ALPORT SYNDROME

A 3-in-1 Medical Reference

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

TO INTERNET REFERENCES

ICON Group International, Inc.

Alport Syndrome

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

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

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FORWARD

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

The Editors

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

CHAPTER 1. STUDIES ON ALPORT SYNDROME

Overview

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

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

What Is Alport Syndrome?[3]

Alport syndrome is a genetic condition characterized by the progressive loss of kidney function and hearing. Alport syndrome can also affect the eyes. The presence of blood in the urine (hematuria) is almost always found in this condition. Many people with Alport syndrome also exhibit high levels of protein in their urine (proteinuria). As this condition progresses, the kidneys become less able to function properly and kidney failure results. Hearing loss is a common feature of Alport syndrome, but the abnormalities in the eyes seldom lead to loss of vision.

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

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

How Common Is Alport Syndrome?

The prevalence of Alport syndrome is approximately 1 in 50,000 newborns.

What Genes Are Related to Alport Syndrome?

Mutations in the **COL4A3** (**http://ghr.nlm.nih.gov/gene=col4a3**), **COL4A4** (**http://ghr.nlm.nih.gov/gene=col4a4**), and **COL4A5** (**http://ghr.nlm.nih.gov/gene=col4a5**) genes cause Alport syndrome.

Mutations in the COL4A3, COL4A4, or COL4A5 genes prevent the proper production or assembly of a specific collagen network composed of alpha3, alpha4, and alpha5 chains of type IV collagen. This network plays an important role in the kidney, specifically in structures called glomeruli. Glomeruli are clusters of specialized blood vessels that remove water and waste products from blood and create urine. When mutations prevent the formation of the type IV collagen network, the kidneys are not able to filter waste products from the blood and create urine normally. This defect allows blood and protein to pass into the urine, and leads to gradual scarring of the kidneys and kidney failure in many people with the disease.

This type IV collagen network is also an important component of inner ear structures, particularly the organ of Corti, that receive sound waves and transform them into nerve impulses. Alterations in type IV collagen often result in inner ear abnormalities that lead to hearing loss. In the eye, this network is important for maintaining the shape of the lens and the normal coloration of the retina (the tissue at the back of the eye that detects light and color). Mutations that disrupt type IV collagen can result in misshapen lenses in the eyes (anterior lenticonus) and abnormal coloration of the retina.

How Do People Inherit Alport Syndrome?

Alport syndrome can have different inheritance patterns that are dependent on the genetic mutation.

Most cases of Alport syndrome are inherited in an X-linked pattern and involve mutations in the COL4A5 gene. A condition is considered X-linked if the mutated gene involved in the disorder is located on the X chromosome (one of the two sex chromosomes). In males, who have only one X chromosome, one mutated copy of the COL4A5 gene is sufficient to cause kidney failure and other severe symptoms of the disorder. In females, who have two X chromosomes, a mutation in one copy of the COL4A5 gene usually results in less severe symptoms. A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked diseases to their sons.

Alport syndrome can be inherited in an autosomal recessive pattern if both copies of the COL4A3 or COL4A4 gene, located on chromosome 2, are mutated. Most often, the parents of a child with an autosomal recessive disorder are not affected but are carriers of one copy of the altered gene.

Alport syndrome can also be inherited in an autosomal dominant pattern, which means one copy of the altered gene, either COL4A3 or COL4A4, can be sufficient to cause the disorder.

Where Can I Find Additional Information about Alport Syndrome?

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

NIH Publications - National Institutes of Health

- National Center for Biotechnology Information: Genes and Disease: **http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=gnd.section.263**
- National Institute of Diabetes and Digestive and Kidney Diseases: **http://kidney.niddk.nih.gov/kudiseases/pubs/glomerular/index.htm#alport**

MedlinePlus - Health Information

- Encyclopedia: Alport syndrome: **http://www.nlm.nih.gov/medlineplus/ency/article/000504.htm**
- Health Topic: Kidney Diseases: **http://www.nlm.nih.gov/medlineplus/kidneydiseases.html**
- Health Topic: Kidney Failure: **http://www.nlm.nih.gov/medlineplus/kidneyfailure.html**

Educational Resources - Information Pages

- Madisons Foundation: **http://www.madisonsfoundation.org/content/3/1/display.asp?did=374**
- National Kidney Foundation: **http://www.kidney.org//kidneydisease/fs/showFS.cfm?id=47**
- Orphanet: **http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=63**

Patient Support - for Patients and Families

- American Association of Kidney Patients: **http://www.aakp.org/AAKP/RenalifeArt/2004/alportsyndrome.htm**
- National Organization for Rare Disorders: **http://www.rarediseases.org/search/rdbdetail_abstract.html?disname=Alport%20Syndrome**

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=alport
- Gene Tests - DNA tests ordered by healthcare professionals:
  http://ghr.nlm.nih.gov/condition=alportsyndrome/show/Gene+Tests;jsessionid=395C1D232B14E5DC29E1E54126369A70
- ClinicalTrials.gov - Linking patients to medical research:
  http://clinicaltrials.gov/search/condition=%22alport+syndrome%22?recruiting=false
- PubMed - Recent literature:
  http://ghr.nlm.nih.gov/condition=alportsyndrome/show/PubMed;jsessionid=395C1D232B14E5DC29E1E54126369A70
- Online Books - Medical and science texts:
  http://books.mcgraw-hill.com/getommbid.php?isbn=0071459960&template=ommbid&c=214
- OMIM - Genetic disorder catalog:
  http://ghr.nlm.nih.gov/condition=alportsyndrome/show/OMIM;jsessionid=395C1D232B14E5DC29E1E54126369A70

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

- Ierino FL, Kanellis J. Thin basement membrane nephropathy and renal transplantation. Semin Nephrol. 2005 May;25(3):184-7. Review. PubMed citation
- Jais JP, Knebelmann B, Giatras I, De Marchi M, Rizzoni G, Renieri A, Weber M, Gross O, Netzer KO, Flinter F, Pirson Y, Dahan K, Wieslander J, Persson U, Tryggvason K, Martin P, Hertz JM, Schroder C, Sanak M, Carvalho MF, Saus J, Antignac C, Smeets H, Gubler MC. X-linked Alport syndrome: natural history and genotype-phenotype correlations in girls and women belonging to 195 families: a "European Community Alport Syndrome Concerted Action" study. J Am Soc Nephrol. 2003 Oct;14(10):2603-10. PubMed citation
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- Kashtan CE. Familial hematuria due to type IV collagen mutations: Alport syndrome and thin basement membrane nephropathy. Curr Opin Pediatr. 2004 Apr;16(2):177-81. Review. PubMed citation
- Kashtan CE. Familial hematurias: what we know and what we don't. Pediatr Nephrol. 2005 Aug;20(8):1027-35. Epub 2005 Apr 27. Review. PubMed citation

- Kashtan CE. The nongenetic diagnosis of thin basement membrane nephropathy. Semin Nephrol. 2005 May;25(3):159-62. Review. PubMed citation
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- Pescucci C, Longo I, Bruttini M, Mari F, Renieri A. Type-IV collagen related diseases. J Nephrol. 2003 Mar-Apr;16(2):314-6. Review. PubMed citation
- Wang YY, Rana K, Tonna S, Lin T, Sin L, Savige J. COL4A3 mutations and their clinical consequences in thin basement membrane nephropathy (TBMN). Kidney Int. 2004 Mar;65(3):786-90. PubMed citation
- Zehnder AF, Adams JC, Santi PA, Kristiansen AG, Wacharasindhu C, Mann S, Kalluri R, Gregory MC, Kashtan CE, Merchant SN. Distribution of type IV collagen in the cochlea in Alport syndrome. Arch Otolaryngol Head Neck Surg. 2005 Nov;131(11):1007-13. PubMed citation

A summary of the genes related to Alport syndrome is provided below:

What Is the Official Name of the COL4A3 Gene?[4]

The official name of this gene is "collagen, type IV, alpha 3 (Goodpasture antigen)."

COL4A3 is the gene's official symbol. The COL4A3 gene is also known by other names, listed below.

What Is the Normal Function of the COL4A3 Gene?

The COL4A3 gene carries the instructions for making one component of type IV collagen, which is a flexible protein that forms complex networks. Specifically, this gene makes the alpha3(IV) chain of type IV collagen. This chain combines with two other types of alpha (IV) chains (the alpha4 and alpha5 chains) to make a complete collagen molecule. Type IV collagen networks make up a large portion of basement membranes, which are thin sheet-like structures that separate and support cells in many tissues. This specific type IV collagen network plays an especially important role in the basement membranes of the kidney, inner ear, and eye.

What Conditions Are Related to the COL4A3 Gene?

Alport Syndrome - Caused by Mutations in the COL4A3 Gene

The autosomal recessive form of Alport syndrome results when two copies of the COL4A3 gene in each cell are mutated. Most of the mutations identified in this gene cause a change in the sequence of amino acids (the building blocks of proteins) in a region of the alpha3(IV)

[4] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/gene=col4a3;jsessionid=395C1D232B14E5DC29E1E54126369A70**.

collagen chain that is critical for combining with other type IV collagen chains. Other mutations severely decrease or prevent the production of any alpha3(IV) chains in the basement membranes of the kidney, inner ear and eye. In the kidney, other types of collagen accumulate in the basement membranes, eventually leading to scarring of the kidneys and kidney failure. Mutations in this gene can also lead to abnormal function in the inner ear, resulting in hearing loss.

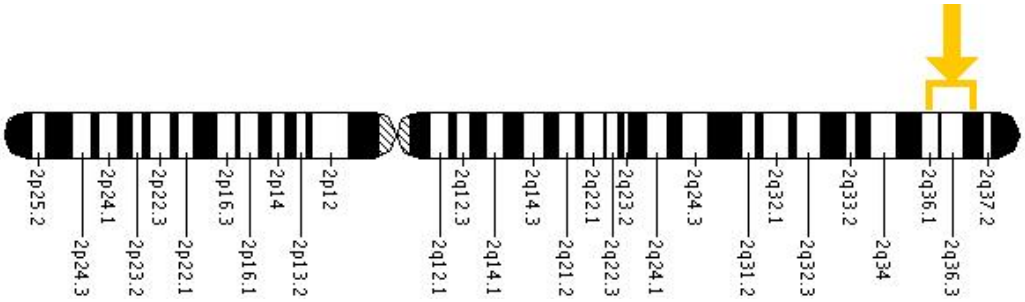
Other Disorders - Associated with the COL4A3 Gene

The autosomal recessive form of Alport syndrome results when two copies of the COL4A3 gene in each cell are mutated. Most of the mutations identified in this gene cause a change in the sequence of amino acids (the building blocks of proteins) in a region of the alpha3(IV) collagen chain that is critical for combining with other type IV collagen chains. Other mutations severely decrease or prevent the production of any alpha3(IV) chains in the basement membranes of the kidney, inner ear and eye. In the kidney, other types of collagen accumulate in the basement membranes, eventually leading to scarring of the kidneys and kidney failure. Mutations in this gene can also lead to abnormal function in the inner ear, resulting in hearing loss.

Where Is the COL4A3 Gene Located?

Cytogenetic Location: 2q36-q37

Molecular Location on chromosome 2: base pairs 227,737,524 to 227,887,750



The COL4A3 gene is located on the long (q) arm of chromosome 2 between positions 36 and 37.

More precisely, the COL4A3 gene is located from base pair 227,737,524 to base pair 227,887,750 on chromosome 2.

References

These sources were used to develop the Genetics Home Reference gene summary on the COL4A3 gene.

- Entrez Gene

- Frasca GM, Onetti-Muda A, Mari F, Longo I, Scala E, Pescucci C, Roccatello D, Alpa M, Coppo R, Li Volti G, Feriozzi S, Bergesio F, Schena FP, Renieri A; Italian Renal Immunopathology Group. Thin glomerular basement membrane disease: clinical significance of a morphological diagnosis--a collaborative study of the Italian Renal Immunopathology Group. Nephrol Dial Transplant. 2005 Mar;20(3):545-51. Epub 2004 Dec 23. PubMed citation
- Gregory MC. The clinical features of thin basement membrane nephropathy. Semin Nephrol. 2005 May;25(3):140-5. Review. PubMed citation
- Kashtan CE. Alport syndrome. An inherited disorder of renal, ocular, and cochlear basement membranes. Medicine (Baltimore). 1999 Sep;78(5):338-60. Review. PubMed citation
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- Tazon Vega B, Badenas C, Ars E, Lens X, Mila M, Darnell A, Torra R. Autosomal recessive Alport's syndrome and benign familial hematuria are collagen type IV diseases. Am J Kidney Dis. 2003 Nov;42(5):952-9. PubMed citation
- Wang YY, Rana K, Tonna S, Lin T, Sin L, Savige J. COL4A3 mutations and their clinical consequences in thin basement membrane nephropathy (TBMN). Kidney Int. 2004 Mar;65(3):786-90. PubMed citation

What Is the Official Name of the COL4A4 Gene?[5]

The official name of this gene is "collagen, type IV, alpha 4."

COL4A4 is the gene's official symbol. The COL4A4 gene is also known by other names, listed below.

What Is the Normal Function of the COL4A4 Gene?

The COL4A4 gene carries the instructions for making one component of type IV collagen, which is a flexible protein that forms complex networks. Specifically, this gene makes the alpha4(IV) chain of type IV collagen. This chain combines with two other types of alpha (IV) chains (the alpha3 and alpha5 chains) to make a complete collagen molecule. Type IV collagen networks make up a large portion of basement membranes, which are thin sheet-like structures that separate and support cells in many tissues. This type IV collagen

[5] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/gene=col4a4**.

network plays an especially important role in the basement membranes of the kidney, inner ear, and eye.

What Conditions Are Related to the COL4A4 Gene?

Alport Syndrome - Caused by Mutations in the COL4A4 Gene

The autosomal recessive form of Alport syndrome occurs when two copies of the COL4A4 gene in each cell are altered. Most COL4A4 mutations cause a change in the sequence of amino acids (the building blocks of proteins) in a region of the alpha4(IV) collagen chain that is critical for combining with other type IV collagen chains. Other mutations severely decrease or prevent the production of any alpha4(IV) chains in the basement membranes of the kidney, inner ear and eye. In the kidney, other types of collagen accumulate in the basement membranes, eventually leading to scarring of the kidneys and kidney failure. Mutations in this gene can also lead to abnormal function in the inner ear, resulting in hearing loss.

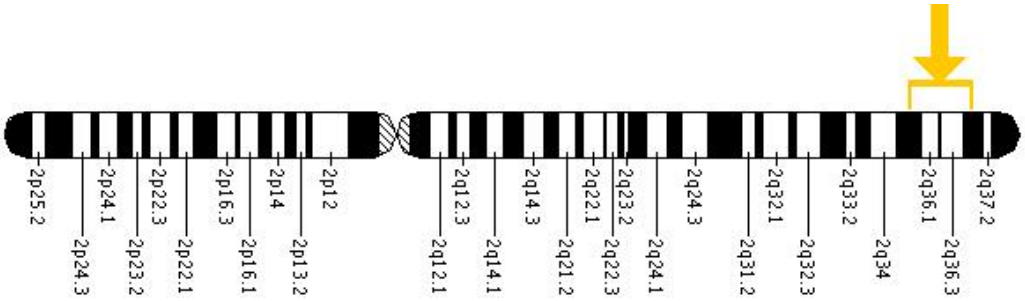
Other Disorders - Caused by Mutations in the COL4A4 Gene

The autosomal recessive form of Alport syndrome occurs when two copies of the COL4A4 gene in each cell are altered. Most COL4A4 mutations cause a change in the sequence of amino acids (the building blocks of proteins) in a region of the alpha4(IV) collagen chain that is critical for combining with other type IV collagen chains. Other mutations severely decrease or prevent the production of any alpha4(IV) chains in the basement membranes of the kidney, inner ear and eye. In the kidney, other types of collagen accumulate in the basement membranes, eventually leading to scarring of the kidneys and kidney failure. Mutations in this gene can also lead to abnormal function in the inner ear, resulting in hearing loss.

Where Is the COL4A4 Gene Located?

Cytogenetic Location: 2q35-q37

Molecular Location on chromosome 2: base pairs 227,578,167 to 227,737,518



The COL4A4 gene is located on the long (q) arm of chromosome 2 between positions 35 and 37.

More precisely, the COL4A4 gene is located from base pair 227,578,167 to base pair 227,737,518 on chromosome 2.

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These sources were used to develop the Genetics Home Reference gene summary on the COL4A4 gene.

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- Gregory MC. The clinical features of thin basement membrane nephropathy. Semin Nephrol. 2005 May;25(3):140-5. Review. PubMed citation
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- OMIM: COL4A4
- Pescucci C, Mari F, Longo I, Vogiatzi P, Caselli R, Scala E, Abaterusso C, Gusmano R, Seri M, Miglietti N, Bresin E, Renieri A. Autosomal-dominant Alport syndrome: natural history of a disease due to COL4A3 or COL4A4 gene. Kidney Int. 2004 May;65(5):1598-603. PubMed citation
- Rana K, Wang YY, Buzza M, Tonna S, Zhang KW, Lin T, Sin L, Padavarat S, Savige J. The genetics of thin basement membrane nephropathy. Semin Nephrol. 2005 May;25(3):163-70. Review. PubMed citation
- Tazon Vega B, Badenas C, Ars E, Lens X, Mila M, Darnell A, Torra R. Autosomal recessive Alport's syndrome and benign familial hematuria are collagen type IV diseases. Am J Kidney Dis. 2003 Nov;42(5):952-9. PubMed citation

What Is the Official Name of the COL4A5 Gene?[6]

The official name of this gene is "collagen, type IV, alpha 5 (Alport syndrome)."

[6] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/gene=col4a5;jsessionid=395C1D232B14E5DC29E1E54126369A70**.

COL4A5 is the gene's official symbol. The COL4A5 gene is also known by other names, listed below.

What Is the Normal Function of the COL4A5 Gene?

The COL4A5 gene carries the instructions for making one component of type IV collagen, which is a flexible protein that forms complex networks. Specifically, this gene makes the alpha5(IV) chain of type IV collagen. This chain combines with two other types of alpha (IV) chains (the alpha3 and alpha4 chains) to make a complete collagen molecule. Type IV collagen networks make up a large portion of basement membranes, which are thin sheet-like structures that separate and support cells in many tissues. This type IV collagen network plays an especially important role in the basement membranes of the kidney, inner ear, and eye.

What Conditions Are Related to the COL4A5 Gene?

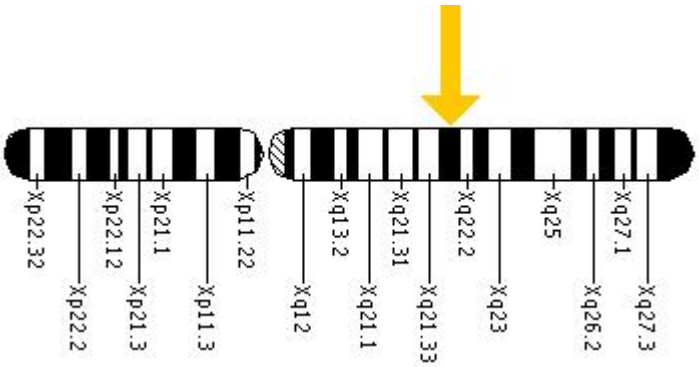
Alport Syndrome - Caused by Mutations in the COL4A5 Gene

Mutations in the COL4A5 gene cause approximately 80 percent of Alport syndrome cases. Several hundred different mutations have been identified, the majority of which cause a change in the sequence of amino acids (the building blocks of proteins) in a region of the alpha5(IV) collagen chain that is critical for combining with other type IV collagen chains. Other mutations severely decrease or prevent the production of the alpha5(IV) chains. As a result, there is a serious deficiency of the type IV collagen network in the basement membranes of the kidney, inner ear, and eye. In the kidney, other types of collagen accumulate in the basement membranes, eventually leading to scarring of the kidneys and kidney failure. Mutations in this gene can also lead to abnormal function in the inner ear, resulting in hearing loss.

Where Is the COL4A5 Gene Located?

Cytogenetic Location: Xq22

Molecular Location on the X chromosome: base pairs 107,569,809 to 107,827,430



The COL4A5 gene is located on the long (q) arm of the X chromosome at position 22.

More precisely, the COL4A5 gene is located from base pair 107,569,809 to base pair 107,827,430 on the X chromosome.

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These sources were used to develop the Genetics Home Reference gene summary on the COL4A5 gene.

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Federally Funded Research on Alport Syndrome

The U.S. Government supports a variety of research studies relating to Alport syndrome. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[7]

[7] 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).

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

- **Project Title: ASSEMBLY OF TYPE IV COLLAGEN IN HEALTH AND DISEASE**

  Principal Investigator & Institution: Kalluri, Raghu; Associate Professor of Medicine; Beth Israel Deaconess Medical Center 330 Brookline Avenue, Br 264 Boston, Ma 02215

  Timing: Fiscal Year 2005; Project Start 15-AUG-1999; Project End 31-JAN-2010

  Summary: (provided by applicant): Type IV collagen is the most abundant protein present in the glomerular basement membrane of the kidney. The basic unit of type IV collagen is a triple helical protomer derived from three a-chains. With six known isoforms of type IV collagen (alpha1-alpha6), 56 theoretical combinations of protomers are possible. Emerging data however, suggests a tissue specific preference for certain protomers. Type IV collagen in the glomerular basement membrane (GBM) is predominantly composed of alpha3, alpha4 and alpha5 isoforms of type IV collagen, with alpha3 chain of type IV collagen being most abundant. Mutations in any one of these isoforms in **Alport syndrome** (a condition associated with progressive kidney disease, occasional hearing loss and eye defects) leads to an absence of all three isoforms from the GBM of these patients, suggesting a molecular association between the three isoforms in the kidney GBM. While in the past five years, biochemical and cell biological experiments have provided further causal support for such protein-protein interactions, molecular drivers that determine specific type IV collagen protomer assembly are still unknown. During the first funding period of this grant application, using human Alport kidneys and kidneys from mice with alpha3(IV) collagen deletion, the relationship between the structure of GBM type IV collagen and its susceptibility of degradation in **Alport syndrome,** was established. Specific type IV collagen isoforms targets for post-transplant alloantibody response in Alport patients were determined in a multi-center study. Further, genetic and biochemical studies with type IV collagen NC1 domains revealed novel insights into the assembly and organization of type IV collagen in the GBM and elsewhere. Collectively, these studies provide evidence that premature turnover of GBM involving altered composition of type IV collagen may contribute to the early pathogenesis of **Alport syndrome.** In this renewal application, we now propose to continue our studies to understand the molecular drivers that determine specific assembly of type IV collagen involving the a3 chain in the GBM, and analyze the impact of disease-associated a3 (IV) NC1 domain mutations on the GBM composition, turnover, and assembly. We will generate gene-targeted mice to probe the contribution of GBM instability for the initiation of progressive renal failure associated with **Alport Syndrome.** We expect this grant application to provide basic understanding of the assembly and function of type IV collagen in the GBM.

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

- **Project Title: DEVELOPMENT OF THE MOUSE COCHLEA DATABASE**

  Principal Investigator & Institution: Santi, Peter A.; Professor; Otolaryngology; University of Minnesota Twin Cities 450 Mcnamara Alumni Center Minneapolis, Mn 554552070

  Timing: Fiscal Year 2007; Project Start 05-DEC-2006; Project End 30-NOV-2010

  Summary: (provided by applicant): Among the five senses, hearing is fundamental for acquiring language, communication, and navigating through our environment. An estimated 28 million Americans are deaf or hearing impaired due to genetic factors, sound-induced trauma, aging or presbycusis, ototoxicity, and viral or bacterial infections. In order to investigate mechanisms involved in hearing dysfunction, and to develop new treatments and therapies for hearing dysfunction, the mouse is rapidly becoming the preferred experimental animal model. However, the anatomy and function of its cochlea has not been well characterized. Thus, the overall goal of this project is to improve our understanding of hearing by facilitating collaboration and multidisciplinary research on the mouse inner ear. Development of the Mouse Cochlea Database (MCD) will provide a web-based repository of comprehensive image and morphometric data on the mouse cochlea and custom-designed software tools to analyze these images. The overall hypothesis of this research is that development of the MCD will provide a new paradigm for learning and performing anatomical research on the cochlea in normal and certain hearing-impaired animals. Five integrated specific aims are proposed. Aim 1 will image cochleas using thin- sheet laser imaging and celloidin sectioning from three strains of mice (CBA/J, C57BL/6, and C57BL/6 COL 4A5). Aim 2 will develop multi-scale, multi-modal, and annotated 2D and 3D anatomical atlases of the cochlea in these mouse strains. Aim 3 will develop a 3D coordinate system of the cochlea in order to generate virtual orthogonal cross sections of the scala media that are morphometrically analyzable. These cross-sections will be produced relative to the basilar membrane and mapped to the frequency/place map of the mouse cochlea. Aim 4 will morphometrically analyze cochlear tissues in the virtual, orthogonal cross sections of the scala media in order to provide normative data and quantitative assessments of cochlear pathologies in age-related, hearing impaired mice, and in an X-linked mouse model of **Alport syndrome.** Aim 5 will distribute data generated from experiments of the previous specific aims and provide online and offline software tools to morphometrically analyze cochlear tissues. Data will be web-based and available as images, searchable database files, movies, QuickTime VR, Acrobat 3D, stereolithography files for rapid prototyping, and stereoscopic files for VMRL displays. Development of the MCD will provide students and investigators with valuable anatomical resources of the cochlea in normal and of certain hearing impaired mice, and it will assist the research community face the challenges posed by the rapid growth in the amount and type of data on the mouse cochlea.

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

- **Project Title: GENE TRANSFER THERAPY FOR ALPORT SYNDROME**

  Principal Investigator & Institution: Lees, George E.; Small Animal Clinical Sciences (Sacs); Texas A&M University System 3578 Tamu College Station, Tx 778433578

  Timing: Fiscal Year 2004; Project Start 01-MAY-2003; Project End 29-FEB-2008

  Summary: (provided by applicant): The long-range goal of this proposal is development of gene transfer therapy for human **Alport syndrome,** a genetic renal disease for which kidney transplantation currently is the only treatment. The disease results from mutations in genes for type IV collagen, which is an integral component of tissue

structures known as basement membranes. Abnormalities leading to renal failure are initiated by deterioration of the glomerular basement membrane (GBM) that occurs because of an absence of normal type IV collagen in the GBM. The central hypothesis of this proposal is that the normal type IV collagen composition of the GBM can be adequately restored by transferring a correct copy of the defective gone into the glomerular cells that synthesize GBM proteins, thus stabilizing GBM structure and slowing or stopping progression of Alport renal disease. In X-linked **Alport syndrome,** the gene (COL4A5) that encodes the a5 chain of type IV collagen is mutated. The objective of this application is to use a new method of achieving gene transfer into glomerular cells to treat dogs with X-linked Aiport syndrome (XLAS). Specific aims of the proposal are to: (1) use a virus vector delivered by an open surgical technique for closed-circuit renal perfusion that successfully transferred a cDNA encoding c_5type IV collagen into the glomeruli of normal pigs to treat dogs with XLAS, (2) construct new viral vectors containing full-length COL4A5 cDNAs that will enable stable transgene expression for up to one year, (3) develop minimally invasive methods for performing closed circuit perfusion of the kidney using trans-vascular catheterization techniques to permit repeated treatment of individual subjects, and (4) perform randomized trials of gene transfer therapy for XLAS in dogs. Effects of transgenic E5(IV) chain expression on the molecular, structural and functional properties of Alport GBM and on the clinical course of Alport renal disease will be determined. The mild renal disease phenotype manifested in female heterozygotes with XLAS suggests that even achieving mosaic expression of normal _5(IV) chains in male hemizygotes will produce a clinically satisfactory treatment result. Because canine XLAS is an animal model of human **Alport syndrome,** successful gene transfer therapy for XLAS in dogs will provide a basis for trials of such treatment for **Alport syndrome** in people. It will also lay the foundation for gene transfer therapy of other glomerular iseases.

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

- **Project Title: GLOMERULAR PERMSELECTIVITY IN ALPORT SYNDROME**

  Principal Investigator & Institution: Kashtan, Clifford E.; Professor; Pediatrics; University of Minnesota Twin Cities 450 Mcnamara Alumni Center Minneapolis, Mn 554552070

  Timing: Fiscal Year 2004; Project Start 15-MAY-2000; Project End 31-MAR-2006

  Summary: (Adapted from the Applicant's Abstract): **Alport syndrome** is a genetic kidney disease that results from mutations in type IV collagen, an integral component of tissue structures known as basement membranes. These mutations result in defects in type IV collagen in the glomerular basement membrane (GBM), a structure that plays a critical role in preventing the leakage of blood proteins into the urine. Proteinuria (the leakage of proteins into the urine) is an important feature of **Alport syndrome.** The goals of this proposal are (1) to understand how proteinuria develops in **Alport syndrome** and (2) to test whether cyclosporine can reduce protienuria and prevent renal failure in **Alport syndrome.** Kidney disease that is indistinguishable genetically, biochemically and pathologically from **Alport syndrome** occurs spontaneously in dogs. We propose to perform three sets of studies on these dogs. (1) We will obtain glomeruli from affected dogs and their normal littermates by serial kidney biopsies, and we will compare the permeability of affected and normal glomeruli to protein. Our hypothesis is that glomerular permeability to protein is normal early in the course of **Alport syndrome,** but increases as certain collagens accumulate abnormally in the GBM. (2) We will isolate GBM from affected and normal glomeruli to test whether the abnormal composition of the Alport GBM interferes with the ability of glomerular epithelial cells (GEC) to attach

to it. GEC also play a role in preventing protein leakage into the urine. Our hypothesis is that GEC do not attach normally to Alport GBM, and that abnormal attachment is associated with proteinuria, and results in changes in the activity of certain genes in these cells (3) There is currently no treatment for Alport kidney disease, other than renal transplantation. A recent report described suppression of proteinuria and stabilization of renal function in Alport patients by long-term treatment with cyclosporine. This study was uncontrolled and included only 8 patients. In addition, cyclosporine itself can cause kidney damage. For these reasons we propose to conduct a controlled trial of cyclosporine therapy in dogs with **Alport syndrome.** This trial will compare urinary protein levels, kidney function, and renal structural changes in treated and untreated dogs.

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

- **Project Title: GORDON RESEARCH CONFERENCE ON BASEMENT MEMBRANES**

  Principal Investigator & Institution: Kramer, James M.; Professor; Gordon Research Conferences West Kingston, Ri 02892

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

  Summary: (provided by applicant): This application requests partial funding for the support of invited speakers for the 2004 Gordon Conference on Basement Membranes. This is the twelfth in a highly successful series of conferences which are a major international forum for dissemination of new ideas and information about the structures and functions of basement membranes (BMs). These are complex, three-dimensional, extracellular structures formed at epithelial-mesenchymal interfaces and around mesenchymal cells, with important roles in the organization and function of most tissues and organs, e.g., muscle, skin, blood vessels, heart, lung, kidney, and peripheral nerves. For example, basement membranes regulate the migration and organization of ceils in the musculoskeletal system, as well as axons and synapses in the nervous system. Mutations in genes encoding basement membrane components result in severe inherited disorders in humans (e.g. epidermolysis bullosa of skin, congenital muscular dystrophies with associated neural defects, **Alport syndrome** of kidney). Acquired defects in basement membranes also contribute to the pathogenesis of diabetic microvascular disease and serve as entry sites for infectious agents, such as leprosy, and for metastatic cancer cells. Traditionally, the conference has attracted scientists from a wide range of fields in basic research, including protein and carbohydrate structure, gene expression, cell and developmental biology, and neurobiology. In addition, it has been attended by clinicians and scientists involved in research and/or treatment of human disorders involving BM components of lung, blood vessels, skin, kidney, bone, muscle and immune systems. Basic studies of BM degradation and turnover are also of interest to scientists investigating dynamic processes such as angiogenesis, cancer metastasis, embryo implantation, and involution of the mammary gland and uterus. There has been substantial interest from clinicians and scientists in the pharmaceutical and biotechnology industries studying the roles of BMs in wound healing, angiogenesis, nerve regeneration, inflammation, and tissue repair. The Conference will present a diverse mixture of sessions on the basic science of basement membrane and extracellular matrix (ECM) structure, biosynthesis, assembly, turnover, and functions. Comparative studies of BM function in vertebrates and invertebrates, and the roles of BM and ECM in embryonic development and embryonic stem cells will be included. In addition, emphasis will be given to studies on the genetic analyses of BM and ECM functions, and the generation of animal models of human BM disorders.

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

- **Project Title: MATRIX OTOPATHOLOGY**

  Principal Investigator & Institution: Gratton, Michaelanne; Otorhinolaryngology Head & Neck Surgery; University of Pennsylvania Office of Research Services Philadelphia, Pa 19104

  Timing: Fiscal Year 2004; Project Start 01-JAN-2004; Project End 31-DEC-2006

  Summary: (provided by applicant): Basement membrane is a unique type of extracellular matrix that underlies the specialized epithelial and supporting cells of the scala media and surrounds endothelial cells and neurons. During cochlea/development, basement membranes play a critical role in cell migration and differentiation. However, the role of cochlear basement membranes post-development has not been studied. In other mature tissues, basement membranes are involved in cell adhesion and polarization as well as tissue permeability. Basement membrane formation requires assembly of a type IV collagen lattice. Other basement membrane proteins bind to the collagen lattice. A mutation in a gene encoding a type IV collagen isoform results in **Alport syndrome,** a disorder exhibiting progressive dysfunction of the auditory, visual and renal systems. The mouse model of **Alport syndrome** exhibits thickened strial capillary basement membranes. The Alport mouse is exploited to achieve the overall goal of this proposal, namely an understanding of basement membrane function in the adult cochlea. Specifically we focus on the impact of matrix thickness followed by investigation of the mechanisms controlling matrix accumulation. Experiments are designed to test three general hypotheses: 1) Strial energy metabolism is reduced in matrix otopathology. The consequences of depleted strial energy production following noise exposure are explored by characterizing electrochemical and transport properties of the stria. 2) The anionic barrier provided by basement membrane proteoglycans is increased by matrix otopathology. The proteoglycan composition of the lateral wall basement membranes is quantified with cationic probes. 3) Matrix accumulates when upregulation of synthesis exceeds degradation in collagen and laminin. Changes in the expression of genes and proteins controlling basement membrane synthesis and degradation are quantified. The proposed work clarifies the relationship of basement membrane to strial function and normal hearing.

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

- **Project Title: MOLECULAR ASPECTS OF ALPORT RENAL DISEASE PROGRESSION**

  Principal Investigator & Institution: Cosgrove, Dominic E.; Staff Scientist Iii & Associate Professo; Father Flanagan's Boys' Home Boys Town, Ne 68010

  Timing: Fiscal Year 2005; Project Start 15-APR-1999; Project End 31-MAY-2009

  Summary: Alport syndrome is a relatively common (1 in 5000) genetic disorder that results in progressive renal disease with hearing loss and retinal flecks. In the past decade, the genes responsible for the syndrome have been identified, and significant progress has been made towards understanding the molecular mechanisms underlying the progressive glomerular and tubulointerstitial disease. This proposal is a focused approach aimed at defining specific aspects that may contribute towards mechanisms underlying glomerular pathogenesis. In the preliminary results section we present evidence that MMP-2, MMP-9, MMP-12 (metalloelastase) and MMP-14 (MT1-MMP) may contribute to glomerular pathogenesis in distinct ways. The role of MMPs in glomerular pathogenesis has been only marginally explored. We suggest dual contributory roles where elevated MMP-2 and MT-1 MMP are protective, while metalloelastase plays a destructive role. Real time PCR analysis of RNA from isolated

glomerular preparations will be used for in situ hybridization and immunofluorescence studies to identify the temporal and spatial regulation of these MMPs in glomerular cells in vivo. Cell culture studies will be employed to probe the mechanism underlying elevated MMP expression in mouse model systems. Double and triple knockout mouse models will be used in an attempt to functionally define the roles of these MMPs in Alport glomerular pathogenesis. In the third aim we explore the mechanism of MMP dysregulation in Alport and integrin alpha1-null Alport mice. We provide evidence that the MAP kinase-signaling pathway is activated in integrin alpha1-null mice. This signaling pathway has been linked to MMP dysregulation in other systems. We will employ specific inhibitors of pp38 and pERK as well as integrin-specific neutralizing antibodies to dissect the role of integrins and MAP kinase activation in MMP dysregulation in glomeruli from integrin a1-null Alport mice. In the preliminary results, we show MMP-12 inhibition arrests the progression of renal disease in Alport mice. We have identified markedly elevated expression of GM-CSF and MCP- 1 in Alport glomeruli, cytokines known to induce expression of MMP-12 in other systems. We show that the receptors for these cytokines (alpha-GMR and CCR2, respectively) are expressed both in Alport glomeruli and on cultured glomerular podocytes. We will employ in vivo and cell culture systems to determine whether this pathway underlies MMP-12 activation in Alport glomeruli. These studies will likely form the basis for related studies in other renal disease models where these same systems have been implicated.

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

- **Project Title: ROLE OF A3A4A5(IV) COLLAGEN IN PODOCYTE BEHAVIOR**

  Principal Investigator & Institution: Borza, Corina M.; Medicine; Vanderbilt University Medical Center Nashville, Tn 372036869

  Timing: Fiscal Year 2004; Project Start 11-SEP-2003; Project End 10-SEP-2006

  Summary: (provided by applicant): Podocytes, endothelial cells, and the glomerular basement membrane (GBM) are the key components of the glomerular filtration barrier. The long term goal of this project is to understand how the composition of collagen IV in the GBM influences the behavior of podocytes (glomerular epithelial cells). Type IV collagen is expressed as an a1a1a2(IV) network in the immature GBM but is replaced by the a3a4a5(IV) network in the mature GBM. Failure to switch to the mature network due to mutations in any of the a3, a4 or a5 chains leads to **Alport syndrome** in humans and Alport-like phenotype in mouse and dog models of the disease. The mechanism whereby the a3a4a5(IV) collagen is required for the long term maintenance of the renal glomerular function is not known. We hypothesize that type IV collagen of the GBM, synthesized by podocytes, in turn provides signals to podocytes through integrins or other cellular receptors, which are required to maintain the appropriate podocyte function. To test this hypothesis, we will pursue two specific aims: (1) to express, isolate, and characterize the a3a4a5(IV) collagen in vitro; and (2) To define the influence of the a3a4a5(IV) collagen on the podocytes phenotype, including comparison of podocytes adhesion and migration on a3a4a5(IV) vs. a1a1a2(IV) collagen, identification of the podocyte integrins interacting with a3a4a5(IV) collagen, and identification of collagen IV domains that interact with podocytes. The successful completion of this project would help improve our understanding of the molecular defects in **Alport syndrome,** while broadening the applicant's research expertise and preparing her for the transition to an independent investigator status.

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

- **Project Title: STRUCTURE-FUNCTION OF TYPE IV COLLAGEN NC1 DOMAINS**

  Principal Investigator & Institution: Sundaramoorthy, Munirathinam; Medicine; Vanderbilt University Medical Center Nashville, Tn 372036869

  Timing: Fiscal Year 2004; Project Start 01-MAY-2002; Project End 31-JAN-2007

  Summary: (provided by applicant): The structure of glomerular basement membrane (GBM) is altered in three notable diseases that affect the kidneys: Goodpasture syndrome (anti-GBM nephritis), **Alport syndrome** (hereditary nephritis), and diabetes mellitus. At least two of them, Goodpasture and Alport syndromes, have been linked to type IV collagen, a major constituent of GBM. Type IV collagen is a family of six alpha chains, alpha1-alpha6, found in various basement membranes (BMs). Three alpha chains form a collagen triple helical protomer and each chain contains a noncollagenous (NC1) globular domain at the C-terminus. The chain stoichiometry of the protomer varies with the origin of the tissue, (alpha1)2.alpha2 being the ubiquitous form and alpha3.alpha4.alpha5 being specific to glomeruli and alveoli. Two triple helical protomers associate at the NC1 region to form tail-to-tail dimer. The NC1 domains are presumed to contain the structural determinants for both triple helix formation and hexamer assembly. The alpha3 NC1 domain harbors the epitope for autoantibodies in patients with Goodpasture syndrome. Mutations in the genes encoding any of the three alpha chains result in the loss of alpha3.alpha4.alpha5 network in the GBM, which is the cause of **Alport syndrome.** Recombinant alpha2, alpha3, and alpha6 NC1 domains show anti-angiogenic and anti-tumor properties. In this study, we propose the following specific aims to determine the structure-function relationships of NC1 domains: Aim 1: To determine the first crystal structure of a NC1 hexamer, ((alpha1)2.alpha2)2 Aim 2: To crystallize and determine the structure of GBM NC1 hexamer, (alpha3.alpha4.alpha5)2 Aim 3: To determine the structure of the Goodpasture antigen, alpha3 NC1 monomer Aim 4: To solve the structures of alpha2 and alpha6 monomers, the angiogenic inhibitors. The accomplishment of these aims requires the application of macromolecular crystallography, computational biology, protein chemistry and molecular biology.

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

- **Project Title: STUDIES ON THE STRUCTURE OF BASEMENT MEMBRANES**

  Principal Investigator & Institution: Hudson, Billy G.; Chairman; Medicine; Vanderbilt University Medical Center Nashville, Tn 372036869

  Timing: Fiscal Year 2004; Project Start 01-SEP-1986; Project End 31-AUG-2005

  Summary: (Verbatim from Investigator's Abstract): Renal disease is a major health problem in the world. Prominent causes are diabetes, hypertension and various forms of glomerular disease, such as Goodpasture syndrome and **Alport syndrome.** These affect the glomerular filtration barrier and lead to end stage renal disease. Goodpasture syndrome, **Alport syndrome,** and diabetic nephropathy directly affect the glomerular basement membrane(GBM), a major component of the filtration barrier. The quest for the molecular bases of these GBM abnormalities had led to the discovery of six alpha(IV) chains (alpha 1-alpha 6) of type IV collagen. These are distributed in distinct networks about the basement membranes and mesangiel matrix of glomerulus. The GBM network formed by alpha 3, alpha 4 and alpha 5 chains is involved in the pathogenesis of Goodpasture and Alport syndromes. In this renewal application, five specific aims are proposed that address structure/function relationships of human type IV collagen and its role in Goodpasture syndrome and **Alport syndrome.** The central research strategy is to express full length alpha(IV) chains and NC1 domains and chimeras in eukaryotic

cells for elucidation of :1) structure and assembly mechanisms of human type IV collagen networks; 2) pathogenic mechanisms of how mutations in alpha5(IV)) chain cause defective assembly in **Alport syndrome;** and 3) location and pathogenicity of the epitopes for Goodpasture autoantibodies. The specific aims are: 1. To express and characterize full-length triple-helical protomers comprised of alpha3, alpha 4, and alpha5 (IV) collagen chains. 2. To identify the molecular recognition sequences of NC1 domain that confer chain specificity of network assembly 3. To determine how mutations in alpha5(IV) chain cause defective assembly of alpha3, alpha4 and alpha5 network in **Alport syndrome.** 4. To elucidate the structural basis by which GP epitopes are inaccessible to antibodies (cryptic) in the NC1 hexamer. 5. To identify the pathogenic epitopes of the alpha3(IV) NC1 domain in the rat model of Goodpasture syndrome. The achievement of these aims requires the application of techniques in molecular biology, protein engineering and physical biochemistry. These techniques include construction of cDNA expression vectors, expression of proteins in cell culture, protein fractionations, and physical characterization of proteins by techniques such as Fourier-transform infrared spectroscopy, circular dichroism spectroscopy, analytical ultra-centrifugation, and electron microscopy.

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

- **Project Title: THE ROLE OF DENDRITIC CELLS IN RENAL IMMUNE RESPONSES**

  Principal Investigator & Institution: Griffin, Matthew D.; Associate Professor of Medicine; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2004; Project Start 01-SEP-2004; Project End 30-JUN-2008

  Summary: (provided by applicant): Infiltration of the renal parenchyma by inflammatory cells, including lymphocytes, is a common feature of kidney diseases even in the apparent absence of exogenous immune stimuli. The mechanisms underlying T-lymphocyte activation in kidney disease are poorly understood, as are the mechanisms that prevent immune activation in the healthy kidney. This experimental protocol will examine the dynamic behavior, responses, and functions of Dendritic cells (DCs) -a migratory population of cells with specialized function in antigen uptake and presentation - within the kidney and its draining lymphoid tissue during health and explore their role in different forms of renal injury. All organs, including the kidney, have a resident population of DCs although the density, distribution and turnover vary. DC "maturation" is induced by the inflammatory products of disease or injury. Mature DCs migrate from an organ to its draining lymph node where they activate T-cells to initiate cellular immune responses. In the absence of maturing stimuli, DCs may also transfer antigens to lymphoid tissue in order to activate regulatory mechanisms that prevent autoimmunity. Modulation of DC-T-cell interactions is recognized as an important therapeutic target for the prevention/treatment of immune-mediated disease. The primary hypotheses of the proposal are that: (a) trafficking of protein antigens from the kidney to the draining Iymph nodes occurs during health and actively maintains immune tolerance to renal tissue, and (b) alterations in renal DC phenotype and turnover result from diverse forms of kidney injury and contribute significantly to inflammatory renal parenchvmal damage. The experimental strategy will focus strongly on the use of in vivo techniques that directly examine DC-mediated antigen trafficking and presentation in the kidney and renal lymph nodes of mice. The first Specific Aim, to determine the biology of renal DCs during health, will employ in vivo BrdU-labeling to determine DC turnover, congenic bone marrow transfer to examine the precursor origins of renal DCs, unilateral inoculation of fluorescent particles or proteins into the kidney to track renal DC-mediated antigen trafficking, generation of transgenic mice

expressing a kidney-restricted neo-antigen, and adoptive transfer of antigen-specific TCR transgenic T-cells. The second Specific Aim, to determine the role of renal DCs in the pathophysiology of diverse form of renal injury, will apply these same in vivo experimental strategies to animals subjected to one of the following four types of renal injury: (a) ischemia, (b) urinary obstruction, (c) acute glomerulonephritis, (d) genetically-based collagen deficiency (a model of Alport's nephritis). In these experiments, the disease-associated alterations to renal DC turnover, surface phenotype, and antigen trafficking as well as antigen-specific T-cell activation within the draining lymph nodes, and infiltration of the renal parenchyma by activated T-cells will be characterized. For both Specific Aims, observational studies will be followed by mechanistic studies involving blockade of specific molecular pathways, depletion of regulatory cell populations, and cross-breeding to genetically modified strains. Analytic tools will include flow cytometry, immunohistochemistry, immunofluorescence microscopy, morphometric analysis, cytokine/chemokine ELISA.

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

The National Library of Medicine: PubMed

One of the quickest and most comprehensive ways to find academic studies in both English and other languages is to use PubMed, maintained by the National Library of Medicine.[8] The advantage of PubMed over previously mentioned sources is that it covers a greater number of domestic and foreign references. It is also free to use. If the publisher has a Web site that offers full text of its journals, PubMed will provide links to that site, as well as to sites offering other related data. User registration, a subscription fee, or some other type of fee may be required to access the full text of articles in some journals.

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

- **3rd International Workshop on Alport syndrome.**
  Author(s): Flinter F.
  Source: Pediatric Nephrology (Berlin, Germany).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7696125&query_hl=21&itool=pubmed_docsum

- **A clinicopathological study of Alport syndrome and detection of type IV collagen chains in Alport patients.**
  Author(s): Chen N, Pan X, Ren H, Dong D.
  Source: Chinese Medical Journal.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11155669&query_hl=21&itool=pubmed_docsum

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

- **A COL4A3 gene mutation and post-transplant anti-alpha 3(IV) collagen alloantibodies in Alport syndrome.**
  Author(s): Kalluri R, van den Heuvel LP, Smeets HJ, Schroder CH, Lemmink HH, Boutaud A, Neilson EG, Hudson BG.
  Source: Kidney International.
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  Author(s): Shimizu Y, Nagata M, Usui J, Hirayama K, Yoh K, Yamagata K, Kobayashi M, Koyama A.
  Source: Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16517570&query_hl=21&itool=pubmed_docsum

- **Topoisomerase I and II consensus sequences in a 17-kb deletion junction of the COL4A5 and COL4A6 genes and immunohistochemical analysis of esophageal leiomyomatosis associated with Alport syndrome.**
  Author(s): Ueki Y, Naito I, Oohashi T, Sugimoto M, Seki T, Yoshioka H, Sado Y, Sato H, Sawai T, Sasaki F, Matsuoka M, Fukuda S, Ninomiya Y.
  Source: American Journal of Human Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9463311&query_hl=21&itool=pubmed_docsum

- **Two CA-dinucleotide polymorphisms at the COL4A5 (Alport syndrome) gene in Xq22.**
  Author(s): Barker DF, Cleverly J, Fain PR.
  Source: Nucleic Acids Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1542599&query_hl=21&itool=pubmed_docsum

- **Type IV collagen alpha 5 chain. Normal distribution and abnormalities in X-linked Alport syndrome revealed by monoclonal antibody.**
  Author(s): Yoshioka K, Hino S, Takemura T, Maki S, Wieslander J, Takekoshi Y, Makino H, Kagawa M, Sado Y, Kashtan CE.
  Source: American Journal of Pathology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8178947&query_hl=21&itool=pubmed_docsum

- **Ultrastructural fragility and type IV collagen abnormality of the anterior lens capsules in a patient with Alport syndrome.**
  Author(s): Takei K, Furuya A, Hommura S, Yamaguchi N.
  Source: Japanese Journal of Ophthalmology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11163053&query_hl=21&itool=pubmed_docsum

- **Ultrastructural immunocytochemistry of collagenous and non-collagenous proteins in fast-frozen, freeze-substituted, and low-temperature-embedded renal tissue in Alport syndrome.**
  Author(s): Muda AO, Rahimi S, Renieri A, Rizzoni G, Massella L, Faraggiana T.
  Source: The Journal of Pathology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9306969&query_hl=21&itool=pubmed_docsum

- **Unequal homologous crossing over resulting in duplication of 36 base pairs within exon 47 of the COL4A5 gene in a family with Alport syndrome.**
  Author(s): Hamalainen ER, Renieri A, Pecoraro C, De Marchi M, Pihlajaniemi T.
  Source: Human Mutation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8889587&query_hl=21&itool=pubmed_docsum

- **Unusual deep intronic mutations in the COL4A5 gene cause X linked Alport syndrome.**
  Author(s): King K, Flinter FA, Nihalani V, Green PM.
  Source: Human Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12436246&query_hl=21&itool=pubmed_docsum

- **Unusual presentation of Alport syndrome.**
  Author(s): Jagose JT, Parekh SJ, Vachharajani TJ, Kulkarni SG, Kirpalani AL.
  Source: J Assoc Physicians India.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7868500&query_hl=21&itool=pubmed_docsum

- **Use of psoralen-coupled nucleotide primers for screening of COL4A5 mutations in Alport syndrome.**
  Author(s): Netzer KO, Seibold S, Gross O, Lambrecht R, Weber M.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8887300&query_hl=21&itool=pubmed_docsum

- **Vitreoretinal degeneration complicated by retinal detachment in Alport syndrome.**
  Author(s): Shaikh S, Garretson B, Williams GA.
  Source: Retina (Philadelphia, Pa.).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12652248&query_hl=21&itool=pubmed_docsum

- **X-linked Alport syndrome in females.**
  Author(s): Meleg-Smith S, Magliato S, Cheles M, Garola RE, Kashtan CE.
  Source: Human Pathology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9563792&query_hl=21&itool=pubmed_docsum

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  Author(s): Naito I, Nomura S, Inoue S, Kagawa M, Matsubara T, Araki T, Taki M, Ohmori H, Manabe K, Kawai S, Osawa G, Sado Y.
  Source: Contrib Nephrol.
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- **X-linked Alport syndrome: an SSCP-based mutation survey over all 51 exons of the COL4A5 gene.**
  Author(s): Renieri A, Bruttini M, Galli L, Zanelli P, Neri T, Rossetti S, Turco A, Heiskari N, Zhou J, Gusmano R, Massella L, Banfi G, Scolari F, Sessa A, Rizzoni G, Tryggvason K, Pignatti PF, Savi M, Ballabio A, De Marchi M.
  Source: American Journal of Human Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8651296&query_hl=21&itool=pubmed_docsum

- **X-linked Alport syndrome: natural history and genotype-phenotype correlations in girls and women belonging to 195 families: a "European Community Alport Syndrome Concerted Action" study.**
  Author(s): Jais JP, Knebelmann B, Giatras I, De Marchi M, Rizzoni G, Renieri A, Weber M, Gross O, Netzer KO, Flinter F, Pirson Y, Dahan K, Wieslander J, Persson U, Tryggvason K, Martin P, Hertz JM, Schroder C, Sanak M, Carvalho MF, Saus J, Antignac C, Smeets H, Gubler MC.
  Source: Journal of the American Society of Nephrology : Jasn.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14514738&query_hl=21&itool=pubmed_docsum

- **X-linked Alport syndrome: natural history in 195 families and genotype- phenotype correlations in males.**
  Author(s): Jais JP, Knebelmann B, Giatras I, De Marchi M, Rizzoni G, Renieri A, Weber M, Gross O, Netzer KO, Flinter F, Pirson Y, Verellen C, Wieslander J, Persson U, Tryggvason K, Martin P, Hertz JM, Schroder C, Sanak M, Krejcova S, Carvalho MF, Saus J, Antignac C, Smeets H, Gubler MC.
  Source: Journal of the American Society of Nephrology : Jasn.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10752524&query_hl=21&itool=pubmed_docsum

- **X-linked inheritance of Alport syndrome: family P revisited.**
  Author(s): Hasstedt SJ, Atkin CL.
  Source: American Journal of Human Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=6650503&query_hl=21&itool=pubmed_docsum

CHAPTER 2. BOOKS ON ALPORT SYNDROME

Overview

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

- **Molecular Pathology and Genetics of Alport Syndrome (Contributions to Nephrology)** Karl Tryggvason (1996); ISBN: 3805561938; http://www.amazon.com/exec/obidos/ASIN/3805561938/icongroupinterna
- **The Molecular Genetics of X-Linked Alport Syndrome (Acta Biomedica Lovaniensia , No 109)** Caiying Guo (1995); ISBN: 9061866812; http://www.amazon.com/exec/obidos/ASIN/9061866812/icongroupinterna

The National Library of Medicine Book Index

The National Library of Medicine at the National Institutes of Health has a massive database of books published on healthcare and biomedicine. Go to the following Internet site, **http://locatorplus.gov/**, and then select **LocatorPlus**. Once you are in the search area, simply

type **Alport syndrome** (or synonyms) into the search box, and select the Quick Limit Option for Keyword, Title, or Journal Title Search: **Books**. From there, results can be sorted by publication date, author, or relevance. The following was recently catalogued by the National Library of Medicine[9]:

- **Hereditaire nefritis met perceptieve slechthorendheid: (Alport-syndroom) en een familie met hereditaire idiopathische schrompelnieren = Hereditary nephritis with perception deafness: (Alport’s syndrome) and a family with idiopathically contracted kidneys: (with a summary in English)** Author: Bokkel Huinink, Jan Adam ten.; Year: 1967; Groningen: Rijksuniversiteit te Groningen, [1967?]

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

APPENDICES

APPENDIX A. HELP ME UNDERSTAND GENETICS

Overview

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

The Basics: Genes and How They Work

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

What Is a Cell?

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

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

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

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

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

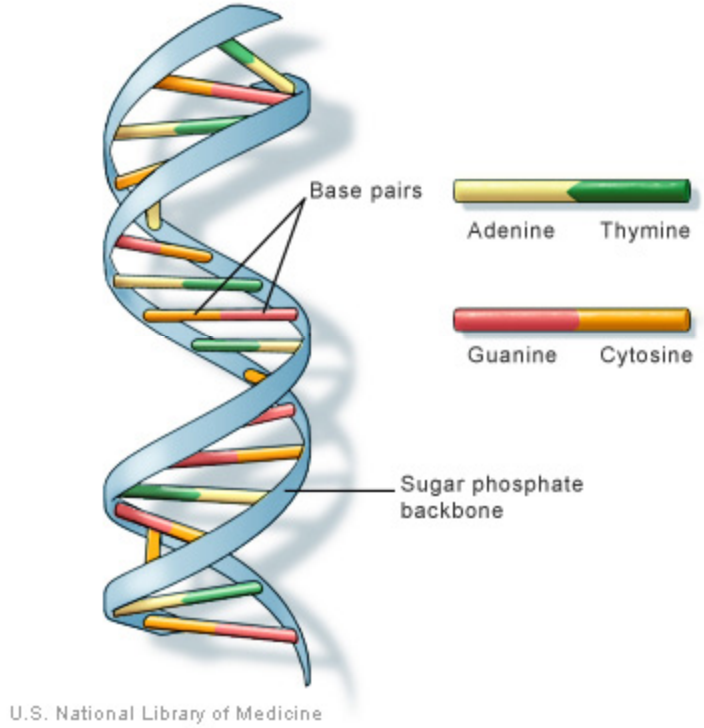
What Is DNA?

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

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

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

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



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

What Is Mitochondrial DNA?

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

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

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

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

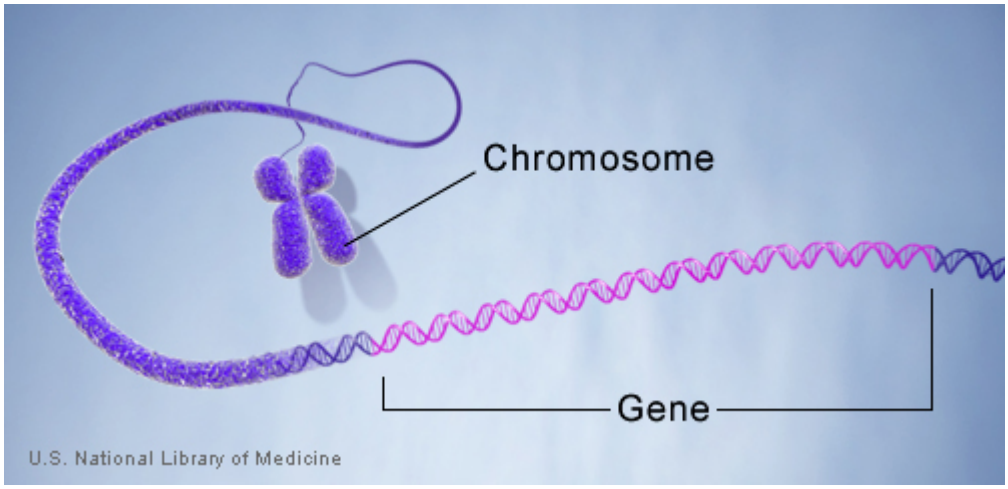
Mitochondrial DNA contains 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation. The remaining genes provide instructions for making molecules called transfer RNAs (tRNAs) and ribosomal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

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

What Is a Gene?

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

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



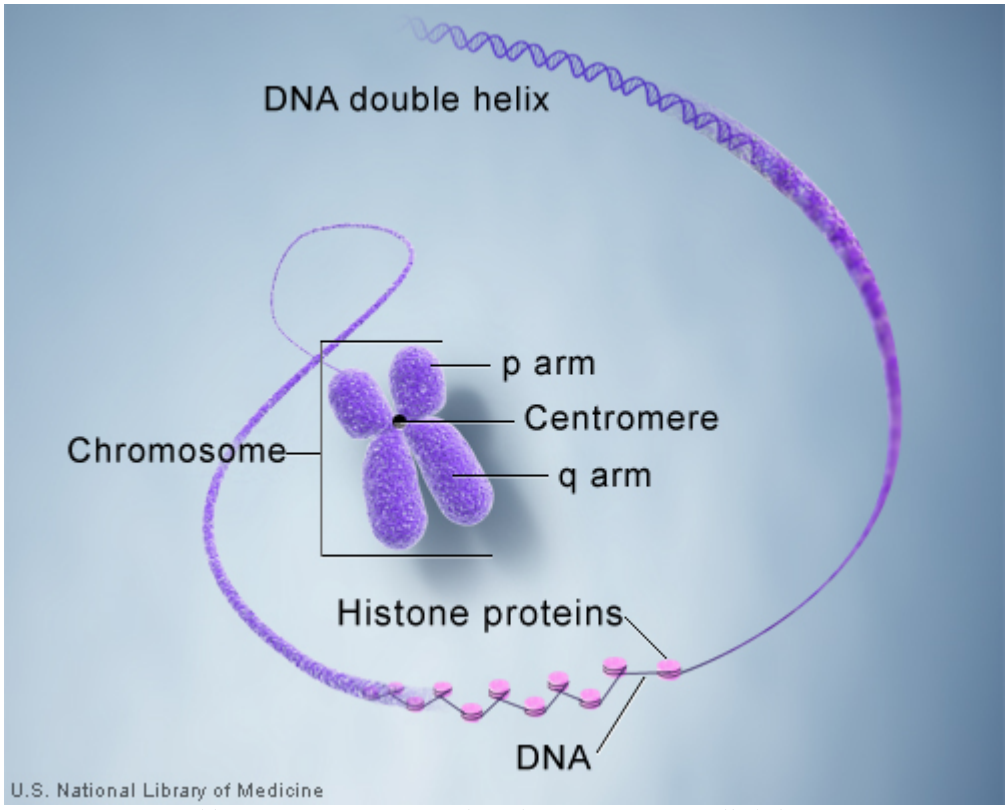
Genes are made up of DNA. Each chromosome contains many genes.

What Is a Chromosome?

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

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

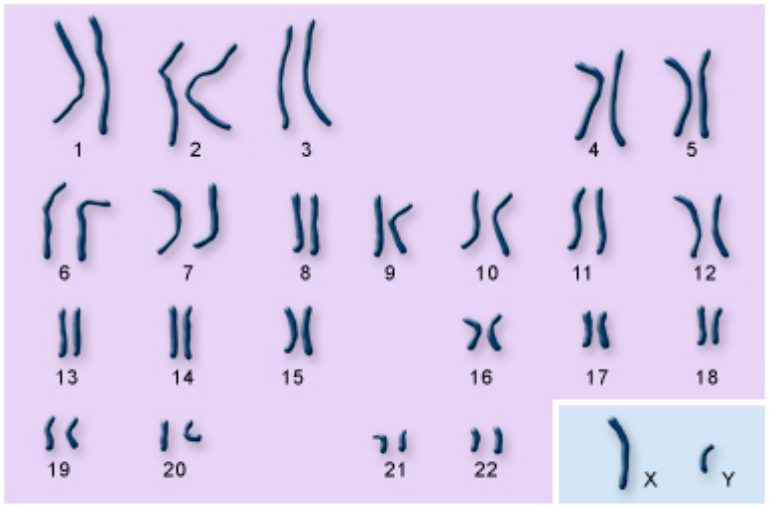
Each chromosome has a constriction point called the centromere, which divides the chromosome into two sections, or "arms." The short arm of the chromosome is labeled the "p arm." The long arm of the chromosome is labeled the "q arm." The location of the centromere on each chromosome gives the chromosome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



DNA and histone proteins are packaged into structures called chromosomes.

How Many Chromosomes Do People Have?

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



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

How Do Geneticists Indicate the Location of a Gene?

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

Cytogenetic Location

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

17q12

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

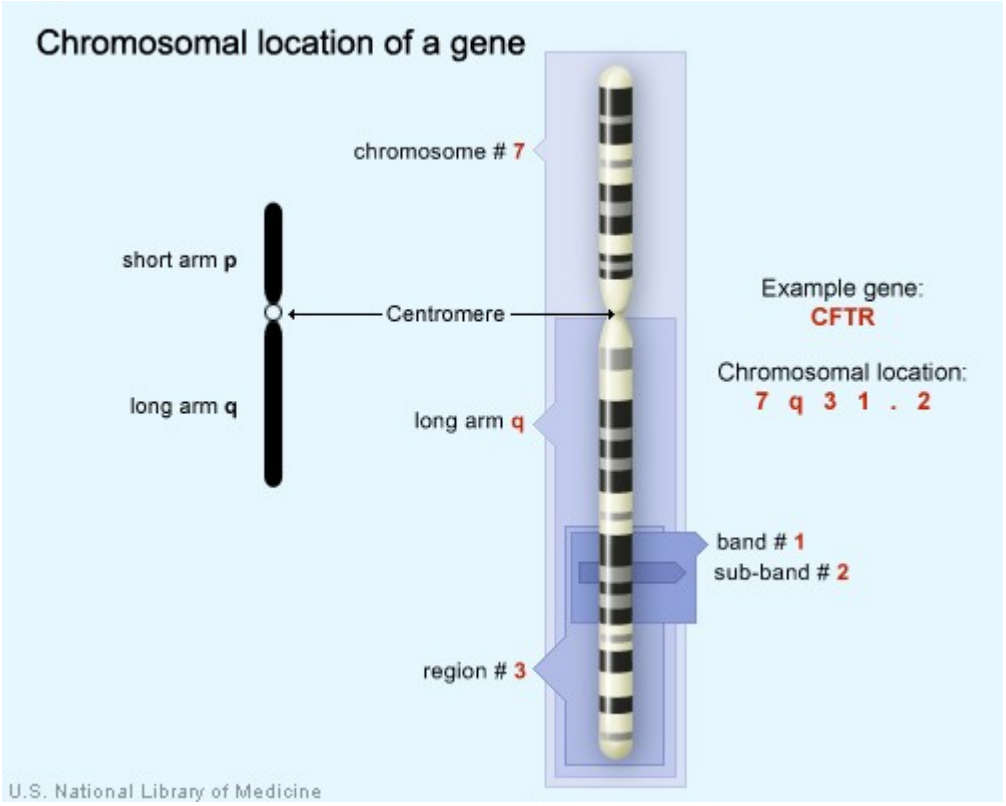
17q12-q21

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

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

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

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



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

Molecular Location

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

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

What Are Proteins and What Do They Do?

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

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

Examples of Protein Functions

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

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

How Does a Gene Make a Protein?

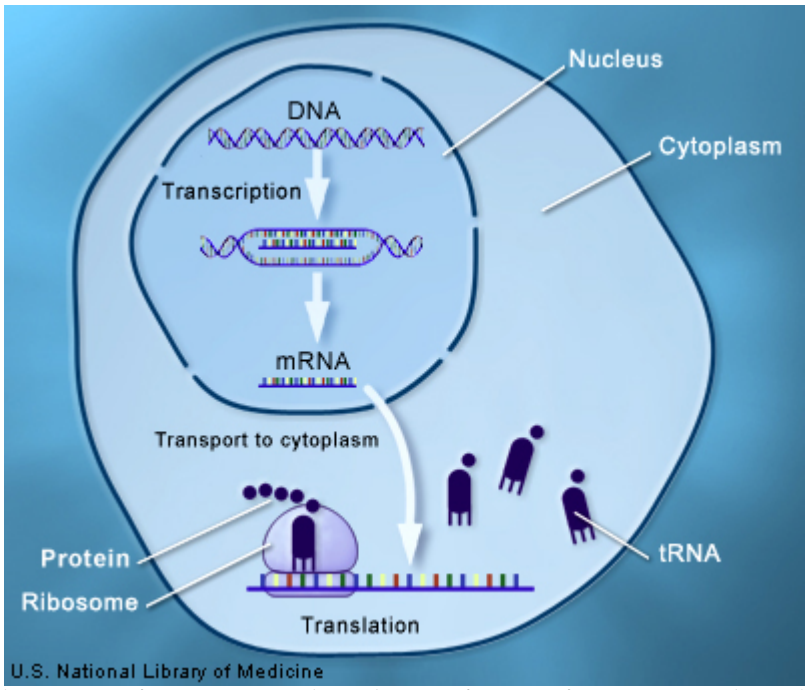
Most genes contain the information needed to make functional molecules called proteins. (A few genes produce other molecules that help the cell assemble proteins.) The journey from gene to protein is complex and tightly controlled within each cell. It consists of two major steps: transcription and translation.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

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

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

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

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



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

Can Genes Be Turned On and Off in Cells?

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

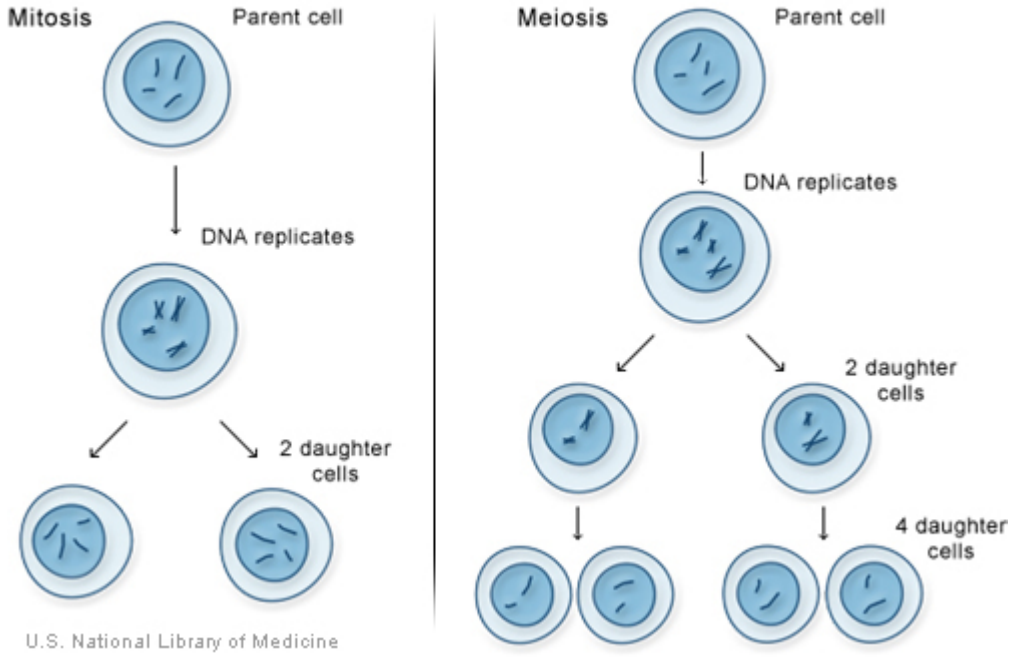
Gene regulation can occur at any point during gene expression, but most commonly occurs at the level of transcription (when the information in a gene's DNA is transferred to mRNA). Signals from the environment or from other cells activate proteins called transcription factors. These proteins bind to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

How Do Cells Divide?

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

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

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



Mitosis and meiosis, the two types of cell division.

How Do Genes Control the Growth and Division of Cells?

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

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

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

Genetic Mutations and Health

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

What Is a Gene Mutation and How Do Mutations Occur?

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

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

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

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

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

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

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

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

How Can Gene Mutations Affect Health and Development?

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

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

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

Do All Gene Mutations Affect Health and Development?

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

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

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

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

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

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

What Kinds of Gene Mutations Are Possible?

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

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

Can Changes in Chromosomes Affect Health and Development?

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

Human cells normally contain 23 pairs of chromosomes, for a total of 46 chromosomes in each cell. A change in the number of chromosomes leads to a chromosomal disorder. These changes can occur during the formation of reproductive cells (eggs and sperm) or in early fetal development. A gain or loss of chromosomes from the normal 46 is called aneuploidy.

The most common form of aneuploidy is trisomy, or the presence of an extra chromosome in each cell. "Tri-" is Greek for "three"; people with trisomy have three copies of a particular chromosome in each cell instead of the normal two copies. Down syndrome is an example of a condition caused by trisomy—people with Down syndrome typically have three copies of chromosome 21 in each cell, for a total of 47 chromosomes per cell.

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

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

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

Can Changes in Mitochondrial DNA Affect Health and Development?

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

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

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

What Are Complex or Multifactorial Disorders?

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

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

What Information about a Genetic Condition Can Statistics Provide?

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

Common Statistical Terms

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

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

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

Naming Genetic Conditions

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

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

- The basic genetic or biochemical defect that causes the condition (for example, alpha-1 antitrypsin deficiency)
- One or more major signs or symptoms of the disorder (for example, sickle cell anemia)
- The parts of the body affected by the condition (for example, retinoblastoma)

- The name of a physician or researcher, often the first person to describe the disorder (for example, Marfan syndrome, which was named after Dr. Antoine Bernard-Jean Marfan)
- A geographic area (for example, familial Mediterranean fever, which occurs mainly in populations bordering the Mediterranean Sea)
- The name of a patient or family with the condition (for example, amyotrophic lateral sclerosis, which is also called Lou Gehrig disease after a famous baseball player who had the condition).

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

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

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

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

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

Inheriting Genetic Conditions

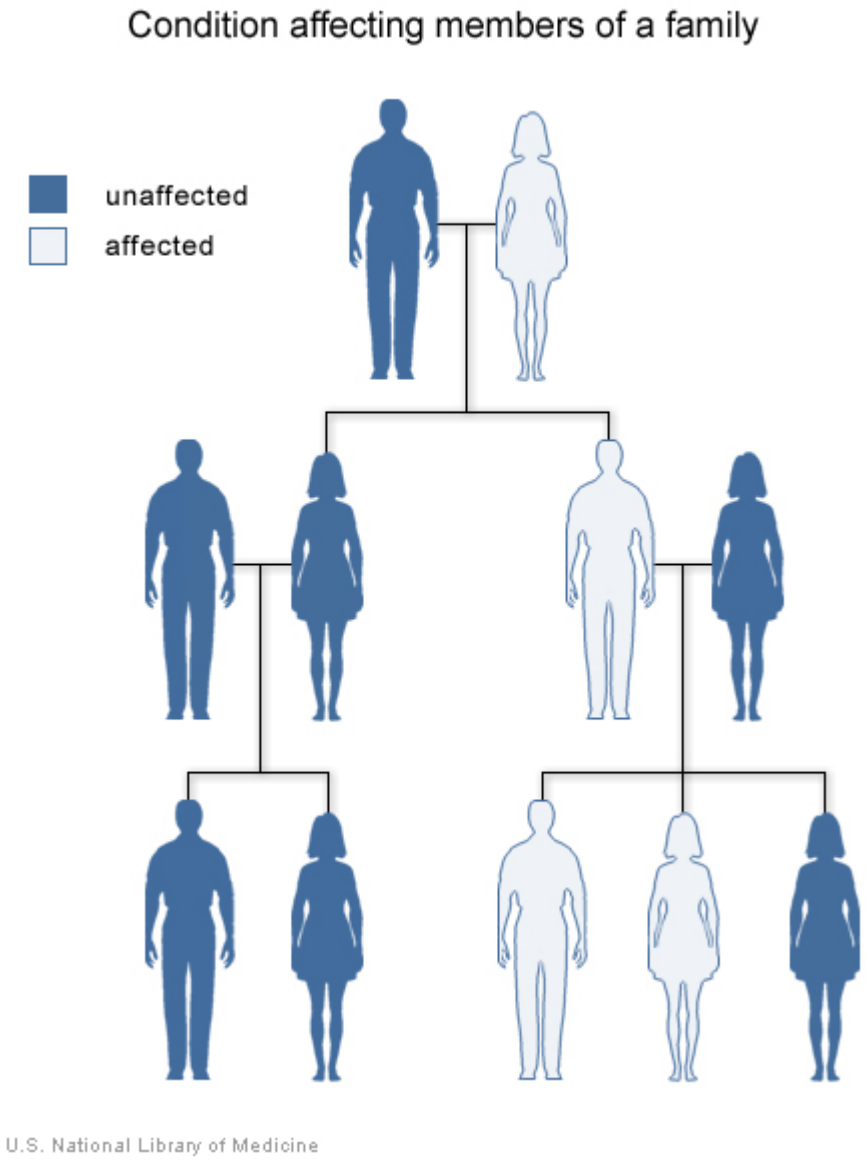
This section gives you information on inheritance patterns and understanding risk.

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

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

such as dietary habits or a combination of genetic and environmental factors are responsible for these disorders.

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



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

Why Is It Important to Know My Family Medical History?

A family medical history is a record of health information about a person and his or her close relatives. A complete record includes information from three generations of relatives,

including children, brothers and sisters, parents, aunts and uncles, nieces and nephews, grandparents, and cousins.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Factors that Influence the Effects of Particular Genetic Changes

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

Reduced Penetrance

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

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

Variable Expressivity

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

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

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

What Do Geneticists Mean by Anticipation?

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

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

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

What Is Genomic Imprinting?

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

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

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

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

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

What Is Uniparental Disomy?

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

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

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

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

Are Chromosomal Disorders Inherited?

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

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

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

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

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

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

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

Genetic Consultation

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

What Is a Genetic Consultation?

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

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

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

Why Might Someone Have a Genetic Consultation?

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

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

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

What Happens during a Genetic Consultation?

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

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

During a consultation, a genetics professional will:

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

A genetics professional will NOT:

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

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

How Can I Find a Genetics Professional in My Area?

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

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

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

Genetic Testing

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

What Is Genetic Testing?

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

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

What Are the Types of Genetic Tests?

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

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

How Is Genetic Testing Done?

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

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

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

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

What Is Direct-to-Consumer Genetic Testing?

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

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

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

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

What Do the Results of Genetic Tests Mean?

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

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

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

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

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

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

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

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

Will Health Insurance Cover the Costs of Genetic Testing?

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

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

What Are the Benefits of Genetic Testing?

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

What Are the Risks and Limitations of Genetic Testing?

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

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

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

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

What Is Genetic Discrimination?

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

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

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

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

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

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

Gene Therapy

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

What Is Gene Therapy?

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

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

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

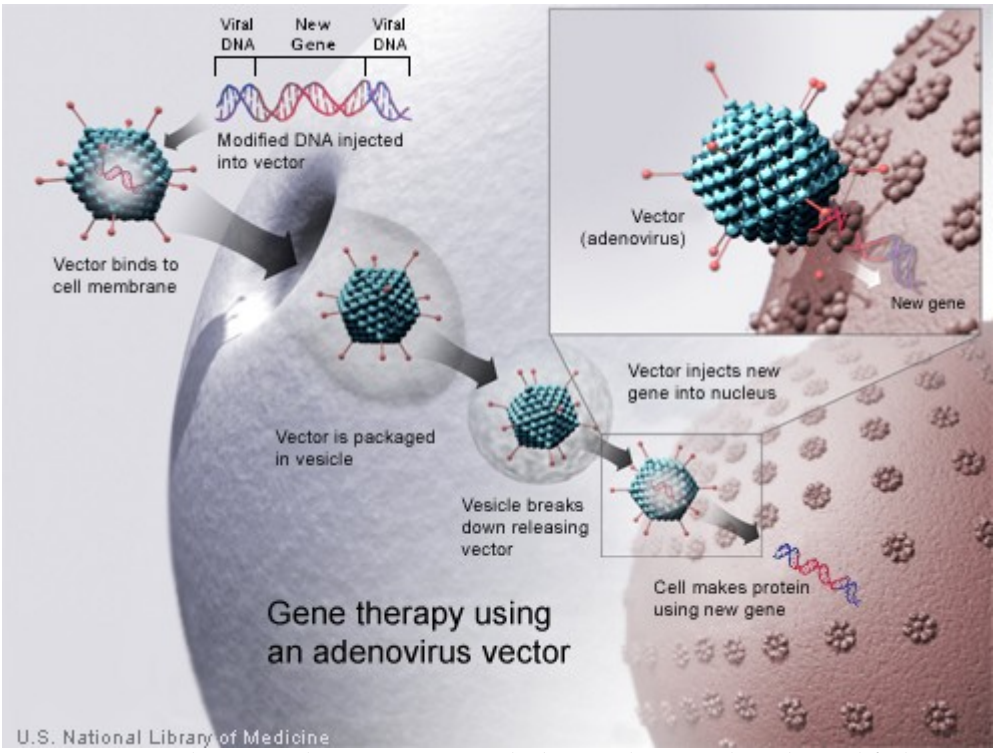
How Does Gene Therapy Work?

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

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

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

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



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

Is Gene Therapy Safe?

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

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

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

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

What Are the Ethical Issues surrounding Gene Therapy?

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

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

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

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

Is Gene Therapy Available to Treat My Disorder?

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

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

You can also search for clinical trials online. ClinicalTrials.gov, a service of the National Institutes of Health, provides easy access to information on clinical trials. You can search for specific trials or browse by condition or trial sponsor. You may wish to refer to a list of gene therapy trials that are accepting (or will accept) patients.

The Human Genome Project and Genomic Research

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

What Is a Genome?

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

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

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

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

What Were the Goals of the Human Genome Project?

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

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

What Did the Human Genome Project Accomplish?

In April 2003, researchers announced that the Human Genome Project had completed a high-quality sequence of essentially the entire human genome. This sequence closed the gaps from a working draft of the genome, which was published in 2001. It also identified the locations of many human genes and provided information about their structure and

organization. The Project made the sequence of the human genome and tools to analyze the data freely available via the Internet.

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

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

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

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

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

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

What Are the Next Steps in Genomic Research?

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

The objectives of continued genomic research include the following:

- Determine the function of genes and the elements that regulate genes throughout the genome.
- Find variations in the DNA sequence among people and determine their significance. These variations may one day provide information about a person's disease risk and response to certain medications.

- Discover the 3-dimensional structures of proteins and identify their functions.
- Explore how DNA and proteins interact with one another and with the environment to create complex living systems.
- Develop and apply genome-based strategies for the early detection, diagnosis, and treatment of disease.
- Sequence the genomes of other organisms, such as the rat, cow, and chimpanzee, in order to compare similar genes between species.
- Develop new technologies to study genes and DNA on a large scale and store genomic data efficiently.
- Continue to explore the ethical, legal, and social issues raised by genomic research.

What Is Pharmacogenomics?

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

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

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

APPENDIX B. PHYSICIAN RESOURCES

Overview

In this chapter, we focus on databases and Internet-based guidelines and information resources created or written for a professional audience.

NIH Guidelines

Commonly referred to as "clinical" or "professional" guidelines, the National Institutes of Health publish physician guidelines for the most common diseases. Publications are available at the following by relevant Institute[12]:

- National Institutes of Health (NIH); guidelines consolidated across agencies available at **http://health.nih.gov/**
- National Institute of General Medical Sciences (NIGMS); fact sheets available at **http://www.nigms.nih.gov/Publications/FactSheets.htm**
- National Library of Medicine (NLM); extensive encyclopedia (A.D.A.M., Inc.) with guidelines: **http://www.nlm.nih.gov/medlineplus/healthtopics.html**
- National Cancer Institute (NCI); guidelines available at **http://www.cancer.gov/cancertopics/pdq**
- National Eye Institute (NEI); guidelines available at **http://www.nei.nih.gov/health/**
- National Heart, Lung, and Blood Institute (NHLBI); guidelines available at **http://www.nhlbi.nih.gov/guidelines/index.htm**
- National Human Genome Research Institute (NHGRI); research available at **http://www.genome.gov/page.cfm?pageID=10000375**
- National Institute on Aging (NIA); guidelines available at **http://www.nia.nih.gov/HealthInformation/Publications/**
- National Institute on Alcohol Abuse and Alcoholism (NIAAA); guidelines available at **http://www.niaaa.nih.gov/Publications/**

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

- National Institute of Allergy and Infectious Diseases (NIAID); guidelines available at **http://www.niaid.nih.gov/publications/**
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); fact sheets and guidelines available at **http://www.niams.nih.gov/hi/index.htm**
- National Institute of Child Health and Human Development (NICHD); guidelines available at **http://www.nichd.nih.gov/publications/pubskey.cfm**
- National Institute on Deafness and Other Communication Disorders (NIDCD); fact sheets and guidelines at **http://www.nidcd.nih.gov/health/**
- National Institute of Dental and Craniofacial Research (NIDCR); guidelines available at **http://www.nidcr.nih.gov/HealthInformation/**
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); guidelines available at **http://www.niddk.nih.gov/health/health.htm**
- National Institute on Drug Abuse (NIDA); guidelines available at **http://www.nida.nih.gov/DrugAbuse.html**
- National Institute of Environmental Health Sciences (NIEHS); environmental health information available at **http://www.niehs.nih.gov/external/facts.htm**
- National Institute of Mental Health (NIMH); guidelines available at **http://www.nimh.nih.gov/healthinformation/index.cfm**
- National Institute of Neurological Disorders and Stroke (NINDS); neurological disorder information pages available at **http://www.ninds.nih.gov/health_and_medical/disorder_index.htm**
- National Institute of Biomedical Imaging and Bioengineering; general information at **http://www.nibib.nih.gov/HealthEdu**
- National Center for Complementary and Alternative Medicine (NCCAM); health information available at **http://nccam.nih.gov/health/**
- National Center for Research Resources (NCRR); various information directories available at **http://www.ncrr.nih.gov/publications.asp**
- Office of Rare Diseases; various fact sheets available at **http://rarediseases.info.nih.gov/html/resources/rep_pubs.html**
- Centers for Disease Control and Prevention; various fact sheets on infectious diseases available at **http://www.cdc.gov/publications.htm**

NIH Databases

In addition to the various Institutes of Health that publish professional guidelines, the NIH has designed a number of databases for professionals.[13] Physician-oriented resources provide a wide variety of information related to the biomedical and health sciences, both past and present. The format of these resources varies. Searchable databases, bibliographic

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

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

- **Bioethics:** Access to published literature on the ethical, legal, and public policy issues surrounding healthcare and biomedical research. This information is provided in conjunction with the Kennedy Institute of Ethics located at Georgetown University, Washington, D.C.: **http://www.nlm.nih.gov/databases/databases_bioethics.html**
- **HIV/AIDS Resources:** Describes various links and databases dedicated to HIV/AIDS research: **http://www.nlm.nih.gov/pubs/factsheets/aidsinfs.html**
- **NLM Online Exhibitions:** Describes "Exhibitions in the History of Medicine": **http://www.nlm.nih.gov/exhibition/exhibition.html**. Additional resources for historical scholarship in medicine: **http://www.nlm.nih.gov/hmd/index.html**
- **Biotechnology Information:** Access to public databases. The National Center for Biotechnology Information conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information for the better understanding of molecular processes affecting human health and disease: **http://www.ncbi.nlm.nih.gov/**
- **Population Information:** The National Library of Medicine provides access to worldwide coverage of population, family planning, and related health issues, including family planning technology and programs, fertility, and population law and policy: **http://www.nlm.nih.gov/databases/databases_population.html**
- **Cancer Information:** Access to cancer-oriented databases: **http://www.nlm.nih.gov/databases/databases_cancer.html**
- **Profiles in Science:** Offering the archival collections of prominent twentieth-century biomedical scientists to the public through modern digital technology: **http://www.profiles.nlm.nih.gov/**
- **Chemical Information:** Provides links to various chemical databases and references: **http://sis.nlm.nih.gov/Chem/ChemMain.html**
- **Clinical Alerts:** Reports the release of findings from the NIH-funded clinical trials where such release could significantly affect morbidity and mortality: **http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html**
- **Space Life Sciences:** Provides links and information to space-based research (including NASA): **http://www.nlm.nih.gov/databases/databases_space.html**
- **MEDLINE:** Bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the healthcare system, and the pre-clinical sciences: **http://www.nlm.nih.gov/databases/databases_medline.html**
- **Toxicology and Environmental Health Information (TOXNET):** Databases covering toxicology and environmental health: **http://sis.nlm.nih.gov/Tox/ToxMain.html**
- **Visible Human Interface:** Anatomically detailed, three-dimensional representations of normal male and female human bodies: **http://www.nlm.nih.gov/research/visible/visible_human.html**

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

The NLM Gateway[15]

The NLM (National Library of Medicine) Gateway is a Web-based system that lets users search simultaneously in multiple retrieval systems at the U.S. National Library of Medicine (NLM). It allows users of NLM services to initiate searches from one Web interface, providing one-stop searching for many of NLM's information resources or databases.[16] To use the NLM Gateway, simply go to the search site at **http://gateway.nlm.nih.gov/gw/Cmd**. Type **Alport 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

Category	Items Found
Journal Articles	1458
Books / Periodicals / Audio Visual	6
Consumer Health	31
Meeting Abstracts	0
Other Collections	0
Total	1495

HSTAT[17]

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.[18] These documents include clinical practice guidelines, quick-reference guides for clinicians, consumer health brochures, evidence reports and technology assessments from the Agency for Healthcare Research and Quality (AHRQ), as well as AHRQ's Put Prevention Into Practice.[19] Simply search by **Alport syndrome** (or synonyms) at the following Web site: **http://text.nlm.nih.gov**.

Coffee Break: Tutorials for Biologists[20]

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

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

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

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

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

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

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

Each report incorporates interactive tutorials that demonstrate how bioinformatics tools are used as a part of the research process. Currently, all Coffee Breaks are written by NCBI staff.[21] Each report is about 400 words and is usually based on a discovery reported in one or more articles from recently published, peer-reviewed literature.[22] This site has new articles every few weeks, so it can be considered an online magazine of sorts. It is intended for general background information. You can access the Coffee Break Web site at the following hyperlink: **http://www.ncbi.nlm.nih.gov/Coffeebreak/**.

Other Commercial Databases

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

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

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

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

APPENDIX C. PATIENT RESOURCES

Overview

Official agencies, as well as federally funded institutions supported by national grants, frequently publish a variety of guidelines written with the patient in mind. These are typically called **Fact Sheets** or **Guidelines**. They can take the form of a brochure, information kit, pamphlet, or flyer. Often they are only a few pages in length. Since new guidelines on Alport 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 Alport 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 Alport 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 **Alport syndrome**:

Bladder Diseases
http://www.nlm.nih.gov/medlineplus/bladderdiseases.html

Colorectal Cancer
http://www.nlm.nih.gov/medlineplus/colorectalcancer.html

Diabetic Kidney Problems
http://www.nlm.nih.gov/medlineplus/diabetickidneyproblems.html

Interstitial Cystitis
http://www.nlm.nih.gov/medlineplus/interstitialcystitis.html

Kidney Cancer
http://www.nlm.nih.gov/medlineplus/kidneycancer.html

Kidney Diseases
http://www.nlm.nih.gov/medlineplus/kidneydiseases.html

Kidney Failure
http://www.nlm.nih.gov/medlineplus/kidneyfailure.html

Kidney Stones
http://www.nlm.nih.gov/medlineplus/kidneystones.html

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

Newborn Screening
http://www.nlm.nih.gov/medlineplus/newbornscreening.html

You may also choose to use the search utility provided by MEDLINEplus at the following Web address: **http://www.nlm.nih.gov/medlineplus/**. Simply type a keyword into the search box and click **Search**. This utility is similar to the NIH search utility, with the exception that it only includes materials that are linked within the MEDLINEplus system (mostly patient-oriented information). It also has the disadvantage of generating unstructured results. We recommend, therefore, that you use this method only if you have a very targeted search.

The 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 Alport 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 **Alport 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/**
- Med Help International: **http://www.medhelp.org/HealthTopics/A.html**
- Open Directory Project: **http://dmoz.org/Health/Conditions_and_Diseases/**
- Yahoo.com: **http://dir.yahoo.com/Health/Diseases_and_Conditions/**
- WebMD®Health: **http://www.webmd.com/diseases_and_conditions/default.htm**

Finding Associations

There are several Internet directories that provide lists of medical associations with information on or resources relating to Alport syndrome. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with Alport 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 Alport 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 **http://sis.nlm.nih.gov/dirline.html**. It is composed of two parts: DIRLINE and Health Hotlines.

The DIRLINE database comprises some 10,000 records of organizations, research centers, and government institutes and associations that primarily focus on health and biomedicine. Simply type in **Alport 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 **Alport 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[23]:

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

For More Information on Genetics

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

- What Is a Genome?: **http://www.ncbi.nlm.nih.gov/About/primer/genetics_genome.html**
- A Science Called Genetics: **http://publications.nigms.nih.gov/genetics/science.html**
- Genetic Mapping: **http://www.genome.gov/10000715**

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

ONLINE GLOSSARIES

The Internet provides access to a number of free-to-use medical dictionaries. The National Library of Medicine has compiled the following list of online dictionaries:

- ADAM Medical Encyclopedia (A.D.A.M., Inc.), comprehensive medical reference: **http://www.nlm.nih.gov/medlineplus/encyclopedia.html**
- MedicineNet.com Medical Dictionary (MedicineNet, Inc.): **http://www.medterms.com/Script/Main/hp.asp**
- Merriam-Webster Medical Dictionary (Inteli-Health, Inc.): **http://www.intelihealth.com/IH/**
- Multilingual Glossary of Technical and Popular Medical Terms in Eight European Languages (European Commission) - Danish, Dutch, English, French, German, Italian, Portuguese, and Spanish: **http://allserv.rug.ac.be/~rvdstich/eugloss/welcome.html**
- On-line Medical Dictionary (CancerWEB): **http://cancerweb.ncl.ac.uk/omd/**
- Rare Diseases Terms (Office of Rare Diseases): **http://ord.aspensys.com/asp/diseases/diseases.asp**
- Technology Glossary (National Library of Medicine) - Health Care Technology: **http://www.nlm.nih.gov/archive//20040831/nichsr/ta101/ta10108.html**

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

- **Basic Guidelines for Alport Syndrome**

  Alport syndrome
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000504.htm

  ESRD
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000500.htm

- **Signs & Symptoms for Alport Syndrome**

  Abnormal urine color
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003139.htm

  Ankle, feet, and leg swelling
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003104.htm

  Blood in the urine
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003138.htm

Bloody urine
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003138.htm

Cough
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003072.htm

Deafness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003044.htm

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

Hearing loss
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003044.htm

Hematuria
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003138.htm

High blood pressure
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003082.htm

Leg swelling
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003104.htm

Loss of hearing
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003044.htm

Loss of vision
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003040.htm

Nerve deafness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003291.htm

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

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

- **Diagnostics and Tests for Alport Syndrome**

ALP
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003470.htm

Audiometry
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003341.htm

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

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

BUN
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003474.htm

Creatinine
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003475.htm

Dialysis
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003421.htm

Hematocrit
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003646.htm

Hematuria test
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003582.htm

Red blood cell count
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003644.htm

Renal biopsy
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003907.htm

Urinalysis
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003579.htm

- **Surgery and Procedures for Alport Syndrome**

  Cataract extraction
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002957.htm

- **Background Topics for Alport Syndrome**

  Anterior
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002232.htm

  Renal
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002289.htm

Online Dictionary Directories

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

- Medical Dictionaries: Medical & Biological (World Health Organization):
  http://www.who.int/hlt/virtuallibrary/English/diction.htm#Medical
- Patient Education: Glossaries (DMOZ Open Directory Project):
  http://dmoz.org/Health/Education/Patient_Education/Glossaries/
- Web of Online Dictionaries (Bucknell University):
  http://www.yourdictionary.com/diction5.html#medicine

ALPORT 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]

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

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

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

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]

Adoptive Transfer: Form of passive immunization where previously sensitized immunologic agents (cells or serum) are transferred to non-immune recipients. When transfer of cells is used as a therapy for the treatment of neoplasms, it is called adoptive immunotherapy (immunotherapy, adoptive). [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]

Air Sacs: Thin-walled sacs or spaces which function as a part of the respiratory system in birds, fishes, insects, and mammals. [NIH]

Albumin: 1. Any protein that is soluble in water and moderately concentrated salt solutions and is coagulable by heat. 2. Serum albumin; the major plasma protein (approximately 60 per cent of the total), which is responsible for much of the plasma colloidal osmotic pressure and serves as a transport protein carrying large organic anions, such as fatty acids, bilirubin, and many drugs, and also carrying certain hormones, such as cortisol and thyroxine, when their specific binding globulins are saturated. Albumin is synthesized in the liver. Low serum levels occur in protein malnutrition, active inflammation and serious hepatic and renal disease. [EU]

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

Allo: A female hormone. [NIH]

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

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

Amino Acid Motifs: Commonly observed structural components of proteins formed by simple combinations of adjacent secondary structures. A commonly observed structure may be composed of a conserved sequence which can be represented by a consensus sequence. [NIH]

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

Amino 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]

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]

Animal model: An animal with a disease either the same as or like a disease in humans. Animal models are used to study the development and progression of diseases and to test new treatments before they are given to humans. Animals with transplanted human cancers or other tissues are called xenograft models. [NIH]

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

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

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]

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

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

Aphakia: Absence of crystalline lens totally or partially from field of vision, from any cause except after cataract extraction. Aphakia is mainly congenital or as result of lens dislocation and subluxation. [NIH]

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]

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]

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

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

Auditory: Pertaining to the sense of hearing. [EU]

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

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

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

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

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

Bacteria: Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccal, rodlike or bacillary, and spiral or spirochetal. [NIH]

Bacterial Infections: Infections by bacteria, general or unspecified. [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]

Basement Membrane: Ubiquitous supportive tissue adjacent to epithelium and around smooth and striated muscle cells. This tissue contains intrinsic macromolecular components such as collagen, laminin, and sulfated proteoglycans. As seen by light microscopy one of its subdivisions is the basal (basement) lamina. [NIH]

Basilar Membrane: A membrane that stretches from the spiral lamina to the basilar crest consisting of an inner and an outer part. The inner part supports the spiral organ of Corti. [NIH]

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

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

Bilateral: Affecting both the right and left side of body. [NIH]

Bile: An emulsifying agent produced in the liver and secreted into the duodenum. Its composition includes bile acids and salts, cholesterol, and electrolytes. It aids digestion of fats in the duodenum. [NIH]

Bilirubin: A bile pigment that is a degradation product of heme. [NIH]

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

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

Biosynthesis: The building up of a chemical compound in the physiologic processes of a living organism. [EU]

Biotechnology: Body of knowledge related to the use of organisms, cells or cell-derived constituents for the purpose of developing products which are technically, scientifically and clinically useful. Alteration of biologic function at the molecular level (i.e., genetic engineering) is a central focus; laboratory methods used include transfection and cloning technologies, sequence and structure analysis algorithms, computer databases, and gene and protein structure function analysis and prediction. [NIH]

Bladder: The organ that stores urine. [NIH]

Blastocyst: The mammalian embryo in the post-morula stage in which a fluid-filled cavity, enclosed primarily by trophoblast, contains an inner cell mass which becomes the embryonic disc. [NIH]

Blood Cell Count: A count of the number of leukocytes and erythrocytes per unit volume in

a sample of venous blood. A complete blood count (CBC) also includes measurement of the hemoglobin, hematocrit, and erythrocyte indices. [NIH]

Blood Coagulation: The process of the interaction of blood coagulation factors that results in an insoluble fibrin clot. [NIH]

Blood Coagulation Factors: Endogenous substances, usually proteins, that are involved in the blood coagulation process. [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 Proteins: Proteins that are present in blood serum, including serum albumin, blood coagulation factors, and many other types of proteins. [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]

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]

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

Bronchioles: The tiny branches of air tubes in the lungs. [NIH]

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

Capillary: Any one of the minute vessels that connect the arterioles and venules, forming a network in nearly all parts of the body. Their walls act as semipermeable membranes for the interchange of various substances, including fluids, between the blood and tissue fluid; called also vas capillare. [EU]

Capsules: Hard or soft soluble containers used for the oral administration of medicine. [NIH]

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

Carcinogenic: Producing carcinoma. [EU]

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

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

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

Case report: A detailed report of the diagnosis, treatment, and follow-up of an individual patient. Case reports also contain some demographic information about the patient (for example, age, gender, ethnic origin). [NIH]

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]

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

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

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

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

Cell Adhesion: Adherence of cells to surfaces or to other cells. [NIH]

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

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

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

Cell Respiration: The metabolic process of all living cells (animal and plant) in which oxygen is used to provide a source of energy for the cell. [NIH]

Cell Size: The physical dimensions of a cell. It refers mainly to changes in dimensions correlated with physiological or pathological changes in cells. [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]

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

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

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

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]

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

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

Chromosomal: Pertaining to chromosomes. [EU]

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

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

Chronic: A disease or condition that persists or progresses over a long period of time. [NIH]

Chronic Disease: Disease or ailment of long duration. [NIH]

Chronic renal: Slow and progressive loss of kidney function over several years, often resulting in end-stage renal disease. People with end-stage renal disease need dialysis or transplantation to replace the work of the kidneys. [NIH]

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

CIS: Cancer Information Service. The CIS is the National Cancer Institute's link to the public, interpreting and explaining research findings in a clear and understandable manner, and providing personalized responses to specific questions about cancer. Access the CIS by calling 1-800-4-CANCER, or by using the Web site at http://cis.nci.nih.gov. [NIH]

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

Clinical 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]

Cochlea: The part of the internal ear that is concerned with hearing. It forms the anterior part of the labyrinth, is conical, and is placed almost horizontally anterior to the vestibule. [NIH]

Cochlear: Of or pertaining to the cochlea. [EU]

Codon: A set of three nucleotides in a protein coding sequence that specifies individual amino acids or a termination signal (codon, terminator). Most codons are universal, but some organisms do not produce the transfer RNAs (RNA, transfer) complementary to all codons. These codons are referred to as unassigned codons (codons, nonsense). [NIH]

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]

Collagen disease: A term previously used to describe chronic diseases of the connective tissue (e.g., rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis), but now is thought to be more appropriate for diseases associated with defects in collagen, which is a component of the connective tissue. [NIH]

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

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

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

Complement: A term originally used to refer to the heat-labile factor in serum that causes immune cytolysis, the lysis of antibody-coated cells, and now referring to the entire functionally related system comprising at least 20 distinct serum proteins that is the effector not only of immune cytolysis but also of other biologic functions. Complement activation occurs by two different sequences, the classic and alternative pathways. The proteins of the classic pathway are termed 'components of complement' and are designated by the symbols C1 through C9. C1 is a calcium-dependent complex of three distinct proteins C1q, C1r and C1s. The proteins of the alternative pathway (collectively referred to as the properdin system) and complement regulatory proteins are known by semisystematic or trivial names. Fragments resulting from proteolytic cleavage of complement proteins are designated with lower-case letter suffixes, e.g., C3a. Inactivated fragments may be designated with the suffix 'i', e.g. C3bi. Activated components or complexes with biological activity are designated by a bar over the symbol e.g. C1 or C4b,2a. The classic pathway is activated by the binding of C1 to classic pathway activators, primarily antigen-antibody complexes containing IgM, IgG1, IgG3; C1q binds to a single IgM molecule or two adjacent IgG molecules. The alternative pathway can be activated by IgA immune complexes and also by nonimmunologic materials including bacterial endotoxins, microbial polysaccharides, and cell walls. Activation of the classic pathway triggers an enzymatic cascade involving C1, C4, C2 and C3; activation of the alternative pathway triggers a cascade involving C3 and factors B, D and P. Both result in the cleavage of C5 and the formation of the membrane attack complex. Complement activation also results in the formation of many biologically active complement fragments that act as anaphylatoxins, opsonins, or chemotactic factors. [EU]

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]

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

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

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

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

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

Consensus Sequence: A theoretical representative nucleotide or amino acid sequence in which each nucleotide or amino acid is the one which occurs most frequently at that site in the different sequences which occur in nature. The phrase also refers to an actual sequence which approximates the theoretical consensus. A known conserved sequence set is represented by a consensus sequence. Commonly observed supersecondary protein structures (amino acid motifs) are often formed by conserved sequences. [NIH]

Conserved Sequence: A sequence of amino acids in a polypeptide or of nucleotides in DNA or RNA that is similar across multiple species. A known set of conserved sequences is represented by a consensus sequence. Amino acid motifs are often composed of conserved sequences. [NIH]

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]

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]

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

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

Cyclosporine: A drug used to help reduce the risk of rejection of organ and bone marrow transplants by the body. It is also used in clinical trials to make cancer cells more sensitive to anticancer drugs. [NIH]

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

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

Cytochrome: Any electron transfer hemoprotein having a mode of action in which the transfer of a single electron is effected by a reversible valence change of the central iron atom of the heme prosthetic group between the +2 and +3 oxidation states; classified as cytochromes a in which the heme contains a formyl side chain, cytochromes b, which contain protoheme or a closely similar heme that is not covalently bound to the protein, cytochromes c in which protoheme or other heme is covalently bound to the protein, and cytochromes d in which the iron-tetrapyrrole has fewer conjugated double bonds than the hemes have. Well-known cytochromes have been numbered consecutively within groups and are designated by subscripts (beginning with no subscript), e.g. cytochromes c, c1, C2, . New cytochromes are named according to the wavelength in nanometres of the absorption maximum of the a-band of the iron (II) form in pyridine, e.g., c-555. [EU]

Cytokine: Small but highly potent protein that modulates the activity of many cell types,

including T and B cells. [NIH]

Cytoplasm: The protoplasm of a cell exclusive of that of the nucleus; it consists of a continuous aqueous solution (cytosol) and the organelles and inclusions suspended in it (phaneroplasm), and is the site of most of the chemical activities of the cell. [EU]

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

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

Defense Mechanisms: Unconscious process used by an individual or a group of individuals in order to cope with impulses, feelings or ideas which are not acceptable at their conscious level; various types include reaction formation, projection and self reversal. [NIH]

Degenerative: Undergoing degeneration : tending to degenerate; having the character of or involving degeneration; causing or tending to cause degeneration. [EU]

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

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]

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

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

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

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

Depth Perception: Perception of three-dimensionality. [NIH]

Developmental Biology: The field of biology which deals with the process of the growth and differentiation of an organism. [NIH]

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

Diastolic: Of or pertaining to the diastole. [EU]

Diffusion: The tendency of a gas or solute to pass from a point of higher pressure or concentration to a point of lower pressure or concentration and to distribute itself throughout the available space; a major mechanism of biological transport. [NIH]

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

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]

Disease Progression: The worsening of a disease over time. This concept is most often used for chronic and incurable diseases where the stage of the disease is an important determinant of therapy and prognosis. [NIH]

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

Disparity: Failure of the two retinal images of an object to fall on corresponding retinal points. [NIH]

Dissection: Cutting up of an organism for study. [NIH]

Duct: A tube through which body fluids pass. [NIH]

Dystrophic: Pertaining to toxic habitats low in nutrients. [NIH]

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

Elastic: Susceptible of resisting and recovering from stretching, compression or distortion applied by a force. [EU]

Elastin: The protein that gives flexibility to tissues. [NIH]

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]

Electrophoresis: An electrochemical process in which macromolecules or colloidal particles with a net electric charge migrate in a solution under the influence of an electric current. [NIH]

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

Endemic: Present or usually prevalent in a population or geographical area at all times; said of a disease or agent. Called also endemial. [EU]

Endothelial cell: The main type of cell found in the inside lining of blood vessels, lymph vessels, and the heart. [NIH]

End-stage renal: Total chronic kidney failure. When the kidneys fail, the body retains fluid and harmful wastes build up. A person with ESRD needs treatment to replace the work of the failed kidneys. [NIH]

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]

Epidermal: Pertaining to or resembling epidermis. Called also epidermic or epidermoid. [EU]

Epidermis: Nonvascular layer of the skin. It is made up, from within outward, of five layers:

1) basal layer (stratum basale epidermidis); 2) spinous layer (stratum spinosum epidermidis); 3) granular layer (stratum granulosum epidermidis); 4) clear layer (stratum lucidum epidermidis); and 5) horny layer (stratum corneum epidermidis). [NIH]

Epidermolysis Bullosa: Group of genetically determined disorders characterized by the blistering of skin and mucosae. There are four major forms: acquired, simple, junctional, and dystrophic. Each of the latter three has several varieties. [NIH]

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

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

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

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

Erythrocyte Indices: Quantification of size and cell hemoglobin content or concentration of the erythrocyte, usually derived from erythrocyte count, blood hemoglobin concentration, and hematocrit. Includes the mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC). Use also for cell diameter and thickness. [NIH]

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

Esophageal: Having to do with the esophagus, the muscular tube through which food passes from the throat to the stomach. [NIH]

Esophagus: The muscular tube through which food passes from the throat to the stomach. [NIH]

Ethnic Groups: A group of people with a common cultural heritage that sets them apart from others in a variety of social relationships. [NIH]

Eukaryotic Cells: Cells of the higher organisms, containing a true nucleus bounded by a nuclear membrane. [NIH]

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

Excitatory: When cortical neurons are excited, their output increases and each new input they receive while they are still excited raises their output markedly. [NIH]

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

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

Exon: The part of the DNA that encodes the information for the actual amino acid sequence of the protein. In many eucaryotic genes, the coding sequences consist of a series of exons alternating with intron sequences. [NIH]

Extracellular: Outside a cell or cells. [EU]

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

Extracellular Space: Interstitial space between cells, occupied by fluid as well as amorphous and fibrous substances. [NIH]

Extraction: The process or act of pulling or drawing out. [EU]

Extrarenal: Outside of the kidney. [EU]

Eye Color: Color of the iris. [NIH]

Eye Infections: Infection, moderate to severe, caused by bacteria, fungi, or viruses, which occurs either on the external surface of the eye or intraocularly with probable inflammation, visual impairment, or blindness. [NIH]

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

Fat: Total lipids including phospholipids. [NIH]

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

Fatty acids: A major component of fats that are used by the body for energy and tissue development. [NIH]

Febrile: Pertaining to or characterized by fever. [EU]

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]

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

Filtration: The passage of a liquid through a filter, accomplished by gravity, pressure, or vacuum (suction). [EU]

Flow Cytometry: Technique using an instrument system for making, processing, and displaying one or more measurements on individual cells obtained from a cell suspension. Cells are usually stained with one or more fluorescent dyes specific to cell components of interest, e.g., DNA, and fluorescence of each cell is measured as it rapidly transverses the excitation beam (laser or mercury arc lamp). Fluorescence provides a quantitative measure of various biochemical and biophysical properties of the cell, as well as a basis for cell sorting. Other measurable optical parameters include light absorption and light scattering, the latter being applicable to the measurement of cell size, shape, density, granularity, and stain uptake. [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]

Fluorescent Dyes: Dyes that emit light when exposed to light. The wave length of the emitted light is usually longer than that of the incident light. Fluorochromes are substances that cause fluorescence in other substances, i.e., dyes used to mark or label other compounds with fluorescent tags. They are used as markers in biochemistry and immunology. [NIH]

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

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

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

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

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

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 Deletion: A genetic rearrangement through loss of segments of DNA or RNA, bringing sequences which are normally separated into close proximity. This deletion may be detected using cytogenetic techniques and can also be inferred from the phenotype, indicating a deletion at one specific locus. [NIH]

Gene Expression: The phenotypic manifestation of a gene or genes by the processes of gene action. [NIH]

Gene Products, rev: Trans-acting nuclear proteins whose functional expression are required for HIV viral replication. Specifically, the rev gene products are required for processing and translation of the HIV gag and env mRNAs, and thus rev regulates the expression of the viral structural proteins. rev can also regulate viral regulatory proteins. A cis-acting antirepression sequence (CAR) in env, also known as the rev-responsive element (RRE), is responsive to the rev gene product. rev is short for regulator of virion. [NIH]

Gene Rearrangement: The ordered rearrangement of gene regions by DNA recombination such as that which occurs normally during development. [NIH]

Gene Therapy: The introduction of new genes into cells for the purpose of treating disease by restoring or adding gene expression. Techniques include insertion of retroviral vectors, transfection, homologous recombination, and injection of new genes into the nuclei of single cell embryos. The entire gene therapy process may consist of multiple steps. The new genes may be introduced into proliferating cells in vivo (e.g., bone marrow) or in vitro (e.g., fibroblast cultures) and the modified cells transferred to the site where the gene expression is required. Gene therapy may be particularly useful for treating enzyme deficiency diseases, hemoglobinopathies, and leukemias and may also prove useful in restoring drug sensitivity, particularly for leukemia. [NIH]

Genes, env: DNA sequences that form the coding region for the viral envelope (env) proteins in retroviruses. The env genes contain a cis-acting RNA target sequence for the rev protein (= gene products, rev), termed the rev-responsive element (RRE). [NIH]

Genetic Engineering: Directed modification of the gene complement of a living organism by such techniques as altering the DNA, substituting genetic material by means of a virus, transplanting whole nuclei, transplanting cell hybrids, etc. [NIH]

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

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

Genital: Pertaining to the genitalia. [EU]

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]

Glomerular: Pertaining to or of the nature of a glomerulus, especially a renal glomerulus. [EU]

Glomeruli: Plural of glomerulus. [NIH]

Glomerulonephritis: Glomerular disease characterized by an inflammatory reaction, with leukocyte infiltration and cellular proliferation of the glomeruli, or that appears to be the result of immune glomerular injury. [NIH]

Glomerulus: A tiny set of looping blood vessels in the nephron where blood is filtered in the kidney. [NIH]

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

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

Glutamate: Excitatory neurotransmitter of the brain. [NIH]

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

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

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

Glycosaminoglycans: Heteropolysaccharides which contain an N-acetylated hexosamine in a characteristic repeating disaccharide unit. The repeating structure of each disaccharide involves alternate 1,4- and 1,3-linkages consisting of either N-acetylglucosamine or N-acetylgalactosamine. [NIH]

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

Graft: Healthy skin, bone, or other tissue taken from one part of the body and used to replace diseased or injured tissue removed from another part of the body. [NIH]

Grafting: The operation of transfer of tissue from one site to another. [NIH]

Graft-versus-host disease: GVHD. A reaction of donated bone marrow or peripheral stem cells against a person's tissue. [NIH]

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

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

Guanine: One of the four DNA bases. [NIH]

Haematological: Relating to haematology, that is that branch of medical science which treats

of the morphology of the blood and blood-forming tissues. [EU]

Haematology: The science of the blood, its nature, functions, and diseases. [NIH]

Haematuria: Blood in the urine. [EU]

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

Haplotypes: The genetic constitution of individuals with respect to one member of a pair of allelic genes, or sets of genes that are closely linked and tend to be inherited together such as those of the major histocompatibility complex. [NIH]

Heart attack: A seizure of weak or abnormal functioning of the heart. [NIH]

Hematocrit: Measurement of the volume of packed red cells in a blood specimen by centrifugation. The procedure is performed using a tube with graduated markings or with automated blood cell counters. It is used as an indicator of erythrocyte status in disease. For example, anemia shows a low hematocrit, polycythemia, high values. [NIH]

Hematuria: Presence of blood in the urine. [NIH]

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

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

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

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

Hemophilia: Refers to a group of hereditary disorders in which affected individuals fail to make enough of certain proteins needed to form blood clots. [NIH]

Hemorrhage: Bleeding or escape of blood from a vessel. [NIH]

Hemorrhagic Fever with Renal Syndrome: An acute febrile disease occurring predominately in Asia. It is characterized by fever, prostration, vomiting, hemorrhagic phenonema, shock, and renal failure. It is caused by any one of several closely related species of the genus Hantavirus. The most severe form is caused by Hantaan virus whose natural host is the rodent Apodemus agrarius. A milder form is caused by Seoul virus and related species and transmitted by the rodents Rattus rattus and R. norvegicus. [NIH]

Hemostasis: The process which spontaneously arrests the flow of blood from vessels carrying blood under pressure. It is accomplished by contraction of the vessels, adhesion and aggregation of formed blood elements, and the process of blood or plasma coagulation. [NIH]

Hepatic: Refers to the liver. [NIH]

Hereditary: Of, relating to, or denoting factors that can be transmitted genetically from one generation to another. [NIH]

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

Heredity: 1. The genetic transmission of a particular quality or trait from parent to offspring. 2. The genetic constitution of an individual. [EU]

Heterodimers: 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]

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]

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]

Hydroxylysine: A hydroxylated derivative of the amino acid lysine that is present in certain collagens. [NIH]

Hydroxyproline: A hydroxylated form of the imino acid proline. A deficiency in ascorbic acid can result in impaired hydroxyproline formation. [NIH]

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]

Immune Tolerance: The specific failure of a normally responsive individual to make an immune response to a known antigen. It results from previous contact with the antigen by an immunologically immature individual (fetus or neonate) or by an adult exposed to extreme high-dose or low-dose antigen, or by exposure to radiation, antimetabolites, antilymphocytic serum, etc. [NIH]

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

Immunofluorescence: A technique for identifying molecules present on the surfaces of cells

or in tissues using a highly fluorescent substance coupled to a specific antibody. [NIH]

Immunohistochemistry: Histochemical localization of immunoreactive substances using labeled antibodies as reagents. [NIH]

Immunologic: The ability of the antibody-forming system to recall a previous experience with an antigen and to respond to a second exposure with the prompt production of large amounts of antibody. [NIH]

Immunotherapy: Manipulation of the host's immune system in treatment of disease. It includes both active and passive immunization as well as immunosuppressive therapy to prevent graft rejection. [NIH]

Impairment: In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [NIH]

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]

Incision: A cut made in the body during surgery. [NIH]

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

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

Infiltration: The diffusion or accumulation in a tissue or cells of substances not normal to it or in amounts of the normal. Also, the material so accumulated. [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]

Inner ear: The labyrinth, comprising the vestibule, cochlea, and semicircular canals. [NIH]

Integrins: A family of transmembrane glycoproteins consisting of noncovalent heterodimers. They interact with a wide variety of ligands including extracellular matrix glycoproteins, complement, and other cells, while their intracellular domains interact with the cytoskeleton. The integrins consist of at least three identified families: the cytoadhesin

receptors, the leukocyte adhesion receptors, and the very-late-antigen receptors. Each family contains a common beta-subunit combined with one or more distinct alpha-subunits. These receptors participate in cell-matrix and cell-cell adhesion in many physiologically important processes, including embryological development, hemostasis, thrombosis, wound healing, immune and nonimmune defense mechanisms, and oncogenic transformation. [NIH]

Interstitial: Pertaining to or situated between parts or in the interspaces of a tissue. [EU]

Intracellular: Inside a cell. [NIH]

Intracellular Membranes: Membranes of subcellular structures. [NIH]

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

Intubation: Introduction of a tube into a hollow organ to restore or maintain patency if obstructed. It is differentiated from catheterization in that the insertion of a catheter is usually performed for the introducing or withdrawing of fluids from the body. [NIH]

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

Invertebrates: Animals that have no spinal column. [NIH]

Involution: 1. A rolling or turning inward. 2. One of the movements involved in the gastrulation of many animals. 3. A retrograde change of the entire body or in a particular organ, as the retrograde changes in the female genital organs that result in normal size after delivery. 4. The progressive degeneration occurring naturally with advancing age, resulting in shrivelling of organs or tissues. [EU]

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

Iris: The most anterior portion of the uveal layer, separating the anterior chamber from the posterior. It consists of two layers - the stroma and the pigmented epithelium. Color of the iris depends on the amount of melanin in the stroma on reflection from the pigmented epithelium. [NIH]

Ischemia: Deficiency of blood in a part, due to functional constriction or actual obstruction of a blood vessel. [EU]

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

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 Disease: Any one of several chronic conditions that are caused by damage to the cells of the kidney. People who have had diabetes for a long time may have kidney damage. Also called nephropathy. [NIH]

Kidney Failure: The inability of a kidney to excrete metabolites at normal plasma levels under conditions of normal loading, or the inability to retain electrolytes under conditions of normal intake. In the acute form (kidney failure, acute), it is marked by uremia and usually by oliguria or anuria, with hyperkalemia and pulmonary edema. The chronic form (kidney failure, chronic) is irreversible and requires hemodialysis. [NIH]

Kidney Failure, Acute: A clinical syndrome characterized by a sudden decrease in glomerular filtration rate, often to values of less than 1 to 2 ml per minute. It is usually associated with oliguria (urine volumes of less than 400 ml per day) and is always associated with biochemical consequences of the reduction in glomerular filtration rate such as a rise in blood urea nitrogen (BUN) and serum creatinine concentrations. [NIH]

Kidney Failure, Chronic: An irreversible and usually progressive reduction in renal function in which both kidneys have been damaged by a variety of diseases to the extent that they are unable to adequately remove the metabolic products from the blood and regulate the body's electrolyte composition and acid-base balance. Chronic kidney failure requires hemodialysis or surgery, usually kidney transplantation. [NIH]

Kidney Transplantation: The transference of a kidney from one human or animal to another. [NIH]

Labyrinth: The internal ear; the essential part of the organ of hearing. It consists of an osseous and a membranous portion. [NIH]

Laminin: Large, noncollagenous glycoprotein with antigenic properties. It is localized in the basement membrane lamina lucida and functions to bind epithelial cells to the basement membrane. Evidence suggests that the protein plays a role in tumor invasion. [NIH]

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

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]

Leprosy: A chronic granulomatous infection caused by Mycobacterium leprae. The granulomatous lesions are manifested in the skin, the mucous membranes, and the peripheral nerves. Two polar or principal types are lepromatous and tuberculoid. [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]

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

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

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]

Lucida: An instrument, invented by Wollaton, consisting essentially of a prism or a mirror through which an object can be viewed so as to appear on a plane surface seen in direct view and on which the outline of the object may be traced. [NIH]

Lupus: A form of cutaneous tuberculosis. It is seen predominantly in women and typically involves the nasal, buccal, and conjunctival mucosa. [NIH]

Lymph: The almost colorless fluid that travels through the lymphatic system and carries cells that help fight infection and disease. [NIH]

Lymph node: A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Also known as a lymph gland. Lymph nodes are spread out along lymphatic vessels and contain many lymphocytes, which filter the lymphatic fluid (lymph). [NIH]

Lymphatic: The tissues and organs, including the bone marrow, spleen, thymus, and lymph nodes, that produce and store cells that fight infection and disease. [NIH]

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

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

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

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

Macrophage: A type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells. [NIH]

Macula: A stain, spot, or thickening. Often used alone to refer to the macula retinae. [EU]

Macula Lutea: An oval area in the retina, 3 to 5 mm in diameter, usually located temporal to the superior pole of the eye and slightly below the level of the optic disk. [NIH]

Macular Degeneration: Degenerative changes in the macula lutea of the retina. [NIH]

Major Histocompatibility Complex: The genetic region which contains the loci of genes which determine the structure of the serologically defined (SD) and lymphocyte-defined (LD) transplantation antigens, genes which control the structure of the immune response-associated (Ia) antigens, the immune response (Ir) genes which control the ability of an animal to respond immunologically to antigenic stimuli, and genes which determine the structure and/or level of the first four components of complement. [NIH]

Malnutrition: A condition caused by not eating enough food or not eating a balanced diet. [NIH]

Mammary: Pertaining to the mamma, or breast. [EU]

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]

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

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

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

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

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

Membrane Proteins: Proteins which are found in membranes including cellular and intracellular membranes. They consist of two types, peripheral and integral proteins. They

include most membrane-associated enzymes, antigenic proteins, transport proteins, and drug, hormone, and lectin receptors. [NIH]

Membranoproliferative: A disease that occurs primarily in children and young adults. Over time, inflammation leads to scarring in the glomeruli, causing proteinuria, hematuria, and sometimes chronic renal failure or end-stage renal disease. [NIH]

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

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

Mental 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]

Mercury: A silver metallic element that exists as a liquid at room temperature. It has the atomic symbol Hg (from hydrargyrum, liquid silver), atomic number 80, and atomic weight 200.59. Mercury is used in many industrial applications and its salts have been employed therapeutically as purgatives, antisyphilitics, disinfectants, and astringents. It can be absorbed through the skin and mucous membranes which leads to mercury poisoning. Because of its toxicity, the clinical use of mercury and mercurials is diminishing. [NIH]

Mesenchymal: Refers to cells that develop into connective tissue, blood vessels, and lymphatic tissue. [NIH]

Metastasis: The spread of cancer from one part of the body to another. Tumors formed from cells that have spread are called "secondary tumors" and contain cells that are like those in the original (primary) tumor. The plural is metastases. [NIH]

Metastatic: Having to do with metastasis, which is the spread of cancer from one part of the body to another. [NIH]

Metastatic cancer: Cancer that has spread from the place in which it started to other parts of the body. [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]

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

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

Migration: The systematic movement of genes between populations of the same species, geographic race, or variety. [NIH]

Miscarriage: Spontaneous expulsion of the products of pregnancy before the middle of the second trimester. [NIH]

Mitochondria: Parts of a cell where aerobic production (also known as cell respiration) takes place. [NIH]

Mitosis: A method of indirect cell division by means of which the two daughter nuclei

normally receive identical complements of the number of chromosomes of the somatic cells of the species. [NIH]

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

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

Musculoskeletal System: Themuscles, bones, and cartilage of the body. [NIH]

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

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

Myopia: That error of refraction in which rays of light entering the eye parallel to the optic axis are brought to a focus in front of the retina, as a result of the eyeball being too long from front to back (axial m.) or of an increased strength in refractive power of the media of the eye (index m.). Called also nearsightedness, because the near point is less distant than it is in emmetropia with an equal amplitude of accommodation. [EU]

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

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]

Neoplasms: New abnormal growth of tissue. Malignant neoplasms show a greater degree of anaplasia and have the properties of invasion and metastasis, compared to benign neoplasms. [NIH]

Nephritis: Inflammation of the kidney; a focal or diffuse proliferative or destructive process which may involve the glomerulus, tubule, or interstitial renal tissue. [EU]

Nephron: A tiny part of the kidneys. Each kidney is made up of about 1 million nephrons, which are the working units of the kidneys, removing wastes and extra fluids from the blood. [NIH]

Nephropathy: Disease of the kidneys. [EU]

Nerve Regeneration: Renewal or physiological repair of damaged nerve tissue. [NIH]

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

Networks: Pertaining to a nerve or to the nerves, a meshlike structure of interlocking fibers or strands. [NIH]

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

Neuronal: Pertaining to a neuron or neurons (= conducting cells of the nervous system). [EU]

Neurons: The basic cellular units of nervous tissue. Each neuron consists of a body, an axon, and dendrites. Their purpose is to receive, conduct, and transmit impulses in the nervous system. [NIH]

Neuropathy: A problem in any part of the nervous system except the brain and spinal cord. Neuropathies can be caused by infection, toxic substances, or disease. [NIH]

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]

Normal Distribution: Continuous frequency distribution of infinite range. Its properties are as follows: 1) continuous, symmetrical distribution with both tails extending to infinity; 2) arithmetic mean, mode, and median identical; and 3) shape completely determined by the mean and standard deviation. [NIH]

Nuclear: A test of the structure, blood flow, and function of the kidneys. The doctor injects a mildly radioactive solution into an arm vein and uses x-rays to monitor its progress through the kidneys. [NIH]

Nuclear Envelope: The membrane system of the cell nucleus that surrounds the nucleoplasm. It consists of two concentric membranes separated by the perinuclear space. The structures of the envelope where it opens to the cytoplasm are called the nuclear pores (nuclear pore). [NIH]

Nuclear Pore: An opening through the nuclear envelope formed by the nuclear pore complex which transports nuclear proteins or RNA into or out of the cell nucleus and which, under some conditions, acts as an ion channel. [NIH]

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

Nucleic acid: Either of two types of macromolecule (DNA or RNA) formed by polymerization of nucleotides. Nucleic acids are found in all living cells and contain the information (genetic code) for the transfer of genetic information from one generation to the next. [NIH]

Nucleus: A body of specialized protoplasm found in nearly all cells and containing the

chromosomes. [NIH]

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

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

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

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

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

Opsin: A protein formed, together with retinene, by the chemical breakdown of meta-rhodopsin. [NIH]

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

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

Osmotic: Pertaining to or of the nature of osmosis (= the passage of pure solvent from a solution of lesser to one of greater solute concentration when the two solutions are separated by a membrane which selectively prevents the passage of solute molecules, but is permeable to the solvent). [EU]

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]

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

Paediatric: Of or relating to the care and medical treatment of children; belonging to or concerned with paediatrics. [EU]

Pancreas: A mixed exocrine and endocrine gland situated transversely across the posterior abdominal wall in the epigastric and hypochondriac regions. The endocrine portion is comprised of the Islets of Langerhans, while the exocrine portion is a compound acinar gland that secretes digestive enzymes. [NIH]

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

Particle: A tiny mass of material. [EU]

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]

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

PDQ: Physician Data Query. PDQ is an online database developed and maintained by the National Cancer Institute. Designed to make the most current, credible, and accurate cancer information available to health professionals and the public, PDQ contains peer-reviewed summaries on cancer treatment, screening, prevention, genetics, and supportive care; a registry of cancer clinical trials from around the world; and directories of physicians, professionals who provide genetics services, and organizations that provide cancer care. Most of this information is available on the CancerNet Web site, and more specific information about PDQ can be found at http://cancernet.nci.nih.gov/pdq.html. [NIH]

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

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

Perception: The ability quickly and accurately to recognize similarities and differences among presented objects, whether these be pairs of words, pairs of number series, or multiple sets of these or other symbols such as geometric figures. [NIH]

Perfusion: Bathing an organ or tissue with a fluid. In regional perfusion, a specific area of the body (usually an arm or a leg) receives high doses of anticancer drugs through a blood vessel. Such a procedure is performed to treat cancer that has not spread. [NIH]

Peripheral Nerves: The nerves outside of the brain and spinal cord, including the autonomic, cranial, and spinal nerves. Peripheral nerves contain non-neuronal cells and connective tissue as well as axons. The connective tissue layers include, from the outside to the inside, the epineurium, the perineurium, and the endoneurium. [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]

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

Phosphorylation: The introduction of a phosphoryl group into a compound through the formation of an ester bond between the compound and a phosphorus moiety. [NIH]

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

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

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

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

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

Plasma protein: One of the hundreds of different proteins present in blood plasma, including carrier proteins (such albumin, transferrin, and haptoglobin), fibrinogen and

other coagulation factors, complement components, immunoglobulins, enzyme inhibitors, precursors of substances such as angiotension and bradykinin, and many other types of proteins. [EU]

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]

Pneumonia: Inflammation of the lungs. [NIH]

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

Polycystic: An inherited disorder characterized by many grape-like clusters of fluid-filled cysts that make both kidneys larger over time. These cysts take over and destroy working kidney tissue. PKD may cause chronic renal failure and end-stage renal disease. [NIH]

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

Polymorphism: The occurrence together of two or more distinct forms in the same population. [NIH]

Polypeptide: A peptide which on hydrolysis yields more than two amino acids; called tripeptides, tetrapeptides, etc. according to the number of amino acids contained. [EU]

Polysaccharide: A type of carbohydrate. It contains sugar molecules that are linked together chemically. [NIH]

Postnatal: Occurring after birth, with reference to the newborn. [EU]

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

Prenatal Diagnosis: Determination of the nature of a pathological condition or disease in the postimplantation embryo, fetus, or pregnant female before birth. [NIH]

Presbycusis: Progressive bilateral loss of hearing that occurs in the aged. Syn: senile deafness. [NIH]

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

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

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

Progression: Increase in the size of a tumor or spread of cancer in the body. [NIH]

Progressive: Advancing; going forward; going from bad to worse; increasing in scope or

severity. [EU]

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]

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

Protein Engineering: Procedures by which nonrandom single-site changes are introduced into structural genes (site-specific mutagenesis) in order to produce mutant genes which can be coupled to promoters that direct the synthesis of a specifically altered protein, which is then analyzed for structural and functional properties and then compared with the predicted and sought-after properties. The design of the protein may be assisted by computer graphic technology and other advanced molecular modeling techniques. [NIH]

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

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

Proteinuria: The presence of protein in the urine, indicating that the kidneys are not working properly. [NIH]

Proteoglycan: A molecule that contains both protein and glycosaminoglycans, which are a type of polysaccharide. Proteoglycans are found in cartilage and other connective tissues. [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]

Psoralen: A substance that binds to the DNA in cells and stops them from multiplying. It is being studied in the treatment of graft-versus-host disease and is used in the treatment of psoriasis and vitiligo. [NIH]

Psoriasis: A common genetically determined, chronic, inflammatory skin disease characterized by rounded erythematous, dry, scaling patches. The lesions have a predilection for nails, scalp, genitalia, extensor surfaces, and the lumbosacral region. Accelerated epidermopoiesis is considered to be the fundamental pathologic feature in psoriasis. [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]

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]

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]

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]

Randomized: Describes an experiment or clinical trial in which animal or human subjects are assigned by chance to separate groups that compare different treatments. [NIH]

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]

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

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

Rectum: The last 8 to 10 inches of the large intestine. [NIH]

Recurrence: The return of a sign, symptom, or disease after a remission. [NIH]

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

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

Remission: A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although there still may be cancer in the body. [NIH]

Renal failure: Progressive renal insufficiency and uremia, due to irreversible and progressive renal glomerular tubular or interstitial disease. [NIH]

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

Retina: The ten-layered nervous tissue membrane of the eye. It is continuous with the optic nerve and receives images of external objects and transmits visual impulses to the brain. Its outer surface is in contact with the choroid and the inner surface with the vitreous body. The outer-most layer is pigmented, whereas the inner nine layers are transparent. [NIH]

Retinal: 1. Pertaining to the retina. 2. The aldehyde of retinol, derived by the oxidative enzymatic splitting of absorbed dietary carotene, and having vitamin A activity. In the retina, retinal combines with opsins to form visual pigments. One isomer, 11-cis retinal combines with opsin in the rods (scotopsin) to form rhodopsin, or visual purple. Another, all-trans retinal (trans-r.); visual yellow; xanthopsin) results from the bleaching of rhodopsin by light, in which the 11-cis form is converted to the all-trans form. Retinal also combines with opsins in the cones (photopsins) to form the three pigments responsible for colour vision. Called also retinal, and retinene1. [EU]

Retinal Detachment: Separation of the inner layers of the retina (neural retina) from the pigment epithelium. Retinal detachment occurs more commonly in men than in women, in eyes with degenerative myopia, in aging and in aphakia. It may occur after an uncomplicated cataract extraction, but it is seen more often if vitreous humor has been lost during surgery. (Dorland, 27th ed; Newell, Ophthalmology: Principles and Concepts, 7th ed, p310-12). [NIH]

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

Retinol: Vitamin A. It is essential for proper vision and healthy skin and mucous membranes. Retinol is being studied for cancer prevention; it belongs to the family of drugs called retinoids. [NIH]

Retinopathy: 1. Retinitis (= inflammation of the retina). 2. Retinosis (= degenerative, noninflammatory condition of the retina). [EU]

Retrograde: 1. Moving backward or against the usual direction of flow. 2. Degenerating, deteriorating, or catabolic. [EU]

Retroviral vector: RNA from a virus that is used to insert genetic material into cells. [NIH]

Rheumatoid: Resembling rheumatism. [EU]

Rheumatoid arthritis: A form of arthritis, the cause of which is unknown, although infection, hypersensitivity, hormone imbalance and psychologic stress have been suggested as possible causes. [NIH]

Rhodopsin: A photoreceptor protein found in retinal rods. It is a complex formed by the binding of retinal, the oxidized form of retinol, to the protein opsin and undergoes a series of complex reactions in response to visible light resulting in the transmission of nerve impulses to the brain. [NIH]

Ribonucleic acid: RNA. One of the two nucleic acids found in all cells. The other is deoxyribonucleic acid (DNA). Ribonucleic acid transfers genetic information from DNA to proteins produced by the cell. [NIH]

Ribose: A pentose active in biological systems usually in its D-form. [NIH]

Ribosome: A granule of protein and RNA, synthesized in the nucleolus and found in the cytoplasm of cells. Ribosomes are the main sites of protein synthesis. Messenger RNA attaches to them and there receives molecules of transfer RNA bearing amino acids. [NIH]

Rods: One type of specialized light-sensitive cells (photoreceptors) in the retina that provide side vision and the ability to see objects in dim light (night vision). [NIH]

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]

Secondary tumor: Cancer that has spread from the organ in which it first appeared to another organ. For example, breast cancer cells may spread (metastasize) to the lungs and cause the growth of a new tumor. When this happens, the disease is called metastatic breast cancer, and the tumor in the lungs is called a secondary tumor. Also called secondary cancer. [NIH]

Secretory: Secreting; relating to or influencing secretion or the secretions. [NIH]

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

Semicircular canal: Three long canals of the bony labyrinth of the ear, forming loops and opening into the vestibule by five openings. [NIH]

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

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

Serine: A non-essential amino acid occurring in natural form as the L-isomer. It is synthesized from glycine or threonine. It is involved in the biosynthesis of purines, pyrimidines, and other amino acids. [NIH]

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

Serum Albumin: A major plasma protein that serves in maintaining the plasma colloidal osmotic pressure and transporting large organic anions. [NIH]

Shock: The general bodily disturbance following a severe injury; an emotional or moral upset occasioned by some disturbing or unexpected experience; disruption of the circulation, which can upset all body functions: sometimes referred to as circulatory shock. [NIH]

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

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

Skull: The skeleton of the head including the bones of the face and the bones enclosing the brain. [NIH]

Small intestine: The part of the digestive tract that is located between the stomach and the large intestine. [NIH]

Smooth muscle: Muscle that performs automatic tasks, such as constricting blood vessels. [NIH]

Social 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]

Sound wave: An alteration of properties of an elastic medium, such as pressure, particle displacement, or density, that propagates through the medium, or a superposition of such alterations. [NIH]

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]

Spinal Nerves: The 31 paired peripheral nerves formed by the union of the dorsal and ventral spinal roots from each spinal cord segment. The spinal nerve plexuses and the spinal roots are also included. [NIH]

Spiral Lamina: The bony plate which extends outwards from the modiolus. It is part of the structure which divides trhe cochlea into sections. [NIH]

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

Stabilization: The creation of a stable state. [EU]

Stem Cells: Relatively undifferentiated cells of the same lineage (family type) that retain the ability to divide and cycle throughout postnatal life to provide cells that can become specialized and take the place of those that die or are lost. [NIH]

Stereoscopic: Accurate depth perception in the presence of binocular single vision, due to the slight disparity in the two retinal images of the same object. [NIH]

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]

Stria: 1. A streak, or line. 2. A narrow bandlike structure; a general term for such longitudinal collections of nerve fibres in the brain. [EU]

Stroke: Sudden loss of function of part of the brain because of loss of blood flow. Stroke may be caused by a clot (thrombosis) or rupture (hemorrhage) of a blood vessel to the brain. [NIH]

Stroma: The middle, thickest layer of tissue in the cornea. [NIH]

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]

Suction: The removal of secretions, gas or fluid from hollow or tubular organs or cavities by means of a tube and a device that acts on negative pressure. [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]

Symptomatic: Having to do with symptoms, which are signs of a condition or disease. [NIH]

Synapses: Specialized junctions at which a neuron communicates with a target cell. At classical synapses, a neuron's presynaptic terminal releases a chemical transmitter stored in synaptic vesicles which diffuses across a narrow synaptic cleft and activates receptors on the postsynaptic membrane of the target cell. The target may be a dendrite, cell body, or axon of another neuron, or a specialized region of a muscle or secretory cell. Neurons may also communicate through direct electrical connections which are sometimes called electrical synapses; these are not included here but rather in gap junctions. [NIH]

Synaptic: Pertaining to or affecting a synapse (= site of functional apposition between neurons, at which an impulse is transmitted from one neuron to another by electrical or chemical means); pertaining to synapsis (= pairing off in point-for-point association of homologous chromosomes from the male and female pronuclei during the early prophase of meiosis). [EU]

Synaptic Vesicles: Membrane-bound compartments which contain transmitter molecules. Synaptic vesicles are concentrated at presynaptic terminals. They actively sequester transmitter molecules from the cytoplasm. In at least some synapses, transmitter release occurs by fusion of these vesicles with the presynaptic membrane, followed by exocytosis of their contents. [NIH]

Systemic: Affecting the entire body. [NIH]

Systolic: Indicating the maximum arterial pressure during contraction of the left ventricle of

the heart. [EU]

Tardive: Marked by lateness, late; said of a disease in which the characteristic lesion is late in appearing. [EU]

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

Temporal: One of the two irregular bones forming part of the lateral surfaces and base of the skull, and containing the organs of hearing. [NIH]

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

Thoracic: Having to do with the chest. [NIH]

Thoracic Surgery: A surgical specialty concerned with diagnosis and treatment of disorders of the heart, lungs, and esophagus. Two major types of thoracic surgery are classified as pulmonary and cardiovascular. [NIH]

Threonine: An essential amino acid occurring naturally in the L-form, which is the active form. It is found in eggs, milk, gelatin, and other proteins. [NIH]

Threshold: For a specified sensory modality (e. g. light, sound, vibration), the lowest level (absolute threshold) or smallest difference (difference threshold, difference limen) or intensity of the stimulus discernible in prescribed conditions of stimulation. [NIH]

Thrombin: An enzyme formed from prothrombin that converts fibrinogen to fibrin. (Dorland, 27th ed) EC 3.4.21.5. [NIH]

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]

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]

Thyroxine: An amino acid of the thyroid gland which exerts a stimulating effect on thyroid metabolism. [NIH]

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

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

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

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

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

Trachea: The cartilaginous and membranous tube descending from the larynx and

branching into the right and left main bronchi. [NIH]

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

Transmitter: A chemical substance which effects the passage of nerve impulses from one cell to the other at the synapse. [NIH]

Transplantation: Transference of a tissue or organ, alive or dead, within an individual, between individuals of the same species, or between individuals of different species. [NIH]

Trauma: Any injury, wound, or shock, must frequently physical or structural shock, producing a disturbance. [NIH]

Trinucleotide Repeat Expansion: DNA region comprised of a variable number of repetitive, contiguous trinucleotide sequences. The presence of these regions is associated with diseases such as Fragile X Syndrome and myotonic dystrophy. Many chromosome fragile sites (chromosome fragility) contain expanded trinucleotide repeats. [NIH]

Trinucleotide Repeats: Microsatellite repeats consisting of three nucleotides dispersed in the euchromatic arms of chromosomes. [NIH]

Trisomy: The possession of a third chromosome of any one type in an otherwise diploid cell. [NIH]

Tryptophan: An essential amino acid that is necessary for normal growth in infants and for nitrogen balance in adults. It is a precursor serotonin and niacin. [NIH]

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]

Urinary: Having to do with urine or the organs of the body that produce and get rid of urine. [NIH]

Urine: Fluid containing water and waste products. Urine is made by the kidneys, stored in the bladder, and leaves the body through the urethra. [NIH]

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

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]

Venous blood: Blood that has given up its oxygen to the tissues and carries carbon dioxide back for gas exchange. [NIH]

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

Vestibule: A small, oval, bony chamber of the labyrinth. The vestibule contains the utricle and saccule, organs which are part of the balancing apparatus of the ear. [NIH]

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

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

Viral vector: A type of virus used in cancer therapy. The virus is changed in the laboratory and cannot cause disease. Viral vectors produce tumor antigens (proteins found on a tumor cell) and can stimulate an antitumor immune response in the body. Viral vectors may also be used to carry genes that can change cancer cells back to normal cells. [NIH]

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

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

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

Visceral: , from viscus a viscus) pertaining to a viscus. [EU]

Vitiligo: A disorder consisting of areas of macular depigmentation, commonly on extensor aspects of extremities, on the face or neck, and in skin folds. Age of onset is often in young adulthood and the condition tends to progress gradually with lesions enlarging and extending until a quiescent state is reached. [NIH]

Vitreous: Glasslike or hyaline; often used alone to designate the vitreous body of the eye (corpus vitreum). [EU]

Vitreous Body: The transparent, semigelatinous substance that fills the cavity behind the crystalline lens of the eye and in front of the retina. It is contained in a thin hyoid membrane and forms about four fifths of the optic globe. [NIH]

Vitreous Humor: The transparent, colorless mass of gel that lies behind the lens and in front of the retina and fills the center of the eyeball. [NIH]

Vitro: Descriptive of an event or enzyme reaction under experimental investigation occurring outside a living organism. Parts of an organism or microorganism are used together with artificial substrates and/or conditions. [NIH]

Vivo: Outside of or removed from the body of a living organism. [NIH]

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]

Wound Healing: Restoration of integrity to traumatized tissue. [NIH]

Xenograft: The cells of one species transplanted to another species. [NIH]

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

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

Zygote: The fertilized ovum. [NIH]

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

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