WERNER SYNDROME

A 3-in-1 Medical Reference

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

TO INTERNET REFERENCES
WERNER SYNDROME

A BIBLIOGRAPHY AND DICTIONARY
FOR PHYSICIANS, PATIENTS, AND GENOME RESEARCHERS

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

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

The Editors

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1 From the NIH, National Cancer Institute (NCI): http://www.cancer.gov/.
CHAPTER 1. STUDIES ON WERNER SYNDROME

Overview

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

The Genetics Home Reference has recently published the following summary for Werner syndrome:

What Is Werner Syndrome?3

Werner syndrome is a rare disorder characterized by the dramatic, rapid appearance of aging. Individuals with this syndrome typically grow and develop normally until they reach puberty. The age of onset of Werner syndrome is variable, but an early sign is the lack of a teenage growth spurt, which results in short stature. Other signs and symptoms appear when affected individuals are in their twenties or thirties and include loss and graying of hair, hoarseness, thickening of the skin, and cloudy lenses (cataracts) in both eyes. Overall, people affected by Werner syndrome have thin arms and legs and a thick trunk. As the syndrome progresses, affected people may experience additional skin problems, type 2

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2 This section has been adapted from the National Library of Medicine: [http://ghr.nlm.nih.gov/](http://ghr.nlm.nih.gov/).
diabetes, diminished fertility, severe hardening of the arteries (arteriosclerosis), thinning bones (osteoporosis), and some types of cancer. Affected individuals typically have a characteristic facial appearance described as "bird-like" by the time they reach their thirties. People affected by Werner syndrome usually live into their late forties or early fifties.

How Common Is Werner Syndrome?

Werner syndrome is estimated to affect 1 in 200,000 individuals in the United States. In Japan, the syndrome occurs more often, affecting between 1 in 20,000 and 1 in 40,000 people.

What Genes Are Related to Werner Syndrome?


The WRN gene provides instructions for the production of Werner protein. This protein is thought to perform several tasks in the cell, including the maintenance and repair of DNA. It also assists in making copies of DNA (replication) in preparation for cell division. Mutations in the WRN gene often lead to the production of an abnormally short Werner protein. Some research suggests that this shortened protein is not sent to the nucleus, where it normally interacts with DNA. Evidence also suggests that the altered protein is broken down quickly in the cell, leading to a loss of Werner protein function. Researchers do not fully understand how WRN mutations cause this syndrome. Cells with an altered Werner protein may divide less often than normal, leading to growth failure. Also, the altered protein may allow DNA damage to accumulate, which could impair normal cell activities and cause health problems related to this condition.

How Do People Inherit Werner Syndrome?

This condition is inherited in an autosomal recessive pattern, which means two copies of the gene in each cell are altered. Most often, the parents of an individual with an autosomal recessive disorder each carry one copy of the altered gene but do not show signs and symptoms of the disorder.

Where Can I Find Additional Information about Werner Syndrome?

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

NIH Publications - National Institutes of Health

  d.section.188
• National Heart, Lung, and Blood Institute:

  **MedlinePlus - Health Information**

  • Health Topic: Cancer:
  • Health Topic: Coronary Artery Disease:

  **Educational Resources - Information Pages**

  • International Registry of Werner Syndrome:
    http://www.wernersyndrome.org/registry/registry.html
  • Madisons Foundation:
    http://www.madisonsfoundation.org/content/3/1/display.asp?did=426
  • Orphanet:
    http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&amp;Expert=902
  • University of Washington Werner Syndrome Research Website:
    http://www.wernersyndrome.org/

  **Patient Support - for Patients and Families**

  • International Registry of Werner Syndrome:
    http://www.wernersyndrome.org/registry/registry.html
  • National Organization for Rare Disorders:
    http://www.rarediseases.org/search/rdbdetail_abstract.html?disname=Werner+Syndrome

  **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=werner
  • ClinicalTrials.gov - Linking patients to medical research:
    http://clinicaltrials.gov/search/condition=%22werner+syndrome%22?recruiting=false
  • PubMed - Recent literature:
  • OMIM - Genetic disorder catalog:
References

These sources were used to develop the Genetics Home Reference condition summary on Werner syndrome.


A summary of the gene related to Werner syndrome is provided below:

**What Is the Official Name of the WRN Gene?**

The official name of this gene is “Werner syndrome.”

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

**What Is the Normal Function of the WRN Gene?**

The WRN gene provides instructions for producing Werner protein, which is a type of enzyme called a helicase. Helicase enzymes generally unwind and separate double-stranded DNA. These activities are necessary before DNA can be copied in preparation for cell division (DNA replication). Helicase enzymes are also critical for making a blueprint of a gene for protein production, a process called transcription. Further evidence suggests that Werner protein plays a critical role in repairing DNA. Overall, this protein helps maintain the structure and integrity of a person’s DNA.

**What Conditions Are Related to the WRN Gene?**

_Werner Syndrome - Caused by Mutations in the WRN Gene_

More than 20 mutations in the WRN gene are known to cause Werner syndrome. Many of these mutations result in an abnormally shortened Werner protein. Evidence suggests that

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4 Adapted from the Genetics Home Reference of the National Library of Medicine: http://ghr.nlm.nih.gov/gene=wrn;jsessionid=02F705788E7034EAD461B37800E420FB.
the altered protein is not transported into the nucleus, where it normally interacts with DNA. This shortened protein may also be broken down too quickly, leading to a loss of Werner protein in the cell. Without normal Werner protein in the nucleus, cells cannot perform the tasks of DNA replication, repair, and transcription. Researchers are still determining how these mutations cause the appearance of premature aging seen in Werner syndrome.

Where Is the WRN Gene Located?

Cytogenetic Location: 8p12-p11.2

Molecular Location on chromosome 8: base pairs 31,010,319 to 31,150,818

The WRN gene is located on the short (p) arm of chromosome 8 between positions 12 and 11.2.

More precisely, the WRN gene is located from base pair 31,010,319 to base pair 31,150,818 on chromosome 8.

References

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

- Entrez Gene
- OMIM

Federally Funded Research on Werner Syndrome

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

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

• Project Title: BIOCHEMICAL BASIS OF WRN AND RECQ HELICASE FUNCTION
  Principal Investigator & Institution: Orren, David K.; Graduate Center for Toxicology; University of Kentucky 109 Kinkead Hall Lexington, Ky 405060057
  Timing: Fiscal Year 2005; Project Start 10-AUG-2004; Project End 31-JUL-2008
  Summary: (provided by applicant): RecQ helicases act to maintain genomic stability by an as yet unknown mechanism. When their function is lost, levels of illegitimate recombination increase significantly. Not surprisingly, the human hereditary RecQ deficiency diseases (Werner, Bloom, and Rothmund-Thomson syndromes, caused by defects in WRN, BLM, and RECQL4, respectively) demonstrate early onset and increased frequency of cancer. Importantly, Werner syndrome also shows accelerated development of many age-related problems. Although these diseases have distinct phenotypes, RecQ family members maintain a high degree of homology within and C terminal to the conserved helicase domain, suggesting that they may have a common mechanistic function and/or DNA substrate specificity. We refer to this extended sequence conservation as the RecQ expanded core. Their illegitimate recombination phenotypes suggest that RecQ helicases function in recombination or anti-recombination pathways, or possibly in resolution of replication fork blockage. Our laboratory has recently uncovered strand pairing and strand exchange activities in WRN and other RecQ helicases consistent with putative roles in these pathways. We hypothesize that the RecQ expanded core forms a functional unit that encompasses DNA binding and catalytic activities. Further, we propose that the function of the RecQ

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).
expanded core is to coordinate DNA binding and unwinding to achieve strand exchange reactions in complex recombination or replication intermediates. This hypothesis fits with the putative roles for RecQ members and current biochemical knowledge regarding these proteins. In this proposal, WRN is used as a model RecQ helicase for 1) characterizing strand exchange activity reflecting putative coordination between strand pairing and unwinding activities, 2) examining DNA binding properties and substrate specificity for replication and recombination intermediates, and 3) generating site-directed mutants that pinpoint the DNA binding, enzymatic, and physiological functions of the RecQ expanded core and its individual domains. Our findings with WRN will be highly relevant to elucidating its DNA metabolic role and specific mechanisms underlying carcinogenesis and certain aging phenotypes. Sequence conservation between RecQ helicases also indicates that our findings will be applicable to the functions of other RecQ helicases (including BLM and RECQL4) and their relationships to human health.

- **Project Title: BIOCHEMISTRY**

  Principal Investigator & Institution: Loeb, Lawrence A.; Professor; University of Washington Office of Sponsored Programs Seattle, Wa 98105

  Timing: Fiscal Year 2005

  Summary: Werner syndrome (WS) is an uncommon autosomal recessive disease characterized by premature aging and genetic instability, and associated with a high incidence of specific, uncommon cancers. The gene mutated in WS, WRN, belongs to the family of RecQ helicases and encodes both 3' -> 5' DNA helicase and 3' -> 5' DNA exonuclease activities. Biochemical studies indicate that the helicase preferentially unwinds DNA harboring alternative structures and that the exonuclease preferentially excises mismatched nucleotides at the 3'-terminus. Cloning and purification of WRN affords us the opportunity to study its biochemistry in detail and use these findings in concert with other projects in this program to understand how the wild-type WS protein, WRN, suppresses genetic instability and cancer. In order to gain insights into the in vivo functions of the WS protein, we will 1. identify and characterize proteins that interact physically and functionally with WRN, and 2. establish model in vitro systems to determine the involvement of WRN in cross-link repair. In addition, we will examine WRN single nucleotide polymorphisms in the general population for functional effects, and analyze polymorphic variants and WRN mutations in cancers associated with WS, in particular, sarcomas. These studies will provide the biochemical foundation for the proposed program project.

- **Project Title: CHARACTERIZATION OF A MOUSE MODEL OF WERNER SYNDROME**

  Principal Investigator & Institution: Chang, Sandy S.; Assistant Professor; Molecular Genetics; University of Texas Md Anderson Can Ctr Cancer Center Houston, Tx 770304009

  Timing: Fiscal Year 2005; Project Start 15-SEP-2004; Project End 30-JUN-2006

  Summary: (provided by applicant): Genetic studies of human progeric syndromes have furthered our understanding of the molecular mechanisms of the aging process. Mutations in Wrn causes Werner Syndrome (WS), a disease characterized by premature aging, elevated genomic instability and cancer. WS fibroblasts prematurely senesce due to telomere shortening, suggesting the possibility that telomere dysfunction collaborates with Wm loss to generate WS. Telomeres function to prevent chromosomal ends from being recognized as double-strand DNA breaks and confer genome stability.
It has been postulated that telomere shortening serves as a molecular clock that eventually signals replicative senescence. WS cells senescence while still possessing long telomeres, suggesting that they may be hypersensitive to telomere shortening. This hypothesis is supported by the observation that the senescence phenotype observed in WS cells can be rescued by overexpression of telomerase, suggesting that one consequence of the WS defect is the acceleration of normal telomere-based senescence. Mice lacking WRN do not display obvious aging phenotypes, and I hypothesize that manifestation of the WS phenotype requires the presence of critically short telomeres. Mouse telomeres are normally too long for the required telomere attrition to take place during the aging process. To test experimentally the hypothesis that manifestation of the WS phenotype in WRN-/- mice requires critical telomere shortening, telomere lengths were shortened genetically via successive intercrossings of WRN-/- mTERC-/- mice. Compound mutant mice with short dysfunctional telomeres exhibited early onset of aging phenotypes, including alopecia, cataract formation and glucose intolerance and died prematurely. These exciting results suggest that our mouse model recapitulates features of WS observed in human patients. Our immediate goal is to characterize additional aging phenotypes in these mice and to correlate the onset of premature aging with genomic instability induced by telomere dysfunction. These studies should establish a role for WRN function in mammalian telomere biology and lend support to the notion that telomeres play a causative role in mammalian aging.

- **Project Title:** DETERMINATION OF REGULATORY MECHANISMS FOR BLM HELICASE

Principal Investigator & Institution: Sengupta, Sagar; National Institute of Immunology Aruna Asaf Ali Marg New Delhi,

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

Summary: (provided by applicant): BLM is a member of the RecQ family of DNA helicases. Germline mutations in BLM and other members of the RecQ helicase family, WRN and RECQ4, result in autosomal-recessive disorders, Bloom syndrome (BS), Werner Syndrome (WS) and Rothmund-Thomson syndrome (RTS) respectively. These syndromes are rare autosomal-recessive disorders that are associated with elevated incidence of cancer. The BS afflicted individuals are predisposed to most types of cancers. Cancer affects about new 700,000 cases every year in India and results in 350,000 deaths per year. BLM is thought to be a "caretaker tumor suppressor" involved in suppressing neoplastic transformation by controlling chromosomal stability. BLM has been proposed to function at the interface of replication and recombination, and to facilitate the repair of DNA damage. Many similar caretakers functionally interact with BLM, thereby indicating a concerted attempt by the various tumor suppressors to maintain genomic stability. Conversely loss of functional interaction of BLM with the other tumor suppressors can lead to enhanced instability of the genome. Inactivation of tumor suppressor, p53, in BS cells causes a significant increase of homologous recombination (HR) compared with BS cells alone, thereby demonstrating that p53 and BLM cooperatively affect HR. Though the downstream effects of BLM on DNA repair and recombination are better characterized, not much information is available about how the signal is transmitted to BLM from the sites of DNA damage. Hence in Module A, I will study the specific role of Chk1-mediated phosphorylation on BLM function(s). The two specific aims of this module are: 1. Determining the Chk1-mediated phosphorylation site(s) of BLM; 2. Functional consequences of Chk1 mediated phosphorylation of BLM. Studies have not yet conclusively deciphered whether and, if so how, BLM modulates HR in combination with other proteins involved in the process. Hence in Module B, I will investigate whether BLM regulates HR in combination with
proteins involved in signal transduction like 53BP1. The specific aims of this module are:
1. Mechanistic analysis of the interaction between BLM and 53BP1 during replication stress;
2. Determine the functional consequence of BLM interaction with 53BP1 during homologous recombination

- **Project Title: DNA REPLICATION, DNA REPAIR AND MICROSATELLITE STABILITY**

  Principal Investigator & Institution: Eckert, Kristin A.; Associate Professor of Pathology; Pathology; Pennsylvania State Univ Hershey Med Ctr 500 University Drive Hershey, Pa 170330850

  Timing: Fiscal Year 2005; Project Start 01-JAN-2005; Project End 31-DEC-2009

  Summary: (provided by applicant): The long-term goal of our research is to elucidate the role of microsatellite DNA sequence variation in neoplastic progression. The objective of this proposal is to identify the full complement of biochemical mechanisms that act to stabilize microsatellite sequences in human cells. Our working hypothesis is that cellular microsatellite mutation rates are the cumulative result of proteins acting to maintain genomic stability during DNA replication. We have developed complementary in vitro/ex vivo assays to study mutagenesis within reporter microsatellites in somatic human cells. Specific Aim 1 will test the hypothesis that DNA polymerase pausing within microsatellite sequences can impede replication fork progression, and that RecQ helicases have a specialized function during microsatellite DNA replication. Biochemical analyses of replication intermediates through microsatellites of differing sequence will be performed using cell lines from normal, Bloom and Werner syndrome donors to the function of BLM and WRN helicases. Mutation rates within the herpes simplex virus thymidine kinase (HSV-tk) gene reporter cassettes will be quantitated to determine whether these helicases function to stabilize microsatellite DNA sequences. Specific Aim 2 will determine the contribution of enzymatic activities associated with the replication fork in maintaining genome stability. We will test the contribution of mismatch repair proteins to the stability of tetranucleotide alleles and microsatellites with potential secondary structure, and test the contribution of the Mre11/NBS/Rad50 complex to human cell replication fidelity. The ex vivo shuttle vector system will be used in naturally occurring MLH1, PMS2, NBS1 and hMre11-defective lymphoblastoid cell lines, and in cells with gene expression down-regulated by antisense methods. Mutation rates and specificities will be determined to establish whether the activities of NBS and hMre11 affect replication fidelity. Specific Aim 3 will determine the relative contribution of replicative and Y family DNA polymerases to spontaneous mutagenesis and microsatellite stability. The in vitro HSV-tk assay will be used to analyze DNA polymerase delta and polymerase kappa (pol kappa) error rates at microsatellites. The effects of pol kappa levels on spontaneous cellular mutagenesis will be analyzed using the ex vivo assay cell lines containing either pol kappa overexpression vectors or stable ribozymes to down-regulated pol kappa expression. These studies will establish whether regulation of pol kappa activity is a potential avenue for therapeutic interventions aimed at regulating genome stability. This proposed research has direct implications for modeling tumor progression, as the loss of genomic surveillance mechanisms will accelerate microsatellite mutagenesis. Microsatellite allele lengths can directly affect gene expression. As microsatellites are polymorphic in human populations, this effect on gene regulation may be an important factor contributing to individual cancer risk.
• Project Title: EUKARYOTIC TOPOISOMERASE I

Principal Investigator & Institution: Champoux, James J.; Microbiology; University of Washington Office of Sponsored Programs Seattle, Wa 98105

Timing: Fiscal Year 2005; Project Start 01-MAY-1994; Project End 31-AUG-2007

Summary: (provided by applicant): The overall goals of the proposed research are to understand in molecular detail how human topoisomerase I functions to control the topological state of the DNA in the cell, and how tyrosyl-DNA phosphodiesterase (Tdp1) repairs the topoisomerase I-DNA covalent complexes that arise when the topoisomerase fails to religate the DNA after certain kinds of DNA damage and in the presence of the anticancer drug, camptothecin. A combination of biochemistry and X-ray crystallography will be used to study the conformational changes in the topoisomerase that accompany DNA binding and to elucidate the mechanism of the topoisomerase I religation reaction. A panel of GST fusions to various human topoisomerase I fragments will be employed to examine interactions of the topoisomerase with the HMG1 and Werner syndrome (WRN) proteins. A number of hypotheses will be tested concerning the functional significance of the interaction between human topoisomerase I and WRN. The identity of the nucleophile and the functions of other conserved active site residues in Tdp1 observed in the recently-solved crystal structure of the enzyme will be investigated by site-directed mutagenesis. Synthetic substrates that provide better leaving groups upon cleavage will be employed to identify the catalytic residue that acts as a general acid to protonate the leaving group when Tdp1 cleaves its DNA-protein substrate. A panel of substrates with different DNA structures and different lengths of topoisomerase I-derived peptides will be tested in kinetic experiments to determine the optimal substrate for Tdp1 cleavage. Finally, a system to study the in vivo fate of the topoisomerase I-DNA covalent complexes produced by the induction of a "toxic" topoisomerase I that cleaves, but fails to religate the DNA will be developed. The identification of intermediates along the pathway for the repair of these covalent complexes will provide important insights regarding how both the protein and the DNA moieties of the complexes are processed prior to cleavage by Tdp1. Information gained on the structure and function of Tdp1 may lead to the development of inhibitors of Tdp1 that could be used in combination anticancer drug therapy regimens with camptothecin.

• Project Title: FUNCTIONAL DYNAMICS OF MAMMALIAN AND VIRAL DNA REPAIR POLYMERASES

Principal Investigator & Institution: Bujalowski, W. M.; Professor; Biochemistry and Molecular Biology; University of Texas Medical Br Galveston 301 University Blvd Galveston, Tx 77555

Timing: Fiscal Year 2007; Project Start 01-FEB-1999; Project End 31-JAN-2011

Summary: (provided by applicant): DNA replication and repair are fundamental processes for transmission of genetic information from one cell generation to the other and for defending the cell against damages in its DNA or against viral infections. At the heart of these processes is the synthesis of the DNA catalyzed by DNA polymerases. Mammalian Polymerase (3 (pol p) and African Swine Fever Virus Polymerase X (pol X) provide outstanding model systems to study the molecular mechanism of the DNA repair polymerase action due to its simplified structures and catalytic repertoires. Because of the fundamental role in human DNA repair and the virus defense against the host reaction to the infection, pol P and pol X are enzymatic systems of a paramount biomedical importance. Mutations and deletions in pol p have been implicated in several human cancers and genetic diseases including breast, prostate, kidney, lung,
Studies

Studies 13 colorectal cancers, and **Werner syndrome**. Mutations in pol X render the virus vulnerable to the DNA-modifying apparatus of the cell, which weakens the progress of the virus infection. In light of the pol (3 key role in human DNA repair and the pol X essential role in the effectiveness of viral infection of the mammalian cell, it is of fundamental importance to understand the molecular mechanism by which pol p and pol X function in performing their activities. Knowledge of mechanistic details of the mechanisms is essential to our understanding of the DNA repair processes in a human cell, the mechanism by which the cell defends itself against diseases, and the mechanism by which the cell fights against viral infections. Studying different steps at the molecular level will provide the necessary knowledge about how to control them. In turn, this knowledge is invaluable for designing rational and efficient therapies for genetic, cancer and viral diseases. The profound and fundamental difference between the replicative and repair polymerases is that the DNA repair enzyme must recognize a specific structure of the damaged DNA prior to the catalysis, in the context of overwhelmingly dsDNA conformation. This indicates that DNA and dNTP recognition, which controls fidelity of DNA synthesis, must precede the catalysis. Thus, elucidation of the energetics, dynamics and structure of pol p - DNA and ASFV pol X - DNA complexes is a prerequisite for understanding the molecular mechanisms of the enzymes, particularly, the efficiency and fidelity of catalysis. The main goal of this project is to elucidate the molecular mechanisms of the recognition of specific DNA structures by pol p and pol X and their role in DNA synthesis. This goal will be achieved through quantitative thermodynamic, kinetic, and structural studies of their complexes with DNA substrates and dNTPs in solution using quantitative fluorescence titrations, analytical centrifugation, fluorescence stopped-flow, rapid-quench-flow, fluorescence energy transfer and site-directed mutagenesis techniques.

- **Project Title: GENETIC INSTABILITY IN WERNER SYNDROME**

Principal Investigator & Institution: Monnat, Raymond J.; Professor of Pathology and Genome Science; Pathology; University of Washington Office of Sponsored Programs Seattle, Wa 98105

Timing: Fiscal Year 2005; Project Start 07-MAR-2000; Project End 28-FEB-2009

Summary: (provided by applicant): The long term goal of research proposed in this Program Project is to provide a detailed description of the **Werner syndrome** protein (WRN) functional pathway in human somatic cells, and to determine how a loss of WRN function leads to the cellular and clinical phenotypes of **Werner syndrome** that include constitutional genetic instability and an elevated risk of cancer. The **Werner Syndrome** Program Project is an integrated research effort consisting of 4 Projects and 2 Cores that are collectively focused on the following questions: 1. what proteins and DNA substrates constitute the WRN functional pathway in human somatic cells? 2. what are the important physiologic functions of WRN in human somatic cells? 3. how does loss of WRN function lead to genetic instability, selective DNA damage hypersensitivity and cell proliferation defects? 4. what role do WRN polymorphisms and mutations play in promoting the risk or pathogenesis of cancer or other diseases in the general population? Results of the proposed research will delineate normal functions of the WRN protein in human somatic cells, and how the loss of function leads to pathogenesis of the **Werner syndrome** cellular and clinical phenotypes. Results of the proposed research will also indicate the potential importance of common heritable alterations in WRN expression—polymorphisms in, or loss of one active copy of, the WRN gene—in promoting cancer risk and pathogenesis in the general population.
• **Project Title:** GENETIC MODIFIERS OF GENOME INSTABILITY & CANCER IN MICE

Principal Investigator & Institution: Preston, Bradley D.; Associate Professor; University of Washington Office of Sponsored Programs Seattle, Wa 98105

Timing: Fiscal Year 2005

Summary: A Wrn "knockout" mouse (Wrn delta) was recently generated that eliminates WRN protein expression (similar to Werner Syndrome) but fails to impart a significant phenotype. This suggests that functional redundancies in mice mask the Wrn4 phenotype. The objective of this project is to characterize potential genetic modifiers of Wrn that affect genome instability and cancer in Wrn delta mice. The SPECIFIC AIMS are: 1. Determine the effect of genetic background on cancer development in Wrn delta mice. We will fast test the hypothesis that genetic background modifies the phenotype of Wrn delta mice. Our approach will be to introduce the Wrn delta allele into congenic inbred strains with different inherent cancer phenotypes. An extensive analysis of Wrn delta in different inbred strains will determine the relative contributions of genetic background and the Wrn delta allele to tissue-specific cancer risk. 2. Examine functional interactions of Wrn with Blm, Atm and Msh2. Studies in yeast show that parallel redundant pathways are often employed to preserve genome stability. A subset of these require the WRN homolog, SGS1. Accordingly, when sgs1 null mutations are combined with defects in parallel pathways, synergistic increases in spontaneous gross chromosomal rearrangements (GCRs) are observed. Using available knockout mouse strains, we will examine three mutants that are predicted to synergize with Wrn delta: Blm delta, Atm delta and Msh2 delta. 3. Determine the effect of DNA polymerase errors in Wrn delta mice. RecQ helicases are closely linked to replicative DNA polymerases (SGS1 is epistatic with DNA polymerase epsilon; WRN binds DNA polymerase delta), and it is hypothesized that spontaneous GCRs result, in large part, from DNA replication errors. This suggests that error-prone DNA replication will amplify the Wrn delta phenotype. We will test this idea by crossing Wrn delta mice with two "mutator" mouse lines recently generated in our laboratory that are defective for Pol delta or Pol epsilon proofreading. Together, these experiments will reveal Wrn functional interactions that affect genome instability and cancer in mice. Our long-term goal is to develop a mouse model that recapitulates fundamental aspects of the Werner Syndrome cancer phenotype. These studies will be integrated with the Cell Function-Monnat and Recombination Mechanisms-Maizels projects to develop a detailed molecular and organismal description of WNR function in rive. Our studies will also lay the groundwork for a collaboration with the first project (Biochemistry-Loeb) evaluating Wrn Exo-, Hel- and SNP "knockin" mice.

• **Project Title:** GENOMIC STABILITY AND RECQ DNA HELICASES IN YEAST

Principal Investigator & Institution: Brill, Steven J.; Professor; Molecular Biology and Biochem; Rutgers the St Univ of Nj New Brunswick 3 Rutgers Plaza New Brunswick, Nj 08901

Timing: Fiscal Year 2005; Project Start 01-MAY-1999; Project End 30-APR-2008

Summary: (provided by applicant): Loss of genome stability is associated with a number of human diseases that predispose patients to cancer. In particular, mutations in the genes encoding the RecQ family of DNA helicases have been shown to cause three distinct genetic diseases [Bloom syndrome (BLM), Werner syndrome (WRN), and a subset of Rothmund-Thomson syndrome (RTS)]. Cells from these patients display excessive DNA rearrangements suggesting that their primary defect is the failure to maintain genome stability. The only RecQ homolog in budding yeast, Sgs1, exists in a
complex with DNA topoisomerase III (Top3) and serves as a model for human BLM which also binds Top3. We have exploited the yeast system to identify genetic pathways that are functionally redundant with the RecQ-Top3 complex. Two of these pathways are defined by the Slx1-Slx4 and Slx5-Slx8 protein complexes. We have shown that Slx1-Slx4 is a 5'-flap endonuclease while Slx5-Slx8 has no known activity. Here we propose to explore the mechanism by which the RecQ-Top3 complex controls genome stability using biochemical and genetic analysis of these three complexes: Slx1-4, Slx5-8, and Sgs1-Top3. In Aim 1 we will purify and characterize the Slx1-Slx4 protein complex from yeast. New subunits will be identified and tested for their effect on 5'-flap endonuclease activity. A structure-function analysis of both subunits will be conducted and the role of these proteins in cell-cycle checkpoint control will be tested. Genome stability will be assayed in mutant cells by measuring recombination frequencies and by investigating the role of the Slx1-4 complex in controlling rDNA repeat structure. The proteins' nuclear localization will also be determined. In Aim 2 we will similarly purify and characterize the Slx5-Slx8 complex. The Slx5 and Slx8 subunits are RING-finger proteins suggesting that the Slx5-8 complex may be involved in protein modification. Using purified recombinant protein we will test Slx5-8 for E3 ligase activity using Smt3 or ubiquitin as ligand. A positive result will be extended by searching for specific substrates of the modification. In Aim 3 Sgs1-Top3 will be purified and tested for DNA helicase and topoisomerase activity using substrates that have been suggested by our genetic analysis.

- **Project Title: INTERNATIONAL REGISTRY OF WERNER SYNDROME**

  Principal Investigator & Institution: Martin, George M.; Professor; Pathology; University of Washington Office of Sponsored Programs Seattle, Wa 98105

  Timing: Fiscal Year 2006; Project Start 30-SEP-1997; Project End 30-JUN-2011

  Summary: (provided by applicant): The International Registry of Werner Syndrome has existed at the University of Washington for the past 15 years to: 1. ascertain and genotype additional pedigrees from around the world (The Registry is the sole organization in the U.S. that provides genetic confirmation of the WS); 2. establish and cryopreserve cell materials including Epstein-Barr virally transformed peripheral blood B lymphocytes cell lines (LCL), primary skin fibroblast cultures and immortalized skin fibroblast cultures from affected patients and other family members from these pedigrees; 3. provide fresh peripheral blood samples, cultured cell materials, WRN cDNA, anti-WRN antibodies to colleagues at the University of Washington and elsewhere; and 4. maintain and expand the University of Washington International Registry of Werner Syndrome Database on the participant information on a secure web server and a separate WorldWeb site with public information for clinicians and for a general audience seeking information regarding Werner syndrome. This proposal would continue these functions with the following enhancements: 1. the establishment of a selection reversible hTERT immortalized WS and control fibroblasts; 2. sequence analysis of candidate genes in Werner syndrome patients and atypical Werner syndrome cases with no apparent WRN or LMNA mutations; 3. as a part of the University of Washington Department of Pathology’s newly developed networked computer system we proposed transfer of the Registry's local secure intranet function (clinical and laboratory data) and the public website to a new system with enhanced security, automated backup, and automated viral screens; and 5. to make a major effort to obtain large numbers of cryopreserved skin explants and other tissues from autopsied WS subjects to provide additional primary cultures and biochemical assayable materials for investigators here at the University of Washington and other institutes.
• **Project Title: LAMIN A MUTATION AND HUTCHINSON-GILFORD PROGERIA**
  Principal Investigator & Institution: Worman, Howard J.; Associate Professor; Medicine; Columbia University Health Sciences Columbia University Medical Center New York, Ny 100323702
  Timing: Fiscal Year 2006; Project Start 01-MAY-2006; Project End 30-APR-2009
  Summary: (provided by applicant): Hutchinson-Gilford progeria syndrome (HGPS), a condition with features of premature aging, is caused by a dominant de novo mutation in LMNA, the gene that encodes lamins A and C, intermediate filament proteins associated with the nuclear envelope. The mutation in HGPS introduces an abnormal splice site that leads the expression of a lamin A mutant with 50 amino acids deleted near its carboxyl-terminal end. The mutant lamin A has been called progerin. Different mutations in lamins A and C cause cardiomyopathy and muscular dystrophy, partial lipodystrophy syndromes, a peripheral neuropathy and atypical Werner syndrome. Some of these disorders share clinical features with HGPS while others are quite different. It is not known how mutations in lamins A and C cause HGPS or other diseases. We hypothesize that different mutations in these proteins cause alterations in nuclear structure and chromatin organization that lead to abnormalities in gene expression. In HGPS, progerin expression, possibly in combination with decreased expression of normal lamins A and C, is responsible for this chain of events. Our goal is to test this hypothesis. In Aim 1, we will study the biochemistry of progerin and its effects on the cell nucleus. We will determine if progerin, like normal prelamin A, is farnesylated and processed by endoproteolysis. We will investigate the effects of progerin on nuclear and chromatin structure and on the dynamics of other nuclear envelope proteins using fluorescent photobleaching methods. In Aim 2, we will generate transgenic mice expressing progerin in epidermis and determine if they develop pathological and functional abnormalities similar to those in skin of human subjects HGPS and normal aging skin. We will also cross progerin transgenic mice to heterozygous Lmna "knockout" mice to determine if reduced wild type protein levels have additional effects. In Aim 3, we will determine if a farnesyltransferase inhibitor blocks prenylation of progerin and determine if blocking progerin prenylation reverses cellular alterations and tissue abnormalities in progerin-expressing transgenic mice, hence connecting the experimental work in Aims 1 and 2. This project will establish how mutations in nuclear lamins A and C cause HGPS, and if inhibition of protein farnesylation is a potential therapeutic intervention.

• **Project Title: MECHANISMS OF TELOMERIC DNA LOSS AND REPAIR**
  Principal Investigator & Institution: Opresko, Patricia Lynn.; Environ & Occupational Health; University of Pittsburgh at Pittsburgh 350 Thackeray Hall Pittsburgh, Pa 15260
  Timing: Fiscal Year 2006; Project Start 01-SEP-2006; Project End 31-JUL-2011
  Summary: (provided by applicant) The long term objective of the proposed research is to understand the molecular mechanisms of genomic instability associated with aging and aging-related diseases. Accelerated telomeric DNA loss occurs in aging-related diseases and after exposure to some environmental DNA damaging agents. Lack of the DNA repair protein WRN accelerates telomere loss and causes the human progeroid Werner syndrome (WS) in which patients prematurely develop multiple aging-related pathologies. The specific goals of this proposal are 1) to determine the molecular mechanisms of telomeric DNA loss associated with DNA damaging agents and WS, and 2) to define the roles for the repair protein WRN in telomere preservation. The hypothesis to be tested is that damage directly to telomeric DNA contributes to telomere attrition, and that WRN protein preserves telomeres by preventing and/or repairing
breaks in telomeric DNA. A shuttle vector mutagenesis assay that measures mutations in a defined target will be used to examine the role of WRN protein in preventing replication-induced telomeric DNA deletions that may occur either spontaneously or after exposure to the environmental mutagen chromium (VI). Exposure to Cr(VI) is associated with respiratory cancers, and induces replication-blocking adducts and breaks in DNA sequences that are prevalent in telomeres. Thus, Cr(VI) is an excellent model for investigating the consequences of environmental DNA damage on telomeric DNA replication. The shuttle vector approach allows for analysis of independent and rare mutation events and eliminates selective pressure against the loss of telomeric repeats. To investigate a role for WRN in repairing breaks at telomeres directly, confocal microscopy will be used to induce DNA double strand breaks selectively at telomeres with a UVA laser in live cells. The broad goals of this proposal are to determine the impact of DNA damage and environmental mutagens on the integrity of telomeric DNA in chromosome ends, and to examine cellular pathways for repairing telomeres. Given the critical role for telomeres in aging and cancer, a mechanistic understanding of the genetic and environmental factors that accelerate telomeric DNA loss should aid in the identification of risk factors for premature aging. Identifying mechanisms of telomere loss and cellular processes that preserve telomeric DNA is crucial for the design of intervention therapies that prevent or delay the onset of diseases associated with aging and cancer.

- **Project Title: MOLECULAR BASIS FOR ACCELERATED AGING IN WERNER SYNDROME**

Principal Investigator & Institution: Szekely, Anna M.; Genetics; Yale University 47 College Street, Suite 203 New Haven, Ct 065208047

Timing: Fiscal Year 2005; Project Start 15-FEB-2001; Project End 30-NOV-2005

Summary: With an increasingly older population there is a significant interest to recognize potential risk factors and develop effective strategies to prevent, postpone or slow down disorders common in elderly. These efforts may depend, in part, on our abilities to unravel patterns of normal aging and to critically resolve, whether common underlying mechanisms govern the physiology and pathology of aging. A powerful approach to investigate the mechanism of human aging is to identify and characterize the biological functions of genes in human genetic disorders that result in premature aging. Information from these studies may have far-reaching implications, as it is conceivable, that these genes may play a role in the rate and variability of normal aging process and the vulnerability to the effect of aging or age-related disorders. **Werner syndrome** is perhaps the single Mendelian disorder that most closely produces a phenotype resembling to human aging. This disorder is one of a class of human progerias, which is due to loss-of-function mutations in a single gene (Wrn). While the encoded Werner protein (WRN) shows significant homology to the RecQ family of DNA helicases, its precise cellular function is poorly understood. We propose that WRN protein may be part of multiple protein complexes with dynamically changing composition and subcellular/subnuclear distribution, thereby participating in diverse cellular functions. In this project we describe our findings and plans to discern the mechanisms, which may link WRN protein directly to DNA replication. These experiments are expected to provide insights into the mechanism(s) by which mutations in Wrn gene promote genetic instability due to a critical role of WRN protein on replication fork progression. In addition, we describe the strategy to characterize several genes and their encoded proteins, some without known homology or function that were isolated by their virtue to bind specifically to the WRN protein and may have significance in vivo. This information may uncover new directions in searching for
aging- and longevity-related, genes. Furthermore, mutations and/or polymorphisms of these genes may define specific pathomechanisms of common disorders of the elderly. This project is expected to define features of genome and cellular maintenance that are particularly susceptible to the effects of normal aging. It is designed to provide an advanced training for the applicant and to enable her to develop an independent carrier in academic gerontology with a focus on the molecular mechanism of aging.

- **Project Title: ROLE OF NUCLEASES IN RNA PRIMER REMOVAL AND MUTAGENESIS**

  Principal Investigator & Institution: Shen, Binghui; Associate Professor; City of Hope/Beckman Research Institute Office of Sponsored Projects Duarte, Ca 910103012
  Timing: Fiscal Year 2005; Project Start 01-JUL-1999; Project End 30-APR-2008
  Summary: (provided by applicant): Cancer research progress, having benefited greatly from studies using powerful model systems, strongly supports the hypothesis that accumulation of mutations leading to decreased genome stability is a critical early event in tumorigenesis. Appropriate implementation of Okazaki fragment maturation during DNA replication in eukaryotic cells is a fundamental mechanism for avoidance of mutations and genome stability. During lagging strand DNA synthesis, multiple RNA primers and extended DNA-fragments are synthesized by DNA polymerase alpha (primase). However, this enzyme lacks proof reading function, different from the other DNA polymerases. Therefore, this initial RNA-DNA fragment (alpha-segment of the Okazaki fragment) is highly mutagenic and has to be processed by nuclease complexes. This proposal aims to define detailed molecular mechanism for the nuclease-driven "alpha-segment" processing or for Okazaki fragment maturation in yeast and mammalian cell systems. For the last funding period, we have defined the roles of three individual nuclease in the process, including S. cerevisiae RNase H(35), ScRad27 or human FEN-1, and exonucleases-1, and mutagenic consequences when these nucleases are defective. The current proposal focuses to test a central hypothesis that two mutually interactive nuclease complexes (DNA2-RPA and FEN-1-ROA1) sequentially process the alpha-segment of the Okazaki fragment. When the FEN-1 nuclease activity is inhibited by genetically built-in blocks, such as simple repeat sequences, Werner syndrome protein (WRN) and FEN-1 nuclease complex takes an alternative route to resolve intrinsic secondary structure of the displaced alpha-segment of the Okazaki fragment. Through a series of vigorous systematic analyses, we intend to obtain a high resolution image of how these three nucleases complexes collectively work towards alpha-segment processing in different scenarios and to relate in vitro and in vivo data using yeast and mammalian systems, including human cell lines and transgenic mice. Information made available from this systematic study will also establish a relationship between this mechanism, unique mutagenic phenotype(s), and development of genetic diseases.

- **Project Title: ROLE OF RECQ HELICASES TO PREVENT SENESCENCE BY C-MYC**

  Principal Investigator & Institution: Galloway, Denise A.; Member and Program Head; Fred Hutchinson Cancer Research Center Box 19024, 1100 Fairview Ave N Seattle, Wa 981091024
  Timing: Fiscal Year 2006; Project Start 15-MAY-2006; Project End 30-APR-2011
  Summary: (provided by applicant): The avoidance of senescence is an essential property of tumor cells. We are planning to determine the role played by the WRN and potentially related RecQ helicases in the avoidance of oncogene-induced senescence. In particular, we will focus on the c-Myc oncogene as we have shown that c-Myc stimulates transcription of the WRN gene and more important, that the WRN protein is
Studies

required to avoid cellular senescence induced by c-Myc overexpression. Loss of function mutations of WRN causes a human premature progeria, **Werner Syndrome** (WS), whose symptoms mimic aspects of natural aging. Cells derived from WS patients also show premature senescence, indicating that the organismal phenotype might be due to accelerated cellular senescence. We hypothesize that WRN function is required for the avoidance of senescence of tumor cells and thus may represent an attractive therapeutic target for cancer treatment. WRN protein participates in DNA repair of abnormal structures generated during DNA replication and aggravated by drugs that cause a DNA replication block. Indeed the preliminary data indicate that the senescence response of WRN deficient cells upon c-Myc overexpression is due to DNA damage and resultant cellular checkpoint responses. In this proposal we plan to test this hypothesis, thus defining the mechanisms of WRN and c-Myc co-dependence. These experiments will involve use of cells derived from WS patients (commercially available) as well as a variety of approaches to interfere with function/or expression of WRN in normal human fibroblasts and in human cancer cell lines. Finally, to assess the role of WRN in tumor development in vivo we will employ an established c-Myc induced lymphoma model in mice together with WRN knock-out mice. Ultimately, our goal is to provide a rational to develop WRN inhibitors to be employed in new therapeutic approaches for cancer. Our proposal is relevant to aging providing information on the basic function of WRN, a gene clearly implicated in organismal aging, and it is also of importance for cancer by defining how cells bypass senescence under oncogenic stimulation. This grant proposal focus on the hypothesis, supported by our previous work, that a gene involved in human aging, called the **Werner Syndrome** gene, is also involved in the "aging" process of tumor cells. In fact, it is known that cells in our body also age. Old cells eventually stop dividing, a condition referred to as irreversible cell-cycle arrest". This is incompatible with tumor cell growth and thus cancer cells have devised ways of avoiding aging. Our previous work demonstrated that the presence of WRN gene was necessary to avoid aging of normal cells when they carry an activated cancer gene. Now we would like to directly test if inhibition of WRN function in cell lines derived from human cancers will cause tumor cells to age or to stop growing. If so, drug inhibitors of WRN function could be proposed for the treatment of cancer.

- **Project Title: SENESCENCE AND LONGEVITY MODULATING GENES, WRN AND BLM**

  Principal Investigator & Institution: Campisi, Judith; Senior Staff Scientist; Molecular Biology; University of Calif-Lawrenc Berkeley Lab C/O Sponsored Projects Office Berkeley, Ca 94720

  Timing: Fiscal Year 2005; Project Start 06-SEP-1993; Project End 30-JUN-2009

  Summary: (provided by applicant): Genomic maintenance systems are important determinants of longevity in all species. In mammals, DNA damage and faulty repair are major causes of cancer and non-cancer aging phenotypes. Normal cells respond to unrepaired DNA damage by apoptosis or cellular senescence, which suppress tumorigenesis but may also contribute to age-related pathology. WRN and BLM are related members of the mammalian RECQ-like family of DNA helicases. Current evidence suggests that both proteins participate in repairing DNA damage, among other possible functions. The phenotypes of humans deficient in these helicases suggest that both proteins prevent certain age-related diseases, including cancer. **Werner syndrome** (WS) and Bloom syndrome (BS) are caused by a deficiency in WRN and BLM, respectively. WS and BS share several features, but also show striking differences, the bases for which are largely unknown. Our overall goal is to better understand the cellular functions of the human WRN and BLM proteins. We propose to focus primarily
on human cells, and determine how WRN and BLM are regulated, and how they regulate responses to DNA damage. We propose to determine effects of wild type and mutant WRN and BLM proteins on the senescence and apoptotic responses, telomere dynamics and genomic integrity of human cells. We will also determine how selected damage-sensing protein kinases regulate the subnuclear localization of WRN and BLM and its response to DNA damage. Our studies will provide important insights into how WRN and BLM postpone the development of aging phenotypes and the development of cancer in humans.

- **Project Title:** STRUCTURAL BIOCHEMISTRY OF RECQ HELICASE INTERACTIONS

Principal Investigator & Institution: Tainer, John A.; Professor; Scripps Research Institute 10550 North Torrey Pines Road La Jolla, Ca 920371000

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

Summary: (provided by applicant): RecQ proteins are a conserved, ubiquitous class of DNA helicases essential for genomic stability. Heritable mutations in RecQ Werner syndrome protein (WRN) or RecQ Bloom syndrome protein (BLM) cause remarkably elevated cancer predispositions and WRN mutations cause an additional aging phenotype. WRN and BLM have divergent roles; yet, both may act as tumor suppressor proteins and maintain genetic integrity by functioning with DNA replication and double-strand break repair proteins. Integrated structural, mutational, and biochemical analyses in the Yannone and Tainer labs will address several unanswered questions as to how WRN and BLM act in preserving genome integrity. We aim to define at the molecular level how WRN and BLM detect and bind DNA substrate, open and unwind target DNA, cleave and resolve DNA intermediates, and coordinate initial protein hand-offs to aid DNA replication and repair pathways. To accomplish this and test specific hypotheses on the molecular basis for WRN and BLM activities, we will biochemically and structurally characterize WRN and BLM components plus their complexes with DNA and key protein partners. Systematic structural and mutational analyses will define functional conformational states and interfaces and suggest mutations to uncouple DNA and/or protein binding events that modulate WRN and BLM activities. We will define the consequences of WRN and BLM conformations and interactions by protein structural studies, biochemical assays in vitro, and functional in vivo assays with our collaborators. These proposed experiments will create a molecular picture of the functional states, protein-DNA, and protein-protein interactions that orchestrate WRN- and BLM-mediated DNA metabolism. Taken together, the anticipated results will provide a detailed molecular understanding of processes underlying the aging and cancer predispositions associated with WRN and BLM helicase deficiencies and create a paradigm for RecQ helicase activities in choreographing replication, recombination and repair events to avoid cancer and aging.

- **Project Title:** STUDIES OF WRN, BLM, RECQ4 AND REPLICATION FORK RESTART

Principal Investigator & Institution: Yan, Hong; Associate Member; Institute for Cancer Research 333 Cottman Avenue Philadelphia, Pa 19112434

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

Summary: (provided by applicant): The long-term objective of the studies in this proposal is to understand how eukaryotic cells coordinate the large number of proteins involved in replication, repair, and homologous recombination to faithfully duplicate their genome. This complicated process is essential to the maintenance of genome
stability, loss of which can lead to cancer or premature aging. Recent studies suggest that a family of proteins, the RecQ-type helicases, might play a role in facilitating DNA replication. In human cells, there are five RecQ family members, three of which are deficient, respectively, in Werner syndrome (WRN), Bloom syndrome (BLM), or a subset of Rothmond-Thompson syndrome (RecQ4). In this proposal, a biochemical approach will be taken to study the roles of WRN, RecQ4, and BLM in replication and, more broadly, the factors and mechanism involved in replication fork restart. The model system to be used is the nuclearplasmic extracts (NPE) derived from nuclei reconstituted in Xenopus egg extracts. This in vitro system recapitulates faithfully the mechanics and regulation of eukaryotic cellular DNA replication. Three specific aims are proposed. The first specific aim seeks to study the roles of FFA-1 (Xenopus WRN) and xRecQ4 (Xenopus RecQ4) in the replication of various defined DNA substrates. The second specific aim seeks to study the role of xBLM (the Xenopus Bloom syndrome protein) in replication fork assembly and characterize the role of topoisomerase 3a (xTopo 3alpha), which interacts with xBLM, in replication. The third specific aim seeks to systematically analyze the factors and mechanism involved in the restart of stalled replication forks using a biochemical system developed in the lab. A variety of methods, including immunodepletion, immunofluorescence staining, affinity protein purification, recombinant protein expression, and biochemical fractionation will be used to accomplish the proposed studies. The results from these studies are expected to significantly advance the understanding of eukaryotic DNA replication fork dynamics and how defective RecQ helicases lead to human diseases like cancer and premature aging.

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

- **Project Title:** TELOMERE MAINTENANCE BY WERNER SYNDROME FAMILY PROTEINS.

Principal Investigator & Institution: Johnson, Frederick Bradley.; Assistant Professor; Pathology and Lab Medicine; University of Pennsylvania Office of Research Services Philadelphia, Pa 19104

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

Summary: (provided by applicant): We will explore connections between telomere biology and disease in the Werner premature aging syndrome, using yeast and cultured human cells as model systems. Telomere shortening accompanies but plays an uncertain causal role in human aging. In contrast, it is clear that prevention of telomere shortening is required for the growth of most cancers. Werner syndrome is characterized by premature features of aging and by elevated rates of cancer, and is caused by loss of the RecQ-family helicase/exonuclease WRN. Evidence is accumulating that Werner cells have telomere defects, which might contribute to the premature aging and elevated cancer incidence, and WRN (and other RecQ helicases) may function in the repair of shortened telomeres. We will dissect the established role of the yeast RecQ homologue, Sgslp, in telomere maintenance. We will map the domains of Sgslp that, in yeast cells lacking telomerase, are required to prevent rapid senescence and telomere shortening, as well as defects in survivors of senescence. We will test alternative mechanisms to explain these defects, including defects in recombination or the formation of G-DNA structures at telomeres. We will also screen for other genetic factors that cooperate with Sgslp in telomere maintenance, including the generation of recombination dependent survivors of senescence. The role in human cells of the mechanisms revealed by studies in yeast, particularly those involving homologous recombination, will be tested by performing experiments in senescing human cultured cells, including those with
mutations in WRN. These studies should illuminate the function of WRN at human telomeres and improve understanding of the role of telomeres in natural human aging and cancer.

• **Project Title: TEOMERIC FUNCTION IN AGING SYNDROMES**
  Principal Investigator & Institution: Karlseder, Jan; Assistant Professor; Salk Institute for Biological Studies 10010 N Torrey Pines Rd La Jolla, Ca 920371099
  Timing: Fiscal Year 2006; Project Start 01-AUG-2006; Project End 31-JUL-2011
  Summary: (provided by applicant): Telomeres are the natural ends of linear chromosomes. In mammals they consist of the repeated sequence TTAGGG that can stretch for up to 150 kb in mice, and 15 kilobase pairs in humans. The very end of the telomeres is made up of a single stranded overhang of the G rich 3' strand that can be up to 300 nucleotides long. A number of proteins bind specifically to the telomeric repeats. The telomeric repeat binding factors TRF1 and TRF2 bind to the double stranded regions of the chromosome ends, and form complexes there with their interacting proteins. TRF1 interacting factors are Tin2, tankyrase 1 and 2 and Pot1, all of which have been implicated in telomere length regulation. TRF2 interacts with the MRN complex hRapl, and has been suggested to play a major role in telomere protection. **Werner Syndrome** is a segmental premature aging disorder, where patients show many signs of old age already with 30 to 40 years. Additionally patients have a high incidence of cancer, and **Werner Syndrome** cells frequently show genome instability. Blooms syndrome is caused by mutations in a helicase related to the Werner protein, and patients also suffer from premature aging and cancer. Our preliminary data suggest that **Werner syndrome** could be caused by a dysfunction in telomere replication, and for the first time links telomere dysfunction to these aging syndromes. In AIM1 we will analyze telomere structure in **Werner Syndrome** cells, investigate the role of telomerase in telomere rescue and maintenance, and define the relationship between telomeres and DNA damage signals. AIM2 focuses on the role of WRN and other RecQ helicases in replication of G rich structures, as well as the interaction of WRN with telomeric proteins. In AIM 3 we plan to study the redundancy of WRN with other members of the RecQ helicase family on replication. Furthermore we will investigate the effects of RecQ helicase dependent telomere dysfunction on genome instability in these syndromes. Relevance: **Werner Syndrome** is a premature aging disease with a high frequency of cancer. Here we aim to investigate the role of telomere function in the syndrome, and to elucidate the connection between telomere replication, aging and cancer in **Werner Syndrome**.

• **Project Title: THE WERNER SYNDROME PROTEIN IN CPT-INDUCED DNA DAMAGE**
  Principal Investigator & Institution: Comai, Lucio; Associate Professor; Molecular Microbiol and Immun; University of Southern California Department of Contracts and Grants Los Angeles, Ca 90033
  Timing: Fiscal Year 2005; Project Start 01-JUN-2004; Project End 31-MAY-2009
  Summary: (provided by applicant): **Werner syndrome** (WS) is an autosomal recessive disorder leading to premature onset aging and aging-related diseases including cancer and atherosclerosis. WS results from the loss of function of the WRN gene. The WRN gene encodes a RecQ helicase protein with a unique exonuclease activity (WRN) whose cellular function is poorly understood. Cells from WS patients demonstrate premature senescence and sensitivity to DNA damaging agents such as camptothecin (CPT). Importantly, we have shown that WRN binds to Ku70/80, a heterodimeric complex
known to play a critical role in the repair of DNA damage. This observation strongly supports the idea that WRN functions in a DNA damage response pathway. We therefore hypothesize that WRN is required for S-phase checkpoint activation or is directly involved in the repair of DNA lesions following exposure of cells to CPT. Specifically, in Aim I we will test whether loss of WRN leads to defective S-phase checkpoint controls in CPT-treated cells. Experiments proposed in Aim 2 will study the dynamics of the recruitment of WRN and its associated factors to chromatin in response to CPT-induced DNA damage. In Aim 3, we will test the hypothesis that loss of WRN results in genetic instability at the rDNA locus leading to aberrant ribosomal RNAs biosynthesis upon DNA damage. In Aim 4, biochemical insights into these processes will be obtained by studying the response to CPT-induced DNA damage of cells expressing mutant WRN proteins deficient in exonuclease or helicase activity, or lacking conserved structural domains. Taken together, these experiments should provide important mechanistic insights into the process of human aging.

- **Project Title:** WERNER SYNDROME FAMILY PROTEINS & TELOMERE RECOMBINATION

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

Summary: (provided by applicant): Telomeres shorten with age in many human tissues and such shortening may play a role in the aging process. Werner syndrome (WS) is a recessive genetic disorder characterized by the premature onset of several features of aging. Cells from Werner patients senesce and shorten telomeres at a much faster rate compared to normal cells. Accumulating evidence indicates that the protein deficient in WS, WRN, functions in telomere maintenance. Since cells must preserve proper telomere function for continued survival, and may use homologous recombination to repair shortened telomeres, this proposal attempts to determine whether WRN and its homologues participate in telomere recombination as a way to repair or protect shortened telomeres. Understanding how the Werner syndrome family proteins are involved in telomere maintenance should yield insight into the natural processes of aging.

**The National Library of Medicine: PubMed**

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6 PubMed was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The PubMed database was developed in conjunction with publishers of biomedical literature as a search tool for accessing literature citations and linking to full-text journal articles at Web sites of participating publishers. Publishers that participate in PubMed supply NLM with their citations electronically prior to or at the time of publication.
To generate your own bibliography of studies dealing with Werner syndrome, simply go to the PubMed Web site at [http://www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed). Type Werner syndrome (or synonyms) into the search box, and click Go. The following is the type of output you can expect from PubMed for Werner syndrome (hyperlinks lead to article summaries):

- **A 2.8 megabase YAC contig spanning D8S339, which is tightly linked to the Werner syndrome locus.**
  Author(s): Bruskiewich R, Schertzer M, Wood S.
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- **A 3.1-Mb YAC contig within the Werner syndrome region, on the short arm of human chromosome 8.**
  Source: Cytogenetics and Cell Genetics.

- **A case of Werner syndrome with three primary lesions of malignant melanoma.**
  Author(s): Shibuya H, Kato A, Kai N, Fujiwara S, Goto M.

- **A comparison of adult and childhood progerias: Werner syndrome and Hutchinson-Gilford progeria syndrome.**
  Author(s): Brown WT, Kieras FJ, Houck GE Jr, Dutkowski R, Jenkins EC.
  Source: Advances in Experimental Medicine and Biology.

- **A conserved and species-specific functional interaction between the Werner syndrome-like exonuclease atWEX and the Ku heterodimer in Arabidopsis.**
  Author(s): Li B, Conway N, Navarro S, Comai L, Comai L.
  Source: Nucleic Acids Research.

- **A genetic analysis of the Werner syndrome region on human chromosome 8p.**
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  Source: The British Journal of Dermatology.

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  Author(s): von Kobbe C, Bohr VA.
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  Source: Development (Cambridge, England).

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  Author(s): Yu CE, Oshima J, Hisama FM, Matthews S, Trask BJ, Schellenberg GD.
  Source: Genomics.
• Abnormal fibroblast aging and DNA replication in the Werner syndrome.
  Author(s): Fujiwara Y, Kano Y, Ichihashi M, Nakao Y, Matsumura T.
  Source: Advances in Experimental Medicine and Biology.

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  Author(s): Schulz VP, Zakian VA, Ogburn CE, McKay J, Jarzebowicz AA, Edland SD, Martin GM.
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  Source: The American Journal of Medicine.

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  Source: Acta Neuropathologica.

• Altered regulation of fibronectin gene expression in Werner syndrome fibroblasts.
  Author(s): Rasoamanantena P, Thweatt R, Labat-Robert J, Goldstein S.
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  Author(s): Bartram CR, Koske-Westphal T, Passarge E.
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  Author(s): von Kobbe C, Harrigan JA, Schreiber V, Stiegler P, Piotrowski J, Dawut L, Bohr VA.
  Source: Nucleic Acids Research.

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Werner Syndrome

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  Source: Human Mutation.  

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  Source: Sci Aging Knowledge Environ.

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  Author(s): Swanson C, Saintigny Y, Emond MJ, Monnat RJ Jr.
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  SH, Bohr VA.
  Source: Nucleic Acids Research.
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  Author(s): Harrigan JA, Opresko PL, von Kobbe C, Kedar PS, Prasad R, Wilson SH, Bohr 
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  Author(s): Degreef H.
  Source: Dermatologica.
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  Author(s): Nehlin JO, Skovgaard GL, Bohr VA.
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  Author(s): Takazawa R, Ajima J, Yamauchi A, Goto M.
  Source: Urologia Internationalis.
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  Author(s): Monnat RJ Jr.
  Source: Cancer.

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  Author(s): Ishikawa Y, Sugano H, Matsumoto T, Furuichi Y, Miller RW, Goto M.
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  Source: Medical Hypotheses.

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   Author(s): Opresko PL, Cheng WH, von Kobbe C, Harrigan JA, Bohr VA.
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   Author(s): Davis T, Kipling D.
   Source: Rejuvenation Res.

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   Author(s): Poot M, Yom JS, Whang SH, Kato JT, Gollahon KA, Rabinovitch PS.

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   Author(s): Von Kobbe C, May A, Grandori C, Bohr VA.

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   Author(s): Kohner EM.
   Source: Archives of Ophthalmology.

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   Author(s): Shen JC, Loeb LA.
   Source: Nucleic Acids Research.

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   Author(s): Suzuki N, Shiratori M, Goto M, Furuichi Y.
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  Author(s): Meguro S, Atsumi Y, Matsuoka K, Ishikawa Y, Sugimoto M, Goto M.
  Source: Diabetes Care.

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  Source: Mechanisms of Ageing and Development.

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  Author(s): Franchitto A, Pichierri P.
  Source: Cell Cycle (Georgetown, Tex.).

• **Werner syndrome protein associates with gamma H2AX in a manner that depends upon Nbs1.**
  Author(s): Cheng WH, Sakamoto S, Fox JT, Komatsu K, Carney J, Bohr VA.
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• **Werner syndrome protein contains three structure-specific DNA binding domains.**
  Author(s): von Kobbe C, Thoma NH, Czyzewski BK, Pavletich NP, Bohr VA.
  Source: The Journal of Biological Chemistry.

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  Author(s): Indig FE, Partridge JJ, von Kobbe C, Aladjem MI, Latterich M, Bohr VA.
  Source: Journal of Structural Biology.

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  Author(s): Brosh RM Jr, von Kobbe C, Sommers JA, Karmakar P, Opresko PL, Piotrowski J, Dianova I, Dianov GL, Bohr VA.
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  Source: Genes & Development.

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  Author(s): Cheng WH, von Kobbe C, Opresko PL, Fields KM, Ren J, Kufe D, Bohr VA.
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  Author(s): Shen JC, Gray MD, Oshima J, Kamath-Loeb AS, Fry M, Loeb LA.
  Source: The Journal of Biological Chemistry.

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  Author(s): Bohr VA, Cooper M, Orren D, Machake A, Piotrowski J, Sommers J, Karmakar P, Brosh R.
  Source: Experimental Gerontology.

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  Author(s): Monnat RJ Jr, Saintigny Y.
  Source: Sci Aging Knowledge Environ.
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  Author(s): Hashimoto K, Ikegami K, Nakajima H, Kitamura T.
  Source: Psychiatry and Clinical Neurosciences.

• **Werner syndrome.**
  Author(s): Samantray SK, Samantray S, Johnson SC, Bhaktaviziam A.
  Source: Aust N Z J Med.

• **Werner syndrome.**
  Author(s): Bullock JD, Howard RO.
  Source: Archives of Ophthalmology.

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  Author(s): Goldstein S, Murano S, Shmookler Reis RJ.
  Source: J Gerontol.

• **Werner syndrome: characterization of mutations in the WRN gene in an affected family.**
  Source: European Journal of Human Genetics : Ejhg.

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  Author(s): Epstein CJ, Motulsky AG.
  Source: Bioessays : News and Reviews in Molecular, Cellular and Developmental Biology.

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  Author(s): Lebel M.
  Source: Cellular and Molecular Life Sciences : Cmls.
• Werner syndrome: molecular genetics and mechanistic hypotheses.
  Author(s): Monnat RJ Jr.
  Source: Experimental Gerontology.

• Werner syndrome: molecular insights into the relationships between defective DNA metabolism, genomic instability, cancer and aging.
  Author(s): Orren DK.

• Werner syndrome: studies in an affected family reveal a cellular phenotype of unaffected siblings.
  Source: Mechanisms of Ageing and Development.

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  Author(s): Barak Y, Sirota P, Kimhi R, Slor H.
  Source: Comprehensive Psychiatry.

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  Author(s): Martin GM, Oshima J, Gray MD, Poot M.
  Source: Journal of the American Geriatrics Society.

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  Source: Nucleic Acids Research.

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  Author(s): Moser MJ, Oshima J, Monnat RJ Jr.
  Source: Human Mutation.
• **WRN or telomerase constructs reverse 4-nitroquinoline 1-oxide sensitivity in transformed Werner syndrome fibroblasts.**
  Author(s): Hisama FM, Chen YH, Meyn MS, Oshima J, Weissman SM.
  Source: Cancer Research.

• **WRN, the protein deficient in Werner syndrome, plays a critical structural role in optimizing DNA repair.**
  Author(s): Chen L, Huang S, Lee L, Davalos A, Schiestl RH, Campisi J, Oshima J.
  Source: Aging Cell.
CHAPTER 2. ALTERNATIVE MEDICINE AND WERNER SYNDROME

Overview

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

- A deletion within the murine Werner syndrome helicase induces sensitivity to inhibitors of topoisomerase and loss of cellular proliferative capacity.
  Author(s): Lebel M, Leder P.
  Source: Proceedings of the National Academy of Sciences of the United States of America.

- A novel flow cytometric technique for drug cytotoxicity gives results comparable to colony-forming assays.
  Author(s): Poot M, Silber JR, Rabinovitch PS.
  Source: Cytometry : the Journal of the Society for Analytical Cytology.
• Camptothecin sensitivity in Werner syndrome fibroblasts as assessed by the COMET technique.
  Author(s): Lowe J, Sheerin A, Jennert-Burston K, Burton D, Ostler EL, Bird J, Green MH, Faragher RG.

• Chromosomal instability in B-lymphoblasotoid cell lines from Werner and Bloom syndrome patients.
  Author(s): Honma M, Tadokoro S, Sakamoto H, Tanabe H, Sugimoto M, Furuichi Y, Satoh T, Sofuni T, Goto M, Hayashi M.
  Source: Mutation Research.

• DNA damage modulates nucleolar interaction of the Werner protein with the AAA ATPase p97/VCP.
  Author(s): PartridgeJJ, Lopreiato JO Jr, Latterich M, Indig FE.
  Source: Molecular Biology of the Cell.

• Effects of topoisomerase II inhibition in lymphoblasts from patients with progeroid and “chromosome instability” syndromes.
  Author(s): Elli R, Chessa L, Antonelli A, Petrinelli P, Ambra R, Marcucci L.
  Source: Cancer Genetics and Cytogenetics.

• Epigenetic inactivation of the premature aging Werner syndrome gene in human cancer.
  Source: Proceedings of the National Academy of Sciences of the United States of America.

• Increased frequency of DNA deletions in pink-eyed unstable mice carrying a mutation in the Werner syndrome gene homologue.
  Author(s): Lebel M.
  Source: Carcinogenesis.

• Posttranscriptional gene silencing in Neurospora by a RecQ DNA helicase.
  Author(s): Cogoni C, Macino G.
• **Severe toxicity following induction chemotherapy for acute myelogenous leukemia in a patient with Werner's syndrome.**
  Source: Leukemia & Lymphoma.

• **The effect of Ninjinyoeito on Werner's syndrome skin fibroblasts.**
  Author(s): Uchiyama Y, Nakajima S, Ohno T, Goto M, Kan M, Haruki E.

• **The Werner syndrome protein confers resistance to the DNA lesions N3-methyladenine and O6-methylguanine: implications for WRN function.**
  Author(s): Blank A, Bobola MS, Gold B, Varadarajan S, D Kolstoe D, Meade EH, Rabinovitch PS, Loeb LA, Silber JR.
  Source: Dna Repair.

• **Thyroid carcinoma after successful treatment of osteosarcoma: a report of three patients.**
  Author(s): Verneris M, McDougall IR, Becton D, Link MP.

• **Werner and Bloom helicases are involved in DNA repair in a complementary fashion.**
  Author(s): Imamura O, Fujita K, Itoh C, Takeda S, Furuichi Y, Matsumoto T.
  Source: Oncogene.

• **Werner helicase relocates into nuclear foci in response to DNA damaging agents and co-localizes with RPA and Rad51.**
  Author(s): Sakamoto S, Nishikawa K, Heo SJ, Goto M, Furuichi Y, Shimamoto A.
  Source: Genes to Cells : Devoted to Molecular & Cellular Mechanisms.

• **Werner protein stimulates topoisomerase I DNA relaxation activity.**
  Author(s): Laine JP, Opresko PL, Indig FE, Harrigan JA, von Kobbe C, Bohr VA.
• Werner syndrome lymphoblastoid cells are sensitive to camptothecin-induced apoptosis in S-phase.
  Author(s): Poot M, Gollahon KA, Rabinovitch PS.
  Source: Human Genetics.

• Werner's syndrome cell lines are hypersensitive to camptothecin-induced chromosomal damage.
  Author(s): Pichierri P, Franchitto A, Mosesso P, Palitti F.
  Source: Mutation Research.

• Werner's syndrome lymphoblastoid cells are hypersensitive to topoisomerase II inhibitors in the G2 phase of the cell cycle.
  Author(s): Pichierri P, Franchitto A, Mosesso P, Proietti de Santis L, Balajee AS, Palitti F.
  Source: Mutation Research.

• Werner's syndrome protein is phosphorylated in an ATR/ATM-dependent manner following replication arrest and DNA damage induced during the S phase of the cell cycle.
  Author(s): Pichierri P, Rosselli F, Franchitto A.
  Source: Oncogene.

• Werner's syndrome protein is required for correct recovery after replication arrest and DNA damage induced in S-phase of cell cycle.
  Author(s): Pichierri P, Franchitto A, Mosesso P, Palitti F.
  Source: Molecular Biology of the Cell.

**Additional Web Resources**

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

• AOL: [http://health.aol.com/healthyliving/althealth](http://health.aol.com/healthyliving/althealth)
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. BOOKS ON WERNER SYNDROME

Overview

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

- Molecular Mechanisms of Werner's Syndrome (Medical Intelligence Unit) Michel Lebel (2004); ISBN: 0306482339; http://www.amazon.com/exec/obidos/ASIN/0306482339/icingroupinterna
APPENDICES
APPENDIX A. HELP ME UNDERSTAND GENETICS

Overview

This appendix presents basic information about genetics in clear language and provides links to online resources.7

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.

• **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.

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.)
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:

<table>
<thead>
<tr>
<th>Function</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody</td>
<td>Antibodies bind to specific foreign particles, such as viruses and bacteria, to help protect the body.</td>
<td>Immunoglobulin G (IgG)</td>
</tr>
<tr>
<td>Enzyme</td>
<td>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.</td>
<td>Phenylalanine hydroxylase</td>
</tr>
<tr>
<td>Messenger</td>
<td>Messenger proteins, such as some types of hormones, transmit signals to coordinate biological processes between different cells, tissues, and organs.</td>
<td>Growth hormone</td>
</tr>
<tr>
<td>Structural component</td>
<td>These proteins provide structure and support for cells. On a larger scale, they also allow the body to move.</td>
<td>Actin</td>
</tr>
<tr>
<td>Transport/storage</td>
<td>These proteins bind and carry atoms and small molecules within cells and throughout the body.</td>
<td>Ferritin</td>
</tr>
</tbody>
</table>

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.

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.8

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

8 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.
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/.

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:

<table>
<thead>
<tr>
<th>Statistical Term</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>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.</td>
<td>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.</td>
</tr>
</tbody>
</table>
Help Me Understand Genetics

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.

**Condition affecting members of a family**

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:

<table>
<thead>
<tr>
<th>Inheritance Pattern</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant</td>
<td>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.</td>
<td>Huntington disease, neurofibromatosis type 1</td>
</tr>
</tbody>
</table>
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:

• 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 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=1000375

• 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/

9 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/hj/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.\textsuperscript{10} 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

\textsuperscript{10} Remember, for the general public, the National Library of Medicine recommends the databases referenced in MEDLINE\textit{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:

- **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](http://www.nlm.nih.gov/databases/databases_bioethics.html)


- **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](http://www.nlm.nih.gov/databases/databases_population.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](http://www.nlm.nih.gov/databases/alerts/clinical_alerts.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](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](http://sis.nlm.nih.gov/Tox/ToxMain.html)


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The NLM Gateway

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. To use the NLM Gateway, simply go to the search site at http://gateway.nlm.nih.gov/gw/Cmd. Type Werner syndrome (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

<table>
<thead>
<tr>
<th>Category</th>
<th>Items Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal Articles</td>
<td>1130</td>
</tr>
<tr>
<td>Books / Periodicals / Audio Visual</td>
<td>9</td>
</tr>
<tr>
<td>Consumer Health</td>
<td>73</td>
</tr>
<tr>
<td>Meeting Abstracts</td>
<td>40</td>
</tr>
<tr>
<td>Other Collections</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1252</td>
</tr>
</tbody>
</table>

HSTAT

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

Coffee Break: Tutorials for Biologists

Coffee Break is a general healthcare site that takes a scientific view of the news and covers recent breakthroughs in biology that may one day assist physicians in developing treatments. Here you will find a collection of short reports on recent biological discoveries.

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13 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 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.
Each report incorporates interactive tutorials that demonstrate how bioinformatics tools are used as a part of the research process. Currently, all Coffee Breaks are written by NCBI staff. 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. 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: \texttt{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 \texttt{http://www.mdconsult.com/}.
- **Medical Matrix**: Lists over 6000 medical Web sites and links to over 1.5 million documents with clinical content, see \texttt{http://www.medmatrix.org/}.
- **Medical World Search**: Searches full text from thousands of selected medical sites on the Internet; see \texttt{http://www.mwsearch.com/}.

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18 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.

19 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 Werner syndrome 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 Werner syndrome. 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 Werner syndrome. 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 Werner syndrome:
Arrhythmia

Birth Defects

Cancer

Coronary Artery Disease

Developmental Disabilities

Down Syndrome

Facial Injuries and Disorders

Genetic Disorders

Head and Brain Malformations

Hearing Disorders and Deafness

Sudden Infant Death Syndrome

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:

• HONselect - Werner Syndrome
  Source: www.hon.ch
  http://www.hon.ch/HONselect/RareDiseases/C16.320.925.html
The NIH Search Utility

The NIH search utility allows you to search for documents on over 100 selected Web sites that comprise the NIH-WEB-SPACE. Each of these servers is “crawled” and indexed on an ongoing basis. Your search will produce a list of various documents, all of which will relate in some way to Werner syndrome. 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 Werner syndrome (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/
- 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 Werner syndrome. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with Werner syndrome.

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 Werner syndrome. 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

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 Werner syndrome (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 Werner syndrome (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:

- 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:

- A Science Called Genetics: http://publications.nigms.nih.gov/genetics/science.html
- Genetic Mapping: http://www.genome.gov/10000715

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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:

- 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

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
WERNER SYNDROME DICTIONARY

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

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

Abdomen: That portion of the body that lies between the thorax and the pelvis. [NIH]

Abdominal: Having to do with the abdomen, which is the part of the body between the chest and the hips that contains the pancreas, stomach, intestines, liver, gallbladder, and other organs. [NIH]

Abdominal fat: Fat (adipose tissue) that is centrally distributed between the thorax and pelvis and that induces greater health risk. [NIH]

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

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]

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

Acute myelogenous leukemia: AML. A quickly progressing disease in which too many immature blood-forming cells are found in the blood and bone marrow. Also called acute myeloid leukemia or acute nonlymphocytic leukemia. [NIH]

Acute myeloid leukemia: AML. A quickly progressing disease in which too many immature blood-forming cells are found in the blood and bone marrow. Also called acute myelogenous leukemia or acute nonlymphocytic leukemia. [NIH]

Acute nonlymphocytic leukemia: A quickly progressing disease in which too many immature blood-forming cells are found in the blood and bone marrow. Also called acute myeloid leukemia or acute myelogenous leukemia. [NIH]

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

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

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

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]

Adipose Tissue: Connective tissue composed of fat cells lodged in the meshes of areolar tissue. [NIH]

Adverse Effect: An unwanted side effect of treatment. [NIH]
**Aerobic**: In biochemistry, reactions that need oxygen to happen or happen when oxygen is present. [NIH]

**Affinity**: 1. Inherent likeness or relationship. 2. A special attraction for a specific element, organ, or structure. 3. Chemical affinity; the force that binds atoms in molecules; the tendency of substances to combine by chemical reaction. 4. The strength of noncovalent chemical binding between two substances as measured by the dissociation constant of the complex. 5. In immunology, a thermodynamic expression of the strength of interaction between a single antigen-binding site and a single antigenic determinant (and thus of the stereochemical compatibility between them), most accurately applied to interactions among simple, uniform antigenic determinants such as haptons. 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]

**Agar**: A complex sulfated polymer of galactose units, extracted from Gelidium cartilagineum, Gracilaria confervoides, and related red algae. It is used as a gel in the preparation of solid culture media for microorganisms, as a bulk laxative, in making emulsions, and as a supporting medium for immunodiffusion and immunoelectrophoresis. [NIH]

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

**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]

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

**Alkaloid**: A member of a large group of chemicals that are made by plants and have nitrogen in them. Some alkaloids have been shown to work against cancer. [NIH]

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

**Alopecia**: Absence of hair from areas where it is normally present. [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 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]
**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]

**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]

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

**Anaphylatoxins:** The family of peptides C3a, C4a, C5a, and C5a des-arginine produced in the serum during complement activation. They produce smooth muscle contraction, mast cell histamine release, affect platelet aggregation, and act as mediators of the local inflammatory process. The order of anaphylatoxin activity from strongest to weakest is C5a, C3a, C4a, and C5a des-arginine. The latter is the so-called "classical" anaphylatoxin but shows no spasmogenic activity though it contains some chemotactic ability. [NIH]

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

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

**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]

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

**Antibiotic:** A drug used to treat infections caused by bacteria and other microorganisms. [NIH]

**Antibodies:** Immunoglobulin molecules having a specific amino acid sequence by virtue of which they interact only with the antigen that induced their synthesis in cells of the lymphoid series (especially plasma cells), or with an antigen closely related to it. [NIH]

**Antibody:** A type of protein made by certain white blood cells in response to a foreign substance (antigen). Each antibody can bind to only a specific antigen. The purpose of this binding is to help destroy the antigen. Antibodies can work in several ways, depending on the nature of the antigen. Some antibodies destroy antigens directly. Others make it easier for white blood cells to destroy the antigen. [NIH]

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

**Antigen:** Any substance which is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibody or specifically sensitized T-lymphocytes, or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (q.v.) combines with antibody or a specific receptor on a lymphocyte. Abbreviated Ag. [EU]

**Antigen-Antibody Complex:** The complex formed by the binding of antigen and antibody molecules. The deposition of large antigen-antibody complexes leading to tissue damage
causes immune complex diseases. [NIH]

**Anti-infective**: An agent that so acts. [EU]

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

**Antineoplastic**: Inhibiting or preventing the development of neoplasms, checking the maturation and proliferation of malignant cells. [EU]

**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]

**Apolipoproteins**: The protein components of lipoproteins which remain after the lipids to which the proteins are bound have been removed. They play an important role in lipid transport and metabolism. [NIH]

**Apoptosis**: One of the two mechanisms by which cell death occurs (the other being the pathological process of necrosis). Apoptosis is the mechanism responsible for the physiological deletion of cells and appears to be intrinsically programmed. It is characterized by distinctive morphologic changes in the nucleus and cytoplasm, chromatin cleavage at regularly spaced sites, and the endonucleolytic cleavage of genomic DNA (DNA fragmentation) at internucleosomal sites. This mode of cell death serves as a balance to mitosis in regulating the size of animal tissues and in mediating pathologic processes associated with tumor growth. [NIH]

**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]

**Arteriolosclerosis**: Sclerosis and thickening of the walls of the smaller arteries (arterioles). Hyaline arteriolosclerosis, in which there is homogeneous pink hyaline thickening of the arteriolar walls, is associated with benign nephrosclerosis. Hyperplastic arteriolosclerosis, in which there is a concentric thickening with progressive narrowing of the lumina may be associated with malignant hypertension, nephrosclerosis, and scleroderma. [EU]

**Arteriosclerosis**: Thickening and loss of elasticity of arterial walls. Atherosclerosis is the most common form of arteriosclerosis and involves lipid deposition and thickening of the intimal cell layers within arteries. Additional forms of arteriosclerosis involve calcification of the media of muscular arteries (Monkeberg medial calcific sclerosis) and thickening of the walls of small arteries or arterioles due to cell proliferation or hyaline deposition (arteriolosclerosis). [NIH]

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

**Ascorbic Acid**: A six carbon compound related to glucose. It is found naturally in citrus fruits and many vegetables. Ascorbic acid is an essential nutrient in human diets, and necessary to maintain connective tissue and bone. Its biologically active form, vitamin C, functions as a reducing agent and coenzyme in several metabolic pathways. Vitamin C is considered an antioxidant. [NIH]

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

**Ataxia:** Impairment of the ability to perform smoothly coordinated voluntary movements. This condition may affect the limbs, trunk, eyes, pharynx, larynx, 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]

**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]

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

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

**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]

**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 craniofacial 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]

**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 amyloids. [NIH]

**Bewilderment:** Impairment or loss of will power. [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]

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

**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 Glucose:** Glucose in blood. [NIH]

**Blood pressure:** The pressure of blood against the walls of a blood vessel or heart chamber. Unless there is reference to another location, such as the pulmonary artery or one of the heart chambers, it refers to the pressure in the systemic arteries, as measured, for example, in the forearm. [NIH]

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

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

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

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

**Bypass:** A surgical procedure in which the doctor creates a new pathway for the flow of body fluids. [NIH]

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

**Calcium:** A basic element found in nearly all organized tissues. It is a member of the alkaline earth family of metals with the atomic symbol Ca, atomic number 20, and atomic weight 40. Calcium is the most abundant mineral in the body and combines with phosphorus to form calcium phosphate in the bones and teeth. It is essential for the normal functioning of nerves and muscles and plays a role in blood coagulation (as factor IV) and in many enzymatic processes. [NIH]

**Camptothecin:** An alkaloid isolated from the stem wood of the Chinese tree, Camptotheca acuminata. This compound selectively inhibits the nuclear enzyme DNA topoisomerase. Several semisynthetic analogs of camptothecin have demonstrated antitumor activity. [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]

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

**Carcinogenic:** Producing carcinoma. [EU]

**Carcinogens:** Substances that increase the risk of neoplasms in humans or animals. Both
genotoxic chemicals, which affect DNA directly, and nongenotoxic chemicals, which induce neoplasms by other mechanism, are included. [NIH]

**Carcinoma:** Cancer that begins in the skin or in tissues that line or cover internal organs. [NIH]

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

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

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

**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]

**Catalytic Domain:** The region of an enzyme that interacts with its substrate to cause the enzymatic reaction. [NIH]

**Cataract:** An opacity, partial or complete, of one or both eyes, on or in the lens or capsule, especially an opacity impairing vision or causing blindness. The many kinds of cataract are classified by their morphology (size, shape, location) or etiology (cause and time of occurrence). [EU]

**Causal:** Pertaining to a cause; directed against a cause. [EU]

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

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

**Cell Aging:** The decrease in the cell's ability to proliferate with the passing of time. Each cell is programmed for a certain number of cell divisions and at the end of that time proliferation halts. The cell enters a quiescent state after which it experiences cell death via the process of apoptosis. [NIH]

**Cell Cycle:** The complex series of phenomena, occurring between the end of one cell division and the end of the next, by which cellular material is divided between daughter cells. [NIH]

**Cell Death:** The termination of the cell's ability to carry out vital functions such as metabolism, growth, reproduction, responsiveness, and adaptability. [NIH]

**Cell Differentiation:** Progressive restriction of the developmental potential and increasing specialization of function which takes place during the development of the embryo and leads to the formation of specialized cells, tissues, and organs. [NIH]

**Cell Division:** The fission of a cell. [NIH]

**Cell 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]

**Centrifugation:** A method of separating organelles or large molecules that relies upon differential sedimentation through a preformed density gradient under the influence of a
gravitational field generated in a centrifuge. [NIH]

**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]

**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]

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

**Chemotactic Factors:** Chemical substances that attract or repel cells or organisms. The concept denotes especially those factors released as a result of tissue injury, invasion, or immunologic activity, that attract leukocytes, macrophages, or other cells to the site of infection or insult. [NIH]

**Chemotherapy:** Treatment with anticancer drugs. [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]

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

**Cholesterol Esters:** Fatty acid esters of cholesterol which constitute about two-thirds of the cholesterol in the plasma. The accumulation of cholesterol esters in the arterial intima is a characteristic feature of atherosclerosis. [NIH]

**Chromatin:** The material of chromosomes. It is a complex of DNA, histones, and non-histone proteins (chromosomal proteins, non-histone) found within the nucleus of a cell. [NIH]

**Chromium:** A trace element that plays a role in glucose metabolism. It has the atomic symbol Cr, atomic number 24, and atomic weight 52. According to the Fourth Annual Report on Carcinogens (NTP85-002,1985), chromium and some of its compounds have been listed as known carcinogens. [NIH]

**Chromosomal:** Pertaining to chromosomes. [EU]

**Chromosome:** Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes. [NIH]

**Chromosome Abnormalities:** Defects in the structure or number of chromosomes resulting in structural aberrations or manifesting as disease. [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]

**Chylomicrons:** A class of lipoproteins that carry dietary cholesterol and triglycerides from the small intestines to the tissues. [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]

Cleave: A double-stranded cut in DNA with a restriction endonuclease. [NIH]

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

Coenzyme: An organic nonprotein molecule, frequently a phosphorylated derivative of a water-soluble vitamin, that binds with the protein molecule (apoenzyme) to form the active enzyme (holoenzyme). [EU]

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

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

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]

Colorectal: Having to do with the colon or the rectum. [NIH]

Colorectal Cancer: Cancer that occurs in the colon (large intestine) or the rectum (the end of the large intestine). A number of digestive diseases may increase a person's risk of colorectal cancer, including polyposis and Zollinger-Ellison Syndrome. [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]

**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]

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

**Constitutional:** 1. Affecting the whole constitution of the body; not local. 2. Pertaining to the constitution. [EU]

**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]

**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]

**Corneum:** The superficial layer of the epidermis containing keratinized cells. [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]

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

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

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]

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

Cytotoxic: Cell-killing. [NIH]

Cytotoxicity: Quality of being capable of producing a specific toxic action upon cells of special organs. [NIH]

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

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

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

Delusions: A false belief regarding the self or persons or objects outside the self that persists despite the facts, and is not considered tenable by one's associates. [NIH]

Dementia: An acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behavior, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive, and initially spares the level of consciousness. [NIH]

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]

**Desmin**: An intermediate filament protein found predominantly in smooth, skeletal, and cardiac muscle cells. Localized at the Z line. MW 50,000 to 55,000 is species dependent. [NIH]

**Deuterium**: Deuterium. The stable isotope of hydrogen. It has one neutron and one proton in the nucleus. [NIH]

**Diabetes Mellitus**: A heterogeneous group of disorders that share glucose intolerance in common. [NIH]

**Digestion**: The process of breakdown of food for metabolism and use by the body. [NIH]

**Diploid**: Having two sets of chromosomes. [NIH]

**Direct**: 1. Straight; in a straight line. 2. Performed immediately and without the intervention of subsidiary means. [EU]

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

**Disorientation**: The loss of proper bearings, or a state of mental confusion as to time, place, or identity. [EU]

**Disposition**: A tendency either physical or mental toward certain diseases. [EU]

**Dissociation**: 1. The act of separating or state of being separated. 2. The separation of a molecule into two or more fragments (atoms, molecules, ions, or free radicals) produced by the absorption of light or thermal energy or by solvation. 3. In psychology, a defense mechanism in which a group of mental processes are segregated from the rest of a person's mental activity in order to avoid emotional distress, as in the dissociative disorders (q.v.), or in which an idea or object is segregated from its emotional significance; in the first sense it is roughly equivalent to splitting, in the second, to isolation. 4. A defect of mental integration in which one or more groups of mental processes become separated off from normal consciousness and, thus separated, function as a unitary whole. [EU]

**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]

**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]

**Effector**: It is often an enzyme that converts an inactive precursor molecule into an active second messenger. [NIH]

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

**Electrolytes**: Substances that break up into ions (electrically charged particles) when they are dissolved in body fluids or water. Some examples are sodium, potassium, chloride, and calcium. Electrolytes are primarily responsible for the movement of nutrients into cells, and the movement of wastes out of cells. [NIH]

**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]

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

**Endogenous**: Produced inside an organism or cell. The opposite is external (exogenous) production. [NIH]

**Endotoxins**: Toxins closely associated with the living cytoplasm or cell wall of certain microorganisms, which do not readily diffuse into the culture medium, but are released upon lysis of the cells. [NIH]

**Environmental Exposure**: The exposure to potentially harmful chemical, physical, or biological agents in the environment or to environmental factors that may include ionizing radiation, pathogenic organisms, or toxic chemicals. [NIH]

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

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

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

**Epidemiological**: Relating to, or involving epidemiology. [EU]

**Epidermis**: Nonvascular layer of the skin. It is made up, from within outward, of five layers: 1) basal layer (stratum basale epidermidis); 2) spinous layer (stratum spinosum epidermidis); 3) granular layer (stratum granulosum epidermidis); 4) clear layer (stratum lucidum epidermidis); and 5) horny layer (stratum corneum epidermidis). [NIH]

**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]

**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]

**Excisional**: The surgical procedure of removing a tumor by cutting it out. The biopsy is then examined under a microscope. [NIH]

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

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

**Exonucleases**: Enzymes that catalyze the release of mononucleotides by the hydrolysis of the terminal bond of deoxyribonucleotide or ribonucleotide chains. EC 3.1.-. [NIH]

**Extracellular**: Outside a cell or cells. [EU]

**Extracellular Matrix**: A meshwork-like substance found within the extracellular space and in association with the basement membrane of the cell surface. It promotes cellular proliferation and provides a supporting structure to which cells or cell lysates in culture dishes adhere. [NIH]
**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]

**Facial:** Of or pertaining to the face. [EU]

**Family Planning:** Programs or services designed to assist the family in controlling reproduction by either improving or diminishing fertility. [NIH]

**Fat:** Total lipids including phospholipids. [NIH]

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

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

**Fibroblasts:** Connective tissue cells which secrete an extracellular matrix rich in collagen and other macromolecules. [NIH]

**Fibronectin:** An adhesive glycoprotein. One form circulates in plasma, acting as an opsonin; another is a cell-surface protein which mediates cellular adhesive interactions. [NIH]

**Fibrosis:** Any pathological condition where fibrous connective tissue invades any organ, usually as a consequence of inflammation or other injury. [NIH]

**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]

**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 deletion 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]

**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]

**Gallbladder:** The pear-shaped organ that sits below the liver. Bile is concentrated and stored in the gallbladder. [NIH]

**Gamma Rays:** Very powerful and penetrating, high-energy electromagnetic radiation of shorter wavelength than that of x-rays. They are emitted by a decaying nucleus, usually between 0.01 and 10 MeV. They are also called nuclear x-rays. [NIH]

**Gamma-interferon:** Interferon produced by T-lymphocytes in response to various mitogens and antigens. Gamma interferon appears to have potent antineoplastic, immunoregulatory and antiviral activity. [NIH]

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

**Gangrene:** Death and putrefaction of tissue usually due to a loss of blood supply. [NIH]

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

**Gastrin:** A hormone released after eating. Gastrin causes the stomach to produce more acid. [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 Silencing:** Interruption or suppression of the expression of a gene at transcriptional or translational levels. [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 testing:** Analyzing DNA to look for a genetic alteration that may indicate an increased risk for developing a specific disease or disorder. [NIH]

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

**Genomics:** The systematic study of the complete DNA sequences (genome) of organisms. [NIH]

**Genotype:** The genetic constitution of the individual; the characterization of the genes. [NIH]

**Germ Cells:** The reproductive cells in multicellular organisms. [NIH]

**Germline mutation:** A gene change in the body’s reproductive cells (egg or sperm) that becomes incorporated into the DNA of every cell in the body of offspring; germline mutations are passed on from parents to offspring. Also called hereditary mutation. [NIH]

**Gland:** An organ that produces and releases one or more substances for use in the body. Some glands produce fluids that affect tissues or organs. Others produce hormones or participate in blood production. [NIH]

**Glucose:** D-Glucose. A primary source of energy for living organisms. It is naturally occurring and is found in fruits and other parts of plants in its free state. It is used therapeutically in fluid and nutrient replacement. [NIH]

**Glucose Intolerance:** A pathological state in which the fasting plasma glucose level is less than 140 mg per deciliter and the 30-, 60-, or 90-minute plasma glucose concentration
following a glucose tolerance test exceeds 200 mg per deciliter. This condition is seen frequently in diabetes mellitus but also occurs with other diseases. [NIH]

Glucose tolerance: The power of the normal liver to absorb and store large quantities of glucose and the effectiveness of intestinal absorption of glucose. The glucose tolerance test is a metabolic test of carbohydrate tolerance that measures active insulin, a hepatic function based on the ability of the liver to absorb glucose. The test consists of ingesting 100 grams of glucose into a fasting stomach; blood sugar should return to normal in 2 to 21 hours after ingestion. [NIH]

Glucose Tolerance Test: Determination of whole blood or plasma sugar in a fasting state before and at prescribed intervals (usually 1/2 hr, 1 hr, 3 hr, 4 hr) after taking a specified amount (usually 100 gm orally) of glucose. [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]

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

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

Hair Color: Color of hair or fur. [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 concentration. 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]
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]

Heterodimer: Zippered pair of nonidentical proteins. [NIH]

Heterogeneity: The property of one or more samples or populations which implies that they are not identical in respect of some or all of their parameters, e.g. heterogeneity of variance. [NIH]

Heterozygotes: Having unlike alleles at one or more corresponding loci on homologous chromosomes. [NIH]

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]

Hoarseness: An unnaturally deep or rough quality of voice. [NIH]

Homologous: Corresponding in structure, position, origin, etc., as (a) the feathers of a bird and the scales of a fish, (b) antigen and its specific antibody, (c) allelic chromosomes. [EU]

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

Horny layer: The superficial layer of the epidermis containing keratinized cells. [NIH]

Hybrid: Cross fertilization between two varieties or, more usually, two species of vines, see also crossing. [NIH]

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

Hydrogen: The first chemical element in the periodic table. It has the atomic symbol H, atomic number 1, and atomic weight 1. It exists, under normal conditions, as a colorless, odorless, tasteless, diatomic gas. Hydrogen ions are protons. Besides the common H1 isotope, hydrogen exists as the stable isotope deuterium and the unstable, radioactive isotope tritium. [NIH]

Hydrogen Peroxide: A strong oxidizing agent used in aqueous solution as a ripening agent, bleach, and topical anti-infective. It is relatively unstable and solutions deteriorate over time unless stabilized by the addition of acetaldehyde or similar organic materials. [NIH]

Hydrolysis: The process of cleaving a chemical compound by the addition of a molecule of water. [NIH]

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

Hypersensitivity: Altered reactivity to an antigen, which can result in pathologic reactions
Hypertension: Persistently high arterial blood pressure. Currently accepted threshold levels are 140 mm Hg systolic and 90 mm Hg diastolic pressure. [NIH]

Hypoplasia: Incomplete development or underdevelopment of an organ or tissue. [EU]

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

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

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]

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 Situ Hybridization: A technique that localizes specific nucleic acid sequences within intact chromosomes, eukaryotic cells, or bacterial cells through the use of specific nucleic acid-labeled probes. [NIH]

In vitro: In the laboratory (outside the body). The opposite of in vivo (in the body). [NIH]

In vivo: In the body. The opposite of in vitro (outside the body or in the laboratory). [NIH]

Induction: The act or process of inducing or causing to occur, especially the production of a specific morphogenetic effect in the developing embryo through the influence of evocators or organizers, or the production of anaesthesia or unconsciousness by use of appropriate agents. [EU]

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

Infantile: Pertaining to an infant or to infancy. [EU]

Infection: 1. Invasion and multiplication of microorganisms in body tissues, which may be clinically unapparent or result in local cellular injury due to competitive metabolism, toxins, intracellular replication, or antigen-antibody response. The infection may remain localized, subclinical, and temporary if the body’s defensive mechanisms are effective. A local infection may persist and spread by extension to become an acute, subacute, or chronic clinical infection or disease state. A local infection may also become systemic when the microorganisms gain access to the lymphatic or vascular system. 2. An infectious disease. [EU]

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

Informed Consent: Voluntary authorization, given to the physician by the patient, with full comprehension of the risks involved, for diagnostic or investigative procedures and medical and surgical treatment. [NIH]

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

**Insulin:** A protein hormone secreted by beta cells of the pancreas. Insulin plays a major role in the regulation of glucose metabolism, generally promoting the cellular utilization of glucose. It is also an important regulator of protein and lipid metabolism. Insulin is used as a drug to control insulin-dependent diabetes mellitus. [NIH]

**Insulin-dependent diabetes mellitus:** A disease characterized by high levels of blood glucose resulting from defects in insulin secretion, insulin action, or both. Autoimmune, genetic, and environmental factors are involved in the development of type I diabetes. [NIH]

**Insulin-like:** Muscular growth factor. [NIH]

**Intercellular Adhesion Molecule-1:** A cell-surface ligand with a role in leukocyte adhesion and inflammation. Its production is induced by gamma-interferon and it is required for neutrophil migration into inflamed tissue. [NIH]

**Intermediate Filament Proteins:** Filaments 7-11 nm in diameter found in the cytoplasm of all cells. Many specific proteins belong to this group, e.g., desmin, vimentin, prekeratin, decamin, skeleton, neurofilin, neurofilament protein, and glial fibrillary acid protein. [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]

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

**Involuntary:** Reaction occurring without intention or volition. [NIH]

**Ions:** An atom or group of atoms that have a positive or negative electric charge due to a gain (negative charge) or loss (positive charge) of one or more electrons. Atoms with a positive charge are known as cations; those with a negative charge are anions. [NIH]

**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]

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

**Kb:** A measure of the length of DNA fragments, 1 Kb = 1000 base pairs. The largest DNA fragments are up to 50 kilobases long. [NIH]

**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]
**Kilobase**: A measure of the length of DNA fragments, 1 Kb = 1000 base pairs. The largest DNA fragments are up to 50 kilobases long. [NIH]

**Kinetic**: Pertaining to or producing motion. [EU]

**Labile**: 1. Gliding; moving from point to point over the surface; unstable; fluctuating. 2. Chemically unstable. [EU]

**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]

**Lens**: The transparent, double convex (outward curve on both sides) structure suspended between the aqueous and vitreous; helps to focus light on the retina. [NIH]

**Lesion**: An area of abnormal tissue change. [NIH]

**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]

**Ligament**: A band of fibrous tissue that connects bones or cartilages, serving to support and strengthen joints. [EU]

**Ligase**: An enzyme that repairs single stranded discontinuities in double-stranded DNA molecules in the cell. Purified DNA ligase is used in gene cloning to join DNA molecules together. [NIH]

**Ligation**: Application of a ligature to tie a vessel or strangulate a part. [NIH]

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

**Linkage Disequilibrium**: Nonrandom association of linked genes. This is the tendency of the alleles of two separate but already linked loci to be found together more frequently than would be expected by chance alone. [NIH]

**Lipid**: Fat. [NIH]

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

**Lipodystrophy**: A collection of rare conditions resulting from defective fat metabolism and characterized by atrophy of the subcutaneous fat. They include total, congenital or acquired, partial, abdominal infantile, and localized lipodystrophy. [NIH]

**Lipoprotein**: Any of the lipid-protein complexes in which lipids are transported in the blood; lipoprotein particles consist of a spherical hydrophobic core of triglycerides or cholesterol esters surrounded by an amphipathic monolayer of phospholipids, cholesterol, and apolipoproteins; the four principal classes are high-density, low-density, and very-low-density lipoproteins and chylomicrons. [EU]

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

**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]
Loss of Heterozygosity: The loss of one allele at a specific locus, caused by a deletion mutation; or loss of a chromosome from a chromosome pair. It is detected when heterozygous markers for a locus appear monomorphic because one of the alleles was deleted. When this occurs at a tumor suppressor gene locus where one of the alleles is already abnormal, it can result in neoplastic transformation. [NIH]

Low-density lipoprotein: Lipoprotein that contains most of the cholesterol in the blood. LDL carries cholesterol to the tissues of the body, including the arteries. A high level of LDL increases the risk of heart disease. LDL typically contains 60 to 70 percent of the total serum cholesterol and both are directly correlated with CHD risk. [NIH]

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]

Lymphoblasts: Interferon produced predominantly by leucocyte cells. [NIH]

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

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

Lymphoma: A general term for various neoplastic diseases of the lymphoid tissue. [NIH]

Lysine: An essential amino acid. It is often added to animal feed. [NIH]

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]

Malignant: Cancerous; a growth with a tendency to invade and destroy nearby tissue and spread to other parts of the body. [NIH]

Malignant tumor: A tumor capable of metastasizing. [NIH]

Mammogram: An x-ray of the breast. [NIH]

Mammography: Radiographic examination of the breast. [NIH]

Manic: Affected with mania. [EU]

Manic-depressive psychosis: One of a group of psychotic reactions, fundamentally marked by severe mood swings and a tendency to remission and recurrence. [NIH]

Medial: Lying near the midsaggital plane of the body; opposed to lateral. [NIH]

Medical Records: Recording of pertinent information concerning patient's illness or illnesses. [NIH]

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

Meiosis: A special method of cell division, occurring in maturation of the germ cells, by means of which each daughter nucleus receives half the number of chromosomes characteristic of the somatic cells of the species. [NIH]

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

Melanocytes: Epidermal dendritic pigment cells which control long-term morphological color changes by alteration in their number or in the amount of pigment they produce and store in the pigment containing organelles called melanosomes. Melanophores are larger cells which do not exist in mammals. [NIH]

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

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

**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]

**Meningioma:** A type of tumor that occurs in the meninges, the membranes that cover and protect the brain and spinal cord. Meningiomas usually grow slowly. [NIH]

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

**Mental Disorders:** Psychiatric illness or diseases manifested by breakdowns in the adaptational process expressed primarily as abnormalities of thought, feeling, and behavior producing either distress or impairment of function. [NIH]

**Mental Retardation:** Refers to sub-average general intellectual functioning which originated during the developmental period and is associated with impairment in adaptive behavior. [NIH]

**Microbe:** An organism which cannot be observed with the naked eye; e.g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

**Microbiology:** The study of microorganisms such as fungi, bacteria, algae, archaea, and viruses. [NIH]

**Microcalcifications:** Tiny deposits of calcium in the breast that cannot be felt but can be detected on a mammogram. A cluster of these very small specks of calcium may indicate that cancer is present. [NIH]

**Microorganism:** An organism that can be seen only through a microscope. Microorganisms include bacteria, protozoa, algae, and fungi. Although viruses are not considered living organisms, they are sometimes classified as microorganisms. [NIH]

**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]

**Mineralization:** The action of mineralizing; the state of being mineralized. [EU]

**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]

**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]

**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]

**Monosomy:** The condition in which one chromosome of a pair is missing. In a normally diploid cell it is represented symbolically as 2N-1. [NIH]

**Morphological:** Relating to the configuration or the structure of live organs. [NIH]

**Morphology:** The science of the form and structure of organisms (plants, animals, and other forms of life). [NIH]

**Mosaicism:** The occurrence in an individual of two or more cell populations of different chromosomal constitutions, derived from a single zygote, as opposed to chimerism in which the different cell populations are derived from more than one zygote. [NIH]

**Mucositis:** A complication of some cancer therapies in which the lining of the digestive system becomes inflamed. Often seen as sores in the mouth. [NIH]

**Mustard Gas:** Severe irritant and vesicant of skin, eyes, and lungs. It may cause blindness and lethal lung edema and was formerly used as a war gas. The substance has been proposed as a cytostatic and for treatment of psoriasis. It has been listed as a known carcinogen in the Fourth Annual Report on Carcinogens (NTP-85-002, 1985) (Merck, 11th ed). [NIH]

**Mutagen:** Any agent, such as X-rays, gamma rays, mustard gas, TCDD, that can cause abnormal mutation in living cells; having the power to cause mutations. [NIH]

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

**Mutagenic:** Inducing genetic mutation. [EU]

**Myelogenous:** Produced by, or originating in, the bone marrow. [NIH]

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

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

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

**Neoplasia:** Abnormal and uncontrolled cell growth. [NIH]

**Neoplasm:** A new growth of benign or malignant tissue. [NIH]

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

**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]

**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]

**Neutrophil:** A type of white blood cell. [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]

**Nucleic Acid Hybridization:** The process whereby two single-stranded polynucleotides form a double-stranded molecule, with hydrogen bonding between the complementary bases in the two strains. [NIH]

**Nucleus:** A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

**Nurse Practitioners:** Nurses who are specially trained to assume an expanded role in providing medical care under the supervision of a physician. [NIH]

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

**Oncogene:** A gene that normally directs cell growth. If altered, an oncogene can promote or allow the uncontrolled growth of cancer. Alterations can be inherited or caused by an environmental exposure to carcinogens. [NIH]

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

**Opacity:** Degree of density (area most dense taken for reading). [NIH]

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

**Osteogenic sarcoma:** A malignant tumor of the bone. Also called osteosarcoma. [NIH]

**Osteoporosis:** Reduction of bone mass without alteration in the composition of bone, leading to fractures. Primary osteoporosis can be of two major types: postmenopausal osteoporosis and age-related (or senile) osteoporosis. [NIH]

**Osteosarcoma:** A cancer of the bone that affects primarily children and adolescents. Also called osteogenic sarcoma. [NIH]

**Ovaries:** The pair of female reproductive glands in which the ova, or eggs, are formed. The ovaries are located in the pelvis, one on each side of the uterus. [NIH]

**Oxidation:** The act of oxidizing or state of being oxidized. Chemically it consists in the increase of positive charges on an atom or the loss of negative charges. Most biological
oxidations are accomplished by the removal of a pair of hydrogen atoms (dehydrogenation) from a molecule. Such oxidations must be accompanied by reduction of an acceptor molecule. Univalent o. indicates loss of one electron; divalent o., the loss of two electrons. [EU]

**Oxidative Phosphorylation:** Electron transfer through the cytochrome system liberating free energy which is transformed into high-energy phosphate bonds. [NIH]

**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]

**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]

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

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

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

**Pathologies:** The study of abnormality, especially the study of diseases. [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]

**Pelvic:** Pertaining to the pelvis. [EU]

**Pelvis:** The lower part of the abdomen, located between the hip bones. [NIH]

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

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

**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]

**Phosphodiesterase:** Effector enzyme that regulates the levels of a second messenger, the cyclic GMP. [NIH]

**Phospholipases:** A class of enzymes that catalyze the hydrolysis of phosphoglycerides or
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, nerves, bones, and teeth, and is a component of adenosine triphosphate (ATP; the primary energy source for the body’s cells.) [NIH]

Phosphorylated: Attached to a phosphate group. [NIH]

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]

Photosensitivity: An abnormal cutaneous response involving the interaction between photosensitizing substances and sunlight or filtered or artificial light at wavelengths of 280-400 nm. There are two main types: photoallergy and photoxicity. [EU]

Physical Examination: Systematic and thorough inspection of the patient for physical signs of disease or abnormality. [NIH]

Physiologic: Having to do with the functions of the body. When used in the phrase "physiologic age," it refers to an age assigned by general health, as opposed to calendar age. [NIH]

Physiology: The science that deals with the life processes and functions of organismus, their cells, tissues, and organs. [NIH]

Pigment: A substance that gives color to tissue. Pigments are responsible for the color of skin, eyes, and hair. [NIH]

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; absence of nervous and sensory systems; and an alteration of haploid and diploid generations. [NIH]

Plaque: A clear zone in a bacterial culture grown on an agar plate caused by localized destruction of bacterial cells by a bacteriophage. The concentration of infective virus in a fluid can be estimated by applying the fluid to a culture and counting the number of. [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]

Plasmid: An autonomously replicating, extra-chromosomal DNA molecule found in many bacteria. Plasmids are widely used as carriers of cloned genes. [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]

Pneumonia: Inflammation of the lungs. [NIH]

Polymerase: An enzyme which catalyses the synthesis of DNA using a single DNA strand
as a template. The polymerase copies the template in the 5'-3' direction provided that sufficient quantities of free nucleotides, dATP and dTTP are present. [NIH]

**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]

**Polyposis:** The development of numerous polyps (growths that protrude from a mucous membrane). [NIH]

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

**Postmenopausal:** Refers to the time after menopause. Menopause is the time in a woman's life when menstrual periods stop permanently; also called "change of life." [NIH]

**Postsynaptic:** Nerve potential generated by an inhibitory hyperpolarizing stimulation. [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]

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

**Prevalence:** The total number of cases of a given disease in a specified population at a designated time. It is differentiated from incidence, which refers to the number of new cases in the population at a given time. [NIH]

**Progeria:** An abnormal congenital condition characterized by premature aging in children, where all the changes of cell senescence occur. It is manifested by premature greying, hair loss, hearing loss, cataracts, arthritis, osteoporosis, diabetes mellitus, atrophy of subcutaneous fat, skeletal hypoplasia, and accelerated atherosclerosis. Many affected individuals develop malignant tumors, especially sarcomas. [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]

**Proline:** A non-essential amino acid that is synthesized from glutamic acid. It is an essential component of collagen and is important for proper functioning of joints and tendons. [NIH]

**Promoter:** A chemical substance that increases the activity of a carcinogenic process. [NIH]

**Prone:** Having the front portion of the body downwards. [NIH]

**Prostate:** A gland in males that surrounds the neck of the bladder and the urethra. It secretes a substance that liquifies coagulated semen. It is situated in the pelvic cavity behind the lower part of the pubic symphysis, above the deep layer of the triangular ligament, and rests upon the rectum. [NIH]
Protein Binding: The process in which substances, either endogenous or exogenous, bind to proteins, peptides, enzymes, protein precursors, or allied compounds. Specific protein-binding measures are often used as assays in diagnostic assessments. [NIH]

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

Protein Kinases: A family of enzymes that catalyze the conversion of ATP and a protein to ADP and a phosphoprotein. EC 2.7.1.37. [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]

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

Psychosis: A mental disorder characterized by gross impairment in reality testing as evidenced by delusions, hallucinations, markedly incoherent speech, or disorganized and agitated behaviour without apparent awareness on the part of the patient of the incomprehensibility of his behaviour; the term is also used in a more general sense to refer to mental disorders in which mental functioning is sufficiently impaired as to interfere grossly with the patient's capacity to meet the ordinary demands of life. Historically, the term has been applied to many conditions, e.g. manic-depressive psychosis, that were first described in psychotic patients, although many patients with the disorder are not judged psychotic. [EU]

Puberty: The period during which the secondary sex characteristics begin to develop and the capability of sexual reproduction is attained. [EU]

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

Pulmonary: Relating to the lungs. [NIH]

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

Pulmonary 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]

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]

Putrefaction: The process of decomposition of animal and vegetable matter by living
organisms. [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]

Quiescent: Marked by a state of inactivity or repose. [EU]

Race: A population within a species which exhibits general similarities within itself, but is both discontinuous and distinct from other populations of that species, though not sufficiently so as to achieve the status of a taxon. [NIH]

Radiation: Emission or propagation of electromagnetic energy (waves/rays), or the waves/rays themselves; a stream of electromagnetic particles (electrons, neutrons, protons, alpha particles) or a mixture of these. The most common source is the sun. [NIH]

Radiation 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]

Reality Testing: The individual's objective evaluation of the external world and the ability to differentiate adequately between it and the internal world; considered to be a primary ego function. [NIH]

Receptor: A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell. [NIH]

Recessive gene: A gene that is phenotypically expressed only when homozygous. [NIH]

Recombinant: A cell or an individual with a new combination of genes not found together in either parent; usually applied to linked genes. [EU]

Recombination: The formation of new combinations of genes as a result of segregation in crosses between genetically different parents; also the rearrangement of linked genes due to crossing-over. [NIH]

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]

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

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

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

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

Risk factor: A habit, trait, condition, or genetic alteration that increases a person's chance of developing a disease. [NIH]

Sarcoma: A connective tissue neoplasm formed by proliferation of mesodermal cells; it is usually highly malignant. [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]

Sclerosis: A pathological process consisting of hardening or fibrosis of an anatomical structure, often a vessel or a nerve. [NIH]

Screening: Checking for disease when there are no symptoms. [NIH]

Sedimentation: The act of causing the deposit of sediment, especially by the use of a centrifugal machine. [EU]

Segmental: Describing or pertaining to a structure which is repeated in similar form in successive segments of an organism, or which is undergoing segmentation. [NIH]

Segmentation: The process by which muscles in the intestines move food and wastes through the body. [NIH]

Segregation: The separation in meiotic cell division of homologous chromosome pairs and their contained allelomorphic gene pairs. [NIH]

Semen: The thick, yellowish-white, viscid fluid secretion of male reproductive organs discharged upon ejaculation. In addition to reproductive organ secretions, it contains spermatozoa and their nutrient plasma. [NIH]

Semisynthetic: Produced by chemical manipulation of naturally occurring substances. [EU]

Senescence: The bodily and mental state associated with advancing age. [NIH]

Senile: Relating or belonging to old age; characteristic of old age; resulting from infirmity of old age. [NIH]

Sequence Analysis: A multistage process that includes the determination of a sequence (protein, carbohydrate, etc.), its fragmentation and analysis, and the interpretation of the resulting sequence information. [NIH]

Sequencing: The determination of the order of nucleotides in a DNA or RNA chain. [NIH]

Serum: The clear liquid part of the blood that remains after blood cells and clotting proteins have been removed. [NIH]

Sex Characteristics: Those characteristics that distinguish one sex from the other. The primary sex characteristics are the ovaries and testes and their related hormones. Secondary sex characteristics are those which are masculine or feminine but not directly related to reproduction. [NIH]

Side effect: A consequence other than the one(s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other than the one sought to be benefited by its administration. [EU]

Signal Transduction: The intercellular or intracellular transfer of information (biological activation/inhibition) through a signal pathway. In each signal transduction system, an
activation/inhibition signal from a biologically active molecule (hormone, neurotransmitter) is mediated via the coupling of a receptor/enzyme to a second messenger system or to an ion channel. Signal transduction plays an important role in activating cellular functions, cell differentiation, and cell proliferation. Examples of signal transduction systems are the GABA-postsynaptic receptor-calcium ion channel system, the receptor-mediated T-cell activation pathway, and the receptor-mediated activation of phospholipases. Those coupled to membrane depolarization or intracellular release of calcium include the receptor-mediated activation of cytotoxic functions in granulocytes and the synaptic potentiation of protein kinase activation. Some signal transduction pathways may be part of larger signal transduction pathways; for example, protein kinase activation is part of the platelet activation signal pathway. [NIH]

**Signs and Symptoms:** Clinical manifestations that can be either objective when observed by a physician, or subjective when perceived by the patient. [NIH]

**Skeletal:** Having to do with the skeleton (boney part of the body). [NIH]

**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]

**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]

**Specialist:** In medicine, one who concentrates on 1 special branch of medical science. [NIH]

**Species:** A taxonomic category subordinate to a genus (or subgenus) and superior to a subspecies or variety, composed of individuals possessing common characters distinguishing them from other categories of individuals of the same taxonomic level. In taxonomic nomenclature, species are designated by the genus name followed by a Latin or Latinized adjective or noun. [EU]

**Specificity:** Degree of selectivity shown by an antibody with respect to the number and types of antigens with which the antibody combines, as well as with respect to the rates and the extents of these reactions. [NIH]

**Spectrum:** A charted band of wavelengths of electromagnetic vibrations obtained by refraction and diffraction. By extension, a measurable range of activity, such as the range of bacteria affected by an antibiotic (antibacterial s.) or the complete range of manifestations of a disease. [EU]

**Sperm:** The fecundating fluid of the male. [NIH]

**Spinal cord:** The main trunk or bundle of nerves running down the spine through holes in the spinal bone (the vertebrae) from the brain to the level of the lower back. [NIH]
Spinous: Like a spine or thorn in shape; having spines. [NIH]

Sporadic: Neither endemic nor epidemic; occurring occasionally in a random or isolated manner. [EU]

Stillbirth: The birth of a dead fetus or baby. [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]

Subacute: Somewhat acute; between acute and chronic. [EU]

Subclinical: Without clinical manifestations; said of the early stage(s) of an infection or other disease or abnormality before symptoms and signs become apparent or detectable by clinical examination or laboratory tests, or of a very mild form of an infection or other disease or abnormality. [EU]

Subcutaneous: Beneath the skin. [NIH]

Subspecies: A category intermediate in rank between species and variety, based on a smaller number of correlated characters than are used to differentiate species and generally conditioned by geographical and/or ecological occurrence. [NIH]

Substrate: A substance upon which an enzyme acts. [EU]

Substrate Specificity: A characteristic feature of enzyme activity in relation to the kind of substrate on which the enzyme or catalytic molecule reacts. [NIH]

Supportive care: Treatment given to prevent, control, or relieve complications and side effects and to improve the comfort and quality of life of people who have cancer. [NIH]

Suppression: A conscious exclusion of disapproved desire contrary with repression, in which the process of exclusion is not conscious. [NIH]

Symphysis: A secondary cartilaginous joint. [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]

Synergistic: Acting together; enhancing the effect of another force or agent. [EU]

Systemic: Affecting the entire body. [NIH]

Telangiectasia: The permanent enlargement of blood vessels, causing redness in the skin or mucous membranes. [NIH]

Telomerase: Essential ribonucleoprotein reverse transcriptase that adds telomeric DNA to the ends of eukaryotic chromosomes. Telomerase appears to be repressed in normal human somatic tissues but reactivated in cancer, and thus may be necessary for malignant transformation. EC 2.7.7.-. [NIH]

Telomere: A terminal section of a chromosome which has a specialized structure and which is involved in chromosomal replication and stability. Its length is believed to be a few
hundred base pairs. [NIH]

**Terminator**: A DNA sequence sited at the end of a transcriptional unit that signals the end of transcription. [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]

**Thioguanine**: An antineoplastic compound which also has antimetabolite action. The drug is used in the therapy of acute leukemia. [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]

**Thymidine**: A chemical compound found in DNA. Also used as treatment for mucositis. [NIH]

**Thymidine Kinase**: An enzyme that catalyzes the conversion of ATP and thymidine to ADP and thymidine 5’-phosphate. Deoxyuridine can also act as an acceptor and dGTP as a donor. (From Enzyme Nomenclature, 1992) EC 2.7.1.21. [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]

**Tic**: An involuntary compulsive, repetitive, stereotyped movement, resembling a purposeful movement because it is coordinated and involves muscles in their normal synergistic relationships; tics usually involve the face and shoulders. [EU]

**Tissue**: A group or layer of cells that are alike in type and work together to perform a specific function. [NIH]

**Topical**: On the surface of the body. [NIH]

**Toxic**: Having to do with poison or something harmful to the body. Toxic substances usually cause unwanted side effects. [NIH]

**Toxicity**: The quality of being poisonous, especially the degree of virulence of a toxic microbe or of a poison. [EU]

**Toxicology**: The science concerned with the detection, chemical composition, and pharmacologic action of toxic substances or poisons and the treatment and prevention of toxic manifestations. [NIH]

**Toxins**: Specific, characterizable, poisonous chemicals, often proteins, with specific biological properties, including immunogenicity, produced by microbes, higher plants, or animals. [NIH]

**Trace element**: Substance or element essential to plant or animal life, but present in
extremely small amounts. [NIH]

**Trachea:** The cartilaginous and membranous tube descending from the larynx and branching into the right and left main bronchi. [NIH]

**Transcriptase:** An enzyme which catalyses the synthesis of a complementary mRNA molecule from a DNA template in the presence of a mixture of the four ribonucleotides (ATP, UTP, GTP and CTP). [NIH]

**Transcription Factors:** Endogenous substances, usually proteins, which are effective in the initiation, stimulation, or termination of the genetic transcription process. [NIH]

**Transduction:** The transfer of genes from one cell to another by means of a viral (in the case of bacteria, a bacteriophage) vector or a vector which is similar to a virus particle (pseudovirion). [NIH]

**Transfection:** The uptake of naked or purified DNA into cells, usually eukaryotic. It is analogous to bacterial transformation. [NIH]

**Translation:** The process whereby the genetic information present in the linear sequence of ribonucleotides in mRNA is converted into a corresponding sequence of amino acids in a protein. It occurs on the ribosome and is unidirectional. [NIH]

**Translational:** The cleavage of signal sequence that directs the passage of the protein through a cell or organelle membrane. [NIH]

**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]

**Tumor suppressor gene:** Genes in the body that can suppress or block the development of cancer. [NIH]

**Type 2 diabetes:** Usually characterized by a gradual onset with minimal or no symptoms of metabolic disturbance and no requirement for exogenous insulin. The peak age of onset is 50 to 60 years. Obesity and possibly a genetic factor are usually present. [NIH]

**Tyrosine:** A non-essential amino acid. In animals it is synthesized from phenylalanine. It is also the precursor of epinephrine, thyroid hormones, and melanin. [NIH]

**Ubiquitin:** A highly conserved 76 amino acid-protein found in all eukaryotic cells. [NIH]

**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]
Urethra: The tube through which urine leaves the body. It empties urine from the bladder. [NIH]

Uterus: The small, hollow, pear-shaped organ in a woman's pelvis. This is the organ in which a fetus develops. Also called the womb. [NIH]

Vaccine: A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. [NIH]

Vacuoles: Any spaces or cavities within a cell. They may function in digestion, storage, secretion, or excretion. [NIH]

Vascular: Pertaining to blood vessels or indicative of a copious blood supply. [EU]

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]

Venules: The minute vessels that collect blood from the capillary plexuses and join together to form veins. [NIH]

Veterinary Medicine: The medical science concerned with the prevention, diagnosis, and treatment of diseases in animals. [NIH]

Vimentin: An intermediate filament protein found in most differentiating cells, in cells grown in tissue culture, and in certain fully differentiated cells. Its insolubility suggests that it serves a structural function in the cytoplasm. MW 52,000. [NIH]

Viral: Pertaining to, caused by, or of the nature of virus. [EU]

Virulence: The degree of pathogenicity within a group or species of microorganisms or viruses as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. [NIH]

Virus: Submicroscopic organism that causes infectious disease. In cancer therapy, some viruses may be made into vaccines that help the body build an immune response to, and kill, tumor cells. [NIH]

Viscera: Any of the large interior organs in any one of the three great cavities of the body, especially in the abdomen. [NIH]

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]

Xeroderma Pigmentosum: A rare, pigmentary, and atrophic autosomal recessive disease affecting all races. It is manifested as an extreme photosensitivity to ultraviolet light as the result of a deficiency in the enzyme that permits excisional repair of ultraviolet-damaged
DNA. [NIH]

**X-ray:** High-energy radiation used in low doses to diagnose diseases and in high doses to treat cancer. [NIH]

**Yeast:** A general term for single-celled rounded fungi that reproduce by budding. Brewers' and bakers' yeasts are Saccharomyces cerevisiae; therapeutic dried yeast is dried yeast. [NIH]

**Zygote:** The fertilized ovum. [NIH]

**Zymogen:** Inactive form of an enzyme which can then be converted to the active form, usually by excision of a polypeptide, e.g. trypsinogen is the zymogen of trypsin. [NIH]
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