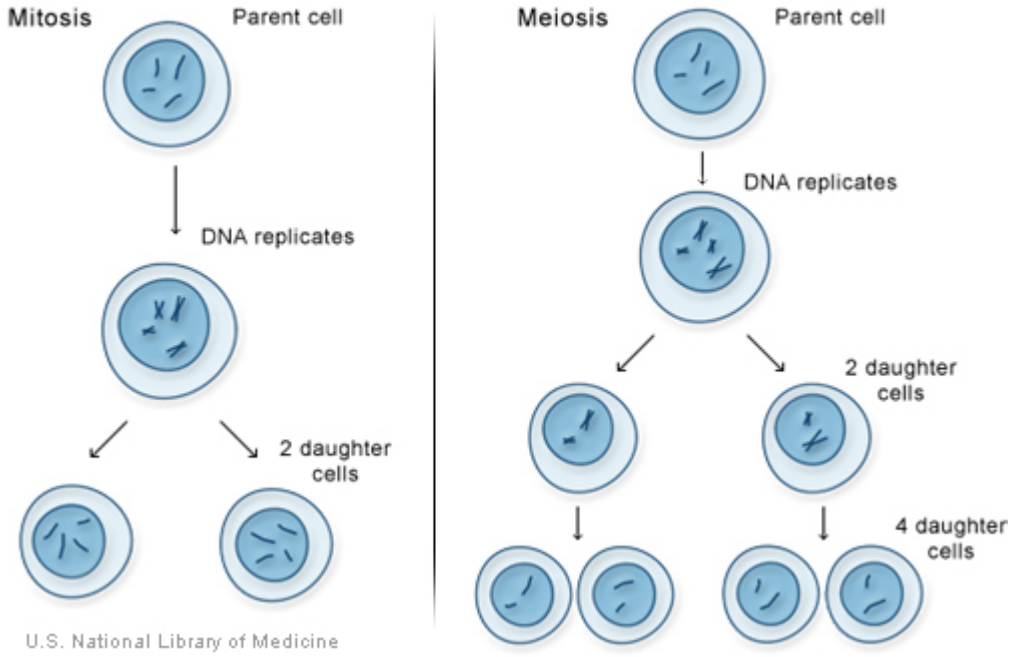
Gene regulation can occur at any point during gene expression, but most commonly occurs at the level of transcription (when the information in a gene's DNA is transferred to mRNA). Signals from the environment or from other cells activate proteins called transcription factors. These proteins bind to 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.[10]

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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[10] 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

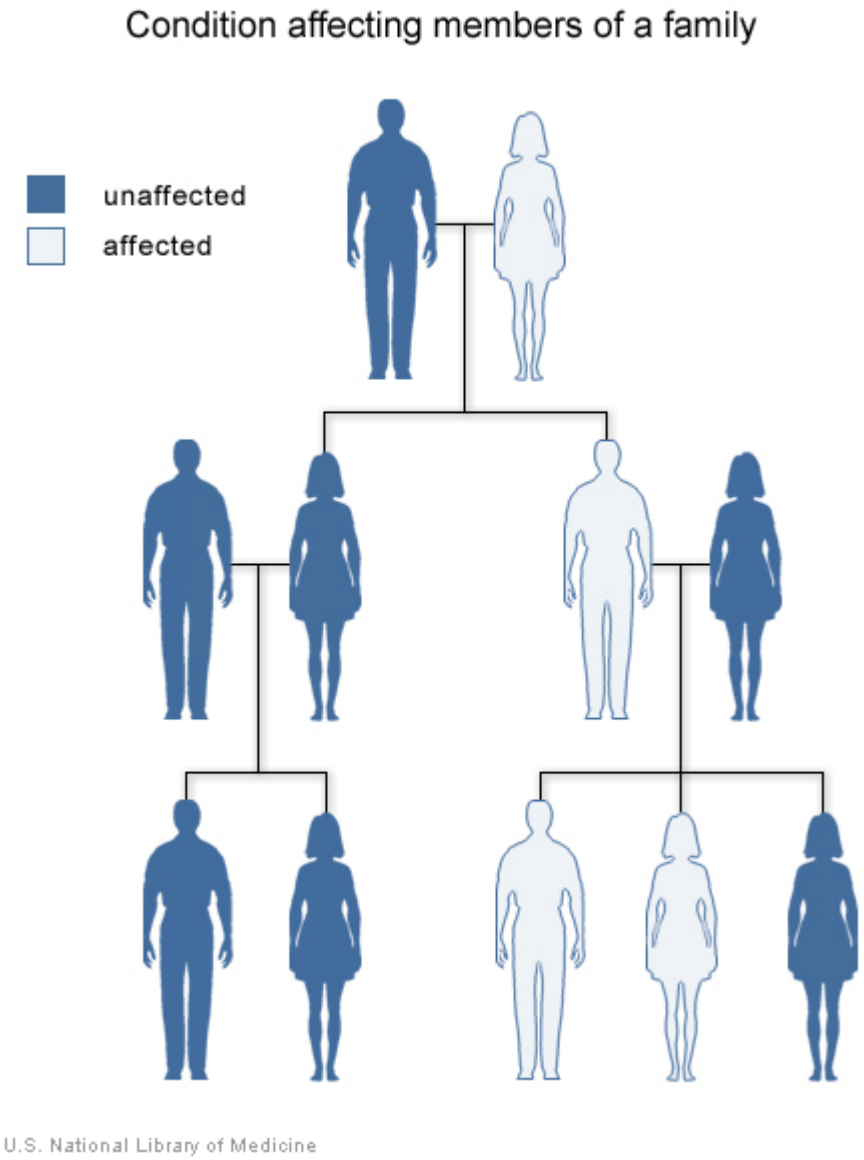
This section gives you information on inheritance patterns and understanding risk.

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.

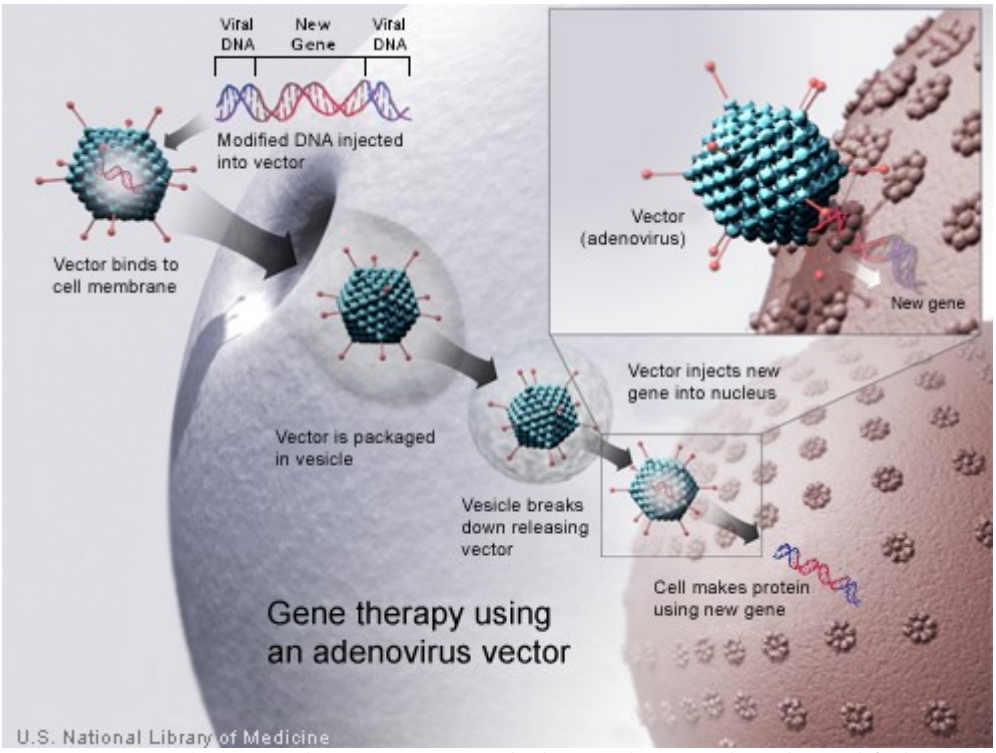
How Does Gene Therapy Work?

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[11]:

- 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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[11] 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.[12] Physician-oriented resources provide a wide variety of information related to the biomedical and health sciences, both past and present. The format of these resources varies. Searchable databases, bibliographic

[12] Remember, for the general public, the National Library of Medicine recommends the databases referenced in MEDLINE*plus* (**http://medlineplus.gov/** or **http://www.nlm.nih.gov/medlineplus/databases.html**).

citations, full-text articles (when available), archival collections, and images are all available. The following are referenced by the National Library of Medicine[13]:

- **Bioethics:** Access to published literature on the ethical, legal, and public policy issues surrounding healthcare and biomedical research. This information is provided in conjunction with the Kennedy Institute of Ethics located at Georgetown University, Washington, D.C.: **http://www.nlm.nih.gov/databases/databases_bioethics.html**
- **HIV/AIDS Resources:** Describes various links and databases dedicated to HIV/AIDS research: **http://www.nlm.nih.gov/pubs/factsheets/aidsinfs.html**
- **NLM Online Exhibitions:** Describes "Exhibitions in the History of Medicine": **http://www.nlm.nih.gov/exhibition/exhibition.html**. Additional resources for historical scholarship in medicine: **http://www.nlm.nih.gov/hmd/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**

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

The NLM Gateway[14]

The NLM (National Library of Medicine) Gateway is a Web-based system that lets users search simultaneously in multiple retrieval systems at the U.S. National Library of Medicine (NLM). It allows users of NLM services to initiate searches from one Web interface, providing one-stop searching for many of NLM's information resources or databases.[15] To use the NLM Gateway, simply go to the search site at **http://gateway.nlm.nih.gov/gw/Cmd**. Type **prion disease** (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	9602
Books / Periodicals / Audio Visual	197
Consumer Health	72
Meeting Abstracts	8
Other Collections	0
Total	9879

HSTAT[16]

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.[17] These documents include clinical practice guidelines, quick-reference guides for clinicians, consumer health brochures, evidence reports and technology assessments from the Agency for Healthcare Research and Quality (AHRQ), as well as AHRQ's Put Prevention Into Practice.[18] Simply search by **prion disease** (or synonyms) at the following Web site: **http://text.nlm.nih.gov**.

Coffee Break: Tutorials for Biologists[19]

Coffee Break is a general healthcare site that takes a scientific view of the news and covers recent breakthroughs in biology that may one day assist physicians in developing treatments. Here you will find a collection of short reports on recent biological discoveries. Each report incorporates interactive tutorials that demonstrate how bioinformatics tools are

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

[15] The NLM Gateway is currently being developed by the Lister Hill National Center for Biomedical Communications (LHNCBC) at the National Library of Medicine (NLM) of the National Institutes of Health (NIH).

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

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

[18] Other important documents in HSTAT include: the National Institutes of Health (NIH) Consensus Conference Reports and Technology Assessment Reports; the HIV/AIDS Treatment Information Service (ATIS) resource documents; the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (SAMHSA/CSAT) Treatment Improvement Protocols (TIP) and Center for Substance Abuse Prevention (SAMHSA/CSAP) Prevention Enhancement Protocols System (PEPS); the Public Health Service (PHS) Preventive Services Task Force's *Guide to Clinical Preventive Services*; the independent, nonfederal Task Force on Community Services' *Guide to Community Preventive Services*; and the Health Technology Advisory Committee (HTAC) of the Minnesota Health Care Commission (MHCC) health technology evaluations.

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

used as a part of the research process. Currently, all Coffee Breaks are written by NCBI staff.[20] Each report is about 400 words and is usually based on a discovery reported in one or more articles from recently published, peer-reviewed literature.[21] This site has new articles every few weeks, so it can be considered an online magazine of sorts. It is intended for general background information. You can access the Coffee Break Web site at the following hyperlink: **http://www.ncbi.nlm.nih.gov/Coffeebreak/**.

Other Commercial Databases

In addition to resources maintained by official agencies, other databases exist that are commercial ventures addressing medical professionals. Here are some examples that may interest you:

- **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/**.

[20] The figure that accompanies each article is frequently supplied by an expert external to NCBI, in which case the source of the figure is cited. The result is an interactive tutorial that tells a biological story.

[21] After a brief introduction that sets the work described into a broader context, the report focuses on how a molecular understanding can provide explanations of observed biology and lead to therapies for diseases. Each vignette is accompanied by a figure and hypertext links that lead to a series of pages that interactively show how NCBI tools and resources are used in the research process.

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 prion disease 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 prion disease. 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 prion disease. 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 **prion disease**:

Animal Diseases and Your Health
http://www.nlm.nih.gov/medlineplus/animaldiseasesandyourhealth.html

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

Degenerative Nerve Diseases
http://www.nlm.nih.gov/medlineplus/degenerativenervediseases.html

Food Contamination and Poisoning
http://www.nlm.nih.gov/medlineplus/foodcontaminationandpoisoning.html

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

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

Viral Infections
http://www.nlm.nih.gov/medlineplus/viralinfections.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.

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:

- **Creutzfeldt-Jakob Disease Fact Sheet for Healthcare Workers**

  Source: www.ninds.nih.gov

  http://www.ninds.nih.gov/disorders/cjd/cjdprecautions.htm

- **Creutzfeldt-Jakob Disease Information Page**

  Source: www.ninds.nih.gov

  http://www.ninds.nih.gov/disorders/cjd/cjd.htm

- **Creutzfeldt-Jakob Disease Press Releases**

  Source: www.ninds.nih.gov

  http://www.ninds.nih.gov/disorders/cjd/press_cjd.htm

- **Dementia: Hope Through Research**
  Source: www.ninds.nih.gov
  http://www.ninds.nih.gov/disorders/dementias/detail_dementia.htm

- **Encephalopathy Press Releases**
  Source: www.ninds.nih.gov
  http://www.ninds.nih.gov/disorders/encephalopathy/press_encephalopathy.htm

- **Gerstmann-Straussler-Scheinker Disease Information Page**
  Source: www.ninds.nih.gov
  http://www.ninds.nih.gov/disorders/gss/gss.htm

- **Kuru Information Page**
  Source: www.ninds.nih.gov
  http://www.ninds.nih.gov/disorders/kuru/kuru.htm

- **Kuru Press Releases**
  Source: www.ninds.nih.gov
  http://www.ninds.nih.gov/disorders/kuru/press_kuru.htm

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

- **NIAID Research on Prion Diseases - NIAID Fact Sheet**
  Source: www.niaid.nih.gov
  http://www.niaid.nih.gov/factsheets/priondis.htm

- **Prion Disease Publications**
  Source: www.niaid.nih.gov
  http://www.niaid.nih.gov/publications/prion.htm

- **Transmissible Spongiform Encephalopathies Information Page**
  Source: www.ninds.nih.gov
  http://www.ninds.nih.gov/disorders/tse/tse.htm

- **Transmissible Spongiform Encephalopathies Press Releases**

  Source: www.ninds.nih.gov

  http://www.ninds.nih.gov/disorders/tse/press_tse.htm

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 prion disease. 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 **prion disease** (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 prion disease. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with prion disease.

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 prion disease. 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 **prion disease** (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 **prion disease** (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[22]:

- 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**

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

- A Science Called Genetics: **http://publications.nigms.nih.gov/genetics/science.html**
- 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**).

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**

PRION DISEASE 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]

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

Aborigines: Native inhabitants or indigenous individuals of a country. [NIH]

Acceptor: A substance which, while normally not oxidized by oxygen or reduced by hydrogen, can be oxidized or reduced in presence of a substance which is itself undergoing oxidation or reduction. [NIH]

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

Actin: Essential component of the cell skeleton. [NIH]

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

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

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

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

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]

Adjustment: The dynamic process wherein the thoughts, feelings, behavior, and biophysiological mechanisms of the individual continually change to adjust to the environment. [NIH]

Adult-Onset Diabetes: Former term for noninsulin-dependent or type II diabetes. [NIH]

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

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

Aerosol: A solution of a drug which can be atomized into a fine mist for inhalation therapy. [EU]

Affinity: 1. Inherent likeness or relationship. 2. A special attraction for a specific element, organ, or structure. 3. Chemical affinity; the force that binds atoms in molecules; the tendency of substances to combine by chemical reaction. 4. The strength of noncovalent chemical binding between two substances as measured by the dissociation constant of the complex. 5. In immunology, a thermodynamic expression of the strength of interaction between a single antigen-binding site and a single antigenic determinant (and thus of the stereochemical compatibility between them), most accurately applied to interactions among simple, uniform antigenic determinants such as haptens. Expressed as the association constant (K litres mole -1), which, owing to the heterogeneity of affinities in a population of antibody molecules of a given specificity, actually represents an average value (mean intrinsic association constant). 6. The reciprocal of the dissociation constant. [EU]

Ageing: A physiological or morphological change in the life of an organism or its parts, generally irreversible and typically associated with a decline in growth and reproductive vigor. [NIH]

Aggressiveness: The quality of being aggressive (= characterized by aggression; militant; enterprising; spreading with vigour; chemically active; variable and adaptable). [EU]

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

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]

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]

Amino Acid Sequence: The order of amino acids as they occur in a polypeptide chain. This is referred to as the primary structure of proteins. It is of fundamental importance in determining protein conformation. [NIH]

Amino Acid Substitution: The naturally occurring or experimentally induced replacement of one or more amino acids in a protein with another. If a functionally equivalent amino acid

is substituted, the protein may retain wild-type activity. Substitution may also diminish or eliminate protein function. Experimentally induced substitution is often used to study enzyme activities and binding site properties. [NIH]

Amino Acids: Organic compounds that generally contain an amino (-NH2) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form proteins. [NIH]

Amino Acids: Organic compounds that generally contain an amino (-NH2) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form proteins. [NIH]

Ammonia: A colorless alkaline gas. It is formed in the body during decomposition of organic materials during a large number of metabolically important reactions. [NIH]

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]

Amplification: The production of additional copies of a chromosomal DNA sequence, found as either intrachromosomal or extrachromosomal DNA. [NIH]

Amyloid: A general term for a variety of different proteins that accumulate as extracellular fibrils of 7-10 nm and have common structural features, including a beta-pleated sheet conformation and the ability to bind such dyes as Congo red and thioflavine (Kandel, Schwartz, and Jessel, Principles of Neural Science, 3rd ed). [NIH]

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

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

Analogous: Resembling or similar in some respects, as in function or appearance, but not in origin or development;. [EU]

Analytes: A component of a test sample the presence of which has to be demonstrated. The term "analyte" includes where appropriate formed from the analyte during the analyses. [NIH]

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]

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]

Anionic: Pertaining to or containing an anion. [EU]

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

Anthelmintic: An agent that is destructive to worms. [EU]

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

Anti-inflammatory: Having to do with reducing inflammation. [NIH]

Antimicrobial: Killing microorganisms, or suppressing their multiplication or growth. [EU]

Antioxidant: A substance that prevents damage caused by free radicals. Free radicals are highly reactive chemicals that often contain oxygen. They are produced when molecules are split to give products that have unpaired electrons. This process is called oxidation. [NIH]

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

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

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

Aphasia: A cognitive disorder marked by an impaired ability to comprehend or express language in its written or spoken form. This condition is caused by diseases which affect the language areas of the dominant hemisphere. Clinical features are used to classify the various subtypes of this condition. General categories include receptive, expressive, and mixed forms of aphasia. [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]

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

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

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

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

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

Asphyxia: A pathological condition caused by lack of oxygen, manifested in impending or

actual cessation of life. [NIH]

Aspirin: A drug that reduces pain, fever, inflammation, and blood clotting. Aspirin belongs to the family of drugs called nonsteroidal anti-inflammatory agents. It is also being studied in cancer prevention. [NIH]

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

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

Ataxia: Impairment of the ability to perform smoothly coordinated voluntary movements. This condition may affect the limbs, trunk, eyes, pharnyx, larnyx, and other structures. Ataxia may result from impaired sensory or motor function. Sensory ataxia may result from posterior column injury or peripheral nerve diseases. Motor ataxia may be associated with cerebellar diseases; cerebral cortex diseases; thalamic diseases; basal ganglia diseases; injury to the red nucleus; and other conditions. [NIH]

Atmospheric Pressure: The pressure at any point in an atmosphere due solely to the weight of the atmospheric gases above the point concerned. [NIH]

Atrophy: Decrease in the size of a cell, tissue, organ, or multiple organs, associated with a variety of pathological conditions such as abnormal cellular changes, ischemia, malnutrition, or hormonal changes. [NIH]

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

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

Autosuggestion: Suggestion coming from the subject himself. [NIH]

Axons: Nerve fibers that are capable of rapidly conducting impulses away from the neuron cell 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]

Bacterial Physiology: Physiological processes and activities of bacteria. [NIH]

Barium: An element of the alkaline earth group of metals. It has an atomic symbol Ba, atomic number 56, and atomic weight 138. All of its acid-soluble salts are poisonous. [NIH]

Basal Ganglia: Large subcortical nuclear masses derived from the telencephalon and located in the basal regions of the cerebral hemispheres. [NIH]

Basal Ganglia Diseases: Diseases of the basal ganglia including the putamen; globus pallidus; claustrum; amygdala; and caudate nucleus. Dyskinesias (most notably involuntary movements and alterations of the rate of movement) represent the primary clinical manifestations of these disorders. Common etiologies include cerebrovascular disease; neurodegenerative diseases; and craniocerebral trauma. [NIH]

Base: In chemistry, the nonacid part of a salt; a substance that combines with acids to form salts; a substance that dissociates to give hydroxide ions in aqueous solutions; a substance whose molecule or ion can combine with a proton (hydrogen ion); a substance capable of donating a pair of electrons (to an acid) for the formation of a coordinate covalent bond. [EU]

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]

Beta-Galactosidase: A group of enzymes that catalyzes the hydrolysis of terminal, non-reducing beta-D-galactose residues in beta-galactosides. Deficiency of beta-Galactosidase A1 may cause gangliodisosis GM1. EC 3.2.1.23. [NIH]

Beta-pleated: Particular three-dimensional pattern of amyloidoses. [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]

Bioassay: Determination of the relative effective strength of a substance (as a vitamin, hormone, or drug) by comparing its effect on a test organism with that of a standard preparation. [NIH]

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

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

Biological 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 transfusion: The administration of blood or blood products into a blood vessel. [NIH]

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

Blood-Brain Barrier: Specialized non-fenestrated tightly-joined endothelial cells (tight junctions) that form a transport barrier for certain substances between the cerebral capillaries and the brain tissue. [NIH]

Blot: To transfer DNA, RNA, or proteins to an immobilizing matrix such as nitrocellulose. [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]

Boron: A trace element with the atomic symbol B, atomic number 5, and atomic weight 10.81. Boron-10, an isotope of boron, is used as a neutron absorber in boron neutron capture therapy. [NIH]

Bowel: The long tube-shaped organ in the abdomen that completes the process of digestion. There is both a small and a large bowel. Also called the intestine. [NIH]

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]

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

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]

Calibration: Determination, by measurement or comparison with a standard, of the correct value of each scale reading on a meter or other measuring instrument; or determination of the settings of a control device that correspond to particular values of voltage, current, frequency, or other output. [NIH]

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

Carcinogenic: Producing carcinoma. [EU]

Cardiac: Having to do with the heart. [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]

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]

Cations: Postively charged atoms, radicals or groups of atoms which travel to the cathode or negative pole during electrolysis. [NIH]

Cause of Death: Factors which produce cessation of all vital bodily functions. They can be analyzed from an epidemiologic viewpoint. [NIH]

Cell: The individual unit that makes up all of the tissues of the body. All living things are made up of one or more cells. [NIH]

Cell Communication: Any of several ways in which living cells of an organism communicate with one another, whether by direct contact between cells or by means of chemical signals carried by neurotransmitter substances, hormones, and cyclic AMP. [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 Fusion: Fusion of somatic cells in vitro or in vivo, which results in somatic cell hybridization. [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]

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]

Cerebellar: Pertaining to the cerebellum. [EU]

Cerebellum: Part of the metencephalon that lies in the posterior cranial fossa behind the brain stem. It is concerned with the coordination of movement. [NIH]

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

Cerebral Cortex: The thin layer of gray matter on the surface of the cerebral hemisphere that develops from the telencephalon and folds into gyri. It reaches its highest development in man and is responsible for intellectual faculties and higher mental functions. [NIH]

Cerebral Palsy: Refers to a motor disability caused by a brain dysfunction. [NIH]

Cerebrospinal: Pertaining to the brain and spinal cord. [EU]

Cerebrospinal fluid: CSF. The fluid flowing around the brain and spinal cord. Cerebrospinal fluid is produced in the ventricles in the brain. [NIH]

Cerebrovascular: Pertaining to the blood vessels of the cerebrum, or brain. [EU]

Cerebrum: The largest part of the brain. It is divided into two hemispheres, or halves, called the cerebral hemispheres. The cerebrum controls muscle functions of the body and also controls speech, emotions, reading, writing, and learning. [NIH]

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

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

Chemical Warfare: Tactical warfare using incendiary mixtures, smokes, or irritant, burning, or asphyxiating gases. [NIH]

Chemical Warfare Agents: Chemicals that are used to cause the disturbance, disease, or death of humans during war. [NIH]

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

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

Chloroquine: The prototypical antimalarial agent with a mechanism that is not well understood. It has also been used to treat rheumatoid arthritis, systemic lupus erythematosus, and in the systemic therapy of amebic liver abscesses. [NIH]

Choleretic: A choleretic agent. [EU]

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]

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]

Clear cell carcinoma: A rare type of tumor of the female genital tract in which the inside of the cells looks clear when viewed under a microscope. [NIH]

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

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

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

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

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]

Cognition: Intellectual or mental process whereby an organism becomes aware of or obtains knowledge. [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]

Combinatorial: A cut-and-paste process that churns out thousands of potentially valuable compounds at once. [NIH]

Complement: A term originally used to refer to the heat-labile factor in serum that causes immune cytolysis, the lysis of antibody-coated cells, and now referring to the entire functionally related system comprising at least 20 distinct serum proteins that is the effector not only of immune cytolysis but also of other biologic functions. Complement activation occurs by two different sequences, the classic and alternative pathways. The proteins of the classic pathway are termed 'components of complement' and are designated by the symbols C1 through C9. C1 is a calcium-dependent complex of three distinct proteins C1q, C1r and C1s. The proteins of the alternative pathway (collectively referred to as the properdin system) and complement regulatory proteins are known by semisystematic or trivial names.

Fragments resulting from proteolytic cleavage of complement proteins are designated with lower-case letter suffixes, e.g., C3a. Inactivated fragments may be designated with the suffix 'i', e.g. C3bi. Activated components or complexes with biological activity are designated by a bar over the symbol e.g. C1 or C4b,2a. The classic pathway is activated by the binding of C1 to classic pathway activators, primarily antigen-antibody complexes containing IgM, IgG1, IgG3; C1q binds to a single IgM molecule or two adjacent IgG molecules. The alternative pathway can be activated by IgA immune complexes and also by nonimmunologic materials including bacterial endotoxins, microbial polysaccharides, and cell walls. Activation of the classic pathway triggers an enzymatic cascade involving C1, C4, C2 and C3; activation of the alternative pathway triggers a cascade involving C3 and factors B, D and P. Both result in the cleavage of C5 and the formation of the membrane attack complex. Complement activation also results in the formation of many biologically active complement fragments that act as anaphylatoxins, opsonins, or chemotactic factors. [EU]

Complementary and alternative medicine: CAM. Forms of treatment that are used in addition to (complementary) or instead of (alternative) standard treatments. These practices are not considered standard medical approaches. CAM includes dietary supplements, megadose vitamins, herbal preparations, special teas, massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Complementary medicine: Practices not generally recognized by the medical community as standard or conventional medical approaches and used to enhance or complement the standard treatments. Complementary medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Complementation: The production of a wild-type phenotype when two different mutations are combined in a diploid or a heterokaryon and tested in trans-configuration. [NIH]

Compulsions: In psychology, an irresistible urge, sometimes amounting to obsession to perform a particular act which usually is carried out against the performer's will or better judgment. [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]

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]

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]

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

Constriction: The act of constricting. [NIH]

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

Contamination: The soiling or pollution by inferior material, as by the introduction of organisms into a wound, or sewage into a stream. [EU]

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

Coordination: Muscular or motor regulation or the harmonious cooperation of muscles or groups of muscles, in a complex action or series of actions. [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]

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]

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

Cultured cells: Animal or human cells that are grown in the laboratory. [NIH]

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

Curcumin: A dye obtained from tumeric, the powdered root of Curcuma longa Linn. It is used in the preparation of curcuma paper and the detection of boron. Curcumin appears to possess a spectrum of pharmacological properties, due primarily to its inhibitory effects on metabolic enzymes. [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]

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

Cystine: A covalently linked dimeric nonessential amino acid formed by the oxidation of cysteine. Two molecules of cysteine are joined together by a disulfide bridge to form cystine. [NIH]

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]

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]

Cytoplasmic Vesicles: Membrane-limited structures derived from the plasma membrane or various intracellular membranes which function in storage, transport or metabolism. [NIH]

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

Cytoskeleton: The network of filaments, tubules, and interconnecting filamentous bridges which give shape, structure, and organization to the cytoplasm. [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]

Decontamination: The removal of contaminating material, such as radioactive materials, biological materials, or chemical warfare agents, from a person or object. [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]

Dentate Gyrus: Gray matter situated above the gyrus hippocampi. It is composed of three layers. The molecular layer is continuous with the hippocampus in the hippocampal fissure. The granular layer consists of closely arranged spherical or oval neurons, called granule cells, whose axons pass through the polymorphic layer ending on the dendrites of pyramidal cells in the hippocampus. [NIH]

Deoxycholic Acid: A bile acid formed by bacterial action from cholate. It is usually conjugated with glycine or taurine. Deoxycholic acid acts as a detergent to solubilize fats for intestinal absorption, is reabsorbed itself, and is used as a choleretic and detergent. [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]

DES: Diethylstilbestrol. A synthetic hormone that was prescribed from the early 1940s until 1971 to help women with complications of pregnancy. DES has been linked to an increased risk of clear cell carcinoma of the vagina in daughters of women who used DES. DES may also increase the risk of breast cancer in women who used DES. [NIH]

Detergents: Purifying or cleansing agents, usually salts of long-chain aliphatic bases or acids, that exert cleansing (oil-dissolving) and antimicrobial effects through a surface action that depends on possessing both hydrophilic and hydrophobic properties. [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]

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]

Dipeptides: Peptides composed of two amino acid units. [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]

Discrete: Made up of separate parts or characterized by lesions which do not become blended; not running together; separate. [NIH]

Discrimination: The act of qualitative and/or quantitative differentiation between two or more stimuli. [NIH]

Disease Susceptibility: A constitution or condition of the body which makes the tissues react in special ways to certain extrinsic stimuli and thus tends to make the individual more than usually susceptible to certain diseases. [NIH]

Disease Transmission: The transmission of infectious disease or pathogens. When transmission is within the same species, the mode can be horizontal (disease transmission, horizontal) or vertical (disease transmission, vertical). [NIH]

Disease Transmission, Horizontal: The transmission of infectious disease or pathogens from one individual to another in the same generation. [NIH]

Disease Transmission, Vertical: The transmission of infectious disease or pathogens from one generation to another. It includes transmission in utero or intrapartum by exposure to blood and secretions, and postpartum exposure via breastfeeding. [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]

Distal: Remote; farther from any point of reference; opposed to proximal. In dentistry, used to designate a position on the dental arch farther from the median line of the jaw. [EU]

Dopamine: An endogenous catecholamine and prominent neurotransmitter in several systems of the brain. In the synthesis of catecholamines from tyrosine, it is the immediate precursor to norepinephrine and epinephrine. Dopamine is a major transmitter in the extrapyramidal system of the brain, and important in regulating movement. A family of dopaminergic receptor subtypes mediate its action. Dopamine is used pharmacologically for its direct (beta adrenergic agonist) and indirect (adrenergic releasing) sympathomimetic effects including its actions as an inotropic agent and as a renal vasodilator. [NIH]

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]

Double-blinded: A clinical trial in which neither the medical staff nor the person knows which of several possible therapies the person is receiving. [NIH]

Drive: A state of internal activity of an organism that is a necessary condition before a given stimulus will elicit a class of responses; e.g., a certain level of hunger (drive) must be present before food will elicit an eating response. [NIH]

Drug Design: The molecular designing of drugs for specific purposes (such as DNA-binding, enzyme inhibition, anti-cancer efficacy, etc.) based on knowledge of molecular properties such as activity of functional groups, molecular geometry, and electronic structure, and also on information cataloged on analogous molecules. Drug design is generally computer-assisted molecular modeling and does not include pharmacokinetics, dosage analysis, or drug administration analysis. [NIH]

Dura mater: The outermost, toughest, and most fibrous of the three membranes (meninges) covering the brain and spinal cord; called also pachymeninx. [EU]

Dyes: Chemical substances that are used to stain and color other materials. The coloring may or may not be permanent. Dyes can also be used as therapeutic agents and test reagents in medicine and scientific research. [NIH]

Dystrophy: Any disorder arising from defective or faulty nutrition, especially the muscular dystrophies. [EU]

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]

Elasticity: Resistance and recovery from distortion of shape. [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]

Elementary Particles: Individual components of atoms, usually subatomic; subnuclear particles are usually detected only when the atomic nucleus decays and then only transiently, as most of them are unstable, often yielding pure energy without substance, i.e., radiation. [NIH]

Embryo: The prenatal stage of mammalian development characterized by rapid morphological changes and the differentiation of basic structures. [NIH]

Empirical: A treatment based on an assumed diagnosis, prior to receiving confirmatory laboratory test results. [NIH]

Encephalopathy: A disorder of the brain that can be caused by disease, injury, drugs, or chemicals. [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]

Endocytosis: Cellular uptake of extracellular materials within membrane-limited vacuoles or microvesicles. Endosomes play a central role in endocytosis. [NIH]

Endorphins: One of the three major groups of endogenous opioid peptides. They are large peptides derived from the pro-opiomelanocortin precursor. The known members of this group are alpha-, beta-, and gamma-endorphin. The term endorphin is also sometimes used to refer to all opioid peptides, but the narrower sense is used here; opioid peptides is used for the broader group. [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-derived: Small molecule that diffuses to the adjacent muscle layer and relaxes it. [NIH]

Enkephalins: One of the three major families of endogenous opioid peptides. The enkephalins are pentapeptides that are widespread in the central and peripheral nervous systems and in the adrenal medulla. [NIH]

Environmental Health: The science of controlling or modifying those conditions, influences, or forces surrounding man which relate to promoting, establishing, and maintaining health. [NIH]

Enzymatic: Phase where enzyme cuts the precursor protein. [NIH]

Enzyme: A protein that speeds up chemical reactions in the body. [NIH]

Enzyme Inhibitors: Compounds or agents that combine with an enzyme in such a manner as to prevent the normal substrate-enzyme combination and the catalytic reaction. [NIH]

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]

Epinephrine: The active sympathomimetic hormone from the adrenal medulla in most species. It stimulates both the alpha- and beta- adrenergic systems, causes systemic vasoconstriction and gastrointestinal relaxation, stimulates the heart, and dilates bronchi and cerebral vessels. It is used in asthma and cardiac failure and to delay absorption of local anesthetics. [NIH]

Epithelial: Refers to the cells that line the internal and external surfaces of the body. [NIH]

Epithelial Cells: Cells that line the inner and outer surfaces of the body. [NIH]

Epithelium: One or more layers of epithelial cells, supported by the basal lamina, which covers the inner or outer surfaces of the body. [NIH]

Epitope: A molecule or portion of a molecule capable of binding to the combining site of an antibody. For every given antigenic determinant, the body can construct a variety of antibody-combining sites, some of which fit almost perfectly, and others which barely fit. [NIH]

Erythrocytes: Red blood cells. Mature erythrocytes are non-nucleated, biconcave disks containing hemoglobin whose function is to transport oxygen. [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]

Excitability: Property of a cardiac cell whereby, when the cell is depolarized to a critical level (called threshold), the membrane becomes permeable and a regenerative inward current causes an action potential. [NIH]

Excitation: An act of irritation or stimulation or of responding to a stimulus; the addition of energy, as the excitation of a molecule by absorption of photons. [EU]

Excitotoxicity: Excessive exposure to glutamate or related compounds can kill brain neurons, presumably by overstimulating them. [NIH]

Excrete: To get rid of waste from the body. [NIH]

Exogenous: Developed or originating outside the organism, as exogenous disease. [EU]

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]

Extremity: A limb; an arm or leg (membrum); sometimes applied specifically to a hand or foot. [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]

Fasciculation: A small local contraction of muscles, visible through the skin, representing a spontaneous discharge of a number of fibres innervated by a single motor nerve filament. [EU]

Fat: Total lipids including phospholipids. [NIH]

Fatal Outcome: Death resulting from the presence of a disease in an individual, as shown by a single case report or a limited number of patients. This should be differentiated from death, the physiological cessation of life and from mortality, an epidemiological or statistical concept. [NIH]

Fathers: Male parents, human or animal. [NIH]

Ferritin: An iron-containing protein complex that is formed by a combination of ferric iron with the protein apoferritin. [NIH]

Fetus: The developing offspring from 7 to 8 weeks after conception until birth. [NIH]

Fibril: Most bacterial viruses have a hollow tail with specialized fibrils at its tip. The tail fibers attach to the cell wall of the host. [NIH]

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]

Fissure: Any cleft or groove, normal or otherwise; especially a deep fold in the cerebral cortex which involves the entire thickness of the brain wall. [EU]

Fluorescence: The property of emitting radiation while being irradiated. The radiation emitted is usually of longer wavelength than that incident or absorbed, e.g., a substance can be irradiated with invisible radiation and emit visible light. X-ray fluorescence is used in diagnosis. [NIH]

Fold: A plication or doubling of various parts of the body. [NIH]

Food Chain: The sequence of transfers of matter and energy from organism to organism in

the form of food. Food chains intertwine locally into a food web because most organisms consume more than one type of animal or plant. Plants, which convert solar energy to food by photosynthesis, are the primary food source. In a predator chain, a plant-eating animal is eaten by a larger animal. In a parasite chain, a smaller organism consumes part of a larger host and may itself be parasitized by smaller organisms. In a saprophytic chain, microorganisms live on dead organic matter. [NIH]

Food Handling: Any aspect of the operations in the preparation, transport, storage, packaging, wrapping, exposure for sale, service, or delivery of food. [NIH]

Forearm: The part between the elbow and the wrist. [NIH]

Fractionation: Dividing the total dose of radiation therapy into several smaller, equal doses delivered over a period of several days. [NIH]

Frameshift: A type of mutation which causes out-of-phase transcription of the base sequence; such mutations arise from the addition or delection of nucleotide(s) in numbers other than 3 or multiples of 3. [NIH]

Frameshift Mutation: A type of mutation in which a number of nucleotides not divisible by three is deleted from or inserted into a coding sequence, thereby causing an alteration in the reading frame of the entire sequence downstream of the mutation. These mutations may be induced by certain types of mutagens or may occur spontaneously. [NIH]

Free Radicals: Highly reactive molecules with an unsatisfied electron valence pair. Free radicals are produced in both normal and pathological processes. They are proven or suspected agents of tissue damage in a wide variety of circumstances including radiation, damage from environment chemicals, and aging. Natural and pharmacological prevention of free radical damage is being actively investigated. [NIH]

Frontal Lobe: The anterior part of the cerebral hemisphere. [NIH]

Fungus: A general term used to denote a group of eukaryotic protists, including mushrooms, yeasts, rusts, moulds, smuts, etc., which are characterized by the absence of chlorophyll and by the presence of a rigid cell wall composed of chitin, mannans, and sometimes cellulose. They are usually of simple morphological form or show some reversible cellular specialization, such as the formation of pseudoparenchymatous tissue in the fruiting body of a mushroom. The dimorphic fungi grow, according to environmental conditions, as moulds or yeasts. [EU]

Gadolinium: An element of the rare earth family of metals. It has the atomic symbol Gd, atomic number 64, and atomic weight 157.25. Its oxide is used in the control rods of some nuclear reactors. [NIH]

Gait: Manner or style of walking. [NIH]

Galactosides: Glycosides formed by the reaction of the hydroxyl group on the anomeric carbon atom of galactose with an alcohol to form an acetal. They include both alpha- and beta-galactosides. [NIH]

Ganglia: Clusters of multipolar neurons surrounded by a capsule of loosely organized connective tissue located outside the central nervous system. [NIH]

Gap Junctions: Connections between cells which allow passage of small molecules and electric current. Gap junctions were first described anatomically as regions of close apposition between cells with a narrow (1-2 nm) gap between cell membranes. The variety in the properties of gap junctions is reflected in the number of connexins, the family of proteins which form the junctions. [NIH]

Gas: Air that comes from normal breakdown of food. The gases are passed out of the body through the rectum (flatus) or the mouth (burp). [NIH]

Gastric: Having to do with the stomach. [NIH]

Gastric Mucosa: Surface epithelium in the stomach that invaginates into the lamina propria, forming gastric pits. Tubular glands, characteristic of each region of the stomach (cardiac, gastric, and pyloric), empty into the gastric pits. The gastric mucosa is made up of several different kinds of cells. [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 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 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 Engineering: Directed modification of the gene complement of a living organism by such techniques as altering the DNA, substituting genetic material by means of a virus, transplanting whole nuclei, transplanting cell hybrids, etc. [NIH]

Genetic testing: Analyzing DNA to look for a genetic alteration that may indicate an increased risk for developing a specific disease or disorder. [NIH]

Genetics: The biological science that deals with the phenomena and mechanisms of heredity. [NIH]

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]

Giardiasis: An infection of the small intestine caused by the flagellated protozoan Giardia lamblia. It is spread via contaminated food and water and by direct person-to-person contact. [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]

Glutamate: Excitatory neurotransmitter of the brain. [NIH]

Glutamic Acid: A non-essential amino acid naturally occurring in the L-form. Glutamic acid (glutamate) is the most common excitatory neurotransmitter in the central nervous system. [NIH]

Glutamine: A non-essential amino acid present abundantly throught the body and is involved in many metabolic processes. It is synthesized from glutamic acid and ammonia. It is the principal carrier of nitrogen in the body and is an important energy source for many cells. [NIH]

Glycerol: A trihydroxy sugar alcohol that is an intermediate in carbohydrate and lipid metabolism. It is used as a solvent, emollient, pharmaceutical agent, and sweetening agent. [NIH]

Glycerophospholipids: Derivatives of phosphatidic acid in which the hydrophobic regions are composed of two fatty acids and a polar alcohol is joined to the C-3 position of glycerol through a phosphodiester bond. They are named according to their polar head groups, such as phosphatidylcholine and phosphatidylethanolamine. [NIH]

Glycine: A non-essential amino acid. It is found primarily in gelatin and silk fibroin and used therapeutically as a nutrient. It is also a fast inhibitory neurotransmitter. [NIH]

Glycoprotein: A protein that has sugar molecules attached to it. [NIH]

Glycosylation: The chemical or biochemical addition of carbohydrate or glycosyl groups to other chemicals, especially peptides or proteins. Glycosyl transferases are used in this biochemical reaction. [NIH]

Goats: Any of numerous agile, hollow-horned ruminants of the genus Capra, closely related to the sheep. [NIH]

Governing Board: The group in which legal authority is vested for the control of health-related institutions and organizations. [NIH]

Gp120: 120-kD HIV envelope glycoprotein which is involved in the binding of the virus to its membrane receptor, the CD4 molecule, found on the surface of certain cells in the body. [NIH]

Granule: A small pill made from sucrose. [EU]

Granulocytes: Leukocytes with abundant granules in the cytoplasm. They are divided into three groups: neutrophils, eosinophils, and basophils. [NIH]

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]

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]

Hemochromatosis: A disease that occurs when the body absorbs too much iron. The body stores the excess iron in the liver, pancreas, and other organs. May cause cirrhosis of the liver. Also called iron overload disease. [NIH]

Hemodialysis: The use of a machine to clean wastes from the blood after the kidneys have failed. The blood travels through tubes to a dialyzer, which removes wastes and extra fluid. The cleaned blood then flows through another set of tubes back into the body. [NIH]

Hemoglobin: One of the fractions of glycosylated hemoglobin A1c. Glycosylated hemoglobin is formed when linkages of glucose and related monosaccharides bind to hemoglobin A and its concentration represents the average blood glucose level over the previous several weeks. HbA1c levels are used as a measure of long-term control of plasma glucose (normal, 4 to 6 percent). In controlled diabetes mellitus, the concentration of glycosylated hemoglobin A is within the normal range, but in uncontrolled cases the level may be 3 to 4 times the normal conentration. Generally, complications are substantially lower among patients with Hb levels of 7 percent or less than in patients with HbA1c levels of 9 percent or more. [NIH]

Hemoglobinopathies: A group of inherited disorders characterized by structural alterations within the hemoglobin molecule. [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]

Hepatic: Refers to the liver. [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 Zoster: Acute vesicular inflammation. [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]

Hippocampus: A curved elevation of gray matter extending the entire length of the floor of the temporal horn of the lateral ventricle (Dorland, 28th ed). The hippocampus, subiculum, and dentate gyrus constitute the hippocampal formation. Sometimes authors include the entorhinal cortex in the hippocampal formation. [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]

Homogeneous: Consisting of or composed of similar elements or ingredients; of a uniform quality throughout. [EU]

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]

Hormonal: Pertaining to or of the nature of a hormone. [EU]

Hormone: A substance in the body that regulates certain organs. Hormones such as gastrin help in breaking down food. Some hormones come from cells in the stomach and small intestine. [NIH]

Hybridization: The genetic process of crossbreeding to produce a hybrid. Hybrid nucleic acids can be formed by nucleic acid hybridization of DNA and RNA molecules. Protein hybridization allows for hybrid proteins to be formed from polypeptide chains. [NIH]

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]

Hydrophilic: Readily absorbing moisture; hygroscopic; having strongly polar groups that readily interact with water. [EU]

Hydrophobic: Not readily absorbing water, or being adversely affected by water, as a hydrophobic colloid. [EU]

Hydroxylation: Hydroxylate, to introduce hydroxyl into (a compound or radical) usually by replacement of hydrogen. [EU]

Hyperbaric: Characterized by greater than normal pressure or weight; applied to gases under greater than atmospheric pressure, as hyperbaric oxygen, or to a solution of greater specific gravity than another taken as a standard of reference. [EU]

Hyperbaric oxygen: Oxygen that is at an atmospheric pressure higher than the pressure at sea level. Breathing hyperbaric oxygen to enhance the effectiveness of radiation therapy is being studied. [NIH]

Hypertension: Persistently high arterial blood pressure. Currently accepted threshold levels are 140 mm Hg systolic and 90 mm Hg diastolic pressure. [NIH]

Hypokinesia: Slow or diminished movement of body musculature. It may be associated with basal ganglia diseases; mental disorders; prolonged inactivity due to illness; experimental protocols used to evaluate the physiologic effects of immobility; and other

conditions. [NIH]

Iatrogenic: Resulting from the activity of physicians. Originally applied to disorders induced in the patient by autosuggestion based on the physician's examination, manner, or discussion, the term is now applied to any adverse condition in a patient occurring as the result of treatment by a physician or surgeon, especially to infections acquired by the patient during the course of treatment. [EU]

Imaging procedures: Methods of producing pictures of areas inside the body. [NIH]

Immune response: The activity of the immune system against foreign substances (antigens). [NIH]

Immune Sera: Serum that contains antibodies. It is obtained from an animal that has been immunized either by antigen injection or infection with microorganisms containing the antigen. [NIH]

Immune system: The organs, cells, and molecules responsible for the recognition and disposal of foreign ("non-self") material which enters the body. [NIH]

Immunity: Nonsusceptibility to the invasive or pathogenic effects of foreign microorganisms or to the toxic effect of antigenic substances. [NIH]

Immunization: Deliberate stimulation of the host's immune response. Active immunization involves administration of antigens or immunologic adjuvants. Passive immunization involves administration of immune sera or lymphocytes or their extracts (e.g., transfer factor, immune RNA) or transplantation of immunocompetent cell producing tissue (thymus or bone marrow). [NIH]

Immunofluorescence: A technique for identifying molecules present on the surfaces of cells or in tissues using a highly fluorescent substance coupled to a specific antibody. [NIH]

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]

Incubation: The development of an infectious disease from the entrance of the pathogen to the appearance of clinical symptoms. [EU]

Incubation period: The period of time likely to elapse between exposure to the agent of the disease and the onset of clinical symptoms. [NIH]

Infancy: The period of complete dependency prior to the acquisition of competence in walking, talking, and self-feeding. [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]

Infection Control: Programs of disease surveillance, generally within health care facilities, designed to investigate, prevent, and control the spread of infections and their causative microorganisms. [NIH]

Inflammation: A pathological process characterized by injury or destruction of tissues caused by a variety of cytologic and chemical reactions. It is usually manifested by typical signs of pain, heat, redness, swelling, and loss of function. [NIH]

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]

Initiation: Mutation induced by a chemical reactive substance causing cell changes; being a step in a carcinogenic process. [NIH]

Innervation: 1. The distribution or supply of nerves to a part. 2. The supply of nervous energy or of nerve stimulus sent to a part. [EU]

Insertional: A technique in which foreign DNA is cloned into a restriction site which occupies a position within the coding sequence of a gene in the cloning vector molecule. Insertion interrupts the gene's sequence such that its original function is no longer expressed. [NIH]

Insight: The capacity to understand one's own motives, to be aware of one's own psychodynamics, to appreciate the meaning of symbolic behavior. [NIH]

Insomnia: Difficulty in going to sleep or getting enough sleep. [NIH]

Insulator: Material covering the metal conductor of the lead. It is usually polyurethane or silicone. [NIH]

Intestinal: Having to do with the intestines. [NIH]

Intestine: A long, tube-shaped organ in the abdomen that completes the process of digestion. There is both a large intestine and a small intestine. Also called the bowel. [NIH]

Intracellular: Inside a cell. [NIH]

Intracellular Membranes: Membranes of subcellular structures. [NIH]

Intracranial Hypertension: Increased pressure within the cranial vault. This may result from several conditions, including hydrocephalus; brain edema; intracranial masses; severe systemic hypertension; pseudotumor cerebri; and other disorders. [NIH]

Intrinsic: Situated entirely within or pertaining exclusively to a part. [EU]

Invasive: 1. Having the quality of invasiveness. 2. Involving puncture or incision of the skin or insertion of an instrument or foreign material into the body; said of diagnostic techniques. [EU]

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]

Isoelectric: Separation of amphoteric substances, dissolved in water, based on their isoelectric behavior. The amphoteric substances are a mixture of proteins to be separated and of auxiliary "carrier ampholytes". [NIH]

Isoelectric Focusing: Electrophoresis in which a pH gradient is established in a gel medium and proteins migrate until they reach the site (or focus) at which the pH is equal to their isoelectric point. [NIH]

Isoelectric Point: The pH in solutions of proteins and related compounds at which the dipolar ions are at a maximum. [NIH]

Karyotype: The characteristic chromosome complement of an individual, race, or species as defined by their number, size, shape, etc. [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]

Language Disorders: Conditions characterized by deficiencies of comprehension or expression of written and spoken forms of language. These include acquired and developmental disorders. [NIH]

Large Intestine: The part of the intestine that goes from the cecum to the rectum. The large intestine absorbs water from stool and changes it from a liquid to a solid form. The large intestine is 5 feet long and includes the appendix, cecum, colon, and rectum. Also called colon. [NIH]

Latency: The period of apparent inactivity between the time when a stimulus is presented and the moment a response occurs. [NIH]

Lectin: A complex molecule that has both protein and sugars. Lectins are able to bind to the outside of a cell and cause biochemical changes in it. Lectins are made by both animals and plants. [NIH]

Lenses: Pieces of glass or other transparent materials used for magnification or increased visual acuity. [NIH]

Lentivirus: A genus of the family Retroviridae consisting of non-oncogenic retroviruses that produce multi-organ diseases characterized by long incubation periods and persistent infection. Lentiviruses are unique in that they contain open reading frames (ORFs) between the pol and env genes and in the 3' env region. Five serogroups are recognized, reflecting the mammalian hosts with which they are associated. HIV-1 is the type species. [NIH]

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]

Ligands: A RNA simulation method developed by the MIT. [NIH]

Linkages: The tendency of two or more genes in the same chromosome to remain together from one generation to the next more frequently than expected according to the law of independent assortment. [NIH]

Lipid: Fat. [NIH]

Lipid Peroxidation: Peroxidase catalyzed oxidation of lipids using hydrogen peroxide as an electron acceptor. [NIH]

Liver: A large, glandular organ located in the upper abdomen. The liver cleanses the blood and aids in digestion by secreting bile. [NIH]

Lobe: A portion of an organ such as the liver, lung, breast, or brain. [NIH]

Localization: The process of determining or marking the location or site of a lesion or disease. May also refer to the process of keeping a lesion or disease in a specific location or site. [NIH]

Localized: Cancer which has not metastasized yet. [NIH]

Locomotor: Of or pertaining to locomotion; pertaining to or affecting the locomotive apparatus of the body. [EU]

Luciferase: Any one of several enzymes that catalyze the bioluminescent reaction in certain marine crustaceans, fish, bacteria, and insects. The enzyme is a flavoprotein; it oxidizes luciferins to an electronically excited compound that emits energy in the form of light. The color of light emitted varies with the organism. The firefly enzyme is a valuable reagent for measurement of ATP concentration. (Dorland, 27th ed) EC 1.13.12.-. [NIH]

Lumbar: Pertaining to the loins, the part of the back between the thorax and the pelvis. [EU]

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]

Lymphatic system: The tissues and organs that produce, store, and carry white blood cells that fight infection and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes and a network of thin tubes that carry lymph and white blood cells. These tubes branch, like blood vessels, into all the tissues of the body. [NIH]

Lymphocytes: White blood cells formed in the body's lymphoid tissue. The nucleus is round or ovoid with coarse, irregularly clumped chromatin while the cytoplasm is typically pale blue with azurophilic (if any) granules. Most lymphocytes can be classified as either T or B (with subpopulations of each); those with characteristics of neither major class are called null cells. [NIH]

Lymphoid: Referring to lymphocytes, a type of white blood cell. Also refers to tissue in which lymphocytes develop. [NIH]

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]

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]

Magnetic Resonance Spectroscopy: Spectroscopic method of measuring the magnetic moment of elementary particles such as atomic nuclei, protons or electrons. It is employed in clinical applications such as NMR Tomography (magnetic resonance imaging). [NIH]

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]

Mange: Sarcoptic infestation of human skin, particularly a contagious skin disease caused by invasion of the epidermis with Sarcoptes scabiei. [NIH]

Mannans: Polysaccharides consisting of mannose units. [NIH]

Meat: The edible portions of any animal used for food including domestic mammals (the major ones being cattle, swine, and sheep) along with poultry, fish, shellfish, and game. [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]

Medical Staff: Professional medical personnel who provide care to patients in an organized facility, institution or agency. [NIH]

MEDLINE: An online database of MEDLARS, the computerized bibliographic Medical Literature Analysis and Retrieval System of the National Library of Medicine. [NIH]

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]

Melanin: The substance that gives the skin its color. [NIH]

Melanoma: A form of skin cancer that arises in melanocytes, the cells that produce pigment. Melanoma usually begins in a mole. [NIH]

Membrane: A very thin layer of tissue that covers a surface. [NIH]

Membrane Lipids: Lipids, predominantly phospholipids, cholesterol and small amounts of glycolipids found in membranes including cellular and intracellular membranes. These lipids may be arranged in bilayers in the membranes with integral proteins between the layers and peripheral proteins attached to the outside. Membrane lipids are required for active transport, several enzymatic activities and membrane formation. [NIH]

Membrane Proteins: Proteins which are found in membranes including cellular and intracellular membranes. They consist of two types, peripheral and integral proteins. They include most membrane-associated enzymes, antigenic proteins, transport proteins, and

drug, hormone, and lectin receptors. [NIH]

Memory: Complex mental function having four distinct phases: (1) memorizing or learning, (2) retention, (3) recall, and (4) recognition. Clinically, it is usually subdivided into immediate, recent, and remote memory. [NIH]

Meninges: The three membranes that cover and protect the brain and spinal cord. [NIH]

Mental: Pertaining to the mind; psychic. 2. (L. mentum chin) pertaining to the chin. [EU]

Mental Health: The state wherein the person is well adjusted. [NIH]

Mental 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]

Microscopy: The application of microscope magnification to the study of materials that cannot be properly seen by the unaided eye. [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]

Mode of Transmission: Contaminated food and water. [NIH]

Modeling: A treatment procedure whereby the therapist presents the target behavior which the learner is to imitate and make part of his repertoire. [NIH]

Modification: A change in an organism, or in a process in an organism, that is acquired from its own activity or environment. [NIH]

Molecular: Of, pertaining to, or composed of molecules : a very small mass of matter. [EU]

Molecular Evolution: Multiple rounds of selection, amplification, and mutation leading to molecules with the desired properties. [NIH]

Molecule: A chemical made up of two or more atoms. The atoms in a molecule can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms. [NIH]

Monitor: An apparatus which automatically records such physiological signs as respiration, pulse, and blood pressure in an anesthetized patient or one undergoing surgical or other procedures. [NIH]

Monoclonal: An antibody produced by culturing a single type of cell. It therefore consists of a single species of immunoglobulin molecules. [NIH]

Monoclonal antibodies: Laboratory-produced substances that can locate and bind to cancer cells wherever they are in the body. Many monoclonal antibodies are used in cancer detection or therapy; each one recognizes a different protein on certain cancer cells. Monoclonal antibodies can be used alone, or they can be used to deliver drugs, toxins, or radioactive material directly to a tumor. [NIH]

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]

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]

Motor Neurons: Neurons which activate muscle cells. [NIH]

Multiple sclerosis: A disorder of the central nervous system marked by weakness, numbness, a loss of muscle coordination, and problems with vision, speech, and bladder control. Multiple sclerosis is thought to be an autoimmune disease in which the body's immune system destroys myelin. Myelin is a substance that contains both protein and fat (lipid) and serves as a nerve insulator and helps in the transmission of nerve signals. [NIH]

Muscle Hypertonia: Abnormal increase in skeletal or smooth muscle tone. Skeletal muscle hypertonicity may be associated with pyramidal tract lesions or basal ganglia diseases. [NIH]

Muscular Diseases: Acquired, familial, and congenital disorders of skeletal muscle and smooth muscle. [NIH]

Mutagenesis: Process of generating genetic mutations. It may occur spontaneously or be induced by mutagens. [NIH]

Mutagens: Chemical agents that increase the rate of genetic mutation by interfering with the function of nucleic acids. A clastogen is a specific mutagen that causes breaks in chromosomes. [NIH]

Myelin: The fatty substance that covers and protects nerves. [NIH]

Myopathy: Any disease of a muscle. [EU]

Myotonic Dystrophy: A condition presenting muscle weakness and wasting which may be progressive. [NIH]

Narcotic: 1. Pertaining to or producing narcosis. 2. An agent that produces insensibility or stupor, applied especially to the opioids, i.e. to any natural or synthetic drug that has morphine-like actions. [EU]

Natural selection: A part of the evolutionary process resulting in the survival and reproduction of the best adapted individuals. [NIH]

NCI: National Cancer Institute. NCI, part of the National Institutes of Health of the United States Department of Health and Human Services, is the federal government's principal agency for cancer research. NCI conducts, coordinates, and funds cancer research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer. Access the NCI Web site at http://cancer.gov. [NIH]

Necrosis: A pathological process caused by the progressive degradative action of enzymes that is generally associated with severe cellular trauma. It is characterized by mitochondrial swelling, nuclear flocculation, uncontrolled cell lysis, and ultimately cell death. [NIH]

Nervous System: The entire nerve apparatus composed of the brain, spinal cord, nerves and ganglia. [NIH]

Neural: 1. Pertaining to a nerve or to the nerves. 2. Situated in the region of the spinal axis, as the neutral arch. [EU]

Neuroblastoma: Cancer that arises in immature nerve cells and affects mostly infants and children. [NIH]

Neurodegenerative Diseases: Hereditary and sporadic conditions which are characterized by progressive nervous system dysfunction. These disorders are often associated with atrophy of the affected central or peripheral nervous system structures. [NIH]

Neurology: A medical specialty concerned with the study of the structures, functions, and diseases of the nervous system. [NIH]

Neuromuscular: Pertaining to muscles and nerves. [EU]

Neuromuscular Diseases: A general term encompassing lower motor neuron disease; peripheral nervous system diseases; and certain muscular diseases. Manifestations include muscle weakness; fasciculation; muscle atrophy; spasm; myokymia; muscle hypertonia, myalgias, and musclehypotonia. [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]

Neuropsychology: A branch of psychology which investigates the correlation between experience or behavior and the basic neurophysiological processes. The term neuropsychology stresses the dominant role of the nervous system. It is a more narrowly defined field than physiological psychology or psychophysiology. [NIH]

Neurotoxic: Poisonous or destructive to nerve tissue. [EU]

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]

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]

Nitrogen Oxides: Inorganic oxides that contain nitrogen. [NIH]

Nitrous Oxide: Nitrogen oxide (N2O). A colorless, odorless gas that is used as an anesthetic and analgesic. High concentrations cause a narcotic effect and may replace oxygen, causing death by asphyxia. It is also used as a food aerosol in the preparation of whipping cream. [NIH]

Norepinephrine: Precursor of epinephrine that is secreted by the adrenal medulla and is a widespread central and autonomic neurotransmitter. Norepinephrine is the principal transmitter of most postganglionic sympathetic fibers and of the diffuse projection system in the brain arising from the locus ceruleus. It is also found in plants and is used pharmacologically as a sympathomimetic. [NIH]

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 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]

Obsessive-Compulsive Disorder: An anxiety disorder characterized by recurrent, persistent obsessions or compulsions. Obsessions are the intrusive ideas, thoughts, or images that are experienced as senseless or repugnant. Compulsions are repetitive and seemingly purposeful behavior which the individual generally recognizes as senseless and from which the individual does not derive pleasure although it may provide a release from tension. [NIH]

Ocular: 1. Of, pertaining to, or affecting the eye. 2. Eyepiece. [EU]

Odds Ratio: The ratio of two odds. The exposure-odds ratio for case control data is the ratio of the odds in favor of exposure among cases to the odds in favor of exposure among noncases. The disease-odds ratio for a cohort or cross section is the ratio of the odds in favor of disease among the exposed to the odds in favor of disease among the unexposed. The prevalence-odds ratio refers to an odds ratio derived cross-sectionally from studies of prevalent cases. [NIH]

Oliguria: Clinical manifestation of the urinary system consisting of a decrease in the amount of urine secreted. [NIH]

Oncogenic: Chemical, viral, radioactive or other agent that causes cancer; carcinogenic. [NIH]

Open Reading Frames: Reading frames where successive nucleotide triplets can be read as

codons specifying amino acids and where the sequence of these triplets is not interrupted by stop codons. [NIH]

Optic Chiasm: The X-shaped structure formed by the meeting of the two optic nerves. At the optic chiasm the fibers from the medial part of each retina cross to project to the other side of the brain while the lateral retinal fibers continue on the same side. As a result each half of the brain receives information about the contralateral visual field from both eyes. [NIH]

Optic Nerve: The 2nd cranial nerve. The optic nerve conveys visual information from the retina to the brain. The nerve carries the axons of the retinal ganglion cells which sort at the optic chiasm and continue via the optic tracts to the brain. The largest projection is to the lateral geniculate nuclei; other important targets include the superior colliculi and the suprachiasmatic nuclei. Though known as the second cranial nerve, it is considered part of the central nervous system. [NIH]

Oral Health: The optimal state of the mouth and normal functioning of the organs of the mouth without evidence of disease. [NIH]

Organ Culture: The growth in aseptic culture of plant organs such as roots or shoots, beginning with organ primordia or segments and maintaining the characteristics of the organ. [NIH]

Organelles: Specific particles of membrane-bound organized living substances present in eukaryotic cells, such as the mitochondria; the golgi apparatus; endoplasmic reticulum; lysomomes; plastids; and vacuoles. [NIH]

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]

Overexpress: An excess of a particular protein on the surface of a cell. [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]

Oxidative Stress: A disturbance in the prooxidant-antioxidant balance in favor of the former, leading to potential damage. Indicators of oxidative stress include damaged DNA bases, protein oxidation products, and lipid peroxidation products (Sies, Oxidative Stress, 1991, pxv-xvi). [NIH]

Oxides: Binary compounds of oxygen containing the anion O(2-). The anion combines with metals to form alkaline oxides and non-metals to form acidic oxides. [NIH]

Palliative: 1. Affording relief, but not cure. 2. An alleviating medicine. [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]

Paradoxical: Occurring at variance with the normal rule. [EU]

Paralysis: Loss of ability to move all or part of the body. [NIH]

Paraparesis: Mild to moderate loss of bilateral lower extremity motor function, which may be a manifestation of spinal cord diseases; peripheral nervous system diseases; muscular

diseases; intracranial hypertension; parasagittal brain lesions; and other conditions. [NIH]

Parasite: An animal or a plant that lives on or in an organism of another species and gets at least some of its nutrition from that other organism. [NIH]

Parenchyma: The essential elements of an organ; used in anatomical nomenclature as a general term to designate the functional elements of an organ, as distinguished from its framework, or stroma. [EU]

Parkinsonism: A group of neurological disorders characterized by hypokinesia, tremor, and muscular rigidity. [EU]

Particle: A tiny mass of material. [EU]

Paternity: Establishing the father relationship of a man and a child. [NIH]

Pathogen: Any disease-producing microorganism. [EU]

Pathologic: 1. Indicative of or caused by a morbid condition. 2. Pertaining to pathology (= branch of medicine that treats the essential nature of the disease, especially the structural and functional changes in tissues and organs of the body caused by the disease). [EU]

Pathologic Processes: The abnormal mechanisms and forms involved in the dysfunctions of tissues and organs. [NIH]

Pathophysiology: Altered functions in an individual or an organ due to disease. [NIH]

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]

Penicillin: An antibiotic drug used to treat infection. [NIH]

Peptide: Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [NIH]

Peripheral blood: Blood circulating throughout the body. [NIH]

Peripheral Nervous System: The nervous system outside of the brain and spinal cord. The peripheral nervous system has autonomic and somatic divisions. The autonomic nervous system includes the enteric, parasympathetic, and sympathetic subdivisions. The somatic nervous system includes the cranial and spinal nerves and their ganglia and the peripheral sensory receptors. [NIH]

Peripheral Nervous System Diseases: Diseases of the peripheral nerves external to the brain and spinal cord, which includes diseases of the nerve roots, ganglia, plexi, autonomic nerves, sensory nerves, and motor nerves. [NIH]

Peripheral Neuropathy: Nerve damage, usually affecting the feet and legs; causing pain, numbness, or a tingling feeling. Also called "somatic neuropathy" or "distal sensory polyneuropathy." [NIH]

Permissiveness: The attitude that grants freedom of expression and activity to another individual, but not necessarily with sanction or approval. [NIH]

Peroneal Nerve: The lateral of the two terminal branches of the sciatic nerve. The peroneal (or fibular) nerve provides motor and sensory innervation to parts of the leg and foot. [NIH]

PH: The symbol relating the hydrogen ion (H+) concentration or activity of a solution to that of a given standard solution. Numerically the pH is approximately equal to the negative logarithm of H+ concentration expressed in molarity. pH 7 is neutral; above it alkalinity increases and below it acidity increases. [EU]

Pharmacokinetics: Dynamic and kinetic mechanisms of exogenous chemical and drug absorption, biotransformation, distribution, release, transport, uptake, and elimination as a function of dosage, and extent and rate of metabolic processes. It includes toxicokinetics, the pharmacokinetic mechanism of the toxic effects of a substance. [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]

Phenylalanine: An aromatic amino acid that is essential in the animal diet. It is a precursor of melanin, dopamine, noradrenalin, and thyroxine. [NIH]

Phosmet: An organothiophosphorus insecticide that has been used to control pig mange. [NIH]

Phospholipases: A class of enzymes that catalyze the hydrolysis of phosphoglycerides or glycerophosphatidates. EC 3.1.-. [NIH]

Phospholipids: Lipids containing one or more phosphate groups, particularly those derived from either glycerol (phosphoglycerides; glycerophospholipids) or sphingosine (sphingolipids). They are polar lipids that are of great importance for the structure and function of cell membranes and are the most abundant of membrane lipids, although not stored in large amounts in the system. [NIH]

Phosphorus: A non-metallic element that is found in the blood, muscles, nevers, bones, and teeth, and is a component of adenosine triphosphate (ATP; the primary energy source for the body's cells.) [NIH]

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]

Plants: Multicellular, eukaryotic life forms of the kingdom Plantae. They are characterized by a mainly photosynthetic mode of nutrition; essentially unlimited growth at localized regions of cell divisions (meristems); cellulose within cells providing rigidity; the absence of organs of locomotion; absense of nervous and sensory systems; and an alteration of haploid and diploid generations. [NIH]

Plasma: The clear, yellowish, fluid part of the blood that carries the blood cells. The proteins that form blood clots are in plasma. [NIH]

Plasma cells: A type of white blood cell that produces antibodies. [NIH]

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]

Plexus: A network or tangle; a general term for a network of lymphatic vessels, nerves, or veins. [EU]

Pneumonia: Inflammation of the lungs. [NIH]

Point Mutation: A mutation caused by the substitution of one nucleotide for another. This results in the DNA molecule having a change in a single base pair. [NIH]

Polymers: Compounds formed by the joining of smaller, usually repeating, units linked by covalent bonds. These compounds often form large macromolecules (e.g., polypeptides, proteins, plastics). [NIH]

Polymorphic: Occurring in several or many forms; appearing in different forms at different stages of development. [EU]

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]

Posterior: Situated in back of, or in the back part of, or affecting the back or dorsal surface of the body. In lower animals, it refers to the caudal end of the body. [EU]

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]

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]

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]

Preleukemia: Conditions in which the abnormalities in the peripheral blood or bone marrow represent the early manifestations of acute leukemia, but in which the changes are not of sufficient magnitude or specificity to permit a diagnosis of acute leukemia by the

usual clinical criteria. [NIH]

Prenatal: Existing or occurring before birth, with reference to the fetus. [EU]

Presynaptic: Situated proximal to a synapse, or occurring before the synapse is crossed. [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]

Prion: Small proteinaceous infectious particles that resist inactivation by procedures modifying nucleic acids and contain an abnormal isoform of a cellular protein which is a major and necessary component. [NIH]

Probe: An instrument used in exploring cavities, or in the detection and dilatation of strictures, or in demonstrating the potency of channels; an elongated instrument for exploring or sounding body cavities. [NIH]

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]

Projection: A defense mechanism, operating unconsciously, whereby that which is emotionally unacceptable in the self is rejected and attributed (projected) to others. [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]

Prostate: A gland in males that surrounds the neck of the bladder and the urethra. It secretes a substance that liquifies coagulated semen. It is situated in the pelvic cavity behind the lower part of the pubic symphysis, above the deep layer of the triangular ligament, and rests upon the rectum. [NIH]

Protease: Proteinase (= any enzyme that catalyses the splitting of interior peptide bonds in a protein). [EU]

Protein C: A vitamin-K dependent zymogen present in the blood, which, upon activation by thrombin and thrombomodulin exerts anticoagulant properties by inactivating factors Va and VIIIa at the rate-limiting steps of thrombin formation. [NIH]

Protein Conformation: The characteristic 3-dimensional shape of a protein, including the secondary, supersecondary (motifs), tertiary (domains) and quaternary structure of the peptide chain. Quaternary protein structure describes the conformation assumed by multimeric proteins (aggregates of more than one polypeptide chain). [NIH]

Protein Folding: A rapid biochemical reaction involved in the formation of proteins. It begins even before a protein has been completely synthesized and proceeds through discrete intermediates (primary, secondary, and tertiary structures) before the final structure (quaternary structure) is developed. [NIH]

Protein S: The vitamin K-dependent cofactor of activated protein C. Together with protein C, it inhibits the action of factors VIIIa and Va. A deficiency in protein S can lead to recurrent venous and arterial thrombosis. [NIH]

Proteins: Polymers of amino acids linked by peptide bonds. The specific sequence of amino acids determines the shape and function of the protein. [NIH]

Proteolytic: 1. Pertaining to, characterized by, or promoting proteolysis. 2. An enzyme that promotes proteolysis (= the splitting of proteins by hydrolysis of the peptide bonds with formation of smaller polypeptides). [EU]

Protocol: The detailed plan for a clinical trial that states the trial's rationale, purpose, drug or vaccine dosages, length of study, routes of administration, who may participate, and other aspects of trial design. [NIH]

Protons: Stable elementary particles having the smallest known positive charge, found in the nuclei of all elements. The proton mass is less than that of a neutron. A proton is the nucleus of the light hydrogen atom, i.e., the hydrogen ion. [NIH]

Pruritus: An intense itching sensation that produces the urge to rub or scratch the skin to obtain relief. [NIH]

Psychiatric: Pertaining to or within the purview of psychiatry. [EU]

Psychiatry: The medical science that deals with the origin, diagnosis, prevention, and treatment of mental disorders. [NIH]

Psychic: Pertaining to the psyche or to the mind; mental. [EU]

Psychology: The science dealing with the study of mental processes and behavior in man and animals. [NIH]

Psychopharmacology: The study of the effects of drugs on mental and behavioral activity. [NIH]

Psychophysiology: The study of the physiological basis of human and animal behavior. [NIH]

Public Health: Branch of medicine concerned with the prevention and control of disease and disability, and the promotion of physical and mental health of the population on the international, national, state, or municipal level. [NIH]

Public Policy: A course or method of action selected, usually by a government, from among alternatives to guide and determine present and future decisions. [NIH]

Pulmonary: Relating to the lungs. [NIH]

Pulmonary Artery: The short wide vessel arising from the conus arteriosus of the right ventricle and conveying unaerated blood to the lungs. [NIH]

Pulmonary Edema: An accumulation of an excessive amount of watery fluid in the lungs, may be caused by acute exposure to dangerous concentrations of irritant gasses. [NIH]

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]

Pyramidal Cells: Projection neurons in the cerebral cortex and the hippocampus. Pyramidal cells have a pyramid-shaped soma with the apex and an apical dendrite pointed toward the pial surface and other dendrites and an axon emerging from the base. The axons may have local collaterals but also project outside their cortical region. [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]

Quantitative Structure-Activity Relationship: A quantitative prediction of the biological,

ecotoxicological or pharmaceutical activity of a molecule. It is based upon structure and activity information gathered from a series of similar compounds. [NIH]

Quaternary: 1. Fourth in order. 2. Containing four elements or groups. [EU]

Quinacrine: N(4)-(6-Chloro-2-methoxy-9-acridinyl)-N(1),N(1)-diethyl-1,4-pentanediamine. An acridine derivative formerly widely used as an antimalarial but superseded by chloroquine in recent years. It has also been used as an anthelmintic and in the treatment of giardiasis and malignant effusions. It is used in cell biological experiments as an inhibitor of phospholipase A2. [NIH]

Rabies: A highly fatal viral infection of the nervous system which affects all warm-blooded animal species. It is one of the most important of the zoonoses because of the inevitably fatal outcome for the infected human. [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]

Racemic: Optically inactive but resolvable in the way of all racemic compounds. [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]

Radioisotope: An unstable element that releases radiation as it breaks down. Radioisotopes can be used in imaging tests or as a treatment for cancer. [NIH]

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]

Reactivation: The restoration of activity to something that has been inactivated. [EU]

Reagent: A substance employed to produce a chemical reaction so as to detect, measure, produce, etc., other substances. [EU]

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]

Recombinant Proteins: Proteins prepared by recombinant DNA technology. [NIH]

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 Nucleus: A pinkish-yellow portion of the midbrain situated in the rostral

mesencephalic tegmentum. It receives a large projection from the contralateral half of the cerebellum via the superior cerebellar peduncle and a projection from the ipsilateral motor cortex. [NIH]

Reductase: Enzyme converting testosterone to dihydrotestosterone. [NIH]

Refer: To send or direct for treatment, aid, information, de decision. [NIH]

Refraction: A test to determine the best eyeglasses or contact lenses to correct a refractive error (myopia, hyperopia, or astigmatism). [NIH]

Regimen: A treatment plan that specifies the dosage, the schedule, and the duration of treatment. [NIH]

Relative risk: The ratio of the incidence rate of a disease among individuals exposed to a specific risk factor to the incidence rate among unexposed individuals; synonymous with risk ratio. Alternatively, the ratio of the cumulative incidence rate in the exposed to the cumulative incidence rate in the unexposed (cumulative incidence ratio). The term relative risk has also been used synonymously with odds ratio. This is because the odds ratio and relative risk approach each other if the disease is rare (5 percent of population) and the number of subjects is large. [NIH]

Reproductive cells: Egg and sperm cells. Each mature reproductive cell carries a single set of 23 chromosomes. [NIH]

Research Design: A plan for collecting and utilizing data so that desired information can be obtained with sufficient precision or so that an hypothesis can be tested properly. [NIH]

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]

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 Ganglion Cells: Cells of the innermost nuclear layer of the retina, the ganglion cell layer, which project axons through the optic nerve to the brain. They are quite variable in size and in the shapes of their dendritic arbors, which are generally confined to the inner plexiform layer. [NIH]

Retinoblastoma: An eye cancer that most often occurs in children younger than 5 years. It occurs in hereditary and nonhereditary (sporadic) forms. [NIH]

Retrograde: 1. Moving backward or against the usual direction of flow. 2. Degenerating, deteriorating, or catabolic. [EU]

Retrospective: Looking back at events that have already taken place. [NIH]

Retroviral vector: RNA from a virus that is used to insert genetic material into cells. [NIH]

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]

Rigidity: Stiffness or inflexibility, chiefly that which is abnormal or morbid; rigor. [EU]

Risk factor: A habit, trait, condition, or genetic alteration that increases a person's chance of developing a disease. [NIH]

Rods: One type of specialized light-sensitive cells (photoreceptors) in the retina that provide side vision and the ability to see objects in dim light (night vision). [NIH]

Ruminants: A suborder of the order Artiodactyla whose members have the distinguishing feature of a four-chambered stomach. Horns or antlers are usually present, at least in males. [NIH]

Salicylate: Non-steroidal anti-inflammatory drugs. [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]

Sciatic Nerve: A nerve which originates in the lumbar and sacral spinal cord (L4 to S3) and supplies motor and sensory innervation to the lower extremity. The sciatic nerve, which is the main continuation of the sacral plexus, is the largest nerve in the body. It has two major branches, the tibial nerve and the peroneal nerve. [NIH]

Sclerosis: A pathological process consisting of hardening or fibrosis of an anatomical structure, often a vessel or a nerve. [NIH]

Scrapie: A fatal disease of the nervous system in sheep and goats, characterized by pruritus, debility, and locomotor incoordination. It is caused by proteinaceous infectious particles called prions. [NIH]

Screening: Checking for disease when there are no symptoms. [NIH]

Secretion: 1. The process of elaborating a specific product as a result of the activity of a gland; this activity may range from separating a specific substance of the blood to the elaboration of a new chemical substance. 2. Any substance produced by secretion. [EU]

Secretory: Secreting; relating to or influencing secretion or the secretions. [NIH]

Self Care: Performance of activities or tasks traditionally performed by professional health care providers. The concept includes care of oneself or one's family and friends. [NIH]

Senile: Relating or belonging to old age; characteristic of old age; resulting from infirmity of old age. [NIH]

Senile Plaques: Spherical masses consisting of amyloid fibrils and neuronal processes. [NIH]

Sequence Homology: The degree of similarity between sequences. Studies of amino acid and nucleotide sequences provide useful information about the genetic relatedness of certain species. [NIH]

Sequencing: The determination of the order of nucleotides in a DNA or RNA chain. [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]

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]

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]

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]

Small intestine: The part of the digestive tract that is located between the stomach and the large intestine. [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]

Sodium salicylate: A drug that belongs to the family of drugs called nonsteroidal anti-inflammatory drugs. Sodium salicylate may be tolerated by people who are sensitive to aspirin. [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]

Spasm: An involuntary contraction of a muscle or group of muscles. Spasms may involve skeletal muscle or smooth muscle. [NIH]

Spastic: 1. Of the nature of or characterized by spasms. 2. Hypertonic, so that the muscles are stiff and the movements awkward. 3. A person exhibiting spasticity, such as occurs in spastic paralysis or in cerebral palsy. [EU]

Spasticity: A state of hypertonicity, or increase over the normal tone of a muscle, with heightened deep tendon reflexes. [EU]

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]

Species Specificity: Restriction of a characteristic or response to the members of one species; it usually refers to that property of the immune response which differentiates one species from another on the basis of antigen recognition, but the concept is not limited to immunology and is used loosely at levels higher than the species. [NIH]

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]

Spectroscopic: The recognition of elements through their emission spectra. [NIH]

Spectrum: A charted band of wavelengths of electromagnetic vibrations obtained by refraction and diffraction. By extension, a measurable range of activity, such as the range of bacteria affected by an antibiotic (antibacterial s.) or the complete range of manifestations of a disease. [EU]

Sperm: The fecundating fluid of the male. [NIH]

Spinal cord: The main trunk or bundle of nerves running down the spine through holes in the spinal bone (the vertebrae) from the brain to the level of the lower back. [NIH]

Spinal Cord Diseases: Pathologic conditions which feature spinal cord damage or dysfunction, including disorders involving the meninges and perimeningeal spaces surrounding the spinal cord. Traumatic injuries, vascular diseases, infections, and inflammatory/autoimmune processes may affect the spinal cord. [NIH]

Spleen: An organ that is part of the lymphatic system. The spleen produces lymphocytes, filters the blood, stores blood cells, and destroys old blood cells. It is located on the left side of the abdomen near the stomach. [NIH]

Sporadic: Neither endemic nor epidemic; occurring occasionally in a random or isolated manner. [EU]

Stabilization: The creation of a stable state. [EU]

Statistically significant: Describes a mathematical measure of difference between groups. The difference is said to be statistically significant if it is greater than what might be

expected to happen by chance alone. [NIH]

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]

Stimulus: That which can elicit or evoke action (response) in a muscle, nerve, gland or other excitable issue, or cause an augmenting action upon any function or metabolic process. [NIH]

Stomach: An organ of digestion situated in the left upper quadrant of the abdomen between the termination of the esophagus and the beginning of the duodenum. [NIH]

Stool: The waste matter discharged in a bowel movement; feces. [NIH]

Strand: DNA normally exists in the bacterial nucleus in a helix, in which two strands are coiled together. [NIH]

Stress: Forcibly exerted influence; pressure. Any condition or situation that causes strain or tension. Stress may be either physical or psychologic, or both. [NIH]

Stroke: Sudden loss of function of part of the brain because of loss of blood flow. Stroke may be caused by a clot (thrombosis) or rupture (hemorrhage) of a blood vessel to the brain. [NIH]

Stroma: The middle, thickest layer of tissue in the cornea. [NIH]

Strontium: An element of the alkaline earth family of metals. It has the atomic symbol Sr, atomic number 38, and atomic weight 87.62. [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]

Subspecies: A category intermediate in rank between species and variety, based on a smaller number of correlated characters than are used to differentiate species and generally conditioned by geographical and/or ecological occurrence. [NIH]

Substance P: An eleven-amino acid neurotransmitter that appears in both the central and peripheral nervous systems. It is involved in transmission of pain, causes rapid contractions of the gastrointestinal smooth muscle, and modulates inflammatory and immune responses. [NIH]

Substrate: A substance upon which an enzyme acts. [EU]

Superoxide: Derivative of molecular oxygen that can damage cells. [NIH]

Superoxide Dismutase: An oxidoreductase that catalyzes the reaction between superoxide anions and hydrogen to yield molecular oxygen and hydrogen peroxide. The enzyme protects the cell against dangerous levels of superoxide. EC 1.15.1.1. [NIH]

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]

Symptomatic: Having to do with symptoms, which are signs of a condition or disease. [NIH]

Symptomatology: 1. That branch of medicine with treats of symptoms; the systematic discussion of symptoms. 2. The combined symptoms of a disease. [EU]

Synapse: The region where the processes of two neurons come into close contiguity, and the nervous impulse passes from one to the other; the fibers of the two are intermeshed, but, according to the general view, there is no direct contiguity. [NIH]

Synapsis: The pairing between homologous chromosomes of maternal and paternal origin

during the prophase of meiosis, leading to the formation of gametes. [NIH]

Synaptic: Pertaining to or affecting a synapse (= site of functional apposition between neurons, at which an impulse is transmitted from one neuron to another by electrical or chemical means); pertaining to synapsis (= pairing off in point-for-point association of homologous chromosomes from the male and female pronuclei during the early prophase of meiosis). [EU]

Synaptic Vesicles: Membrane-bound compartments which contain transmitter molecules. Synaptic vesicles are concentrated at presynaptic terminals. They actively sequester transmitter molecules from the cytoplasm. In at least some synapses, transmitter release occurs by fusion of these vesicles with the presynaptic membrane, followed by exocytosis of their contents. [NIH]

Systemic: Affecting the entire body. [NIH]

Taurine: 2-Aminoethanesulfonic acid. A conditionally essential nutrient, important during mammalian development. It is present in milk but is isolated mostly from ox bile and strongly conjugates bile acids. [NIH]

Terminator: A DNA sequence sited at the end of a transcriptional unit that signals the end of transcription. [NIH]

Testosterone: A hormone that promotes the development and maintenance of male sex characteristics. [NIH]

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]

Thalamic: Cell that reaches the lateral nucleus of amygdala. [NIH]

Thalamic Diseases: Disorders of the centrally located thalamus, which integrates a wide range of cortical and subcortical information. Manifestations include sensory loss, movement disorders; ataxia, pain syndromes, visual disorders, a variety of neuropsychological conditions, and coma. Relatively common etiologies include cerebrovascular disorders; craniocerebral trauma; brain neoplasms; brain hypoxia; intracranial hemorrhages; and infectious processes. [NIH]

Thalamus: Paired bodies containing mostly gray substance and forming part of the lateral wall of the third ventricle of the brain. The thalamus represents the major portion of the diencephalon and is commonly divided into cellular aggregates known as nuclear groups. [NIH]

Therapeutics: The branch of medicine which is concerned with the treatment of diseases, palliative or curative. [NIH]

Third Ventricle: A narrow cleft inferior to the corpus callosum, within the diencephalon, between the paired thalami. Its floor is formed by the hypothalamus, its anterior wall by the lamina terminalis, and its roof by ependyma. It communicates with the fourth ventricle by the cerebral aqueduct, and with the lateral ventricles by the interventricular foramina. [NIH]

Thoracic: Having to do with the chest. [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]

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]

Thymus: An organ that is part of the lymphatic system, in which T lymphocytes grow and multiply. The thymus is in the chest behind the breastbone. [NIH]

Thyroid: A gland located near the windpipe (trachea) that produces thyroid hormone, which helps regulate growth and metabolism. [NIH]

Thyroid Gland: A highly vascular endocrine gland consisting of two lobes, one on either side of the trachea, joined by a narrow isthmus; it produces the thyroid hormones which are concerned in regulating the metabolic rate of the body. [NIH]

Thyroid Hormones: Hormones secreted by the thyroid gland. [NIH]

Tibial Nerve: The medial terminal branch of the sciatic nerve. The tibial nerve fibers originate in lumbar and sacral spinal segments (L4 to S2). They supply motor and sensory innervation to parts of the calf and foot. [NIH]

Tissue: A group or layer of cells that are alike in type and work together to perform a specific function. [NIH]

Tissue Culture: Maintaining or growing of tissue, organ primordia, or the whole or part of an organ in vitro so as to preserve its architecture and/or function (Dorland, 28th ed). Tissue culture includes both organ culture and cell culture. [NIH]

Tissue Transplantation: Transference of tissue within an individual, between individuals of the same species, or between individuals of different species. [NIH]

Tooth Preparation: Procedures carried out with regard to the teeth or tooth structures preparatory to specified dental therapeutic and surgical measures. [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]

Toxin: A poison; frequently used to refer specifically to a protein produced by some higher plants, certain animals, and pathogenic bacteria, which is highly toxic for other living organisms. Such substances are differentiated from the simple chemical poisons and the vegetable alkaloids by their high molecular weight and antigenicity. [EU]

Tracer: A substance (such as a radioisotope) used in imaging procedures. [NIH]

Trachea: The cartilaginous and membranous tube descending from the larynx and branching into the right and left main bronchi. [NIH]

Transcription Factors: Endogenous substances, usually proteins, which are effective in the initiation, stimulation, or termination of the genetic transcription process. [NIH]

Transduction: The transfer of genes from one cell to another by means of a viral (in the case of bacteria, a bacteriophage) vector or a vector which is similar to a virus particle (pseudovirion). [NIH]

Transfection: The uptake of naked or purified DNA into cells, usually eukaryotic. It is analogous to bacterial transformation. [NIH]

Transfer Factor: Factor derived from leukocyte lysates of immune donors which can transfer both local and systemic cellular immunity to nonimmune recipients. [NIH]

Transferases: Transferases are enzymes transferring a group, for example, the methyl group or a glycosyl group, from one compound (generally regarded as donor) to another compound (generally regarded as acceptor). The classification is based on the scheme "donor:acceptor group transferase". (Enzyme Nomenclature, 1992) EC 2. [NIH]

Transfusion: The infusion of components of blood or whole blood into the bloodstream. The blood may be donated from another person, or it may have been taken from the person earlier and stored until needed. [NIH]

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]

Translocate: The attachment of a fragment of one chromosome to a non-homologous chromosome. [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]

Tremor: Cyclical movement of a body part that can represent either a physiologic process or a manifestation of disease. Intention or action tremor, a common manifestation of cerebellar diseases, is aggravated by movement. In contrast, resting tremor is maximal when there is no attempt at voluntary movement, and occurs as a relatively frequent manifestation of Parkinson disease. [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]

Ubiquitin: A highly conserved 76 amino acid-protein found in all eukaryotic cells. [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]

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]

Urinary: Having to do with urine or the organs of the body that produce and get rid of urine. [NIH]

Urine: Fluid containing water and waste products. Urine is made by the kidneys, stored in the bladder, and leaves the body through the urethra. [NIH]

Uterus: The small, hollow, pear-shaped organ in a woman's pelvis. This is the organ in which a fetus develops. Also called the womb. [NIH]

Vaccination: Administration of vaccines to stimulate the host's immune response. This includes any preparation intended for active immunological prophylaxis. [NIH]

Vaccine: A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. [NIH]

Vacuoles: Any spaces or cavities within a cell. They may function in digestion, storage, secretion, or excretion. [NIH]

Vagina: The muscular canal extending from the uterus to the exterior of the body. Also called the birth canal. [NIH]

Valine: A branched-chain essential amino acid that has stimulant activity. It promotes muscle growth and tissue repair. It is a precursor in the penicillin biosynthetic pathway. [NIH]

Vascular: Pertaining to blood vessels or indicative of a copious blood supply. [EU]

Vasodilators: Any nerve or agent which induces dilatation 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]

Venter: Belly. [NIH]

Ventral: 1. Pertaining to the belly or to any venter. 2. Denoting a position more toward the belly surface than some other object of reference; same as anterior in human anatomy. [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]

Venules: The minute vessels that collect blood from the capillary plexuses and join together to form veins. [NIH]

Vertebrae: A bony unit of the segmented spinal column. [NIH]

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]

Viroids: A group of pathogens comprising the smallest known agents of infectious disease. They are unencapsulated and are capable of replicating autonomously in susceptible cells. Positively identified viroids composed of single-stranded RNA have been isolated from

higher plants, but the existence of DNA viroids pathogenic to animals is suspected. [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]

Virulent: A virus or bacteriophage capable only of lytic growth, as opposed to temperate phages establishing the lysogenic response. [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]

Visual Acuity: Acuteness or clearness of vision, especially of form vision, which is dependent mainly on the sharpness of the retinal focus. [NIH]

Vitro: Descriptive of an event or enzyme reaction under experimental investigation occurring outside a living organism. Parts of an organism or microorganism are used together with artificial substrates and/or conditions. [NIH]

Vivo: Outside of or removed from the body of a living organism. [NIH]

White blood cell: A type of cell in the immune system that helps the body fight infection and disease. White blood cells include lymphocytes, granulocytes, macrophages, and others. [NIH]

Windpipe: A rigid tube, 10 cm long, extending from the cricoid cartilage to the upper border of the fifth thoracic vertebra. [NIH]

Womb: A hollow, thick-walled, muscular organ in which the impregnated ovum is developed into a child. [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]

Zoonoses: Diseases of non-human animals that may be transmitted to man or may be transmitted from man to non-human animals. [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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