POLYCYSTIC KIDNEY DISEASE

A 3-in-1 Medical Reference

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

TO INTERNET REFERENCES

ICON Group International, Inc.

POLYCYSTIC KIDNEY DISEASE

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

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

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

Printed in the United States of America.

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

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

Cataloging-in-Publication Data

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

Polycystic Kidney Disease: A Bibliography and Dictionary for Physicians, Patients, and Genome Researchers/ James N. Parker and Philip M. Parker, editors
p. cm.
Includes bibliographical references, glossary, and index.
ISBN: 0-497-11275-2
1. Polycystic Kidney Disease-Popular works. I. Title.

Disclaimer

This publication is not intended to be used for the diagnosis or treatment of a health problem. It is sold with the understanding that the publisher, editors, and authors are not engaging in the rendering of medical, psychological, financial, legal, or other professional services.

References to any entity, product, service, or source of information that may be contained in this publication should not be considered an endorsement, either direct or implied, by the publisher, editors, or authors. ICON Group International, Inc., the editors, and the authors are not responsible for the content of any Web pages or publications referenced in this publication.

Copyright Notice

Acknowledgements

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

About the Editors

James N. Parker, M.D.

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

Philip M. Parker, Ph.D.

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

About ICON Health Publications

To discover more about ICON Health Publications, simply check with your preferred online booksellers, including Barnes&Noble.com and Amazon.com which currently carry all of our titles. Or, feel free to contact us directly for bulk purchases or institutional discounts:

ICON Group International, Inc.
7404 Trade Street
San Diego, CA 92121 USA
Fax: 858-635-9414
Web site: **www.icongrouponline.com/health**

Table of Contents

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 polycystic kidney disease is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about polycystic kidney disease, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to polycystic kidney disease, from the essentials to the most advanced areas of research. Special attention has been paid to present the genetic basis and pattern of inheritance of polycystic kidney disease. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on polycystic kidney disease. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to polycystic kidney disease, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. We hope these resources will prove useful to the widest possible audience seeking information on polycystic kidney disease.

The Editors

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

CHAPTER 1. STUDIES ON POLYCYSTIC KIDNEY DISEASE

Overview

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

Genetics Home Reference

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

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

What Is Polycystic Kidney Disease?[3]

Polycystic kidney disease is a disorder that affects the kidneys and other organs. Clusters of fluid-filled sacs, called cysts, develop in the kidneys and interfere with their ability to filter waste products from the blood. The growth of cysts causes the kidneys to become enlarged and can lead to kidney failure. Cysts may also develop in other organs, particularly the liver.

Frequent complications of polycystic kidney disease include dangerously high blood pressure (hypertension), pain in the back or sides, blood in the urine (hematuria), recurrent urinary tract infections, kidney stones, and heart valve abnormalities. Additionally, people

---

[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=polycystickidneydisease**.

with polycystic kidney disease have an increased risk of an abnormal bulging (an aneurysm) in a large blood vessel called the aorta or in blood vessels at the base of the brain. Aneurysms can be life-threatening if they tear or rupture.

The two major forms of polycystic kidney disease are distinguished by the usual age of onset and their pattern of inheritance. The autosomal dominant form (sometimes called ADPKD) has signs and symptoms that typically begin in adulthood, although cysts in the kidney are often present from childhood. Autosomal dominant polycystic kidney disease can be further divided into type 1 and type 2, depending on which gene is mutated. The autosomal recessive form of polycystic kidney disease (sometimes called ARPKD) is much rarer and is often lethal early in life. The signs and symptoms of this condition are usually apparent at birth or in early infancy.

How Common Is Polycystic Kidney Disease?

Polycystic kidney disease is one of the most common disorders caused by mutations in a single gene. It affects about 500,000 people in the United States. The autosomal dominant form of the disease is much more common than the autosomal recessive form. Autosomal dominant polycystic kidney disease affects 1 in 500-1,000 people, while the autosomal recessive type occurs in an estimated 1 in 20,000-40,000 people.

What Genes Are Related to Polycystic Kidney Disease?

Mutations in the **PKD1** (**http://ghr.nlm.nih.gov/gene=pkd1**), **PKD2** (**http://ghr.nlm.nih.gov/gene=pkd2**), and **PKHD1** (**http://ghr.nlm.nih.gov/gene=pkhd1**) genes cause polycystic kidney disease.

Mutations in either the PKD1 or PKD2 gene can cause autosomal dominant polycystic kidney disease. These genes provide instructions for making proteins whose functions are not fully understood. Researchers believe that they are involved in transmitting chemical signals from outside the cell to the cell's nucleus. The two proteins work together to promote normal kidney development, organization, and function. Mutations in the PKD1 or PKD2 gene lead to the formation of thousands of cysts, which disrupt the normal functions of the kidneys and other organs. People with mutations in the PKD2 gene, particularly women, typically have a less severe form of the disease than people with PKD1 mutations. The signs and symptoms, including a decline in kidney function, tend to appear later in adulthood in people with a PKD2 mutation.

Mutations in the PKHD1 gene cause autosomal recessive polycystic kidney disease. This gene provides instructions for making a protein whose exact function is unknown; however, the protein likely transmits chemical signals from outside the cell to the cell nucleus. Researchers have not determined how mutations in the PKHD1 gene lead to the formation of numerous cysts characteristic of polycystic kidney disease.

Although polycystic kidney disease is usually a genetic disorder, a small percentage of cases are not caused by gene mutations. These nonhereditary cases are called acquired polycystic kidney disease. This form of the disorder occurs most often in people who have been treated for several years with hemodialysis (a procedure that filters the blood in people with kidney failure).

How Do People Inherit Polycystic Kidney Disease?

Most cases of polycystic kidney disease have an autosomal dominant pattern of inheritance. People with this condition are born with one mutated copy of the PKD1 or PKD2 gene in each cell. In about 90 percent of these cases, an affected person inherits the mutation from one affected parent. The other 10 percent of cases result from new mutations in one of the genes and occur in people with no history of the disorder in their family.

Although one altered copy of a gene in each cell is sufficient to cause the disorder, an additional mutation in the second copy of the PKD1 or PKD2 gene may make cysts grow faster and increase the severity of the disease. The rate at which cysts enlarge and cause a loss of kidney function varies widely, and may be influenced by mutations in other, as yet unidentified, genes.

Polycystic kidney disease also can be inherited in an autosomal recessive pattern. People with this form of the condition have two altered copies of the PKHD1 gene in each cell. The parents of a child with an autosomal recessive disorder are not affected but are carriers of one copy of the altered gene.

Where Can I Find Additional Information about Polycystic Kidney Disease?

You may find the following resources about polycystic kidney disease 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.109
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK):
  http://kidney.niddk.nih.gov/kudiseases/pubs/polycystic/index.htm

MedlinePlus - Health Information

- Encyclopedia: Polycystic kidney disease:
  http://www.nlm.nih.gov/medlineplus/ency/article/000502.htm
- Health Topic: Kidney Diseases:
  http://www.nlm.nih.gov/medlineplus/kidneydiseases.html

Educational Resources - Information Pages

- American Academy of Family Physicians:
  http://familydoctor.org/142.xml
- Children's Hospital Boston:
  http://www.childrenshospital.org/az/Site1464/mainpageS1464P0.html

- Merck Manual of Medical Information, Second Home Edition:
  http://www.merck.com/mmhe/sec11/ch146/ch146k.html
- New York Online Access to Health:
  http://www.noah-health.org/en/kidver/kidney/specific/cysts.html
- Orphanet: Polycystic kidney disease, dominant type:
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=730
- Orphanet: Polycystic kidney disease, recessive type:
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=731

Patient Support - for Patients and Families

- American Association of Kidney Patients:
  http://www.aakp.org/
- Kidney and Urology Foundation of America:
  http://www.kidneyurology.org/Patient_Resources/PaR_Lib_KidneyCysts.htm
- Kidney Research UK:
  http://www.nkrf.org.uk/
- National Kidney Foundation:
  http://www.kidney.org/atoz/atozItem.cfm?id=102
- National Organization for Rare Disorders:
  http://www.rarediseases.org/search/rdbdetail_abstract.html?disname=Polycystic+Kidney+Diseases
- PKD Foundation:
  http://www.pkdcure.org/
- Resource list from the University of Kansas Medical Center:
  http://www.kumc.edu/gec/support/polycyst.html

Professional Resources

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

- Gene Reviews - Clinical summary:
  http://ghr.nlm.nih.gov/condition=polycystickidneydisease/show/Gene+Reviews;jsessionid=7A8E7723938821FA1993B0541B8BCE6D
- Gene Tests - DNA tests ordered by healthcare professionals:
  http://ghr.nlm.nih.gov/condition=polycystickidneydisease/show/Gene+Tests;jsessionid=7A8E7723938821FA1993B0541B8BCE6D
- Genetic Tools - Teaching cases:
  http://www.genetests.org/servlet/access?fcn=y&filename=/tools/cases/renal-33/
- ClinicalTrials.gov - Linking patients to medical research:
  http://clinicaltrials.gov/search/condition=%22polycystic+kidney+disease%22?recruiting=false

- PubMed - Recent literature:
  http://ghr.nlm.nih.gov/condition=polycystickidneydisease/show/PubMed;jsessionid=7A8E7723938821FA1993B0541B8BCE6D
- Online Books - Medical and science texts:
  http://books.mcgraw-hill.com/getommbid.php?isbn=0071459960&template=ommbid&c=215
- OMIM - Genetic disorder catalog:
  http://ghr.nlm.nih.gov/condition=polycystickidneydisease/show/OMIM;jsessionid=7A8E7723938821FA1993B0541B8BCE6D

References

These sources were used to develop the Genetics Home Reference condition summary on polycystic kidney disease.

- Adeva M, El-Youssef M, Rossetti S, Kamath PS, Kubly V, Consugar MB, Milliner DM, King BF, Torres VE, Harris PC. Clinical and molecular characterization defines a broadened spectrum of autosomal recessive polycystic kidney disease (ARPKD). Medicine (Baltimore). 2006 Jan;85(1):1-21. PubMed citation
- Boucher C, Sandford R. Autosomal dominant polycystic kidney disease (ADPKD, MIM 173900, PKD1 and PKD2 genes, protein products known as polycystin-1 and polycystin-2). Eur J Hum Genet. 2004 May;12(5):347-54. Review. PubMed citation
- Gene Review: Polycystic Kidney Disease, Autosomal Dominant
- Gene Review: Polycystic Kidney Disease, Autosomal Recessive
- Hateboer N, v Dijk MA, Bogdanova N, Coto E, Saggar-Malik AK, San Millan JL, Torra R, Breuning M, Ravine D. Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. Lancet. 1999 Jan 9;353(9147):103-7. PubMed citation
- Horie S. ADPKD: molecular characterization and quest for treatment. Clin Exp Nephrol. 2005 Dec;9(4):282-91. Review. PubMed citation
- Igarashi P, Somlo S. Genetics and pathogenesis of polycystic kidney disease. J Am Soc Nephrol. 2002 Sep;13(9):2384-98. Review. No abstract available. PubMed citation
- Lina F, Satlinb LM. Polycystic kidney disease: the cilium as a common pathway in cystogenesis. Curr Opin Pediatr. 2004 Apr;16(2):171-6. Review. PubMed citation
- Scriver, Charles R; The metabolic & molecular bases of inherited disease; 8th ed.; New York : McGraw-Hill, c2001. p5467-5489. NLM Catalog
- Tahvanainen E, Tahvanainen P, Kaariainen H, Hockerstedt K. Polycystic liver and kidney diseases. Ann Med. 2005;37(8):546-55. Review. PubMed citation
- Wilson PD. Polycystic kidney disease. N Engl J Med. 2004 Jan 8;350(2):151-64. Review. No abstract available. PubMed citation

A summary of the genes related to polycystic kidney disease is provided below:

What Is the Official Name of the PKD1 Gene?[4]

The official name of this gene is "polycystic kidney disease 1 (autosomal dominant)."

PKD1 is the gene's official symbol. The PKD1 gene is also known by other names, listed below.

What Is the Normal Function of the PKD1 Gene?

The PKD1 gene provides instructions for making a protein called polycystin-1. This protein is most active in kidney cells before birth; much less of the protein is made in normal adult kidneys. Although its exact function is not well understood, polycystin-1 appears to interact with a smaller, somewhat similar protein called polycystin-2.

Polycystin-1 spans the cell membrane of kidney cells, so that one end of the protein remains inside the cell and the other end projects from the outer surface of the cell. This positioning of the protein allows it to interact with other proteins, carbohydrates, and fat molecules (lipids) outside the cell and to receive signals that help the cell respond to its environment. When a molecule binds to polycystin-1 on the surface of the cell, the protein interacts with polycystin-2 to trigger a cascade of chemical reactions inside the cell. These chemical reactions instruct the cell to undergo certain changes, such as maturing to take on specialized functions. Polycystin-1 and polycystin-2 likely work together to help regulate cell growth and division (proliferation), cell movement (migration), and interactions with other cells.

Polycystin-1 is also found in cell structures called primary cilia. Primary cilia are tiny, fingerlike projections that line the small tubes where urine is formed (renal tubules). Researchers believe that primary cilia sense the movement of fluid through these tubules, which appears to help maintain the tubules' size and structure. The interaction of polycystin-1 and polycystin-2 in renal tubules promotes the normal development and function of the kidneys.

What Conditions Are Related to the PKD1 Gene?

Polycystic Kidney Disease - Caused by Mutations in the PKD1 Gene

More than 250 mutations in the PKD1 gene have been identified in people with polycystic kidney disease. These mutations are responsible for about 85 percent of cases of autosomal dominant polycystic kidney disease (ADPKD), which is the most common type of this disorder. Mutations in the PKD1 gene include deletions or insertions of DNA building blocks (base pairs) and alterations of one or more base pairs. Most PKD1 mutations are predicted to produce an abnormally small, nonfunctional version of the polycystin-1 protein. Although researchers are uncertain how a lack of polycystin-1 leads to the

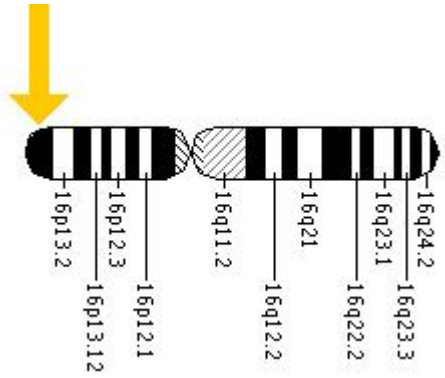
[4] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/gene=pkd1;jsessionid=7A8E7723938821FA1993B0541B8BCE6D**.

formation of cysts, it probably disrupts the protein's signaling function within the cell and in primary cilia. As a result, cells lining the renal tubules may grow and divide abnormally, leading to the growth of numerous cysts characteristic of polycystic kidney disease.

Where Is the PKD1 Gene Located?

Cytogenetic Location: 16p13.3

Molecular Location on chromosome 16: base pairs 2,078,711 to 2,125,899



The PKD1 gene is located on the short (p) arm of chromosome 16 at position 13.3.

More precisely, the PKD1 gene is located from base pair 2,078,711 to base pair 2,125,899 on chromosome 16.

References

These sources were used to develop the Genetics Home Reference gene summary on the PKD1 gene.

- Al-Bhalal L, Akhtar M. Molecular basis of autosomal dominant polycystic kidney disease. Adv Anat Pathol. 2005 May;12(3):126-33. Review. PubMed citation
- Bissler JJ, Dixon BP. A mechanistic approach to inherited polycystic kidney disease. Pediatr Nephrol. 2005 May;20(5):558-66. Epub 2005 Feb 18. Review. PubMed citation
- Boucher C, Sandford R. Autosomal dominant polycystic kidney disease (ADPKD, MIM 173900, PKD1 and PKD2 genes, protein products known as polycystin-1 and polycystin-2). Eur J Hum Genet. 2004 May;12(5):347-54. Review. PubMed citation
- Gene Review
- Horie S. ADPKD: molecular characterization and quest for treatment. Clin Exp Nephrol. 2005 Dec;9(4):282-91. Review. PubMed citation
- Lina F, Satlinb LM. Polycystic kidney disease: the cilium as a common pathway in cystogenesis. Curr Opin Pediatr. 2004 Apr;16(2):171-6. Review. PubMed citation

- Nauli SM, Alenghat FJ, Luo Y, Williams E, Vassilev P, Li X, Elia AE, Lu W, Brown EM, Quinn SJ, Ingber DE, Zhou J. Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. Nat Genet. 2003 Feb;33(2):129-37. PubMed citation
- Nauli SM, Rossetti S, Kolb RJ, Alenghat FJ, Consugar MB, Harris PC, Ingber DE, Loghman-Adham M, Zhou J. Loss of polycystin-1 in human cyst-lining epithelia leads to ciliary dysfunction. J Am Soc Nephrol. 2006 Apr;17(4):1015-25. PubMed citation
- Ong AC, Harris PC. Molecular pathogenesis of ADPKD: the polycystin complex gets complex. Kidney Int. 2005 Apr;67(4):1234-47. PubMed citation
- Scriver, Charles R; The metabolic & molecular bases of inherited disease; 8th ed.; New York : McGraw-Hill, c2001. p5467-5489. NLM Catalog
- Wilson PD. Polycystic kidney disease. N Engl J Med. 2004 Jan 8;350(2):151-64. Review. No abstract available. PubMed citation

What Is the Official Name of the PKD2 Gene?[5]

The official name of this gene is "polycystic kidney disease 2 (autosomal dominant)."

PKD2 is the gene's official symbol. The PKD2 gene is also known by other names, listed below.

What Is the Normal Function of the PKD2 Gene?

The PKD2 gene provides instructions for making a protein called polycystin-2. This protein is found in the kidneys before birth and in many adult tissues. Although its exact function is not well understood, polycystin-2 can be regulated by a larger, somewhat similar protein called polycystin-1.

Polycystin-2 likely functions as a channel spanning the cell membrane of kidney cells. In conjunction with polycystin-1, the channel transports positively charged atoms (ions), particularly calcium ions, into the cell. This influx of calcium ions triggers a cascade of chemical reactions inside the cell that may instruct the cell to undergo certain changes, such as maturing to take on specialized functions. Polycystin-1 and polycystin-2 likely work together to help regulate cell growth and division (proliferation), cell movement (migration), and interactions with other cells.

Polycystin-2 is also active in other parts of the cell, including cellular structures called primary cilia. Primary cilia are tiny, fingerlike projections that line the small tubes where urine is formed (renal tubules). Researchers believe that primary cilia sense the movement of fluid through these tubules, which appears to help maintain the tubules' size and structure. The interaction of polycystin-1 and polycystin-2 in renal tubules promotes the normal development and function of the kidneys.

---

[5] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/gene=pkd2**.

What Conditions Are Related to the PKD2 Gene?

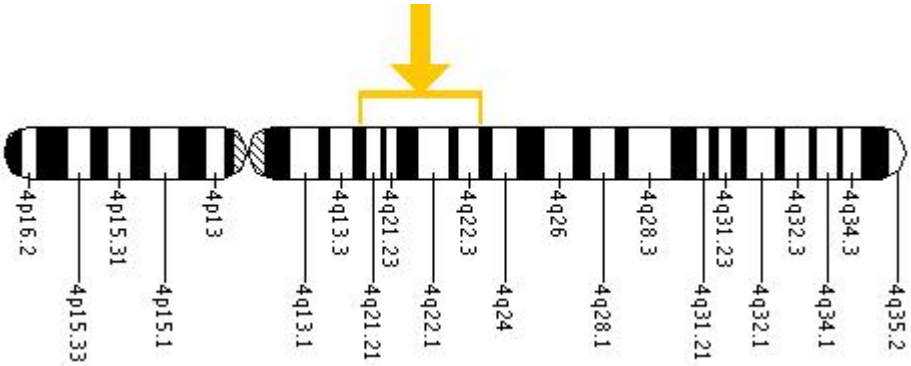
Polycystic Kidney Disease - Caused by Mutations in the PKD2 Gene

More than 75 mutations in the PKD2 gene have been identified in people with polycystic kidney disease. These mutations are responsible for about 15 percent of all cases of autosomal dominant polycystic kidney disease (ADPKD), which is the most common type of this disorder. Mutations in the PKD2 gene include changes in single DNA building blocks (base pairs) and deletions or insertions of a small number of base pairs in the gene. Most PKD2 mutations are predicted to result in the production of an abnormally small, nonfunctional version of the polycystin-2 protein. Although researchers are uncertain how a lack of polycystin-2 leads to the formation of cysts, it likely disrupts the protein's interaction with polycystin-1 and alters signaling within the cell and in primary cilia. As a result, cells lining the renal tubules may grow and divide abnormally, leading to the growth of numerous cysts characteristic of polycystic kidney disease.

Where Is the PKD2 Gene Located?

Cytogenetic Location: 4q21-q23

Molecular Location on chromosome 4: base pairs 89,147,843 to 89,217,952



The PKD2 gene is located on the long (q) arm of chromosome 4 between positions 21 and 23.

More precisely, the PKD2 gene is located from base pair 89,147,843 to base pair 89,217,952 on chromosome 4.

References

These sources were used to develop the Genetics Home Reference gene summary on the PKD2 gene.

- Al-Bhalal L, Akhtar M. Molecular basis of autosomal dominant polycystic kidney disease. Adv Anat Pathol. 2005 May;12(3):126-33. Review. PubMed citation
- Bissler JJ, Dixon BP. A mechanistic approach to inherited polycystic kidney disease. Pediatr Nephrol. 2005 May;20(5):558-66. Epub 2005 Feb 18. Review. PubMed citation

- Boucher C, Sandford R. Autosomal dominant polycystic kidney disease (ADPKD, MIM 173900, PKD1 and PKD2 genes, protein products known as polycystin-1 and polycystin-2). Eur J Hum Genet. 2004 May;12(5):347-54. Review. PubMed citation
- Gene Review
- Grimm DH, Karihaloo A, Cai Y, Somlo S, Cantley LG, Caplan MJ. Polycystin-2 regulates proliferation and branching morphogenesis in kidney epithelial cells. J Biol Chem. 2006 Jan 6;281(1):137-44. Epub 2005 Nov 8. PubMed citation
- Lina F, Satlinb LM. Polycystic kidney disease: the cilium as a common pathway in cystogenesis. Curr Opin Pediatr. 2004 Apr;16(2):171-6. Review. PubMed citation
- Nauli SM, Alenghat FJ, Luo Y, Williams E, Vassilev P, Li X, Elia AE, Lu W, Brown EM, Quinn SJ, Ingber DE, Zhou J. Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. Nat Genet. 2003 Feb;33(2):129-37. PubMed citation
- Ong AC, Harris PC. Molecular pathogenesis of ADPKD: the polycystin complex gets complex. Kidney Int. 2005 Apr;67(4):1234-47. PubMed citation
- Scriver, Charles R; The metabolic & molecular bases of inherited disease; 8th ed.; New York : McGraw-Hill, c2001. p5467-5489. NLM Catalog
- Wilson PD. Polycystic kidney disease. N Engl J Med. 2004 Jan 8;350(2):151-64. Review. No abstract available. PubMed citation

What Is the Official Name of the PKHD1 Gene?[6]

The official name of this gene is "polycystic kidney and hepatic disease 1 (autosomal recessive)."

PKHD1 is the gene's official symbol. The PKHD1 gene is also known by other names, listed below.

What Is the Normal Function of the PKHD1 Gene?

The PKHD1 gene provides instructions for making a protein called fibrocystin (sometimes known as polyductin). This protein is present in fetal and adult kidney cells, and is also present at low levels in the liver and pancreas.

Fibrocystin spans the cell membrane of kidney cells, so that one end of the protein remains inside the cell and the other end projects from the outer surface of the cell. Based on its structure, fibrocystin may act as a receptor, interacting with molecules outside the cell and receiving signals that help the cell respond to its environment. This protein also may be involved in connecting cells together (adhesion), keeping cells apart (repulsion), and promoting the growth and division of cells (proliferation).

Fibrocystin is also found in cell structures called primary cilia. Primary cilia are tiny, fingerlike projections that line the small tubes where urine is formed (renal tubules).

---

[6] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/gene=pkhd1;jsessionid=7A8E7723938821FA1993B0541B8BCE6D**.

Researchers believe that primary cilia play an important role in maintaining the size and structure of these tubules; however, the function of fibrocystin in primary cilia remains unclear.

What Conditions Are Related to the PKHD1 Gene?

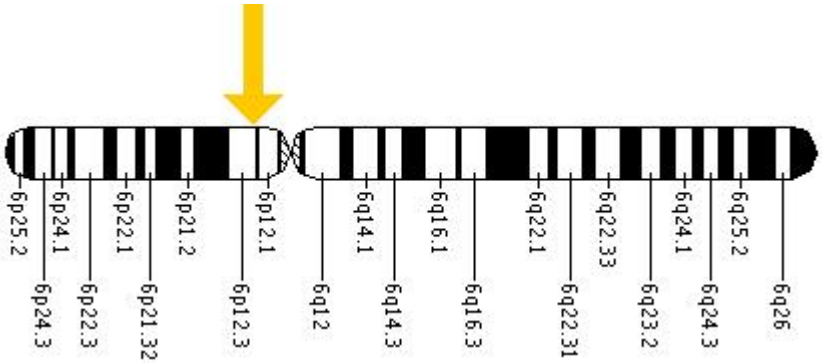
Polycystic Kidney Disease - Caused by Mutations in the PKHD1 Gene

More than 270 mutations in the PKHD1 gene have been identified in people with polycystic kidney disease. These mutations cause autosomal recessive polycystic kidney disease (ARPKD), which is a severe type of the disorder that is usually evident at birth or in early infancy. PKHD1 mutations include changes in single DNA building blocks (base pairs) and insertions or deletions of a small number of base pairs in the gene. These mutations disrupt the normal structure and function of the fibrocystin protein, or lead to the production of an abnormally small, nonfunctional version of the protein. Researchers have not determined how these genetic changes lead to the formation of numerous cysts characteristic of polycystic kidney disease.

Where Is the PKHD1 Gene Located?

Cytogenetic Location: 6p12.2

Molecular Location on chromosome 6: base pairs 51,588,103 to 52,060,381



The PKHD1 gene is located on the short (p) arm of chromosome 6 at position 12.2.

More precisely, the PKHD1 gene is located from base pair 51,588,103 to base pair 52,060,381 on chromosome 6.

References

These sources were used to develop the Genetics Home Reference gene summary on the PKHD1 gene.

- Bergmann C, Senderek J, Kupper F, Schneider F, Dornia C, Windelen E, Eggermann T, Rudnik-Schoneborn S, Kirfel J, Furu L, Onuchic LF, Rossetti S, Harris PC, Somlo S, Guay-Woodford L, Germino GG, Moser M, Buttner R, Zerres K. PKHD1 mutations in

autosomal recessive polycystic kidney disease (ARPKD). Hum Mutat. 2004 May;23(5):453-63. Review. PubMed citation

- Bergmann C, Senderek J, Windelen E, Kupper F, Middeldorf I, Schneider F, Dornia C, Rudnik-Schoneborn S, Konrad M, Schmitt CP, Seeman T, Neuhaus TJ, Vester U, Kirfel J, Buttner R, Zerres K; APN (Arbeitsgemeinschaft fur Padiatrische Nephrologie). Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). Kidney Int. 2005 Mar;67(3):829-48. PubMed citation
- Gene Review
- Harris PC, Rossetti S. Molecular genetics of autosomal recessive polycystic kidney disease. Mol Genet Metab. 2004 Feb;81(2):75-85. Review. PubMed citation
- Lina F, Satlinb LM. Polycystic kidney disease: the cilium as a common pathway in cystogenesis. Curr Opin Pediatr. 2004 Apr;16(2):171-6. Review. PubMed citation
- Sharp AM, Messiaen LM, Page G, Antignac C, Gubler MC, Onuchic LF, Somlo S, Germino GG, Guay-Woodford LM. Comprehensive genomic analysis of PKHD1 mutations in ARPKD cohorts. J Med Genet. 2005 Apr;42(4):336-49. No abstract available. PubMed citation
- Ward CJ, Hogan MC, Rossetti S, Walker D, Sneddon T, Wang X, Kubly V, Cunningham JM, Bacallao R, Ishibashi M, Milliner DS, Torres VE, Harris PC. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. Nat Genet. 2002 Mar;30(3):259-69. PubMed citation
- Ward CJ, Yuan D, Masyuk TV, Wang X, Punyashthiti R, Whelan S, Bacallao R, Torra R, LaRusso NF, Torres VE, Harris PC. Cellular and subcellular localization of the ARPKD protein; fibrocystin is expressed on primary cilia. Hum Mol Genet. 2003 Oct 15;12(20):2703-10. Epub 2003 Aug 12. PubMed citation
- Wilson PD. Polycystic kidney disease. N Engl J Med. 2004 Jan 8;350(2):151-64. Review. No abstract available. PubMed citation

Federally Funded Research on Polycystic Kidney Disease

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

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 polycystic kidney disease.

---

[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).

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

- **Project Title: "THE EARLY COLLABORATIVE CLINICAL STUDIES IN PKD**

  Principal Investigator & Institution: Chapman, Arlene B.; Professor of Medicine; Medicine; Emory University 1784 North Decatur Road, Suite 510 Atlanta, Ga 30322

  Timing: Fiscal Year 2006; Project Start 01-FEB-2000; Project End 31-DEC-2010

  Summary: (provided by applicant): Autosomal dominant **polycystic kidney disease** (ADPKD) is a major cause of disabling morbidity and is the fourth leading cause of end-stage renal failure in the world, affecting more than 500,000 U.S. citizens and millions more worldwide. Researchers at the University of Alabama, Emory University, University of Kansas, Mayo Clinic and Washington University St. Louis joined together in 2000 to create the Consortium for Radiologic Studies of **Polycystic Kidney Disease** (CRISP-I). The primary objectives of this investigation were to: (1) Develop and test the accuracy and reproducibility of imaging techniques to monitor changes in renal cyst size and parenchymal involvement. (2) Establish and maintain a database of uniformly and accurately collected information. (3) Maintain and make available such data to facilitate the planning and implementation of clinically appropriate interventions in the near future. The goals of CRISP-I I are to extend the observations of CRISPI in order to: 1) Draw unequivocal linkage between the rate of kidney/cyst enlargement and qualitative and quantitative end-points. 2) Provide a marker of disease progression (kidney volume) sensitive and accurate enough to be used as a primary outcome marker in clinical trials aiming to forestall disease progression. 3) Develop and test other bio-markers of disease progression. The specific aims are: Aim 1: Extend the preliminary observations of CRISP-I to ascertain the extent to which quantitative (kidney volume and hepatic and kidney cyst volume) or qualitative (cyst distribution and character) structural parameters predict renal insufficiency. Aim 2: Extend the preliminary observations of CRISP-I to ascertain the extent to which age and sex-adjusted measurements of renal blood flow by MR technology predict the rate of renal growth; and, renal blood flow and kidney volume predict the rate of renal function decline in ADPKD. Aim 3: Exhaustively analyze the living database and stored biologic samples derived from CRISP-I and the CRISP-II extension to develop and test new metrics to quantify and monitor disease progression, and collect DMA samples and clinical information from CRISP family members known to have ADPKD for use in future studies to examine genotype-phenotype correlations and to identify genetic modifiers.

- **Project Title: 2005 CILIA, MUCUS, AND MUCOCILIARY INTERACTIONS GRC**

  Principal Investigator & Institution: Salathe, Matthias A.; Associate Professor; Gordon Research Conferences West Kingston, Ri 02892

  Timing: Fiscal Year 2005; Project Start 18-FEB-2005; Project End 31-JAN-2006

  Summary: The Gordon Research Conference on Cilia, Mucus, and Mucociliary Interactions, held from February 27 to March 4, 2005, at the Rancho Santa Barbara Marriott in Buellton, California, will provide a unique opportunity for scientists involved in ciliary, mucous and mucociliary research to present their latest progress and to exchange ideas, thus bringing together a very diverse group of scientists who usually do not meet. Abnormal cilia and mucus contribute to a variety of human diseases including diseases of the airways, abnormal left-right asymmetry, and **polycystic**

kidney disease to name a few. Many of these diseases have no effective or only limited treatment options. Thus, there is a clear need for a small meeting focusing on these topics. As a Gordon Research Conference, the meeting will follow the highly successful model of such conference layouts and will offer 9 plenary sessions and additional poster sessions. Three of the plenary sessions will be devoted to cilia, one to primary ciliary dyskinesia, three to mucus and mucins, and two to mucociliary interactions. The organizing committee has invited an international and diverse group of many young but also established investigators to present their work during plenary sessions. Discussions have been recognized to be vital to the success of the conference and ample time for these will be allowed between speakers during plenary sessions, facilitated by discussion leaders. Finally, poster sessions will complement the plenary sessions and free afternoons will further enable idea exchanges between scientists.

- **Project Title: A NEW GENE FAMILY AS MODIFIERS OF POLYCYSTIN SIGNALING**

  Principal Investigator & Institution: Miller, Renee M.; Neurology; University of Rochester 517 Hylan Bldg., Box 270140 Rochester, Ny 14627

  Timing: Fiscal Year 2006; Project Start 01-JAN-2007; Project End 31-DEC-2009

  Summary: (provided by applicant): Our lab is interested in the mechanosensory signaling pathways initiated at the lov-1/PC1 and pkd-2/PC2 polycystin cation channel complex. We will exploit the nematode, C. elegans, in a series of behavioral, genetic, and biochemical experiments to elucidate the role of several novel gene products in these pathways. C. elegans males exhibit a complex mating behavior program which requires intact polycystins for two distinct steps, response to contact and location of the hermaphrodite vulva. We have recently discovered five new genes named cwp1-5, expressed exclusively in male worms in the identical set of 21 sensory neurons as the polycystins, lov-1 and pkd-2. CWP1-4 proteins contain a signal sequence at the N-terminal and are predicted to be secreted, while CWP-5 contains a transmembrane domain. Behavioral analysis of cwp mutant strains reveals strong effects on mating behavior in wild type and pkd-2 (null) males. A deletion removing both cwp-2 & cwp-3 suppresses the location of vulva defect in pkd-2(null) worms. An in- frame deletion that removes the transmembrane domain of CWP-5 causes a severe (50%) response to contact defect in wild-type worms, and further reduces the response frequency in pkd-2 (null) males from 37% to 3%. This proposal focuses on uncovering the mechanistic details of how CWPs interact with polycystins and other, alternative (as yet undescribed) mechanosensory signaling pathways. Knowledge of polycystin independent pathways for mechanosensation has great relevance for the treatment of **polycystic kidney disease** (PKD), in which PC1 and/or PC2 function is lost. The two specific aims dissect the mechanisms of suppression of location of vulva defects by cwp-2&cwp-3 deletion and the response to contact defect in cwp-5(mutant) males, respectively. Each aim is composed of several sub-aims, directly testing specific hypotheses about CWP interactions, localization, and function. We propose experiments that take advantage of the unique genetic tractablity of C. elegans, such as transgenesis, RNAi, and epistasis tests. We also propose a forward genetic suppressor screen to identify additional components of signaling pathways for polycystin-dependent behaviors. The experiments we propose will provide important new data regarding the transduction of mechanical stimuli into behavioral output. PKD is the most common genetic disease in the USA. Through analysis of cwp and polycystin genes, our project will aid in the understanding of how loss of the ability to sense fluid flow in the kidney leads to dysfunction in PKD. Furthermore, characterizing new pathways that allow for

normal sensation in the absence of polycystin proteins might lead to new therapeutic approaches.

- **Project Title: ADPKD: DISEASE SPECTRUM & GENOTYPE-PHENOTYPE CORRELATIONS**

  Principal Investigator & Institution: Harris, Peter C.; Professor of Medicine; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2005; Project Start 01-AUG-2001; Project End 31-MAY-2006

  Summary: (provided by applicant): Molecular diagnosis of autosomal dominant **polycystic kidney disease** (ADPKD) has proven difficult because of genetic and allelic heterogeneity and the complex structure of the major gene, PKD1. Consequently, the degree to which the marked phenotypic variability in the severity of renal disease and expression of extrarenal manifestations correlates with genotype is largely unknown. Using recent improvements to specifically amplify the PKDI gene and temperature modulated heteroduplex analysis (TMHA), we propose to develop rapid and accurate genetic characterization of the ADPKD genes. Mutation detection rates of >80 percent for PKD1 and >90 percent for PKD2 will be achieved during the project. The fate and stability of mutant ADPKD proteins, polycystin-1 and -2, will be investigated in patient-derived lymphoblastoid cell lines, epithelial cell lines derived from a single cyst lining, and knockout mouse models of PkdI. The mutational mechanism will be further explored by the isolation of individual cyst lining, characterized by their immuno-reactivity to the polycystin proteins, using laser capture microdissection. Genetic analysis of these cells will reveal the importance of somatic events at the ADPKD genes and elsewhere for cyst initiation and expansion. Phenotype/genotype correlations will be explored in defined patient groups: renal insufficient; geographically defined without referral or recognition bias; very early onset disease; late onset disease; severe liver disease and vascular abnormalities. The ADPKD gene is known to be a strong indicator of renal disease severity (PKD1 more severe than PKD2) but the relative contribution of the two genes to extra-renal disease is unknown. The prevalence of PKD2 in the general population is also largely unknown. Correlations between the type and position of mutation in PKD1 and PKD2 will be made to the severity of renal disease and to the different phenotypic groups. These results will show if there are clear phenotype/genotype correlations, that may have prognostic implications, reveal more about the mutational mechanism and highlight important regions of the polycystin proteins. Specific mutational mechanisms, such as an early embryonic somatic mutation or the modifying effect of variants at the ADPKD allele inherited from the normal parent, will be analyzed in early onset cases. This study will help resolve questions about the mutational mechanism in ADPKD, determine the role of somatic events, show the extent to which the ADPKD genotype dictates clinical outcomes and generate phenotypically and genotypically well characterized ADPKD populations that will be suitable for testing the role of other genetic modifying factors.

- **Project Title: ANALYSIS OF CENTROSOME DYNAMICS**

  Principal Investigator & Institution: Oegema, Karen; Ludwig Institute for Cancer Research 9500 Gilman Drive La Jolla, Ca 920930660

  Timing: Fiscal Year 2006; Project Start 29-SEP-2006; Project End 31-AUG-2011

  Summary: (provided by applicant): Centrioles perform two critical functions in eukaryotes: (1) they direct the accumulation of microtubule nucleating/anchoring material to form centrosomes that play a critical role during cell division, and (2) they serve as basal bodies that direct the formation of microtubule-based cellular projections

called cilia, which perform a variety of motile and sensory functions. Centrioles duplicate precisely once per cell cycle in a process that remains poorly understood at a molecular level. Specific Aims 1 and 2 of the proposed research use the C. elegans embryo as a model system to perform a molecular characterization of the steps in the centriole duplication cycle. Comprehensive RNAi-based screens and genetic analysis in C. elegans have identified 5 proteins, in addition to ct/p-tubulin, that localize to centrioles and are required for their assembly. Of these, only two (SAS-4 and SAS-6) have the properties of stably-associated structural components. In the first aim, steps in the duplication cycle will be defined by using fluorescence-microscopy based methods to monitor the kinetics of incorporation of SAS-4 and SAS-6 into centrioles. Like SAS-4 and SAS-6, o/p-tubulin is stably incorporated into centrioles and is required for their duplication, y-tubulin, a specialized tubulin isoform implicated in microtubule nucleation also has a conserved role in centriole assembly. In the second aim, the ability to monitor the formation of centriolar substructures in living embryos will be used to identify the step(s) in the duplication cycle that require microtubule assembly and y-tubulin. A comparison of these results will indicate whether the primary role of y-tubulin is nucleation of centriolar microtubules. A mutation in the putative human homolog of SAS-4 was recently linked to autosomal recessive primary microcephaly (MCPH), a disorder associated with reduced brain size. Our work has also implicated a SAS-4-associated protein in a lethal fetal brain developmental disorder. In the final aim, a series of parallel experiments performed in C. elegans and mammalian cells will determine whether the mutations in these human disorders are associated with defects in the duplication of centrioles, or in one of their two critical functions, centrosome assembly or ciliogenesis. In humans, centrioles template the assembly of least 8 different types of cilia that propel mucus and fluids, coordinate developmental events, and move the egg and sperm during reproduction. In addition to contributing to our understanding of the regulation of brain size, characterizing how centrioles form and function during cell division and ciliogenesis will likely provide insight relevant to the diagnosis and treatment of the large spectrum of diseases associated with ciliary defects including: progressive blindness, infertility, **polycystic kidney disease,** Bardet- Biedel syndrome, hydrocephalus, and Kartagener's triad.

- **Project Title: AUTOSOMAL MUTAGENESIS AND POLYCYSTIC KIDNEY DISEASE**

  Principal Investigator & Institution: Turker, Mitchell S.; Senior Scientist; None; Oregon Health & Science University 3181 Sw Sam Jackson Pk Rd Portland, or 972393098

  Timing: Fiscal Year 2006; Project Start 15-APR-2006; Project End 31-MAR-2008

  Summary: (provided by applicant): **Polycystic kidney disease** (PKD) is characterized by kidney cysts and may account for 5-8% of all end stage renal disease in the United States. The autosomal dominant form of PKD is due to inherited mutation of either PKD1 or PKD2 and cyst formation is believed to begin with "second step" autosomal mutations that occur in kidney epithelial cells. The relationship between second step autosomal mutation and kidney cyst development in two mouse models of autosomal dominant PKD is the focus of this exploratory R21 application. The major hypothesis to be tested is that environmental and genetic approaches that increase somatic mutations in renal epithelial cells will proportionally increase cyst formation in mice heterozygous for Pkd1 or Pkd2. Two specific aims are offered. The first will use ionizing radiation to induce mutations in the right kidneys of mice whose left kidneys will be shielded from exposure. Cyst formation will then be quantified with histological methods in the exposed and shielded kidneys as a function of time after exposure. By controlling mutation induction with ionizing radiation exposure the amount of time necessary for a

somatic mutational event to translate into a kidney cyst can be determined. The second aim will use mismatch repair deficiency to increase autosomal mutations 10-fold or greater in the kidney cells. The presence of mononucleotide runs in the coding sequence of Pkd1, but not in Pkd2, is predicted to make the Pkd1 gene significantly more mutable in the mismatch repair deficient background, and thereby demonstrate a potential role for gene structure in cyst formation. Immunohistochemistry will be used in both specific aims to provide evidence that the types of mutations present in the cells surrounding the kidney cysts are consistent with the mutational approaches taken because the presence or absence of PKD protein will reflect small and large mutational events, respectively. Successful completion of the proposed experiments will provide basic information about the etiology and pathogenesis of PKD by directly demonstrating quantitative and temporal relationships between autosomal mutation and cyst formation.

- **Project Title: BUILDING A 3-DIMENSIONAL MODEL OF THE PORE OF CFTR**

  Principal Investigator & Institution: Mccarty, Nael A.; Associate Professor; School of Biology; Georgia Institute of Technology 505 10Th St Nw Atlanta, Ga 303320420

  Timing: Fiscal Year 2005; Project Start 15-SEP-2001; Project End 31-AUG-2007

  Summary: The CFTR protein forms a chloride ion channel in the plasma membranes of many epithelial cells, including cells of the kidney and gut. Mutation of the gene encoding CFTR is the primary defect in Cystic Fibrosis (CF), the most common lethal, autosomal recessive disease among Caucasians, affecting approximately 30,000 Americans. Alteration in CFTR function also plays an important role in the pathophysiology of secretory diarrhea and **polycystic kidney disease** (PKD). The basic mechanisms of permeation in this channel are not clear. It is not known which portions of the protein contribute to forming the pore, and which amino acids in those domains are involved in the biophysical processes of ion permeation. The long-term objective of this laboratory is to determine the mechanisms of permeation in CFTR. For this proposal, Specific Aim number 1 is to determine the oligometric structure of the functional CFTR channel. Specific Aim number 2 is to identify transmembrane (TM) helices that line the pore, by localization of binding sites for open-channel blockers. Specific Aim number 3 is to identify groups of amino acids that serve as determinants of anion selectivity. The proposed approach relies upon the use of molecular biological techniques (site-directed mutagenesis) combined with expression in Xenopus oocytes and quantitative biophysical assays. The working hypothesis is that the pore is lined by TM domains 5, 6, 11, and 12. To achieve these goals, whole-cell and single-channel currents will be measured to determine the kinetics of two structurally-distinct classes of pore-blocking molecules, and to determine whether their binding domains contribute to the permeation pathway. Structural elements that contribute to the architecture of the pore will be defined by comparing the ability of wildtype and mutant channels to interact with open-channel blockers. Previous studies from this laboratory have shown that blocker kinetics are highly sensitive to the structure of the pore. A region within TM6 has been identified that is critical for discrimination between different anions. This region also appears to lie close to the binding sites for pore-blocking molecules. To accurately describe the structure of this region of the channel, it is necessary to consider to contributions made from portions of the channel other than TM6. These studies will be guided by a three- dimensional model of the pore, proposed in the application, which takes into account the experimental data for TM domains 5, 6, 11, and 12. This approach hypothesizes that multiple helical domains contribute both to the binding sites for drugs and to the determinants of selectivity in the channel. A specific subset of residues that may determine the biophysical features of permeation is proposed. Testing the

importance of these residues will allow the construction of a detailed map of the conduction pathway. An improved understanding of the function of this channel will aid in the design of novel therapies for Cystic Fibrosis, secretory diarrhea, and **polycystic kidney disease.**

- **Project Title: CALCIUM REGULATION OF CAMP-DEPENDENT PROLIFERATION**

  Principal Investigator & Institution: Wallace, Darren P.; University of Kansas Medical Center Msn 1039 Kansas City, Ks 66160

  Timing: Fiscal Year 2005; Project Start 30-SEP-2005; Project End 31-AUG-2010

  Summary: Polycystic kidney diseases (PKDs) are lethal, hereditary disorders characterized by hyperplasia of the tubule epithelium, cyst formation and massive kidney enlargement. cAMP agonists, including arginine vasopressin, accelerate the proliferation of epithelial cells from PKD cysts but not from normal human kidneys (NHK). We discovered that cAMP activates extracellular signal-regulated kinases1/2[2] (ERK) in human PKD, but inhibits ERK activation in NHK cells. The molecular mechanisms underlying this phenotypic difference between PKD and NHK cells are linked to cAMP/ protein kinase A-dependent B-Raf activation of MEK and ERK, leading to increased cell proliferation. Recent studies in animals with four different genetic types of PKD showed that inhibition of renal cAMP production by vasopressin V2 receptor antagonist OPC-31260 dramatically halted cyst and kidney enlargement, demonstrating a central role for cAMP in renal cystic disease. Mutated gene products of hereditary cystic disorders are thought to cause abnormal Ca2+ levels in renal tubule cells. Recently, we found that inhibition of Ca2+ entry in mouse cortical collecting duct cells (M-1) with channel blockers or reduced extracellular [Ca2+] caused a phenotypic switch in the proliferation response to cAMP. cAMP inhibited the proliferation of M-1 cells with normal intracellular [Ca2+]; however, in M-1 cells with reduced [Ca2+] cAMP stimulated B-Raf, the MEK-ERK pathway and cell proliferation, mimicking the PKD phenotype. The central hypothesis is that in human ADPKD and ARPKD, dysfunctional Ca2+ metabolism by renal epithelial cells induces and maintains a "phenotypic switch" that uncovers a common cellular pathway leading to cAMP-dependent activation of B-Raf and ERK, and increased cell proliferation. The strength of this proposal is the use of cyst epithelial cells from two different types of human hereditary disease, ADPKD and ARPKD, to address the following specific aims: Aim 1: Determine if [Ca2+]i modifies cAMP-dependent B-Raf signaling through the MEK-ERK pathway and contributes to the phenotypic difference in between PKD and NHK cells in the cAMP mitogenic response. Aim 2. Elucidate mechanisms by which vasopressin V2 receptor agonists and antagonists adjust intracellular Ca2+ and modulate cAMP-dependent B-Raf activation and the proliferation of human PKD cells. Aim 3. Determine if selective reduction of B-Raf abundance and inhibition of B-Raf kinase activity diminish cAMP-dependent ERK activation and cell proliferation in PKD cells. The results from these studies will provide fundamentally new opportunities for developing novel small molecule therapies to slow, and possibly halt the progression of PKD in patients.

- **Project Title: CELL INTERACTIONS IN DEVELOPMENT OF THE MAMMALIAN KIDNEY**

  Principal Investigator & Institution: Mcmahon, Andrew P.; Professor; Molecular and Cellular Biology; Harvard University 1350 Massachusetts Ave Cambridge, Ma 02138

  Timing: Fiscal Year 2005; Project Start 01-SEP-1998; Project End 31-AUG-2008

  Summary: (provided by applicant): About 20 million Americans are affected each year by kidney and urological diseases. The societal and monetary cost of kidney disease is

substantial. Our interest lies in elucidating the molecular and cellular mechanisms that establish a physiological competent organ during fetal life. Simply put, how do nephrons form? A variety of experiments over the last fifty years have highlighted the importance of cell-cell interactions. In these, the ureteric bud, which gives rise to the collecting duct network of the mature kidney, induces mesenchymal precursors to transform into small epithelial tubules, the renal vesicles. The mesenchyme in turn stimulates branching growth of the ureteric epithelium leading to new rounds of tubule induction. Several members of the Wnt-family of secreted glycoproteins are expressed in different positions along the proximo-distal (cortical to medullary) axis of the ureteric epithelium. The proximal boundary of Wnt15 expression is positioned just beneath the branch tips while that of Wnt7b is more distal and extends into the ureter. We have generated mutant alleles that allow the conditional removal of Wnt l5 and Wnt7b activities and we will utilize these genetic tools to characterize the renal functions of these Wnts. One class of Wnt signal utilizes a beta-catenin:Lef/TCF transcriptional complex. B-catenin is also a possible downstream mediator of the action of **polycystic kidney disease** genes. We have developed a mouse model that removes beta-catenin activity from collecting duct epithelia. We will explore the mechanism underlying the resulting cystic phenotype. Wnt4 plays a key role in the induction of renal vesicles. Subsequent morphogenesis and patterning establishes a segmental organization that is critical to normal renal function whereby various channels, transporters and pumps are expressed at specific positions along the length of the nephron. We propose to undertake large-scale gene-expression analysis with libraries of transcriptional regulators and renal tubule specific cDNAs identified by transcriptional profiling on oligonucleotide microarrays to both characterize the process of renal tubule development and to identify potential regulatory factors of this process.

- **Project Title: CHARACTERIZATION OF THE MURINE PCY MUTATION**

  Principal Investigator & Institution: Woo, David D.; Associate Professor; Medicine; University of California Los Angeles Office of Research Administration Los Angeles, Ca 90024

  Timing: Fiscal Year 2005; Project Start 01-MAR-2002; Project End 30-NOV-2006

  Summary: Polycystic kidney diseases (PKD) are among the leading causes of progressive renal failure in children and adults. Currently, there is no known therapy that can inhibit or retard the progression to renal failure in PKD patients. Despite the recent molecular identification of PKD1 and PKD2, the two genes most commonly mutated in human PKD, the genetics and pathogenesis of renal failure in PKD remains poorly understood. Homozygous pcy/pcy mice develop a slowly progressive form PKD that has many characteristics resembling human PKD. Understanding the molecular lesion in pcy mice will provide important additional insights into the genetics and pathogenic pathways involved in the development of renal failure in PKD. This proposal aim to elucidate the molecular defect in the pcy mouse and to improve our understanding of modifier genes that determine the severity of the renal cystic disease phenotype. Towards the identification and characterization of the pcy mutation at the molecular level, we will (1) isolate the minimal pcy interval in BACs contigs using the RPCI-23 mouse genomic library for sequencing by the NIH mouse genome sequencing project and (2) identify the pcy gene by systematically characterize; candidate genes located within our pcy interval. Towards improving our understanding of modifier genes that regulates the severity of the **polycystic kidney disease** phenotype, we will (1) isolate the two mapped modifier loci into separate congenic strains using marker assisted selective breeding approaches and (2) use gene expression profiling to catalog

the set of genes that are differentially expressed in the kidneys of congenic mice with the mild PKD and in the kidneys of age matched congenic mice with the severe PKD.

- **Project Title: CILIA AND CYSTIC KIDNEY DISEASE**

  Principal Investigator & Institution: Yoder, Bradley K.; Associate Professor; Cell Biology; University of Alabama at Birmingham 1530 3Rd Avenue South Birmingham, Al 35294

  Timing: Fiscal Year 2005; Project Start 01-FEB-2004; Project End 31-JAN-2008

  Summary: (provided by applicant): The formation of cysts in the kidney is common to a number of disorders in humans, the most prominent of which is **polycystic kidney disease** (PKD). Several genes associated with PKD have been cloned and the corresponding proteins have been localized to a number of different subcellular domains; however, recent data has raised the possibility that their localization in cilia is important for normal renal physiology and for cilia function. Cilia are highly conserved organelles found on many different cell types in mammals as well as lower eukaryotic organisms where they are involved in a wide range of functions from fluid and cell movement to sensory perception and developmental patterning. In spite of these important roles, very little research has been conducted on how proteins become localized to this structure. This issue is becoming increasingly important with regards to normal tissue physiology, embryogenesis, and disease as evidenced by the developmental defects and severe pathologies seen in mice lacking normal cilia, and the recent localization of a number of proteins to cilia that are associated with human disorders such as PKD and cystic fibrosis. In light of these findings, this proposal centers on two major themes, which are to elucidate the mechanism by which proteins become targeted to cilia and to determine whether cilia dysfunction is a key contributing factor to the formation of cysts in the mammalian kidney. As a consequence of the high degree of evolutionary conservation of cilia, the approaches used in this application involve a combination of in vivo studies in mice and C. elegans as well as in vitro experiments using a cell culture system. In the first aim of this proposal, critical domains required for cilia localization will be identified within two cystic kidney disease related proteins that are found in the cilia of both C. elegans and mice. The goal of the second aim is to elucidate how these proteins are transported from their site of synthesis in the cytosol to their location in the cilia where they function. The third aim will explore whether two recently identified proteins involved in a non-PKD form of renal cystic disease in humans are also present in cilia, thus evaluating the universal nature of the association between cilia and renal cystogenesis. Finally, the fourth aim will directly evaluate the importance of cilia in the etiology of renal cystic disease using a series of conditional mutations in mice that specifically disrupt cilia formation in the kidney. These conditional mutant mice have additional benefits in that they can be used to evaluate the importance of cilia in other pathologies associated with cystic kidney disease as well as provide critical reagents, such as conditional cell lines, that will allow us to further study the role of cilia in normal physiology.

- **Project Title: CLONING & IN VIVO ROLE OF FLAGELLAR PROTEIN KINASE A**

  Principal Investigator & Institution: Howard, David R.; Biology; University of Wisconsin La Crosse La Crosse, Wi 54601

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

  Summary: Numerous diseases are caused by defective cilia and/or flagella, including primary ciliary dyskinesia, **polycystic kidney disease,** lateralization defects, Bardet-Biedl syndrome, retinal degeneration, and male infertility. All of these diseases can be caused by a variety of molecular defects, some of which have recently been uncovered

and some of which remain unknown. Progress in understanding cilia and flagella in health is largely due to the knowledge gained through basic science done in the model organism Chlamydomonas reinhardtii. The regulation of motility in cilia and flagella remains relatively poorly understood, both at a basic level and in the relationship to disease. This proposal is focused on determining the identity and the in vivo role of flagellar cAMP dependent protein kinase (PKA) in Chlamydomonas. Abundant evidence indicates that PKA regulates flagellar motility in both Chlamydomonas and humans. In Chlamydomonas, it has been shown that PKA slows the activity of dynein motors in vitro, but the in vivo role of PKA in flagella is not known. In addition, the PKA protein or gene has not been positively identified or characterized. In Aim 1, flagellar PKA proteins will be identified in an affinity-based approach using the same tools that were used to show PKA's function in vitro. This method allows the discoveries to be immediately related to previously established in vitro data. Identified PKA(s) will be partially sequence using tandem MS, and their full sequence located. A gene exists in the Chlamydomonas database that could possibly be PKA, but its predicted protein sequence does not clearly classify it as a PKA. Based on our preliminary data, there seems to be multiple PKAs in flagella. In Aim 2, cDNAs coding for flagellar PKA will be cloned and used to determine the number of different PKA transcripts that are made. In Aim 3, the in vivo role of flagellar PKA will be determined by disrupting its function, either by electroporatirig cells with biotin-PKI to inhibit kinase activity or by RNA-mediated interference (RNAi). Swimming velocity, phototaxis ability, and beat waveform parameters will then be measured. Together, this project will allow data about the in vitro control of dynein activity to be related to changes in flagellar beating in vivo. In addition the project will provide critical information about a key component of the pathway that regulates flagellar notility. An integral component of this project is the involvement of undergraduates in all aspects of the work.

- **Project Title: CONTROL OF ORIENTATION OF EPITHELIAL POLARITY**

  Principal Investigator & Institution: Mostov, Keith E.; Professor; Anatomy; University of California San Francisco 3333 California St., Ste. 315 San Francisco, Ca 941430962

  Timing: Fiscal Year 2005; Project Start 01-APR-2004; Project End 31-MAR-2009

  Summary: (provided by applicant): The kidney consists mainly of polarized epithelial cells. Proper polarization of these epithelial cells is essential for normal kidney function and is deranged in several renal diseases, such as autosomal dominant **polycystic kidney disease.** The polarization of individual cells is coordinated to form multicellular structures. For instance, the cells that line the tubules of the nephron are all oriented such that their apical surfaces face the central lumen of the tubule, while their basal surface faces towards the periphery. We have found that the establishment of cell polarity and the coordinated orientation of that polarity can be experimentally separated. We use Madin-Darby canine kidney (MDCK) cells grown in three-dimensional collagen gels, where the MDCK cells form hollow cysts lined by a monolayer of polarized epithelial cells. Expression of a dominant negative (DN) form of the small GTPase Racl causes an inversion of the orientation of polarity, so that the apical surface now points toward the periphery of the cyst, rather than towards the central lumen. DN Racl also causes impaired assembly of laminin around the cyst. Addition of exogenous laminin rescues the orientation of cell polarity. We also found that inhibition of beta1 integrin, Cdc42, or atypical Protein Kinase C (aPKC); all result in inversion of orientation of polarity. This leads to a hypothesis of a pathway that controls orientation of polarity: Raclr-> beta1-> integrin-> laminin assembly-> laminin receptor (probably beta1 integrin) -> Cdc42-> aPKC/Par3/Par6 complex. The aPKC/Par3/Par6 complex is a conserved module that controls polarization in nearly all-metazoan cells.

We will test most aspects of this model in this grant. We will test the hypothesis that laminin assembly is downstream of Racl and upstream of Cdc42. We will test the hypothesis that integrins act both upstream and downstream of laminin assembly. We will use a powerful collection of mutants in Cdc42, aPKC, Par3 and Par6 test the hypothesis that all of these proteins control orientation of polarity. This work will lead to important advances in understanding cell polarization and how the polarization of individual cells is coordinated to organize multicellular structures, such as tubules and cysts. This will be invaluable in understanding the pathogenesis of renal diseases where this polarity is deranged.

- **Project Title: CORE--PROTEOMICS RESOURCE**

  Principal Investigator & Institution: Kim, Helen; Research Associate Professor and Directo; University of Alabama at Birmingham 1530 3Rd Avenue South Birmingham, Al 35294

  Timing: Fiscal Year 2005; Project Start 30-SEP-2005; Project End 31-AUG-2010

  Summary: This Core will provide proteomics technology and support to the investigators in this proposed **polycystic kidney disease** (PKD) research group. While specific genes and mutations in the proteins encoded by the genes have been identified as starting points for ARPKD and ADPKD, the mutations affect multiple tissues, and therefore almost certainly multiple proteins other than the primary ones encoded by the mutated gene. Proteomics technology allows analysis of patterns of protein changes downstream of a primary genetic defect; we will utilize the resources and personnel of the existing DAB Comprehensive Cancer Center (CCC) Proteomics/Mass Spectrometry Shared Facility to provide proteomics and mass spectrometry capabilities toward the PKD research effort. These efforts will be directed by the existing Shared Facility directors, Drs. Helen Kim and Stephen Barnes, who bring substantial experience in providing such services to the UAB biomedical research community. The rationale for this Core is that systematic proteomic analysis of biological samples from PKD experiments that are hypothesis-driven will enhance the likelihood of identifying previously unidentified proteins or protein modifications that involved in the pathogenesis of the PKD phenotype. Such results can then identify proteins for followup studies, or to which antibodies can be raised for use by the PKD community. An important function of this Core is to provide educational support to the PKD community regarding proteomics technologies and to enable informed utilization of the core technologies by the investigators, particularly for those who have not previously accessed the technologies. These will be in the form of tutorials and/or a workshop, as well as consultation sessions involving the Core directors and individual researchers. PKD this Core services will be enhanced by having a biostatistician working closely with the Core, Dr. Meleth; PKD investigators will be strongly encouraged to consult with Dr.Meleth prior to carrying out an experiment, to insure that various quality control and experimental design issues are addressed. Finally, a research associate will be dedicated to this Core, who will process PKD samples through the appropriate 2D separations and the MS protein identifications. She will coordinate the generation of reports of the final data for each set of samples. This Core will also maintain a database of PKD proteomics data, as part of an ongoing effort by the Shared Facility.

- **Project Title: CUX-1 AND CELL CYCLE REGULATION IN PKD**

  Principal Investigator & Institution: Vanden Heuvel, Gregory B.; Assistant Professor; University of Kansas Medical Center Msn 1039 Kansas City, Ks 66160

  Timing: Fiscal Year 2005; Project Start 30-SEP-2005; Project End 31-AUG-2010

Summary: The overall aim of this proposal is to determine the role of the homeobox gene Cux-1 in cell cycle regulation in **polycystic kidney disease.** Cux-1 is the murine homologue of the Drosophila gene Cut, which is required for the proper development of the Malpighian tubules, the insect excretory and osmoregulatory organs. Mammalian Cut homologues function as transcriptional repressers of genes specifying terminal differentiation in multiple cell lineages. Cux-1 represses the expression of the cyclin kinase inhibitor (CKI) p21 in S phase and is part of the network controlling G1-S transition. Cux-1 also represses the CKI p27, and ectopic expression of Cux-1 in transgenic mice results in multiorgan hyperplasia from the aberrant down regulation of p27kip1 expression. Our recent studies demonstrate that Cux-1 is ectopically expressed in Pkd1 null kidneys, both in cystic and in normal tubule epithelial cells. Moreover, p27 is down regulated in Pkd1 null kidneys. Cux-1 is proteolytically processed during the cell cycle by a nuclear isoform of Cathepsin L, converting Cux-1 from a full length protein that represses p27, to a truncated protein with a distinct DNA binding activity. Recent studies show that Cathepsin L is reduced in nuclear extracts of human ADPKD cells, compared to normal human kidney cells, and this is associated with increased levels of the full length Cux-1 protein. Moreover, cpk mice bearing a deletion of one Cathepsin L site in Cux-1, called Cux-1 DCR1, exhibit cystic kidneys significantly larger than cystic kidneys of cpk mice alone. The proposed studies will test the hypotheses that deregulation of Cux-1 is required for the proliferative defects observed in **polycystic kidney disease** and that changes in Cux-1 expression and/or function modify the severity of the disease. We will use a genetic approach to introduce a loss-of-function Cux-1 mutation into kidney specific Pkd1 null murine models of **polycystic kidney disease** to determine whether Cux-1 is required to develop cysts. We will analyze cells isolated from these mice to determine the functional role of Cux-1 in regulating the cell cycle in PKD. Finally, we will analyze cell cycle regulated proteolytic processing of Cux-1 to determine whether reduced processing of Cux-1 in PKD contributes to deregulated cell proliferation. These studies will provide novel insights into the mechanisms of cell proliferation in **polycystic kidney disease.**

- **Project Title: CYSTIC DILATATION OF NEPHRONS IN TRANSGENIC INV MICE**

  Principal Investigator & Institution: Phillips, Carrie L.; Assistant Professor; Medicine; Indiana Univ-Purdue Univ at Indianapolis 620 Union Drive, Room 618 Indianapolis, in 462025167

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

  Summary: (provided by applicant): Congenital and inherited polycystic renal disorders are among the most frequent primary diagnoses in children with chronic kidney disease and are responsible for 15% of renal transplants. Inherited polycystic kidney diseases (PKD) of childhood include nephronophthisis, autosomal recessive **polycystic kidney disease** and medullary cystic kidney disease. Nephronophthisis is the most common cause of end stage renal disease in children and young adults and the infantile form (NPHP2) has recently been linked to mutations in the inv gene. The function of inversin, the inv gene product, is not known. We developed antibodies to inversin that localized to plasma membranes, nuclei, perinuclear cytoplasm and primary cilia, and co-immunoprecipitated with proteins involved in junctional complexes, axis development and PKD, i.e. N-cadherin and beta-catenin. We found fusiform cysts in proximal tubules and collecting ducts of inv/inv mice. Cilia are implicated in the formation of renal cysts and many PKD-associated proteins have been localized to cilia, including polaris, cystin and polycystins-1 and -2. We propose to define the function of inversin by determining its interaction with other PKD-associated proteins. Our long-term objective is to determine how defective proteins in cilia or plasma membranes lead to PKD so that

therapeutic modalities may be developed. Our immediate objective is to establish the molecular and cellular basis of PKD by investigating the functional relationship of inversin with known PKD-associated proteins including the polycystins, cadherins and catenins. We hypothesize that inversin interacts with the polycystins, cadherins and catenins in normal development and maturation of renal epithelium. This interaction allows renal epithelial cells to progress through developmental checkpoints by integrating junctional complexes with cilia. Our general strategy is to study the potential role of inversin in the multi-protein polycystin/PKD complex by applying techniques of functional genomics to established culture model systems. We propose one overall specific aim with two components. First, we will determine the structural and functional significance of inversin in renal development by blocking in vitro translation of inversin in cultured renal epithelial cells and transfilter embryonic kidney cultures. Second, we will identify crucial binding partners of inversin in these cultured systems by blocking in vitro translation and assaying for changes in PKD-associated proteins.

- **Project Title: CYSTIN, A LIPID RAFT AND CILIA-ASSOCIATED PROTEIN IN PKD**

  Principal Investigator & Institution: Guay-Woodford, Lisa M.; Professor of Medicine; Medicine; University of Alabama at Birmingham 1530 3Rd Avenue South Birmingham, Al 35294

  Timing: Fiscal Year 2005; Project Start 15-MAR-2000; Project End 30-JUN-2009

  Summary: (provided by applicant): Primary cilia are dynamic, complex structures that contain >250 proteins, including several **polycystic kidney disease** (PKD)-related proteins. In renal epithelial cells, the primary apical cilium appears to be a major effector of differentiation signals and to play a critical role in PKD pathogenesis. Recent in vitro studies demonstrate that the primary cilium acts as a cellular sensor, transducing apical mechanical signals through a polycystin-1/polycystin-2-dependent Ca++ signaling pathway. However, the precise mechanisms involved in cilia formation, stabilization, and signal transduction are not well-defined and even less is known about how these cilia-associated proteins are targeted to cilia and functionally assembled. We have identified Cys1 as the disease-gene in cpk mice; demonstrated that its novel protein product, cystin, localizes to the primary apical cilium; and determined that cystin fractionates with lipid rafts through an N-terminal domain, probably the predicted N-myristoylation/ polybasic motif. We hypothesize that cystin traffics to the primary cilium via lipid raft-mediated mechanisms, associates with the cilial membrane, and serves as part of the molecular framework that stabilizes the microtubular scaffold of the ciliary axoneme. Using a suite of stably transfected cell lines that express wild-type cystin and various truncation mutants as GFP-tagged fusion proteins, we have determined that the N-terminal domain is necessary but not sufficient for targeting cystin to cilia and a second, novel signal is required. Since cystin is expressed at low levels and no functional assays currently exist, we have developed an innovative set of strategies to further characterize this novel protein and its intracellular trafficking itinerary as first steps toward defining its function. Specifically, in this proposal, we will: 1) Determine whether cystin tagged with green fluorescent protein (cystin-GFP) rescues the cpk phenotype and targets correctly to the primary cilium of renal epithelia in vivo; 2) Characterize cystin with respect to the predicted N-myristoylation site, putative cilia-targeting signals, and putative interacting partners; and 3) Examine the dynamics of cystin intracellular trafficking to the primary apical cilium. The central hypotheses underlying the proposed studies are that defects in primary cilia function impair the terminal phases of renal tubulo-epithelial differentiation and the epithelial response to this developmental arrest is cyst formation. Therefore, primary apical cilium represents

a new focal point for dissecting the complex mechanisms involved in renal cystic disease and ultimately, perhaps a new target for therapeutic interventions.

- **Project Title: DATA COORDINATING AND IMAGE ANALYSIS FOR CRISP-II**

  Principal Investigator & Institution: Bae, Kyongtae T.; Associate Professor; Radiology; Washington University 1 Brookings Dr, Campus Box 1054 Saint Louis, Mo 631304899

  Timing: Fiscal Year 2006; Project Start 30-SEP-1999; Project End 31-JUL-2006

  Summary: (provided by applicant): Autosomal dominant **polycystic kidney disease** (ADPKD) is a major cause of disabling morbidity and is the fourth leading cause of end-stage renal failure in the world, affecting more than 500,000 U.S. citizens and millions more worldwide. Researchers at the University of Alabama, Emory University, University of Kansas, Mayo Clinic and Washington University St. Louis joined together in 2000 to create the Consortium for Radiologic Studies of **Polycystic Kidney Disease** (CRISP-I). The primary objectives of this investigation were to: (1) Develop and test the accuracy and reproducibility of imaging techniques to monitor changes in renal cyst size and parenchymal involvement. (2) Establish and maintain a database of uniformly and accurately collected information. (3) Maintain and make available such data to facilitate the planning and implementation of clinically appropriate interventions in the near future. The goals of CRISP-I I are to extend the observations of CRISPI in order to: 1) Draw unequivocal linkage between the rate of kidney/cyst enlargement and qualitative and quantitative end-points. 2) Provide a marker of disease progression (kidney volume) sensitive and accurate enough to be used as a primary outcome marker in clinical trials aiming to forestall disease progression. 3) Develop and test other bio-markers of disease progression. The specific aims are: Aim 1: Extend the preliminary observations of CRISP-I to ascertain the extent to which quantitative (kidney volume and hepatic and kidney cyst volume) or qualitative (cyst distribution and character) structural parameters predict renal insufficiency. Aim 2: Extend the preliminary observations of CRISP-I to ascertain the extent to which age and sex-adjusted measurements of renal blood flow by MR technology predict the rate of renal growth; and, renal blood flow and kidney volume predict the rate of renal function decline in ADPKD. Aim 3: Exhaustively analyze the living database and stored biologic samples derived from CRISP-I and the CRISP-II extension to develop and test new metrics to quantify and monitor disease progression, and collect DMA samples and clinical information from CRISP family members known to have ADPKD for use in future studies to examine genotype-phenotype correlations and to identify genetic modifiers.

- **Project Title: DATA COORDINATING CENTER FOR PKD TREATMENT NETWORK**

  Principal Investigator & Institution: Miller, J. Philip.; Professor; Biostatistics; Washington University 1 Brookings Dr, Campus Box 1054 Saint Louis, Mo 631304899

  Timing: Fiscal Year 2005; Project Start 15-AUG-2002; Project End 31-JAN-2009

  Summary: (provided by applicant): Washington University proposes to establish the Data Coordinating Center (DCC) for the **Polycystic Kidney Disease** Treatment Network (PKD-TN) within the Division of Biostatistics. WU performs a similar function for the NIDDK-sponsored CRISP study that is developing imaging parameters to follow the progression of **Polycystic Kidney Disease** (PKD). WU generally, and this investigative team specifically, has a strong record of experience as the DCC for multicenter studies. The DCC will participate as a key member of the Steering Committee, taking a leadership role in planning the studies, leading the statistical analyses and reporting of these studies. A web-based data entry system, based on the one currently being used for

CRISP, will be customized for the needs of the PKD-TN. The DCC will serve as the communications hub for the PKD-TN, arranging meetings, telephone and electronic communications and producing and archiving study-related documents. A three-group, double-masked, randomized, multicenter, placebo-controlled trial will address whether either an ACE inhibitor or an angiotensenin 2 antangonist will retard the progression of renal impairment in PKD. The trial will enroll 1,800 PKD subjects with a wide range of renal function and follow them for 3-5 years. The primary endpoint will be that of time to death, ESRD or a doubling of the serum creatinine level. GFR levels will be assessed annually with a central laboratory and will be used as a secondary endpoint. The GFR measurements will allow us to address questions about variations in treatment effect according to the severity of renal impairment and the presence of common features of the disease such as hypertension and proteinuria. Blood and urine samples will be collected at baseline and annually and stored in the NIDDK's repository for future pharmocogenitic studies and future studies of biomarkers of the progression of PKD. An early Phase II trial of BMP-7, a cytokine which has an essential role in coordinating the formation of the emerging metanephos, is proposed. BMP-7 has been shown to maintain renal function in animal models with acute and chronic renal disease and to reduce renal hypertrophy. A simple, two-group, placebo controlled, randomized clinical trial will be conducted to determine whether BMP-7 can retard the growth rate of the kidneys in PKD subjects. MRI-based imaging will be used to measure kidney size for the trial.

- **Project Title: FIBROTIC SEQUELAE OF CHILDHOOD RENAL DISEASE**

  Principal Investigator & Institution: Fogo, Agnes B.; Professor; Pathology; Vanderbilt University Medical Center Nashville, Tn 372036869

  Timing: Fiscal Year 2005; Project Start 01-APR-1992; Project End 31-MAR-2007

  Summary: (provided by applicant) This competing renewal of our Pediatric Center Grant will focus on fibrotic sequelae of childhood renal diseases. The first project, with Dr. Fogo as the PI will focus on tubular interstitial fibrosis mechanisms related to angiotensin and plasminogen activator inhibitor-1. The second project with Dr. Ichikawa as PI will focus on the function of the renin angiotensin system in the macrophage and its contribution to interstitial fibrosis. The third project, headed by Dr. Kon, will focus on the role of the renin angiotensin system in the macrophage in atherosclerosis. The fourth project headed by a new member of the center grant, Dr. Allison Eddy at the Children's and Regional Medical Center, Seattle, will focus on macrophage scavenger receptors and their processing of low density lipoproteins and impact on renal fibrosis. Three pilot projects include a clinical pilot study (Dr. Jabs, PI) to establish measures of carotid artery intima media thickness in children with chronic kidney disease as a marker of cardiovascular disease risk; a basic science study (Dr. Upadhya, PI) investigating pathogenesis of fibrosis in a model of **polycystic kidney disease** and lastly a pilot study (Dr. Matsusaka, PI) to determine mechanisms of podocyte injury in novel transgenic animal models with HIV infection. These projects will be supported by an animal genotyping and phenotyping core and administrative core.

- **Project Title: FLOW EFFECTS ON PRIMARY CILIUM DEFLECTION**

  Principal Investigator & Institution: Resnick, Andrew; Physiology and Biophysics; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

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

Summary: (provided by applicant): Dr. Resnick is a physicist committed to establishing a career in systems biology research and a research program designed to study cell signaling. His short-term career goals are to develop solid foundations in electrophysiological and immunostaining experimental techniques, protein function, cell biology and current medical practices. The proposed career development plan will train Dr. Resnick in 1) electrophysiological experimental techniques and immunofluorescent methods; 2) Cell biology, and the functional roles of cell signaling molecules; and 3) independent career development and translational research. Mentors at Case Western Reserve University (CWRU), and University Hospitals (UH) will provide training and expertise, and monitor and support Dr. Resnick's career advancement. The existing collaborative nature of this research and training environment is suited to the multi-disciplinary nature of the project and Dr. Resnick's career goals in biomedical research. The research plan will investigate the possible role of the primary cilium in renal epithelial cells as a mechanical sensor of the cell's external fluid environment, and the metabolic pathways that are regulated by that sensing mechanism. First, renal epithelial cells will be cultured and placed within a calibrated flow chamber, and their cilia monitored. Second, laser tweezers will be used to manipulate the cilia in a controlled fashion. Calcium imaging will be performed to determine the metabolic effects of cilia deformation. It is theorized that improper functioning of the cilia leads to **polycystic kidney disease** via improper regulation of angiotensin II; understanding and validating this model could lead to effective treatments by developing targeted drugs. This career development plan will establish Dr. Resnick as an independent investigator in biomedical research and prepare him to lead research efforts in the development of cell regulatory models.

- **Project Title: FUNCTION AND REGULATION OF POLYCYSTIN-2**

  Principal Investigator & Institution: Ehrlich, Barbara E.; Professor; Yale University 47 College Street, Suite 203 New Haven, Ct 065208047

  Timing: Fiscal Year 2005; Project Start 30-SEP-2005; Project End 31-AUG-2010

  Summary: This project examines the properties of polycystin-2 (PC2) as an intracellular calcium channel. In this project two classes of potential regulators will be tested where each regulator is part of the complex or cascade. The consequences of disrupting the regulation on the intracellular calcium signaling and on the subsequent downstream signaling will be tested. The results obtained from these experiments will identify regulatory factors that modulate the activity of PC2, will outline the molecular basis for these interactions and how they are regulated, and will suggest downstream targets for the siganling cascade. The hypotheses to be tested are: 1) The interactions between PC1 and PC2 are functional and can be predicted from the molecular properties of PC2. 2) PC2 and the ryanodine receptor (RyR) make a channel complex where PC2 regulates the activity of the RyR which then can modulate global intracellular calcium signaling. 3) Changes in the regulation of the channel complex will modify intracellular calcium signaling, and downstream signaling in intact cell. These changes will have consequences on organs in the intact animal. The preliminary results presented here show that PC2 has several protein partners and that these associated proteins are important for regulating the channel complex. The experiments outlined in this project will investigate the functional properties of PC2 at the single channel level and will correlate the channel properties with cell and organ function. The results to be obtained may determine the mechanism of action of PC2 at a molecular level and may suggest useful treatments for individuals affected with **polycystic kidney disease.**

- **Project Title: FUNCTION OF THE RAS RELATED RAL PROTEINS**

  Principal Investigator & Institution: Feig, Larry A.; Professor; Biochemistry; Tufts University Boston 136 Harrison Avenue Boston, Ma 02111

  Timing: Fiscal Year 2005; Project Start 01-FEB-1992; Project End 31-MAR-2009

  Summary: (provided by applicant): The overall goal of this proposal is to gain a better understanding of the functions of the Ras related Ral- GTPase family. RalA and RalB have been implicated in diverse cell functions including the control of vesicle sorting, gene expression and cell proliferation. As GTPases, Ral proteins function as molecular switches to transmit extracellular signals to specific intracellular signaling cascades. Ral proteins reach the active GTP bound state in cells by interacting with one of a family of Ral-specific guanine nucleotide exchange factors (Ral-GEFs). One class of Ral-GEFs binds to and is activated by GTP-bound Ras, and a growing body of evidence supports the idea that elevated Ral-GEF/Ral signaling has the potential to contribute to human oncogenesis. This proposal will attempt to reveal the mechanisms underlying two newly identified processes by which the Ral-GEF, Ral-GDS, is regulated. One process positively regulates Ral-GEF activity through interaction with the PDK1 protein kinase, and the other negatively regulates Ral-GEF activity through protein kinase D-mediated phosphorylation. Active GTP-bound Ral proteins bind to and alter the activity of a set of downstream "effector" proteins to influence cellular processes. Studies in this proposal will expand upon our recent finding that RalA but not RalB functions in the maintenance of cellular polarity by enhancing the rate of delivery of membrane proteins to the basolateral surface of epithelial cells through its newly identified effector, the exocyst, and possibly through an exocyst-independent mechanism. Thus, one set of goals is to define the biochemical basis for the difference in activities of these two closely related Ral family members. Another goal is to identify the additional RalA "effector" that participates in basolateral membrane delivery. We also plan to define how RalA binding to the exocyst or other Ral effectors promotes membrane delivery in MDCK epithelial cells. Understanding how Ral functions in this process is important because faulty delivery and polarization of membrane proteins can lead to serious diseases including cystic fibrosis, I cell disease, familial, **polycystic kidney disease** and possibly cancer. Finally, there is a growing appreciation that Ral-GEFs contribute to downstream signaling from GTPases by mechanisms that are independent from their ability to activate GTPases. Therefore, another aim of this proposal is to evaluate the contribution of Ral-GEF binding proteins for their ability to contribute functions that complement those of active Ral in cell processes mediated by the Ral-GEF/Ral signaling cascade.

- **Project Title: FUNCTIONAL CHARACTERIZATION OF THE GENE NPHP4**

  Principal Investigator & Institution: Hildebrandt, Friedhelm; Professor; Pediatrics and Communicable Diseases; University of Michigan at Ann Arbor 3003 South State Street, Room 1040 Ann Arbor, Mi 481091274

  Timing: Fiscal Year 2005; Project Start 01-JUN-2004; Project End 31-MAY-2008

  Summary: (provided by applicant): Functional characterization of the gene (NPHP4) causing nephronophthisis type 4. Nephronophthisis (NPHP), an autosomal-recessive cystic kidney disease, constitutes the most frequent genetic cause of chronic renal failure in the first two decades of life. Histologically, the disease is characterized by disrupted tubular basement membrane structure, renal tubular cell atrophy, interstitial fibrosis and cyst formation. In a subset of patients with NPHP there is an association with retinitis pigrnentosa, known as Senior-Loken syndrome (SLS). We have previously identified by positional cloning the gene (NPHP1) for juvenile nephronophthisis. Its gene product "nephrocystin" interacts with signaling proteins that regulate actin

organization in the cytoskeleton. We have also identified by positional cloning the gene (NPHP3), mutations in which cause NPHP type 3 and the mouse renal cystic phenotype pcy. In addition, using a candidate approach, we have identified mutations in the human inversin gene as causing NPHP type 2 and demonstrated its expression in primary cilia of renal tubule cells, thus linking the pathogenesis of NPHP to disease mechanisms of **polycystic kidney disease.** Recently, we have identified by positional cloning the gene (NPHP4) causing NPHP type 4 and SLS type 4. NPHP4 is unique to human and mouse genomes and encodes a novel protein, nephroretinin, which is conserved in the nematode C. elegans. We generated first functional data by demonstrating that, i) nephroretinin is expressed in primary cilia of renal epithelial cells, ii) nephroretinin localizes to specific cUiated neurons in C. elegans which express other proteins relevant for renal cystic disease, and iii), NPHP4 mutations exhibit oligogenic inheritance with other NPHP genes. This proposal is aimed at the functional characterization of the novel NPHP4 gene product "nephroretinin" that we identified. Specifically, we propose to: 1) Determine how oligogenic mutations in nephronophthisis genes influence genotype/phenotype relationships; 2) Characterize the function of the NPHP4 gene and its role in the pathogenesis of NPHP type 4; 3) Generate and characterize mouse models of targeted disruption of the Nphp4 and Nphpl genes. Since nephroretinin represents a novel gene product, we expect these studies to provide new insights into disease mechanisms of renal interstitial fibrosis and cyst development in developing and adult kidney and into the function of the retina.

- **Project Title: G PROTEIN SIGNALING IN POLYCYSTIC KIDNEY DISEASE**

  Principal Investigator & Institution: Denker, Bradley M.; Associate Physician; Brigham and Women's Hospital Research Administration Boston, Ma 02115

  Timing: Fiscal Year 2005; Project Start 30-SEP-2005; Project End 31-AUG-2010

  Summary: Polycystic kidney disease (PKD) accounts for 5-10% of patients on dialysis and is an enormous personal and economic burden. Autosomal dominant PKD results from mutations in two genes, PKD1 or PKD2 and their protein products polycystin-1, and -2 (PC1, PC2). Cysts develop in PKD, in part, from abnormalities in cell growth and apoptosis signaling pathways. G proteins mediate numerous signaling pathways including growth/apoptosis. We have identified important roles for Ga12 in epithelial cells and identified novel activation of ser/thre phosphatase (PP2A). PC1 signals through G proteins, and we have confirmed binding of both Ga12 and PP2A to the C-terminus of PC1. We hypothesize that the PC1 C-terminus organizes a multiprotein signaling complex containing Ga12 and PP2A, and we predict that PC1/Ga12/PP2A interactions are critical for PC1 functions. The long-term objectives are to identify mechanisms (and potential therapies) mediated by these interactions that lead to changes in cell growth and apoptosis. The goals of this proposal are to characterize how PC1/Ga12/PP2A modulates down stream signaling and affects protein interactions and phosphorylation within the PC1 signaling complex. In Aim 1, the domains of Ga12 and PC1 necessary for interaction will identified through mutatgenesis and chimera studies, and effects of PC1 on Ga12 function characterized. The mechanism of PP2A binding to PC1 C-terminus will also be elucidated. In Aim 2, MDCK cell lines with inducible Ga12 and activated Ga12 (Q229L) will be used with adenoviral expression of PC1 and the PC1 C-terminal domain to determine the role of Ga12 and PP2A (with inhibitors) on phosphorylation of PC1 and interacting proteins, PC2, fibrocystin, E-cadherin and b-catenin. In Aim 3, growth and apoptosis mediated by PC1/Ga12/PP2A will be determined in cultured cells. In addition, a proximal tubule animal model of activated Ga12 will be established by creating a floxed Q229L Ga12 transgenic mouse that will be crossed gGT-Cre mice. This model will extend findings obtained from in-vitro studies.

Therapies to stop or reverse the enlarging cysts in patients with PKD have been lacking. Disturbances in cell growth and cell death in the kidney are fundamental to cyst formation and the development of kidney failure. Results from these studies will permit new understanding of how certain signals that normally regulate cell growth and death are altered in PKD. This will lead to new approaches for treatment of PKD.

- **Project Title: GENETIC ANALYSIS /EARLY DEVELOPMENT /DISEASES IN ZEBRAFI**

  Principal Investigator & Institution: Sun, Zhaoxia; Assistant Professor; Yale University 47 College Street, Suite 203 New Haven, Ct 065208047

  Timing: Fiscal Year 2005; Project Start 30-SEP-2005; Project End 31-AUG-2010

  Summary: PKD (**polycystic kidney disease**) is characterized by the formation of multiple kidney cysts that are thought to result from over-proliferation of renal epithelial cells. PKD affects more than 600,000 Americans and half of the patients will progress into end stage renal disease by the age of 60. Presently, no cure is available for this devastating illness. Recent progresses in PKD research suggest that in vertebrates, the cilium, protruding from apical surface of epithelial cells into tube lumen, may act as a sensor for environmental antiproliferative signals. Defects in cilia formation and function can therefore lead to cell over-proliferation and eventual cyst formation. Presently, the best understood aspect of cilia assembly is IFT (intraflagellar transport), microtubule based motility essential for transporting cargoes for cilia assembly. However, how this motility is regulated is poorly understood. This project focuses on seahorse, a cystic kidney mutant we isolated in a genetic screen in zebrafish along with three IFT genes, seahorse mutant show almost identical phenotypes as IFT mutants, indicating that Seahorse protein may be involved in the same pathway as IFT proteins. Interesting, seahorse encodes a highly conserved novel non-IFT protein. In addition, Seahorse protein contains leucine-rich repeats, suggesting that it may be involved in multi-protein complexes. In this project, we will start by characterizing seahorse gene and gene product in detail with in situ, immuno-staining and eGFP tagging. In Aim 2, we will analyze the cellular basis of seahorse phenotype by examining cell proliferation, apoptosis and cilia formation in seahorse mutants. In Aim 3, we will dissect the function seahorse first by testing its interaction with IFT genes. We will then use yeast two-hybrid screen and tandem affinity purification to identify binding partners of Seahorse. Finally, in Aim 4, we will collaborate with Somlo lab to test whether the function of seahorse is conserved in mammalian cells. Together, these experiments will shed light on the function of seahorse, a non-IFT gene, in cilia assembly and cyst formation.

- **Project Title: GENETIC AND MOLECULAR MECHANISMS OF RENAL INJURY**

  Principal Investigator & Institution: Abboud, Hanna E.; Professor; Medicine; University of Texas Hlth Sci Ctr San Ant 7703 Floyd Curl Dr San Antonio, Tx 78229

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

  Summary: (provided by applicant) This is a revised application in response to RFA: DK-02-028 for the establishment of the George M. O'Brien Kidney Research Center at the University of Texas Health Science Center. The application focuses on the response of the kidney to diverse forms of injury with the goal of identifying genetic factors and mechanisms of development of diabetic and **polycystic kidney disease.** The Center is composed of three scientific projects, one core, and three feasibility/developmental projects that bring together scientists from the Departments of Medicine, Cell and Structural Biology, Physiology, and the Institute of Biotechnology at the University of Texas Health Science Center at San Antonio and the Department of Genetics at the

Southwest Foundation for Biomedical Research. In Project 1, Dr. Abboud will investigate a positional candidate gene, tight junction protein-1 (TJP-1) to identify DNA sequence variants that are responsible for the linkage to albuminura. In Project 2, Dr. Kasinath will explore the signaling mechanisms by which hyperinsulinemia results in protein translation and matrix accumulation in the db/db mouse model of type II diabetes. In Project 3, Dr. Chen, will explore the role of nekl kinase in the pathogenesis of **polycystic kidney disease.** In Project 4 (Development/Feasibility) Dr. Pergola explores microcirculatory responses to manipulations of the renin-angiotensin system as a potential tool to identify patients at risks for development of diabetic nephropathy. In Project 5 (Development/Feasibility), Dr. Gooch will study the role of calcineurin in IGF1 and TGFbeta signaling as it pertains to diabetic nephropathy. Project 6 (Development/Feasibility), Dr. Rincon-Choles will characterize kidney phenotype and identify quantitative trait loci influencing diabetic nephropathy in a pedigreed and genotyped colony of baboons with type II diabetes. Four of the six projects will utilize the services of the Morphology Core, and three of the six projects will utilize the Transgenic Core Facility. It is anticipated that the studies will advance the understanding of genetic, biochemical, and cellular factors that modulate renal response to injury.

- **Project Title: HUMAN UREMIC PERSISTENT HYPERPARATHYROIDISM: FUNCTIONAL AND MOLECULAR ASPECTS**

  Principal Investigator & Institution: Egbuna, Ogo; Brigham and Women's Hospital Research Administration Boston, Ma 02115

  Timing: Fiscal Year 2006; Project Start 25-SEP-2006; Project End 31-AUG-2011

  Summary: (provided by applicant): Patients receiving dialysis for end stage kidney failure often develop overactivity of their parathyroid glands, which can persist long after successful kidney transplantation and contributes to adverse graft and recipient outcomes. Causes of the abnormal, poorly suppressible parathyroid function after transplantation have been little studied and are incompletely understood. Patients with post-transplant, persistent secondary hyperparathyroidism (PSHPT) would be expected to show alterations in parathyroid cell (PTC) function due to changes in protein/gene expression and/or function influencing proliferation, PTH gene expression and set-point of secretion. Transplant recipients with autosomal dominant **polycystic kidney disease** (ADPKD) are at higher risk for post transplant parathyroidectomy. The identification of polycystins (PC) in PTC's, and their function as plasma membrane calcium sensors/channels have been well described. PC's also utilize intracellular signaling pathways similar to those of the calcium-sensing receptor (CaR). These observations support the hypothesis that PCL's play a role in parathyroid function. Elucidating the molecular basis of PSHPT and the role of PCL's in PTC function will assist in developing therapies and strategies that could optimize patient and graft outcomes. These issues will be addressed by undertaking the following specific aims: Aim 1: Elucidate the characteristics of persistent hypersecretion and proliferation characteristic of PSHPT in renal transplant patients relative to dialysis patients, by quantifying the parathyroid secretory and proliferative responses in vitro to changes in the extracellular calcium concentration (Ca2+) and 1,25 (OH)2 vitamin D3. Aim 2: Investigate the key qualitative and quantitative differences between parathyroid glands of transplant and dialysis patients with or without ADPKD and PSHPT with regard to CaR-regulated signaling pathways that have been implicated in the abnormal Ca2+-regulated PTH release in primary HPT and dialysis patients. Specific Aim 3: Determine the relationship between abnormal Ca2+-regulated processes and the expression of key genes implicated in the control of parathyroid function in PTC's of dialysis and

transplant patients with and without PKD. If these genes are over- or underexpressed, we will assess the effect of correcting their expression using adeno-associated viral vectors or RNA silencing. Specific Aim 4: Identify novel genes contributing to PSHPT using DNA microarrays.

- **Project Title: IMAGING POLYCYSTIN-MEDIATED CA TRANSIENTS IN C. ELEGANS**

  Principal Investigator & Institution: Portman, Douglas Stuart.; Assistant Professor; Biomedical Genetics; University of Rochester 517 Hylan Bldg., Box 270140 Rochester, Ny 14627

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

  Summary: (provided by applicant): **Polycystic kidney disease** (ADPKD) results from mutations in the human PKD1 and PKD2 genes, which encode the proteins polycystin-1 and -2. The polycystins are thought to act in the primary cilia of the renal epithelium, where they transduce mechanical bending of the cilium by fluid flow into cytoplasmic calcium signals. Cystogenesis is hypothesized to result from the disruption of this signaling pathway. However, the molecular mechanisms by which the polycystins respond to mechanical cues are not well understood. In the nematode C. elegans, the polycystin orthologs LOV-1 and PKD-2 are required for the function of twenty-one male-specific sensory neurons that sense contact with hermaphrodites. The polycystins localize to the primary cilia at the dendritic tips of these cells. As in vertebrates, it is thought that these proteins transduce the deformation of cilia into downstream calcium signals. Because of its sophisticated and rapid experimental accessibility, the nematode model has great potential for exploring the molecular nature of polycystin signaling. Our goal in this application is to develop and implement a system to directly measure polycystin-dependent calcium signaling in vivo using the genetically-encoded calcium indicator cameleon. In the first aim, we will measure calcium transients in C. elegans males in real time in response to a variety of stimuli, including contact with hermaphrodites, artificial mechanical stimuli, and transverse fluid flow. By comparing calcium responses between wild-type animals and those carrying null mutations in the polycystins, we will test the hypothesis that these responses depend on polycystin function. In the second aim, we will apply this assay to test the hypothesis that two recently-identified C. elegans genes specifically expressed in male sensory neurons, cwp-4 and cwp-5, have roles in polycystin-mediated Ca2+ signaling. These studies will establish C. elegans as a unique system for the in vivo genetic and molecular analysis of the molecular mechanisms of signaling by the polycystins in response to mechanical stimuli.

- **Project Title: IN VIVO PIV: A PLATFORM TECHNOLOGY FOR PHENOTYPING FLOW IN ANIMAL MODEL SYSTEMS**

  Principal Investigator & Institution: Hove, Jay R.; Genome Science; University of Cincinnati Sponsored Research Services Cincinnati, Oh 45221

  Timing: Fiscal Year 2006; Project Start 06-SEP-2006; Project End 30-JUN-2010

  Summary: (provided by applicant): Flow-induced forces resulting from intravital biofluids (e.g., blood, urine, cerebrospinal fluid) are widely acknowledged to be critical for proper embryonic development. Defects in embryonic biofluid flow are associated with renal, cardiovascular and nervous system disorders. Genetic, surgical, and pharmacological animal models exist or are being developed for both normal development and disease states. However, existing methods for intravital flow imaging are inadequate as all current modalities lack the spatial and/or temporal resolution

necessary to describe the wide range of complex developmental flows that exist in biological organisms. We propose to create a cutting-edge, cross-platform technology for 4-D imaging (3-D + time) of biofluid flows within the living embryonic zebrafish, a widely-used animal model for developmental studies. The foundation of this critically-needed technology will be a laser-based multidimensional microscopic imaging system to visualize and track the motions of submicron fluorescent tracer particles suspended within the anatomical flows of interest. We will utilize a unique defocusing digital particle image velocimetry (DDPIV) technique to obtain the required spatial and temporal sensitivity. In addition, by developing new image analysis algorithms we will, for the first time, be able to account for the large velocity gradients and moving boundaries that are so prevalent in living systems and which have been so problematic for existing in vivo imaging technologies. The creation of a novel in vivo micro-DDPIV technology will greatly impact our ability to understand how biofluid flow affects development in both healthy and flow-compromised animals. This is an area of great need as we are currently capable of creating large numbers of flow-related mutants in zebrafish, but are far less able to reliably quantify the resulting dynamic flow changes in order to understand their effects on developmental pathogenesis. This work will significantly aid a wide-range of biomedical research efforts, as flow-dependent phenomena are key factors in a great many diseases including **polycystic kidney disease,** atherosclerosis, syringomyelia, cardiomyopathy, and hydrocephalus-related disorders.

- **Project Title: INTEGRIN AND CADHERIN IN POLYCYSTIC KIDNEY DISEASE**

  Principal Investigator & Institution: Kreidberg, Jordan A.; Associate Professor of Pediatrics; Brigham and Women's Hospital Research Administration Boston, Ma 02115

  Timing: Fiscal Year 2005; Project Start 30-SEP-2005; Project End 31-AUG-2010

  Summary: Polycystic kidney disease (PKD) is characterized by loss of normal epithelial morphology and function in kidney tubules, and resultant cyst formation. Polycystins 1 and 2 are, therefore, among the groups of molecules required to maintain normal epithelial morphology and function. In our laboratory, a major focus has been on how integrins and cadherins, normally thought of as cell-extracellular matrix (ECM) and cell-cell adhesion molecules, respectively, cooperate to maintain normal epithelial morphology. As a component of these studies, we have recently published that alphas betal integrin, apart from its role as a receptor for laminin, a component of the ECM, also functions as part of the adherens junction where it associates with the cadherin:catenin complex, and stimulates cadherin mediated cell-cell adhesion. In this grant we now turn our focus to the role of integrins and cadherins in PKD, and in particular, how polycystins 1 and 2 may function in signal transduction pathways that affect integrin and cadherin function. Understanding the role of integrins and cadherins in PKD may eventually lead to pharmacological interventions that ameliorate cystogenesis. PKD is a cause of a significant portion of chronic renal failure that leads to dialysis and transplantation. This research aimed at understanding how PKD causes kidney damage, will yield information that should lead to treatments that help prevent kidney damage in PKD.

- **Project Title: INTRAFLAGELLAR TRANSPORT PROTEINS IN MICE**

  Principal Investigator & Institution: Pazour, Gregory J.; Assistant Professor; Cell Biology; Univ of Massachusetts Med Sch Worcester Medical School Worcester, Ma 01655

  Timing: Fiscal Year 2005; Project Start 01-JUN-2001; Project End 31-MAY-2006

Summary: (provided by applicant): The long-term objective of this work is to understand the role of the intraflagellar transport (IFT) proteins in vertebrates, with a focus on their role in the primary cilia of kidney and the connecting cilium of photoreceptor cells. In Chlamydomonas and Caenorhabditis elegans these proteins form a multisubunit complex that is transported along flagellar and ciliary microtubules. This transport is essential for assembly and maintenance of cilia and flagella. The IFT particle proteins are conserved in mice and humans. These proteins are found at the connecting cilium in photoreceptor rod cells suggesting that they are important for transport of opsin or other proteins from the cell body to the outer segment. Furthermore, the **polycystic kidney disease** gene Tg737 encodes the IFT88 subunit of the IFT particle. Mutations in this gene interfere with ciliary assembly in mouse kidneys, suggesting that the primary cilium plays an important role in kidney physiology. The proposed work will determine if the IFT57 and IFT88 proteins are required for intraphotoreceptor transport by examining the effect of mutations on mouse rod cells. The proposed work will also examine the role of IFT57 in formation of kidney primary cilia and will test the hypothesis that the kidney primary cilium is a sensory organelle by determining if osmolarity detectors and somatostatin receptors are localized on primary cilia in the kidney as they are in other cells.

- **Project Title: ION TRANSPORT DYSREGULATION IN CILIUM-DEFICIENT ARPKD**

  Principal Investigator & Institution: Schwiebert, Erik M.; Associate Professor; Physiology and Biophysics; University of Alabama at Birmingham 1530 3Rd Avenue South Birmingham, Al 35294

  Timing: Fiscal Year 2005; Project Start 01-SEP-2005; Project End 31-AUG-2010

  Summary: (provided by applicant): Both genetic forms of **polycystic kidney disease** (PKD) present in human or mouse models as a profound change in renal tubule or epithelial cell morphology and architecture due to mutations in proteins that localize, at least in part, to the apical central monocilium of the cortical collecting duct (CCD) principal cell (PC cell). Once the genetic and biochemical consequences of PKD are manifested in this change in morphology, the change in cellular or tubular architecture affects transepithelial ion transport profoundly. In human autosomal recessive PKD (ARPKD) monolayers, there is evidence of sodium hyperabsorption, although the sodium transport mechanisms are not yet clearly defined. This abnormality may explain early onset hypertension observed in the majority of human ARPKD patients. Using mouse renal epithelial cells that are immortalized due to genetic cross with the Immortomouse and form polarized epithelial cell monolayers from wild-type, mutant, and genetically rescued PC cells from the Oak Ridge polycystic kidney (orpk) mouse CCD of very high electrical resistance, our laboratory has gathered preliminary data showing upregulated absorptive sodium transport in mouse orpk ARPKD mutant cortical collecting duct (CCD) principal epithelial cells (PC cells) grown as polarized monolayers and lacking apical central monocilia versus control cilium-competent PC cell monolayers. These upregulated sodium currents may represent ENaC- and NHE-mediated sodium hyperabsorption. Taken together, the literature, the experience of our collaborative research group, our current preliminary work, and the constructive criticism of the reviewers of our original application led us to formulate the following working hypothesis: CCDs from mouse models of ARPKD that lack apical central monocilia have upregulated ENaC- and NHE-mediated sodium absorption and resultant hypertension. Interrelated specific aims derive from this hypothesis and are designed to understand the cellular and molecular mechanisms that underlie this ARPKD disease phenotype.

- **Project Title: JADE-1 IN CYSTIC RENAL DISEASE**

  Principal Investigator & Institution: Cohen, Herbert Tod.; Associate Professor; Boston Medical Center One Boston Medical Center Place Boston, Ma 02118

  Timing: Fiscal Year 2005; Project Start 01-APR-2004; Project End 31-MAR-2009

  Summary: (provided by applicant): Autosomal dominant **polycystic kidney disease** (ADPKD) is a common cause of end-stage renal disease. Loss of the polycystin-1 - polycystin-2 interaction is central to disease pathogenesis, but the precise mechanism of cyst formation remains unclear. Intriguingly, disordered renal tubule cell proliferation and apoptosis are consistent features of all the cystic renal diseases. Our laboratory has been closely studying the molecular basis of von HippeI-Lindau (VHL) renal disease, which includes a polycystic kidney phenotype. The similarities between the cystogenic pathways in VHL disease and ADPKD are striking. Jade-1 (gene for Apoptosis and Differentiation in Epithelia) encodes a short-lived, highly-regulated pro-apoptotic transcription factor that is stabilized by the VHL tumor suppressor. Jade-1 resides in prominent nuclear speckles and is most highly expressed in renal tubular epithelial cells. Intriguingly, the pattern of naturally occurring VHL mutations that stabilize Jade-1 suggest a correlation with VHL renal disease risk, which has not been previously described. Jade-1 protein alters the monolayer morphology of renal cells and promotes apoptosis that is blocked by VHL. Jade-1 may help propel a pre-apoptotic epithelial cell off a monolayer, promoting anoikis. Remarkably, wild-type polycystin-1 strongly regulates Jade-1 much like VHL, and this effect is blocked by a disease-causing polycystin-1 mutation in the coiled-coil domain that prevents interaction with polycystin-2. Moreover, Jade-1 is the target of a novel polycystin-1 dominant-negative mechanism. Thus, pro-apoptotic Jade-1 is downstream of both VHL and a common polycystin-1 / polycystin-2 regulatory pathway. Jade-1 may therefore be a central regulator of renal cyst formation in VHL disease and ADPKD, and perhaps in other cystic renal diseases. The Jade-1 - polycystin relationship in cystic disease will be explored through the following Aims: AIM 1: The mechanism of Jade-1 regulation by polycystin-1 AIM 2:Jade-1 effects on the cell cycle and modulation by polycystin-1 AIM 3: Direct role of Jade-1 in renal cyst formation.

- **Project Title: KANSAS INTERDISCIPLINARY CENTER FOR PKD RESEARCH**

  Principal Investigator & Institution: Calvet, James P.; Professor; Biochemistry and Molecular Biology; University of Kansas Medical Center Msn 1039 Kansas City, Ks 66160

  Timing: Fiscal Year 2005; Project Start 30-SEP-1999; Project End 31-AUG-2010

  Summary: OF OVERALL CENTER (provided by applicant): The Kansas Interdisciplinary Center for PKD Research (Kansas PKD Center) was established to provide support for highly meritorious new research programs to explore the basic mechanisms causing **polycystic kidney disease** (PKD); to provide opportunities to bring new investigators into PKD research; and to foster opportunities for more interdisciplinary research in a dynamic, enriching, and interactive setting. The long term goal for the Kansas PKD Center is to find a treatment for PKD that will alleviate the suffering of patients and families affected by the disease. The central theme of the research projects in the Kansas PKD Center is "cell proliferation in **polycystic kidney disease.**" This theme was chosen because Center investigators have been able to identify the cell proliferation defect in PKD as one that involves a cyclic AMP- and calcium-dependent mechanism. The focus will be on using the mouse as a model organism, and on human PKD cyst cells. The Kansas PKD Center is comprised of eight components. The Administrative Core will provide administrative support for Center investigators.

The Biomaterials Research Core will establish and maintain a repository of human and animal biological materials for PKD research including primary cultured cells and tissues, and DMA and RNA from ADPKD, ARPKD, and normal human kidney tissues. The Core will also establish and maintain immortalized cell lines from mice carrying unique PKD gene mutations and will provide technical assistance and training in cell culture methodology for all Center investigators. There will be four Biomedical Research Projects: Project 1, "Calcium Regulation of cAMP-Dependent Proliferation," Project 2, "Polycystin-1 Mediated Calcium and cAMP Signaling," Project 3, "Role of Oxidant Stress in Progression of PKD," and Project 4, "Cux-1 and Cell Cycle Regulation in PKD."

- **Project Title: KANSAS POLYCYSTIC KIDNEY IMAGING PROGRAM (CRISPII)**

  Principal Investigator & Institution: Grantham, Jared J.; Distinguished Professor; Internal Medicine; University of Kansas Medical Center Msn 1039 Kansas City, Ks 66160

  Timing: Fiscal Year 2006; Project Start 01-FEB-2000; Project End 31-DEC-2010

  Summary: (provided by applicant): Autosomal dominant **polycystic kidney disease** (ADPKD) is a major cause of disabling morbidity and is the fourth leading cause of end-stage renal failure in the world, affecting more than 500,000 U.S. citizens and millions more worldwide. Researchers at the University of Alabama, Emory University, University of Kansas, Mayo Clinic and Washington University St. Louis joined together in 2000 to create the Consortium for Radiologic Studies of **Polycystic Kidney Disease** (CRISP-I). The primary objectives of this investigation were to: (1) Develop and test the accuracy and reproducibility of imaging techniques to monitor changes in renal cyst size and parenchyma! involvement. (2) Establish and maintain a database of uniformly and accurately collected information. (3) Maintain and make available such data to facilitate the planning and implementation of clinically appropriate interventions in the near future. The goals of CRISP-I I are to extend the observations of CRISPI in order to: 1) Draw unequivocal linkage between the rate of kidney/cyst enlargement and qualitative and quantitative end-points. 2) Provide a marker of disease progression (kidney volume) sensitive and accurate enough to be used as a primary outcome marker in clinical trials aiming to forestall disease progression. 3) Develop and test other bio-markers of disease progression. The specific aims are: Aim 1: Extend the preliminary observations of CRISP-I to ascertain the extent to which quantitative (kidney volume and hepatic and kidney cyst volume) or qualitative (cyst distribution and character) structural parameters predict renal insufficiency. Aim 2: Extend the preliminary observations of CRISP-I to ascertain the extent to which age and sex-adjusted measurements of renal blood flow by MR technology predict the rate of renal growth; and, renal blood flow and kidney volume predict the rate of renal function decline in ADPKD. Aim 3: Exhaustively analyze the living database and stored biologic samples derived from CRISP-I and the CRISP-II extension to develop and test new metrics to quantify and monitor disease progression, and collect DMA samples and clinical information from CRISP family members known to have ADPKD for use in future studies to examine genotype-phenotype correlations and to identify genetic modifiers.

- **Project Title: KIDNEY DEVELOPMENT AND CYSTOGENESIS IN MEDAKA**

  Principal Investigator & Institution: Obara, Tomoko; Assistant Rofessor; Medicine; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

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

  Summary: (provided by applicant): Autosomal dominant **polycystic kidney disease** (ADPKD) is a hereditary disease occurring at a frequency of 1:1000 in humans and characterized by cyst formation in kidney tubules, deregulated fluid transport and

alteration of extracellular adhesion. ADPKD is caused by mutations in the PKD1 or PKD2 gene that encode polycystin-1 and polycystin-2, respectively. The primary causes and mechanisms of cyst formation in ADPKD remain elusive. Our attempts to knockdown pkdl in zebrafish failed because of gene redundancy. Medaka is a unique inbred aquatic vertebrate fish model system, which shows lower redundancy in gene number compared to zebrafish. The use of medaka provides an opportunity to develop a novel system to study organogenesis and to understand the mechanisms of cystogenesis. Given that PKD1 mutations account for 85% of all ADPKD cases in humans, we have targeted pkdl in medaka to understand its function(s). Preliminary results demonstrate that targeting pkdl in medaka (in contrast to zebrafish) causes prronephric cysts formation. We have also established a system using medaka for studies of kidney, cystogenesis that is sensitive for the defect of polycystin-1 interacting proteins such as polycystin-2, which can be used to assess the in vivo relevance of the large number of polycystin-1 interacting proteins. In specific aim 1, we will test the in vivo function of specific polycystin-1 motifs by disrupting pkdl mRNA splicing and generate an allelic series of deletions in medaka. For this purpose, we propose to use our urogenital specific medaka transgenic GFP line to monitor the progress of cyst formation, and to analyze the kidney phenotypes as well as other potential defects in organogenesis caused by the defers. In specific aim 2, we will validate the biological significance of polycystin-1 interacting proteins.

- **Project Title: KIDNEY INJURY MOLECULE-1 IN EPITHELIAL REPAIR**

  Principal Investigator & Institution: Bonventre, Joseph V.; Professor; Brigham and Women's Hospital Research Administration Boston, Ma 02115

  Timing: Fiscal Year 2005; Project Start 01-JUN-2005; Project End 31-MAY-2010

  Summary: (provided by applicant): Kidney injury molecule-1 (KIM-1) is strongly upregulated in proximal tubular epithelial cells in various states characterized by epithelial cell dedifferentiation: ischemia, toxic renal injury, **polycystic kidney disease** and renal cell carcinoma. It is upregulated more than any other known protein with renal injury. KIM-1 protein is a Type I cell membrane glycoprotein containing extracellular immunoglobulin-like and mucin domains suggesting functional roles in cell-cell and/or cell-matrix interactions. We have cloned, and generated monoclonal and polyclonal antibodies to, the human, mouse and rat KIM-1. KIM-1 is upregulated in vitro in MDCK cells adjacent to a mechanical "wound". The ectodomain of KIM-1 is cleaved and found in urine of patients with acute tubular necrosis or renal cell carcinoma. Gene transfer of KIM-1 in LLC-PK1 epithelial cells results in an increased number of cells with mesenchymal morphology and confers growth in soft agar. The goal of this proposal is to characterize the functional role of KIM-1 during the processes of adhesion and differentiation of epithelial cells. We hypothesize that KIM-1 reduces cell-cell and increases cell-matrix adhesion and potentiates epithelial to mesenchymal transition. In Specific Aim 1, we will characterize the effects of KIM-1 on cell-cell and cell-matrix interactions of epithelial cells. In pilot experiments, we found decreased cell-cell aggregation of LLC-PK1 cells expressing KIM-1. CHO cells overexpressing KIM-1 "scatter" on various matrix substrates. KIM-1 expression results in loss of E-cadherin and increased cell-matrix adhesion. The roles of ERM proteins, integrins, Rho, integrin-linked and mitogen-activated protein (MAP) kinases as effectors of KIM-1 actions on cell-cell and cell-matrix adhesion will be explored. The contributions of the extracellular and intracellular domains of KIM-1 and tyrosine phosphorylation of the intracellular domain of KIM-1 in KIM-l's effects on adhesion will be evaluated. In the second specific aim, we will analyze the role of KIM-1 in the processes associated with dedifferentiation of renal tubular epithelial cells that are important for repair of the epithelium with both

positive and potentially negative consequences. We will explore the role of TGF-beta in potentiating the effects of KIM-1 on cell differentiation and epithelial to mesenchymal transition. A mechanism is proposed that implicates ERM proteins, Rho, integrin-linked and MAP family kinases as well as a-catenin and the transcription factor Snail, in the effect of KIM-1 on the differentiation status of the renal epithelial cell. KIM-1-expressing proximal tubules localize in areas of the kidney with increased fibrosis in a model of **polycystic kidney disease** and we will explore if there is an effect of KIM-1 expression on matrix protein production and extracellular matrix remodeling. Understanding the function of KIM-1 will provide important insight into the role of this protein in injury and repair processes of the kidney, and may identify KIM-1 as an important therapeutic target not only for acute and chronic renal disease but also for malignant transformation of the epithelial cell.

- **Project Title: LAMININ ALPHA5 AND POLYCYSTIC KIDNEY DISEASE**

  Principal Investigator & Institution: Miner, Jeffrey H.; Associate Professor; Internal Medicine; Washington University 1 Brookings Dr, Campus Box 1054 Saint Louis, Mo 631304899

  Timing: Fiscal Year 2006; Project Start 04-APR-2006; Project End 31-MAR-2008

  Summary: (provided by applicant): Laminin a5 is a component of essentially all basement membranes in the kidney. It is particularly important in the glomerular basement membrane (GBM), where we have shown that it is necessary for maintenance of GBM integrity, for vascularization of glomeruli, and for mesangial cell organization of glomerular capillary loops. During the course of generating a conditional, floxed LamaS allele, we have serendipitously created a new mouse model for autosomal recessive **polycystic kidney disease.** This stems from the insertion of a FRT-flanked PGKneo selectable marker into an intron of LamaS, thus generating a hypomorphic LamaS allele, which we call LamaSneo. Preliminary studies show that LamaSneo/neo mice die at ~23 days of age with multiple large cysts, proteinuria, hematuria, and reduced levels of laminin a5 in most kidney basement membranes. Evidence that cysts are forming can be detected as early as the time of birth. The purpose of this limited two year Pilot and Feasibility Study is to segregate the putative epithelial cell/matrix defects in the tubular compartment of the nephron that result in cystogenesis, from the GBM defects that likely exacerbate kidney damage and speed the onset of renal failure in LamaSneo/neo mice. This will allow for a more meaningful analysis of cystogenesis and testing of hypotheses as to its origin. We will accomplish this by generating new transgenic mice that express the enhanced FLP recombinase specifically in podocytes, using the 2.5 kilobase podocin promoter. The FRT sites flanking the PGKneo are substrates for FLP recombinase, which will splice them together and delete the intervening PGKneo insertion specifically; in podocytes, thus restoring normal levels of laminin alphas in the GBM. We hypothesize this will also restore the integrity of the glomerular filtration barrier and allow a focused study of tubule defects that result in cystogenesis. In addition, the transgenic mice we will generate will serve as a useful resource to the nephrology research community, as they will provide a unique additional tool for manipulating podocyte gene expression.

- **Project Title: MECHANISMS OF RENAL TUMORIGENESIS IN TUBEROUS SCLEROSIS**

  Principal Investigator & Institution: Henske, Elizabeth P.; Member; Fox Chase Cancer Center 333 Cottman Avenue Philadelphia, Pa 191112434

  Timing: Fiscal Year 2006; Project Start 30-SEP-1995; Project End 31-MAR-2009

Summary: (provided by applicant): This A2 proposal is focused on renal disease in Tuberous Sclerosis Complex (TSC). TSC is an autosomal dominant disorder in which the renal manifestations include angiomyolipomas, **polycystic kidney disease,** and carcinoma. We and others have shown that loss of tuberin (TSC2) upregulates Rheb activity. Rheb activates the mammalian target of rapamycin (mTOR). In published work, we demonstrated mitotic regulation of hamartin (TSC1) by the cyclin-dependent kinase CDK1. In unpublished work, we have found that hamartin is centrosome-localized and interacts with the mitotic kinase Plk1. Consistent with a central role of hamartin (TSC1) in mitosis, we also found that Tsc1-/- mouse embryonic fibroblasts (MEFs) have mitotic and centrosome defects. This proposal centers on two inter-related central hypotheses: 1) mitotic regulation of hamartin plays a key role in the function of the hamartin/tuberin complex, and 2) Rheb is the critical downstream target through which hamartin (TSC1) and tuberin (TSC2) function as tumor suppressors. To address these hypotheses, we propose the following Specific Aims. Aim 1: To define the impact of mitotic phosphorylation of hamartin (TSC1) on Rheb activity and the hamartin-Plk1 interaction. Aim 2: To test the hypothesis that loss of hamartin (TSC1) results in centrosomal and mitotic defects. Aim 3: To determine whether Rheb-dependent pathways are activated in sporadic human renal tumors. Aim 4: To determine whether Rheb expression in the kidney induces tumors. Our published and preliminary data point toward a critical role of hamartin in regulation of mitosis (Aims 1 and 2), with broad potential cancer relevance. In Aims 3 and 4 we will examine the role of Rheb in renal tumorigenesis in vivo, using both human tumors and transgenic mice. We anticipate that this project will elucidate the central pathways leading to tumorigenesis in TSC. Lay summary. TSC is a genetic disease in which patients can develop kidney tumors, kidney cancer, and kidney cysts. This project will use biochemistry, cell culture, human specimens, and animal models to elucidate the cause of kidney disease in TSC. The cellular and biochemical pathways that cause kidney disease in TSC are likely to be closely related to the pathways that cause kidney tumors and cysts in other individuals.

- **Project Title: MOLECULAR ANALYSES OF TWO MOUSE KIDNEY DISEASE MODELS**

  Principal Investigator & Institution: Davisson, Muriel T.; Senior Staff Scientist; Jackson Laboratory 600 Main St Bar Harbor, Me 046091500

  Timing: Fiscal Year 2005; Project Start 01-AUG-2003; Project End 31-MAY-2007

  Summary: (provided by applicant): Over 600,000 people in the U.S. suffer from kidney diseases; more than 50,000 die each year. Mouse models are the paradigm for characterizing the etiology and pathogenesis of kidney diseases. The purpose of this project is to identify the mutated genes in two novel mouse models for kidney disease. Bilateral polycystic kidneys (bpck) is a spontaneous recessive mutation that causes classic **polycystic kidney disease.** It is a new model because it maps to a region of the mouse genome that has no other kidney disease gene. Based on conserved homology, bpck will likely indicate a new human **polycystic kidney disease** gene. Variable hydronephrosis (vhn) is a recessive mutation caused by one of the breakpoints of a reciprocal translocation. vhn presents uni- or bilateral hydronephrosis and renal agenesis/dysgenesis. Preliminary genetic analyses indicate that each of the phenotypes is caused by mutation in a single major gene. Aim 1 is to refine the chromosomal positions of the mutations with a high resolution genetic intercross for bpck and BAC/FISH physical mapping for vhn. Aim 2 is to identify the mutated genes using the positional candidate gene approach and standard molecular protocols. Human orthologues and gene locations will be predicted from the results. Aim 3 is to analyze in detail the disease phenotypes and progression. Gene expression patterns will be

determined by TISH and protein localization by immunochemistry. Aim 4 is to analyze gene function by identifying interacting genes using microarrays and quantitative RT-PCR.

- **Project Title: MOLECULAR GENETICS OF HUMAN ARPKD**

  Principal Investigator & Institution: Germino, Gregory G.; Associate Professor; Medicine; Johns Hopkins University W400 Wyman Park Building Baltimore, Md 212182680

  Timing: Fiscal Year 2005; Project Start 01-MAY-1996; Project End 31-MAR-2010

  Summary: (provided by applicant): Autosomal recessive **polycystic kidney disease** (ARPKD) is a significant cause of pediatric morbidity and mortality. Affected children suffer from HTN, renal insufficiency and portal tract fibrosis. The clinical spectrum of ARPKD is widely variable with most cases presenting in infancy. Our Consortium, supported by two previous awards, has used genetic approaches to define its molecular basis. In our most recent cycle, we identified the gene, PKHD1, and determined that it maps to a >400kb genomic interval, encodes a >13kb mRNA, undergoes a complicated pattern of splicing with a 67 exon transcript which encodes the longest ORF and a 4074 aa protein. We have shown that the gene is most highly expressed in kidney at all developmental stages, though it is also expressed at low levels in multiple other tissues. The gene product, polyductin, (PD), is a type I membrane protein thought likely to be a ligand or receptor. Immunolocalization studies have placed the protein in the basal body/primary cilia. In studies using epitope-tagged full length recombinant PD, we found evidence that the molecule undergoes a complicated pattern of proteolytic processing. Our genotype/phenotype studies found that individuals with biallelic truncating PKHD1 mutations have more severe disease. We isolated the mouse orthologue, determined that it also has complex splicing and generated mice with targeted mutations of the 5' end. Surprisingly, homozygous mutant mice only developed biliary and pancreatic disease. Preliminary data suggest that the targeted allele is not a true null. In this renewal, we seek to follow-up on these observations. In Aim 1, we will test the hypothesis that PD undergoes regulated proteolysis mediated by proprotein convertases, TACE or other metalloprotease, and secretase using a variety of epitope-tagged recombinant molecules, metabolic labeling, engineered mutations and mutant cell lines. We will also examine whether endogenous PD has the same properties. In Aim 2, we will develop a cell culture model system that can be used to assess the functional consequences of regulated intramembrane proteolysis. Aim 3 tests the hypothesis that complete loss of Pkhdl will result in renal and other organ dysfunction. We will characterize a newly developed line of mice with a functional floxed allele targeting exons 3 and 4. If cre-mediated deletion does not result in a complete null allele, we will generate one by introducing lox p sites flanking the entire gene. The last aim will characterize the complex pattern of splicing since this is such a prominent feature of the gene, likely explains the surprising results of recent gene targeting studies, and may account for some of the observed clinical variability.

- **Project Title: NOVEL CARDIAC RISK FACTORS & ENDOTHELIAL FUNCTION IN CKD**

  Principal Investigator & Institution: Menon, Vandana; New England Medical Center Hospitals 750 Washington St Boston, Ma 021111533

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

  Summary: (provided by applicant): Cardiovascular disease is the leading cause of morbidity and mortality among patients with chronic kidney disease. This excess risk is

only partly attributable to a high prevalence of traditional cardiovascular risk factors. The principal investigator's goal is to establish a career as an independent investigator with the broad objectives of understanding of the pathophysiologic mechanisms leading to cardiovascular disease and developing effective preventive strategies to reduce the burden of cardiovascular disease in kidney disease. The proposed study will investigate the mechanisms underlying development of cardiovascular disease in the earlier stages of non-diabetic chronic kidney disease utilizing data from two National Institutes of Diabetes & Digestive & Kidney Diseases (NIDDK) sponsored trials. The overall hypothesis is that: Non-diabetic chronic kidney disease is characterized by early elevation of markers of inflammation, oxidative stress and insulin resistance, and that these risk factors are associated with cardiovascular disease in this patient population. The Modification of Diet in Renal Disease (MDRD) Study was a large randomized controlled trial of patients in the earlier stages of chronic kidney disease. Participants in the MDRD Study had predominantly non-diabetic kidney disease of varying etiologies. The Halt Progression of **Polycystic Kidney Disease** trial is a randomized trial to slow the progression of kidney disease in patients with autosomal dominant **polycystic kidney disease** (ADPKD). These two patient populations provide a unique opportunity to examine the relationship between kidney disease and novel cardiac risk factors, and to study the role of these novel risk factors in the pathophysiology of cardiovascular disease, in the absence of important confounders such as diabetes, dialysis and malnutrition. The study hypothesis will be tested using three specific aims: 1. To determine whether inflammation, oxidative stress, insulin resistance, and endothelial dysfunction in the earlier stages of chronic kidney disease are associated with cardiovascular disease. 2. To determine whether ADPKD is associated with inflammation, insulin resistance, and oxidative stress 3. To determine whether inflammation, insulin resistance, and oxidative stress are associated with endothelial dysfunction, measured as brachial artery reactivity and peripheral artery tonometry, in ADPKD. The novel risk factors under investigation in this proposal could serve to identify high-risk patients for targeted interventions to prevent or delay the adverse outcomes associated with cardiovascular disease. The applicant has chosen a group of distinguished mentors and collaborators to support this project. This award will provide Dr. Menon with the final training necessary for her to make the transition from trainee to principal investigator.

- **Project Title: NOVEL THERAPEUTIC STRATEGIES FOR PKD**

  Principal Investigator & Institution: Wilson, Patricia D.; Professor; Medicine; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 100296574

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

  Summary: Polycystic kidney diseases (PKD) affect greater than or equal too 500,000 patients in the US and > 6 million worldwide, but the only form of "therapy" is renal replacement by dialysis or transplantation. The most common and important renal malformations are genetic in origin. Autosomal dominant (AD)PKD has an incidence of greater than or equal too1:500 and accounts for greater than or equal too 7% of all patients on dialysis, while autosomal recessive (AR)PKD) has an incidence of greater than or equal too 1: 20,000 with a mortality of greater than or equal too50% in the newborn period and accounts for >5% cases of endstage renal failure in children. The overall goal of this program project is to establish a multidisciplinary team to develop and apply the expanding new understanding of the molecular cellular and physiological basis of polycystic kidney diseases to the development of novel, rational therapeutic approaches. The ultimate goal is to develop preventive and/or therapeutic treatments to slow disease progression and thus offer treatment that is at present lacking. Medical

scientists from the Departments of Medicine, Pediatrics, Urology, Gene Therapy Institute and Cancer Center have established a critical mass with a multifaceted approach to study renal morphogenesis and malformations ranging from molecular, cellular, physiological, genetic and clinical approaches, thus constituting a combined basic and translational program. The five projects and two cores will be highly interactive and are scientifically integrated in a scheme that focuses on the regulation of the function of the PKD 1 gene product, polycystin by phosphorylation, Project 1; the role of polycystin- 1 in the control of renal morphogenesis, Project 2; the role of the WTl-target protein "sprouty" in cystic kidney devlopment, Project 3; the analysis of sodium and potassium transport in ARPKD, project 4; and the functional consequences of apical EGF receptor signalling in ARPKD, Project 5. The Core will provide and develop viral vectors, renal cell lines and organ cultures as well as transgenic, knock-out and other mouse models In addition, this Core will centralize services and functional assays including adhesion, migration, 3D gel tubulogenesis, embryonic mouse kidney organ culture and microinjections. These integrated studies will increase our understanding of the underlying biology of polycystic kidney diseases sufficiently to lead to testing of therapeutic approaches in human cells in vitro and mice in organ culture and in vivo by small molecule and/or gene therapy strategies.

- **Project Title: OSMOLYTES ON PROTEIN STRUCTURE AND ENERGETICS**

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

  Timing: Fiscal Year 2006; Project Start 01-AUG-1993; Project End 31-MAR-2010

  Summary: (provided by applicant): Protecting osmolytes are responsible for the kidney medulla's extraordinary ability to cope with intracellular urea concentration as high as 1.5M. These small organic molecules are common in cells of many tissues, and an important part of their action in kidney is to stabilize intracellular proteins against the deleterious effects of urea. Besides being essential for our survival, imbalances in osmolyte levels play key roles in such conditions as **polycystic kidney disease,** diabetes mellitus, and brain edema. Though many biological roles of osmolytes arise from their solvation of proteins, it is unknown how protein solvation facilitates these roles. This gap in knowledge prevents a complete understanding of osmolyte effects and their roles in normal and disease states. Our long-term goal is to understand how interactions among osmolytes, water, and biomolecules give rise to osmotic stress response on the one hand, and disease on the other. Using measurements of the transfer free energy of protein side-chain and peptide backbone groups (GTFEs) from water to osmolyte solution, we recently made the remarkable discovery of how to predict the energetics of protein-stability in osmolytes. Our aims are to consolidate and use this ability to determine the underlying forces responsible for protein stability, and to the predict energetic effects of osmolytes on contraction and accretion of structure in denatured ensembles. We will extend our use of GTFEs to enable predictions of protein-protein interaction free energies, to better understand how fluctuating osmolyte concentrations affect key protein-protein interactions vital to cellular responses, and determine the extent to which kidney osmolytes act synergistically, negatively, or independently in affecting the properties of proteins. We aim to merge our ability to predict the energetics of protein stability and solvation effects with Kirkwood-Buff approaches that structurally relate water*osmolyte*protein interaction with the energetics, to give a considerably more detailed mechanistic understanding of protein solvation than currently exists. Relevance: This project will lead to a better understanding of how osmolytes protect proteins from unfolding under harsh condition, and how imbalances

in osmolyte levels can contribute to the pathology of such conditions as **polycystic kidney disease,** diabetes mellitus, and brain swelling. Our work will have practical applications in the pharmaceutical industry for stabilization of vaccines and protein/ peptide drugs.

- **Project Title: PATHOBIOLOGY OF HEPATIC EPITHELIA**

  Principal Investigator & Institution: Larusso, Nicholas F.; Professor and Chair; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2005; Project Start 01-DEC-1978; Project End 31-MAR-2009

  Summary: (provided by applicant): Our long-term objectives remain to apply the fundamental concepts and broad technologies of cell and molecular biology to understand hepatic epithelial cell function and dysfunction. We continue to focus on cholangiocytes, the epithelial cells lining intrahepatic bile ducts, because of their biologic and clinical importance, and because of the new concepts, hypotheses, and techniques we have developed to study, cholangiocyte pathobiology, an underserved area of liver research. Recent evidence from our lab indicates that: (i) aquaporins (AQPs), a family of water channels, are important in ductal bile formation; and (ii) cholangiocytes contain primary cilia that act as sensory organelles and participate in normal bile formation and in biliary cystogenesis. Thus, we will test the central hypothesis that ductal bile formation: (i) is the net result of solute-driven, passive movement of water molecules through AQPs constitutively expressed in or recycled among distinct cellular compartments; (ii) is influenced by luminal mechanical, chemical, and osmotic signals sensed via primary cilia on the apical cholangiocyte membrane; and (iii) is abnormal in genetic spontaneous or experimental animal models of autosomal recessive **polycystic kidney disease** (ARPKD) when cholangiocyte ciliary structure and/or function is disturbed. Our three distinct but integrated specific aims test the hypotheses that: (i) ductal bile formation involves the normal function of primary cilia expressed on the apical membrane of each cholangiocyte to detect mechanical (e.g., bile flow rate), chemical (e.g., nucleotides, bile acids, glucose), and/or osmotic (e.g., bile hypo/hyperosmolarity) signals from bile; (ii) cellular expression, compartmentalization, and recycling of key 'flux' proteins (e.g., AQPs, AE2, CFTR) regulating ductal bile formation are influenced by ciliary stimulation; and (iii) abnormalities in structure, expression, and/or cellular localization of cilia-associated proteins (e.g., fibrocystin, the protein product of PKHD1, the gene mutated in ARPKD) contribute to disturbances in cholangiocyte water, solute, and ion transport promoting biliary cystogenesis. We will employ established and new methods, models, and probes, including: perfused bile duct units, isolated biliary cysts, isolated cholangiocyte cilia, spontaneous (i.e., the PCK rat) and transgenic (i.e., fibrocystin knockout mouse) animal models of ARPKD, gene silencing using small-interfering RNAs (siRNAs), novel cholangiocyte culture systems, and innovative morphologic techniques. Our results will further clarify the role of AQPs in cholangiocyte bile formation, address directly the potential importance of cholangiocyte cilia in ductal bile production, and explore the relationship of cholangiocyte cilia to possible disturbances of water, ion, and solute transport in biliary cystogenesis. Innovative aspects of our program include novel methodologies and animal models, and new concepts regarding the importance of cholangiocyte AQPs and cilia in ductal bile formation and biliary cystogenesis. We will generate information to yield new insights into normal cholangiocyte function, explore highly promising, selected aspects of cholangiocyte dysfunction, and continue to provide a broad theoretical framework for understanding and managing the cholangiopathies, a group of genetic and acquired hepatobiliary diseases in which the cholangiocyte is the principal target of diverse pathologic processes.

- **Project Title: PATHOGENESIS OF WPK-INDUCED RENAL AND CEREBRAL DISEASE**

  Principal Investigator & Institution: Gattone, Vincent H.; Professor; Anatomy and Cell Biology; Indiana Univ-Purdue Univ at Indianapolis 620 Union Drive, Room 618 Indianapolis, in 462025167

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

  Summary: (provided by applicant): Inherited renal cystic diseases, including the various forms of **polycystic kidney disease** (PKD) are prevalent conditions that usually affects multiple organs. There are numerous human genes, which when mutated, lead to a variety of cystic phenotypes with variable extrarenal manifestations. There are several rodent models, some with mutations in known human PKD genes. Others models represent rodent PKD genes, but could also function as modifier genes for other rodent models and human PKD. However, all of these models have made important contributions to our knowledge of PKD. The present proposal will isolate the rat wpk gene which causes renal changes similar to human autosomal recessive PKD. Additionally, affected rats have a cerebral defect (hydrocephalus with agenesis or hypoplasia of the corpus callosum) similar to that seen in human oro-facial-digital, genitopatellar and cerebro-renal-digital syndromes. Currently we localized the wpk gene to a 2Mb region of rat Chromosome 5, a location known to harbor a rodent PKD modifier locus and about 20 genes. The long term goal of our research is to identify genes and pathways involved in renal cystogenesis in order to develop therapeutic interventions. We hypothesize that the Wpk gene represents a human PKD gene and/or a modifier locus. Our Specific Aim is to: 1) Identify, clone and characterize the Wpk gene by crossing the Wistar-wpk rat with inbred Brown Norway rats and using chromosomal markers to localize the gene. Aside from the positional approach, we will identify candidate genes from with the 2Mb regions to test using RT-PCR as well as by screening rat ESTs from that region. Once identified, 9organ expression and immunohistochemistry will be used to identify the tissues and cells that express this gene product. The identification of the Wpk gene and its protein product will allow insight into cystogenesis as well as important information on shared pathways in kidney and brain development. This model and the Wpk gene are important for 2 major reasons, a) they have cystic disease and unique cerebral pathology similar to a few human conditions and b) the Wpk lies in a chromosomal region known to modify other rodent forms of PKD and may be an important modifier locus for PKD (rodent and human).

- **Project Title: PATHOLOGIC MECHANISMS OF POLYCYSTIC KIDNEY DISEASE**

  Principal Investigator & Institution: Wandinger-Ness, Angela; Associate Professor; Pathology; University of New Mexico Albuquerque Health Sciences Ctr, Financial Srvs Div. Albuquerque, Nm 87131

  Timing: Fiscal Year 2006; Project Start 15-AUG-1995; Project End 30-NOV-2010

  Summary: (provided by applicant): Autosomal Dominant **Polycystic Kidney Disease** (ADPKD) is caused by mutations in the genes encoding polycystin-1 and/or polycystin-2, but results in epithelial cells with disrupted adherens junctions and compromised beta-catenin signaling pathways. Our data show the polycystins in a multiprotein complex with adherens junction components. The complexes are associated with plasma membrane microdomains containing the structural lipid raft protein flotillin-2, but not similar microdomains containing caveolin. Disruption of the adherens junction complexes is linked to down regulation of LAR family receptor tyrosine phosphatases and hyperphosphorylation of the proteins in the complex. Since adherens junctions

provide structural stability to the epithelial sheet through connections to the actin cytoskeleton, and such connections are compromised in ADPKD, these alterations are likely to contribute to the disease pathology. We hypothesize that flotillin-2 membrane microdomains represent sites where the polycystins are activated and cooperate with signaling molecules to bring about stable cell-cell adhesion. Consequently, when polycystin-1 function is mutant or absent, the signaling to initiate cell adhesion is altered and changes in renal cystogenic potential result. The experiments in this proposal will elucidate the organization and function of the polycystin-containing multiprotein complexes associated with the flotillin-2 membrane microdomains by probing for colocalized tyrosine kinases and phosphatases and by monitoring the contribution of flotillin-2 rafts to actin remodeling, membrane trafficking and stable cell-cell adhesion. Successful completion of the proposed experiments will provide new, mechanistic information on the temporal sequence of events leading from polycystin-1 activation to the stabilization of E-cadherin mediated adhesion. These mechanistic insights are expected to be useful for designing therapeutic interventions, particularly those that make use of kinase inhibitors.

- **Project Title: PAX2 INTERACTING PROTEINS IN DEVELOPMENT AND DISEASE**

  Principal Investigator & Institution: Dressler, Gregory R.; Associate Professor; Pathology; University of Michigan at Ann Arbor 3003 South State Street, Room 1040 Ann Arbor, Mi 481091274

  Timing: Fiscal Year 2005; Project Start 15-JAN-1999; Project End 31-MAR-2007

  Summary: (provided by applicant): Understanding the genetic basis of mammalian development is not only important from a basic biological view but is also relevant to human disease. The development of the mammalian embryo from a single fertilized egg utilizes the entire spectrum of genetic and biochemical regulatory mechanisms. Pluripotent precursor cells, or stem cells, must proliferate to renew the embryonic population and also differentiate to generate the highly specialized cell types unique to particular tissues and structures. Many types of human diseases result from the aberrant proliferation of cells that appear more de-differentiated, assuming an embryonic phenotype. In cancer, such dedifferentiated cells are also prone to migration and invasion, two processes oft seen in the developing embryo. Growth and differentiation of precursor cells are controlled both by intrinsic proteins, such as transcriptional activators and repressors, and by extrinsic factors, such as secreted cell signaling molecules. The interplay between cell-cell signaling and gene activation by transcription lies at the heart of genetic regulatory mechanisms controlling differentiation, proliferation, cell death, and morphogenesis. The developing kidney is an excellent model system to study epithelial cell differentiation and morphogenesis of a complex organ system. Pax2 is a transcription factor transiently expressed in the early kidney precursor cells, the metanephric mesenchyme, and in the proliferating epithelial derivatives of this mesenchyme. While Pax2 is absolutely essential for kidney development, failure to suppress Pax2 expression in more differentiated renal tubules is associated with a variety of disease including renal cell carcinoma, **polycystic kidney disease,** and juvenile cystic dysplastic kidneys. The activity of Pax2 is stimulated by phosphorylation of the transactivation domain by the c-Jun N-terminal kinase (JNK). Furthermore, the interaction of Pax2 with the Groucho family of transcriptional repressor molecules inhibits phosphoprylation of the Pax2 activation domain. Thus, Pax2 activity is regulated by both extrinsic signaling, through JNK, and by intrinsic nuclear factors, such as Groucho, to control the activation or repression of downstream Pax2 target genes. This proposal will map the specific serine residues of Pax2 phosphorylation within the large activation domain. Phospho-Pax2 specific antibodies

will be generated to localize the active form of the Pax2 protein in vivo and to determine the interactions of Phospho-Pax2 with the cellular transcription machinery. We will also address the role of the Pax2 interacting protein PTIP in modulating Pax2 activity. PTIP is an essential nuclear factor for cell proliferation that associates with actively expressed chromatin. Given the role of Pax2 in the proliferation of renal epithelial cells and in renal disease, controlling Pax2 activity through its interactions with other cellular proteins can potentially lead to novel therapeutic interventions for cancer, PKD and other kidney disease.

- **Project Title: PKD INNOVATIVE IMAGING TO ASSESS PROGRESSION (PCC)**

  Principal Investigator & Institution: Torres, Vicente E.; Chairman; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2006; Project Start 01-FEB-2000; Project End 31-DEC-2010

  Summary: (provided by applicant): Autosomal dominant **polycystic kidney disease** (ADPKD) is a major cause of disabling morbidity and is the fourth leading cause of end-stage renal failure in the world, affecting more than 500,000 U.S. citizens and millions more worldwide. Researchers at the University of Alabama, Emory University, University of Kansas, Mayo Clinic and Washington University St. Louis joined together in 2000 to create the Consortium for Radiologic Studies of **Polycystic Kidney Disease** (CRISP-I). The primary objectives of this investigation were to: (1) Develop and test the accuracy and reproducibility of imaging techniques to monitor changes in renal cyst size and parenchymal involvement. (2) Establish and maintain a database of uniformly and accurately collected information. (3) Maintain and make available such data to facilitate the planning and implementation of clinically appropriate interventions in the near future. The goals of CRISP-I I are to extend the observations of CRISPI in order to: 1) Draw unequivocal linkage between the rate of kidney/cyst enlargement and qualitative and quantitative end-points. 2) Provide a marker of disease progression (kidney volume) sensitive and accurate enough to be used as a primary outcome marker in clinical trials aiming to forestall disease progression. 3) Develop and test other bio-markers of disease progression. The specific aims are: Aim 1: Extend the preliminary observations of CRISP-I to ascertain the extent to which quantitative (kidney volume and hepatic and kidney cyst volume) or qualitative (cyst distribution and character) structural parameters predict renal insufficiency. Aim 2: Extend the preliminary observations of CRISP-I to ascertain the extent to which age and sex-adjusted measurements of renal blood flow by MR technology predict the rate of renal growth; and, renal blood flow and kidney volume predict the rate of renal function decline in ADPKD. Aim 3: Exhaustively analyze the living database and stored biologic samples derived from CRISP-I and the CRISP-II extension to develop and test new metrics to quantify and monitor disease progression, and collect DMA samples and clinical information from CRISP family members known to have ADPKD for use in future studies to examine genotype-phenotype correlations and to identify genetic modifiers.

- **Project Title: POLYCYSTIC KIDNEY DISEASE CLINICAL TRIALS NETWORK**

  Principal Investigator & Institution: Perrone, Ronald D.; Associate Professor; New England Medical Center Hospitals 750 Washington St Boston, Ma 021111533

  Timing: Fiscal Year 2005; Project Start 15-AUG-2002; Project End 31-JAN-2009

  Summary: (provided by applicant): Autosomal dominant **polycystic kidney disease** (ADPKD) is the most common lethal monogenetic disease, affecting 1/500 to 1/1000 of the US population. 50% of those affected with ADPKD will develop end-stage renal disease by the 6th decade of life. There are no proven therapies to slow the inexorable

loss of kidney function in those with progressive disease. Interruption of the renin-angiotensin-aldosterone system (RAAS) has been shown to reduce the progressive decline in renal function in both diabetic and non-diabetic kidney diseases, but it is unknown whether these results extend to ADPKD. Abundant evidence implicates angiotensin II in the pathogenesis of hypertension, but small single-center studies of limited duration have reported inconsistent results of ACE inhibitor (ACE-I) therapy on disease progression. This application is submitted in response to RFA DK-01-029 to establish a PKD Clinical Trials Network of clinical centers that will each enroll 500 ADPKD patients and conduct a clinical trial to assess the efficacy of therapeutic interruption of the RAAS on renal progression. We have proposed a randomized, double-blinded trial to compare ACE-I vs. active control in hypertensive ADPKD patients with renal insufficiency (GFR 30-65 ml/min/1.73 m2) on the time to reach a composite outcome of doubling of serum creatinine, ESRD, or death. The Clinical Center will be based at the New England Medical Center and Beth Israel Deaconess Medical Center. The Principal and Co-Principal Investigators have had career-long interests in ADPKD and personally care for large numbers of ADPKD patients. We have identified 107 potentially eligible patients within our clinical sites. Additional strategies will be used to target patients locally and within contiguous New England States. Strong institutional support is available at the highest levels, including the General Clinical Research Centers at NEMC and BIDMC. As part of this RFA, we have proposed a pilot study to assess the safety of cyclooxygenase-2 inhibition, which has been implicated in angiogenesis and cyst development in animal models of ADPKD. Thirty ADPKD patients with GFR >70 ml/min/1.73 m2 will be randomized to treatment with celecoxib vs. placebo and followed for 16 weeks. Change in GFR is the primary outcome measure and incidence of hyperkalemia, fluid retention, and elevated blood pressure will be assessed.

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

- **Project Title: POLYCYSTIN-1, ATP-INDUCED CA2+ ENTRY & C1 - CONDUCTANCE**

  Principal Investigator & Institution: Sutters, Michael; Medicine; Johns Hopkins University W400 Wyman Park Building Baltimore, Md 212182680

  Timing: Fiscal Year 2005; Project Start 01-SEP-2004; Project End 31-AUG-2009

  Summary: (provided by applicant): Autosomal dominant **polycystic kidney disease** (ADPKD) is one of the most common hereditary diseases, causing loss of renal function that leads to dialysis treatment in some 1800 new patients a year. The disease, arising from mutations in the PKD 1 gene encoding polycystin-1, is characterized by the presence of multiple renal cysts. Expansion of these cysts correlates closely with loss of renal function and is driven by transepithelial fluid secretion. The objective of this KO8 proposal is to understand why loss of polyeystin-1 results in fluid secretion and cyst expansion. ATP is a potent and universal stimulus for fluid secretion and might therefore play a role in ADPKD: All the components required for ATP-stimulated chloride secretion are resident in the cyst environment. ATP acts through heterotrimeric G proteins (Glphabetagamma) to cause an initial burst of calcium release from the endoplasmic reticulum (ER), which in turn triggers a prolonged phase of calcium entry from outside the cell (agonist induced calcium entry or ACE). ACE is also triggered by ER store-independent pathways linked to Galphabetagamma. Increased ATP-stimulated chloride secretion could arise from loss of polycystin-1 through disruption of its known effects upon ACE-type channels and Galphabetagamma. In preliminary experiments it was demonstrated that expression of the isolated C-terminal 193 amino acids of

polycystin-1 (sIg-PKD193 fusion protein) augmented ATP-stimulated chloride secretion through up-regulation of store independent ACE in a cortical collecting duct cell line. Over-expressed polycystin-1 had the opposite effect, abbreviating the cell calcium response to ATP, suggesting that the slg-PKD193 fusion protein effect was the result of dominant negative inhibition of endogenous polycystin-1. It is hypothesized that: Polyeystin-1 down-regulates ATPstimulated chloride secretion through attenuation of store-independent agonist-induced calcium entry, and acts via modulation of heterotrimerie G protein coupled pathways. The experiments in Specific Aim #1 will define the effects of polycystin-1 upon the ER store dependent and independent components of ACE, and correlate these effects with the regulation of chloride channel activity. This will be done through over-expression and inhibition of polycystin-1. Specific aim #2 will identify the mechanism of the effect of polycystin-1 upon ACE, thereby providing a direct link between genetic lesion and fluid secretion. Dr. Michael Sutters has dedicated his career to becoming both a clinician and a scientist. He will be the principle investigator in this KO8 application. The long-term aim of his work is to facilitate the design of new therapeutic strategies to control disease progression through delineation of the mechanism of cyst expansion in ADPKD

- **Project Title: POLYCYSTIN2 FUNCTION IN KIDNEY DEVELOPMENT**

  Principal Investigator & Institution: Drummond, Iain A.; Assistant Professor of Medicine; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2005; Project Start 01-SEP-2004; Project End 31-AUG-2008

  Summary: Autosomal dominant **polycystic kidney disease** is caused primarily by mutations in two genes, Pkd1 and Pkd2, which function together as a calcium channel complex. Subcellular localization studies suggest that the polycystin2 protein may act in the apical cell membrane associated with cilia or in internal cell membranes as a calcium release channel. However, it is currently not known where polycystin2 channel activity acts in epithelia or which cellular signaling systems may impinge on polycystin2 function. Disruption of zebrafish polycystin2 gene expression using antisense morpholino oligos results in rapid kidney cyst development, randomized organ laterality, hydrocephalus, and body axis curvature. These defects are rescued by co-injection of the human pkd2 mRNA. In Aim 1. we propose using the zebrafish as an in vivo system for structure function analysis of polycystin2. We hypothesize that specific amino acid motifs in polycystin2 target it to its cellular site of action. By disrupting these either in the endogenous zebrafish polycystin2 or in rescuing human polycystin2 mRNAs we will test whether subcellular localization affects the cellular function of polycystin2. In Aim 2. we hypothesize that polycystin 2, acting as a calcium channel, mediates the effects of physical forces on the epithelium. We will measure calcium responses in isolated kidney tubules that lack polycystin2 function or that express altered pkd2 alleles. Finally we propose that mutations in polycytin2 interacting proteins or downstream mediators may effect signaling or function of polycystin2. In Aim 3. we outline a plan to identify cellular components that interact with polycystin2 by screening for dominant suppressors of the zebrafish polycystin2 phenotype. This proposal exploits unique advantages of the zebrafish as a model organism to more fully explore the function of polycystin2 in vivo and further our understanding of the cellular mechanisms of autosomal dominant **polycystic kidney disease.**

- **Project Title: POLYPEPTIDES OF THE FLAGELLAR TIP COMPLEX**

  Principal Investigator & Institution: Sloboda, Roger D.; Professor; Biological Sciences; Dartmouth College Office of Sponsored Projects Hanover, Nh 03755

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

Summary: (provided by applicant): Intraflagellar transport (IFT) is a process that is fundamental to the proper function of many cell types in the body, among them cells of the kidney where it is required for the assembly and maintenance of the primary cilia of the cells lining the nephron. Defects in the components of these primary cilia and defects in the machinery of IFT have been shown to cause **polycystic kidney disease.** The long term goals of this new project are to identify and characterize proteins of the flagellar tip complex and learn how they are involved in controlling particle movement during IFT. Why direct these studies to the flagellar tip? The microtubules (MTs) of the flagellar axoneme assemble and continuously turn over at the flagellar tip. The supply to and removal from the flagella of IFT components requires two motors: the MT-based motor protein kinesin-ll moves cargo from the base to the tip, and cytoplasmic dynein 1b moves cargo from the tip back to the base. Important activities relevant to the proper functioning of IFT occur at the flagellar tip, and these include MT assembly and disassembly, motor protein regulation, and cargo loading and unloading. Because an abrupt change in the direction of particle movement occurs only at the flagellar tip, the motor proteins must be regulated at the tip. Kinesin must be down regulated or turned off, and cytoplasmic dynein must be upregulated or turned on. The mechanisms used to control motor protein regulation and cargo unloading at the tip are unknown, but it is likely that a complex of proteins restricted to the flagellar tip, herein referred to as the flagellar tip complex (FTC), plays a definitive role in these processes. To test this hypothesis, three aims are proposed here: Having identified a polypeptide, CrEB1, that is localized at the flagellar tip. I will use rEB1 as a hook to fish out and identify other FTC proteins that are specific to the flagellar tip. The second aim will employ different approaches to identify structural and enzymatic components of the FTC that do not depend on an interaction with CrEBl. The third aim will characterize the FTC proteins identified via the first two aims and determine their function in IFT. Understanding more about the process of IFT is very important, as recent studies have shown that IFT defects cause **polycystic kidney disease** specifically, and defects in primary cilia are associated with a range of human disorders in addition to cystic diseases of the kidney, including retinal degeneration, obesity, hypertension, and diabetes, etc.

- **Project Title: REGULATION OF CA++ SIGNALING BY THE PDK 2 GENE PRODUCT**

  Principal Investigator & Institution: Tsiokas, Leonidas; Assistant Professor; Cell Biology; University of Oklahoma Hlth Sciences Ctr Health Sciences Center Oklahoma City, Ok 731171213

  Timing: Fiscal Year 2005; Project Start 01-MAR-2002; Project End 31-DEC-2006

  Summary: (provided by applicant): The function(s) of the genes responsible for the vast majority of cases of autosomal dominant **polycystic kidney disease** (ADPKD) are unknown. Based on sequence analysis, the gene product of the **polycystic kidney disease** gene 1 (PKD1) has been proposed to encode a protein with a role in cell-cell and/or cell - extracellular matrix interactions while PKD2 is thought to function as a cation channel. We have shown that PKD2 physically associated with PKD1 and only in the presence of PKD1, PKD2 was able to form a Ca++ permeable cation channel. In addition to PKD 1, PKD2 was also able to associate with the transient receptor potential channel 1 (TRPC1). We now show that TRPC1 has a widespread distribution in epithelial structures, primarily the ductal cells of the kidney and liver. TRPC 1 was shown to enhance Ca++ entry in response to store depletion (or capacitative Ca++ entry, CCE). CCE is the major route by which non-excitable cells regulate their intracellular

Ca++ concentration. Among the many cellular functions regulated by CCE, regulation of cAMP accumulation is a well-characterized and specific physiological target of CCE. Notably, the involvement of cAMP in cyst formation in kidney and liver epithelial cells has been well established. We propose that PKD1, PKD2 and TRPC1 assemble to a functional complex to enhance CCE. Naturally occurring mutations in PKD2 may result in the disruption of this complex and thereby in alterations in CCE. We will test our model by showing the existence of an endogenous complex and identifying protein-protein interactions responsible for complex assembly. Next, we will measure CCE in cells transfected with PKD1, PKD2 and TRPC1. We will evaluate an effect of PKD2 on CCE by introducing dominant negative constructs of PKD2 in cell lines that endogenously express PKD1, PKD2 and TRPC1 and testing whether wild type or mutant PKD2 can regulate cAMP accumulation in kidney epithelial cells. Our ultimate goal is to develop a biologically significant system that would allow us to probe the mechanisms by which pathogenic mutations in PKD2 alter its normal function, and to design therapeutic interventions in diseases such as ADPKD.

- **Project Title: REGULATION OF CALCIUM-ACTIVATED CHLORIDE CHANNELS**

  Principal Investigator & Institution: Hartzell, H Criss.; Professor; Cell Biology; Emory University 1784 North Decatur Road, Suite 510 Atlanta, Ga 30322

  Timing: Fiscal Year 2005; Project Start 01-JUL-2000; Project End 31-AUG-2009

  Summary: (provided by applicant): Our long-term goal is to understand the structure and function of a new family of Cl channels, the bestrophins. We have evidence that bestrophins are Ca-activated Cl channels. CaC channels play established roles in many physiological processes, including epithelial secretion. Specific Aim 1 will perform a structure-function analysis of mouse bestrophin 2 (mBest2). Two hypotheses will be tested: (1 A): The pore of the mBest2 Cl channel is formed by several different non-contiguous hydrophobic sequences, including parts of segments B, C, and E. Cysteine-scanning mutagenesis and analysis of bestrophin currents by patch clamp will be employed to understand how the channel selects among ions. Epitope-tagging will be used to establish mBest2 topology. (1B): Native CaC channels are heteromultimers of bestrophin subunits. We will use co-expression of bestrophin subunits, co-immunoprecipitation of interacting subunits, and interference with the expression or function of native bestrophin subunits using siRNA and dominant negative constructs. This aim will (i) provide concepts about the mechanisms of anion selectivity of ion channels, (ii) yield insights into how the channel functions physiologically, and (iii) give additional support for the role of bestrophins as Cl-selective pores. The second specific aim is to understand the physiological and pathophysiological functions of mBest2. Native CaC currents and bestrophin currents are both regulated by extracellular osmolarity as well as cytosolic Ca. Cells in the kidney are subject to widely varying extracellular osmotic environments depending on the animal's hydration state. Two hypotheses will be tested. (2A): CaC and bestrophin currents are modulated by cell membrane tension and play a novel role in cell volume regulation. This hypothesis will be tested by determining the relationships between osmolarity, cell volume, membrane tension, Ca, mBest2 currents, and compensatory cell volume changes. (2B): CaC currents and bestrophins are involved in cyst expansion in autosomal dominant **polycystic kidney disease** (ADPKD). This hypothesis will be explored using immunocytochemcial, electrophysiological, and pharmacological analysis of Best2 expression in normal and polycystic kidney tissue and cultured epithelial cells from cysts. This aim will establish the role of CaC channels and bestrophins in kidney physiology and disease.

- **Project Title: REGULATION OF CFTR TRAFFICKING**

  Principal Investigator & Institution: Stanton, Bruce A.; Professor; Physiology; Dartmouth College Office of Sponsored Projects Hanover, Nh 03755

  Timing: Fiscal Year 2005; Project Start 30-SEP-1992; Project End 31-JUL-2009

  Summary: (provided by applicant): Our long-term objective is to elucidate the endocytic trafficking pathway of CFTR and to identify a drug that corrects defective endocytic trafficking of detaF508-CFTR. DeltaF508, the most common mutation in CF, reduces the expression of CFTR in the apical plasma membrane in epithelial cells because deltaF508-CFTR is not exported efficiently from the endoplasmic reticulum and because the endocytic trafficking of CFTR is abnormal. However, very little is known about the mechanisms regulating the endocytic trafficking of CFTR. In preliminary studies we demonstrate that myosin VI regulates CFTR endocytosis, that myosin Vc regulates CFTR endocytic recycling and that the deltaF508 mutation facilitates CFTR endocytosis. Accordingly, the hypothesis to be tested in this proposal is that a complex of interacting proteins including myosin VI and Vc regulates the endocytic trafficking of CFTR and that the deltaF508 mutation perturbs the endocytic trafficking pathway. To test this hypothesis we propose three specific aims: Specific Aim #1. Test the hypothesis that a macromolecular complex of proteins including myosin Vl, Dab2, AP-2 and clathrin regulate the endocytosis of CFTR. The goal of this specific aim is to elucidate how myosin Vl, the adaptor proteins Dab2 and AP-2, and clathrin regulate the endocytosis of CFTR, Specific Aim #2. Test the hypothesis that a macromolecular complex of proteins including myosin Vc and EBP50 regulate the endocytic recycling of CFTR. The goal of this specific aim is to elucidate how myosin Vc and EBP50 regulate the endocytic recycling of CFTR, and Specific Aim #3. Test the hypothesis that the half-life of deltaF508-CFTR in the plasma membrane is reduced due to an increase in endocytosis and/or a reduction in endocytic recycling. The goal of this specific aim is to determine if the deltaF508 mutation perturbs CFTR endocytosis and/or endocytic recycling. We anticipate that our studies will provide new insight into the mechanisms involved in cargo selection and vesicle trafficking as well as the etiology of several other "trafficking" disorders such as autosomal dominant distal renal tubular acidosis, Huntington's disease, Tangier's disease, Niemann-Pick disease type C, and **polycystic kidney disease.**

- **Project Title: REGULATION OF FLAGELLAR ASSEMBLY IN CHLAMYDOMONAS**

  Principal Investigator & Institution: Lefebvre, Paul A.; Professor; Genetics, Cell Biology & Develpmnt; University of Minnesota Twin Cities 450 Mcnamara Alumni Center Minneapolis, Mn 554552070

  Timing: Fiscal Year 2005; Project Start 01-DEC-1984; Project End 31-AUG-2008

  Summary: (provided by applicant): The long-term goal of this research is to understand the mechanisms eukaryotic cells use to regulate the assembly of cilia and flagella. The flagella of Chlamydomonas are maintained at a constant length, but mutations in four different genes: LF1, LF2, LF3 and LF4, cause the cells to lose control of assembly and grow flagella up to three times normal length. Two of these genes encode members of well-studied gene families: a MAP kinase and a kinase of the CDK family. Analysis of the four LF genes leads to the conclusion that LF4, a novel MAP kinase, acts to enforce flagellar length control by shortening the flagella. LF1, LF2 and LF3 appear to act together to regulate length, perhaps by regulating retrograde intraflagellar transport (IFT). During the next project period the specific aims of this project will address the following questions:l) What proteins regulate the MAP kinase enzyme encoded by the LF4 gene, and what proteins does LF4p phosphorylate? 2) How do the proteins in the

putative LF1/LF2/LF3 cytoplasmic complex interact, and how does this complex regulate the LF2 protein kinase? 3) What are the protein substrates of the LF2 protein kinase and how does phosphorylation of these targets regulate flagellar length? 4) Do the long-flagella mutants show alterations in intraflagellar transport (IFT)? Cilia and flagella have long been known to play key roles in processes that involve the movement of fluids over surfaces or the movement of cells through fluids. More recently it has become clear that cilia and flagella have critical functions early in development. Defects in the assembly of cilia and flagella have been connected to **polycystic kidney disease** retinal degeneration, situs inversus, and other problems in mammalian development. Understanding the regulation of flagellar assembly in Chlamydomonas provides a powerful model for understanding this assembly in mammalian systems.

- **Project Title: REGULATION OF KIDNEY-SPECIFIC GENE EXPRESSION**

  Principal Investigator & Institution: Igarashi, Peter; Professor and Chief; Internal Medicine; University of Texas Sw Med Ctr/Dallas 5323 Harry Hines Blvd. Dallas, Tx 753909105

  Timing: Fiscal Year 2006; Project Start 15-APR-1991; Project End 30-NOV-2010

  Summary: (provided by applicant): The overall goal of this project is to understand the roles of hepatocyte nuclear factor-1 3 (HNF-1 (3) in kidney-specific gene expression, renal cell differentiation, and kidney organogenesis. HNF-1 (3 belongs to a family of homeodomain-containing transcription factors that regulate tissue-specific gene expression in the kidney, liver, pancreas, and other organs. Humans with mutations of HNF-13 develop maturity-onset diabetes of the young type 5 (MODY5) and congenital cystic abnormalities of the kidney. Transgenic mice expressing mutant HNF-13 under the control of a kidney-specific promoter develop kidney cysts and renal failure, which is similar to the phenotype of humans with MODY5. Similarly, kidney-specific deletion of HNF- 1(3 using Cre/loxP recombination results in renal cyst formation. HNF-1 {3 mutant mice show decreased expression of Pkhdl, the gene mutated in autosomal recessive **polycystic kidney disease** (ARPKD), and HNF-13 directly regulates the Pkhdl promoter. These studies identify Pkhdl as a novel gene target of HNF- 13 in the kidney. They establish a previously unrecognized link between two renal cystic diseases, MODY5 and ARPKD, and suggest that the mechanism of cyst formation in humans with MODY5 involves down- regulation of PKHD1 gene expression. To test this hypothesis and to further define the functions of HNF-13 in the kidney, we will complete the following specific aims: 1. Define the roles of coactivators and histone acetylation in the regulation of Pkhdl gene transcription. 2. Determine how the activity of HNF-13 is reciprocally regulated by SUMO ligases and ubiquitin ligases. 3. Determine how HNF-13 regulates the tissue-specific expression of Pkhdl in the kidney and liver. 4. Elucidate the molecular pathogenesis of the kidney and genitourinary tract abnormalities caused by mutations of HNF-13. The proposed studies will utilize genetically-modified mice to define in vivo expression patterns and disease phenotypes and biochemical studies to elucidate molecular mechanisms. Understanding the functions of HNF-13 and the regulation of Pkhdl gene transcription will provide insights into the pathogenesis of congenital kidney abnormalities and ARPKD, which is one of the most common genetic causes of renal failure in infants and children.

- **Project Title: REGULATION OF POLYCYSTIN-2**

  Principal Investigator & Institution: Anyatonwu, Georgia I.; Pharmacology; Yale University 47 College Street, Suite 203 New Haven, Ct 065208047

  Timing: Fiscal Year 2005; Project Start 01-SEP-2003; Project End 30-SEP-2005

Summary: (provided by applicant): Autosomal dominant **polycystic kidney disease** (ADPKD) affects millions of people and it is the fourth leading cause of kidney failure in the United States. The two genes encoded in this disease are PKD1 and PKD2, and mutations in either gene are associated with the phoenotype seen in ADPKD. The long-term objective entails PKD2 gene product, polycystin-2, functions as a calcium permeable nonselective cation channel. Dysregulation of this channel provides mechanism for the onset and progression of ADPKD. The specific aims of this research include to (1) Determine the interaction between polycystin-2 and the ryanodine receptor (RYR); (2) What effects mutated variants of polycystin-2 would impact on the function of polycystin-2; (3) Develop a screening assay for putative agonists and antagonists of PKD2. Since these channels are intracellular calcium channels, planar lipid bilayer and calcium imaging techniques will be used to perform this study.

- **Project Title: REGULATION OF POLYCYSTIN-2 TRAFFICKING**

  Principal Investigator & Institution: Youker, Robert T.; None; Oregon Health & Science University 3181 Sw Sam Jackson Pk Rd Portland, or 972393098

  Timing: Fiscal Year 2007; Project Start 01-FEB-2007; Project End 31-JAN-2009

  Summary: (provided by applicant): Polycystin-2 is a non-selective calcium channel that regulates tubulogenesis and maintains homeostasis in several organ systems, including the liver, heart, and kidneys. Mutations in polycystin-2 account for 15% of the cases of people with autosomal dominant **polycystic kidney disease** (ADPKD), a genetically inherited disorder causing renal failure. Most polycystin-2 in epithelial cells localizes to the endoplasmic reticulum (ER) where it combines with the IPS receptor to control calcium homeostasis. Yet little is known about the mechanisms that localize this polytopic membrane channel to the ER. Our laboratory identified PACS-2 as a novel sorting protein and recently discovered that it binds to the cytosolic domain of polycystin-2 and is required to localize the channel to the ER. PACS-2 connects polycystin-2 to COPI, a vesicular coat protein that controls Golgi-to-ER retrieval. PACS-2/COPI may control the ER localization of polycystin-2 by directing an efficient Golgi-to-ER trafficking step. To test this hypothesis, experiments in Aim 1 will determine whether ER localization of polycystin-2 requires COPI and whether PKD2 is localized to the ER through a retentionor retrieval-based mechanism. To test the role of COPI in controlling the ER localization of full-length polycystin-2, we will use siRNA depletion of the beta-COP subunit and develop two polycystin-2 reporter constructs will be developed to determine quantitatively whether polycystin-2 is localized to the ER by a Golgi-to-ER retrieval step and the role of PACS-2 and COPI in directing this pathway. Specific aim 2 will determine which of the seven COPI subunits and residues in the polycystin-2 cytosolic domain-in addition to phosphorylated Ser812-are important for binding to PACS-2 and directing ER localization of polycystin-2. Yeast two-hybrid genetic screens and protein binding assays will identify COPI subunits and amino acid residues within the polycystin-2 cytosolic domain essential for complex formation. Polycystin-2 reporter molecules containing mutations of identified amino acids will be expressed to rigorously determine their role in the ER localization of polycystin-2 and their potential role in the targeting of polycystin-2 to the TGN, cell surface and primary cilia. Together, these studies will identify the fundamental mechanisms that control the subcellular localization of polycystin-2 and may provide a foundation to understand how intracellular signaling pathways are disrupted in **polycystic kidney disease.** The proposed studies are relevant to public health because insight into how polycystin-2 action is regulated is crucial for understanding kidney function and for developing therapies that can protect ADPKD patients from the devastating effect of this disease.

- **Project Title: REGULATION OF THE MOLECULAR MOTOR KINESIN-1**

  Principal Investigator & Institution: Verhey, Kristen J.; Cell and Developmental Biology; University of Michigan at Ann Arbor 3003 South State Street, Room 1040 Ann Arbor, Mi 481091274

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

  Summary: (provided by applicant): Motor proteins carry cellular cargoes along the cytoskeleton to their destination. Disregulation of these processes underlies a number of diseases ranging from cancer to **polycystic kidney disease** to neurodegenerative diseases. The long-term goal of our research is to understand how motor protein transport is controlled and coordinated in cells. We will use molecular, biochemical and cell biological analyses to address the mechanisms that control cargo binding and motor activity of the microtubule-based motor kinesin-1. Our hypothesis is that spatially segregated protein complexes control kinesin-1 transport at the point of departure and at the destination. We will analyze the mechanisms by which cargo binding leads to motor activation at the point of departure. We will explore the possibility that modifications of the microtubule cytoskeleton play a role in directing motor protein transport to the correct cellular destination. We will analyze the role of newly-identified protein complexes in the release of cargo and inactivation of kinesin-1 at the destination. This work will provide exciting new insights into the function of kinesin-1 in nerve cells. This work will also increase our understanding of how the regulation of motor proteins gives rise to coordinated transport of protein complexes in cells and will suggest therapeutic targets in human disease.

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

- **Project Title: RENAL AND ELECTROLYTE DISEASE AND HYPERTENSION**

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

  Timing: Fiscal Year 2005; Project Start 01-JUL-1983; Project End 30-JUN-2008

  Summary: (provided by applicant): The training program of the Division of Renal Diseases and Hypertension at the University of Colorado Health Sciences Center provides and integrated 3-4 year experience in clinical nephrology (1 year) and academic research (2-3 years). The program is designed to prepare postdoctoral fellows for careers in academic medicine. The clinical training, by utilizing 3 different hospitals with varied populations (University Hospital, Veterans Affairs Medical Center, and Denver Health Medical Center) exposes the trainees to a great range of patients with parenchymal renal disease, fluid and electrolyte disorders, acid-base disorders, hypertension, acute and chronic renal failure, acute renal replacement therapies, and chronic dialysis (peritoneal, hemodialysis both at home and in-center), and all medical aspects of transplantation. Thereafter the fellows choose to pursue their research training in the laboratory of any faculty member in the Division or in other Divisions with which we closely interact, such as rheumatology, immunology. The laboratories have modern, state of the art equipment and staff that provide the best possible research environment. The fellows can choose from a large number of laboratories or clinical investigation projects. Very broadly stated these include: a) laboratories studying the pathogenesis of acute renal failure; b) laboratories exploring the role of aquaporins in disorders of water balance; c) laboratories focused on signaling pathways in vascular smooth muscle cells, tumor cells, inner medullary collecting ducts cells; d) laboratories that study the pathogenesis of renal cyst formation; e) laboratories that study the immunology of graft rejection; and f) clinical studies in patients with diabetes, diabetic

nephropathy, acute renal failure, **polycystic kidney disease,** and graft rejection. Fellows are encouraged to enter a program leading to a Ph.D. in human biology that further broadens the research options available to them. The fellowship program chooses 4 trainees each year, all of who commit to at least a 3-year fellowship and express interest in an academic career. Interviewees are chosen from applicants who have completed at least three years of postdoctoral training in internal medicine. This ensures that the individual is ready for his or her initial clinical training, which is then followed by their research training.

- **Project Title: REVERSE GENETICS OF CHLAMYDOMONAS USING TILLING**

  Principal Investigator & Institution: Niyogi, Krishna K.; Plant and Microbial Biology; University of California Berkeley 2150 Shattuck Avenue, Room 313 Berkeley, Ca 947045940

  Timing: Fiscal Year 2006; Project Start 01-SEP-2006; Project End 31-AUG-2009

  Summary: (provided by applicant): Project Summary: The unicellular green alga Chlamydomonas reinhardtii is the model organism of choice for studying many fundamental aspects of eukaryotic cell biology, physiology, and biochemistry. As examples, the biogenesis and function of flagella/cilia, basal bodies, and plastids are most easily investigated using Chlamydomonas. A draft sequence of the Chlamydomonas nuclear genome at >9X coverage has been released by the DOE's Joint Genome Institute, but the lack of reverse genetic resources is currently a major limitation for functional genomics of Chlamydomonas. TILLING is a high-throughput reverse genetics approach that combines traditional mutagenesis with modern technology for detection of point mutations. TILLING can provide an allelic series of mutations in any gene of interest. The goal of this project is to establish a publicly available TILLING resource for the Chlamydomonas research community, in collaboration with the Seattle TILLING Project, which has successfully developed similar resources for the Arabidopsis, Drosophila, and zebrafish communities. The specific aims of this proposal are (1) to optimize UV/chemical mutagenesis of haploid Chlamydomonas and generate mutant populations for TILLING, (2) to perform pilot TILLING projects to determine if the haploid mutation density is sufficient for cost-effective TILLING, (3) to optimize UV/chemical mutagenesis of diploid Chlamydomonas and generate mutant populations for TILLING, (4) to perform pilot TILLING projects using a mutagenized diploid population, and (5) to provide a TILLING service to the Chlamydomonas research community. There is broad community support for the development of a TILLING resource for Chlamydomonas. The mutant populations and data generated by this project will be publicly available from the Chlamydomonas stock center and database. Relevance: Chlamydomonas is an important model for basic biological mechanisms and for human disease processes such as **polycystic kidney disease,** primary cilia dyskinesia, and Rh null disease. This project will generate a resource that will enable the determination of gene function for many genes that have been discovered by sequencing the Chlamydomonas genome.

- **Project Title: ROLE OF CELL ADHESION IN ORGANIZING MEMBRANE GROWTH**

  Principal Investigator & Institution: Yeaman, Charles; Anatomy and Cell Biology; University of Iowa Iowa City, Ia 52242

  Timing: Fiscal Year 2005; Project Start 01-SEP-2004; Project End 31-AUG-2009

  Summary: (provided by applicant): The long-term goal of this proposal is to understand the molecular mechanisms that regulate exocytosis in order to comprehend and develop

therapies for devastating human diseases in which exocytosis is defective, such as diabetes and **polycystic kidney disease.** The overall objective of this work is to dissect the spatio-temporal regulation of exocytosis at a molecular level during development of epithelial cell polarity. This proposal focuses on three components of the trafficking machinery: the Exocyst (a putative vesicle tethering factor), Munc18c (a regulator of tethering/fusion machinery), and Syntaxin 4 (a component of the fusion machinery). Based upon results of preliminary studies, a working hypothesis has been developed for how polarized trafficking to the basal-lateral membrane is established. Cell-cell adhesion promotes assembly, movement and association of Exocyst with intercellular contact sites defined by E-cadherin-associated protein complexes; association of transport vesicles with these sites coincides with an interaction between an Exocyst subunit (Sec6) and Munc18c, and this in turn regulates the activity of Syntaxin 4, leading to membrane fusion. The specific aims of this study are to: 1) identify mechanisms that specify targeting patch assembly at sites of cell-cell adhesion; 2) determine the functional significance of Sec6 binding to Munc18c in basal-lateral membrane trafficking; and 3) determine whether conformational changes in Sec6 regulate its association with Munc18c. The research plan to achieve these aims involves a combination of cell biology, biochemistry and molecular biology approaches. The significance of these studies is that they will define signaling pathways and specific interactions that couple an extracellular spatial cue (cell adhesion) to organization of components involved in membrane trafficking (vesicle docking/fusion machinery) leading to establishment of cell polarity. In the long term these studies will provide new insights into understanding the basis for abnormalities in membrane protein organizations characteristic of epithelial diseases. Also, because this proposal focuses on how information is transferred from vesicle to plasma membrane to initiate exocytosis, it has broad implications for many processes including antigen presentation, neurotransmission and hormone secretion.

- **Project Title: ROLE OF PACS PROTEINS IN POLYCYSTIN-2 TRAFFICKING AND ADPKD**

  Principal Investigator & Institution: Thomas, Gary; Scientist/Professor; None; Oregon Health & Science University 3181 Sw Sam Jackson Pk Rd Portland, or 972393098

  Timing: Fiscal Year 2006; Project Start 01-DEC-1985; Project End 31-MAY-2011

  Summary: (provided by applicant): The long-term goal of this project is to determine the role of the sorting proteins PACS-1 and PACS-2 in autosomal dominant **polycystic kidney disease** (ADPKD). This inherited disorder manifests in formation of numerous cysts in the kidney, culminating in excessive apoptosis and destruction of normal tissue. ADPKD is frequently caused by mutation of polycystin-2, a calcium-permeable ion channel that functions in multiple subcellular organelles. We recently identified the molecular trafficking machinery-PACS-1 and PACS-2- governing the stepwise movement of polycystin-2 between the endoplasmic reticulum (ER), Golgi and the cell surface. In addition, we discovered that PACS-1 and PACS-2 integrate protein trafficking with apoptosis and cell differentiation. We hypothesize that PACS-1 and PACS-2 are multifunctional sorting proteins that control the subcellular localization of polycystin-2 in the normal kidney, and that misregulation of PACS-1 and PACS-2 contributes to the cystogenesis and excess apoptosis observed in the polycystic kidney. We identified PACS-2 as the first COPI connector, and experiments in Aim 1 will determine how PACS-2 and COPI combine to localize polycystin-2 to the ER-the principle cellular reservoir for this ion channel. Also, we showed that PACS-1 is an AP-1 connector that localizes polycystin-2 to the trans-Golgi network (TGN). Studies in Aim 2 will determine how regulation of PACS-1 and PACS-2 sorting activity effects polycystin-

2 calcium spikes in multiple subcellular compartments. Despite the causal relationship between polycystin-2 mutations and ADPKD, the steps leading from channel dysfunction to cystogenesis and disease are poorly understood. We recently found that PACS-1 expression is severely reduced in the ADPKD kidney, while PACS-2 expression is relatively little changed-a combination that favors apoptosis in cultured cells. Studies in Aim 3 will determine the cellular expression of PACS-1 and PACS-2 in the ADPKD kidney and will test whether loss of PACS-2 inhibits cystogenesis using a mouse model of **polycystic kidney disease.** Successful completion of our proposed studies will illuminate for the first time the multifunctional trafficking machinery- PACS-1 and PACS-2-that regulates the ability of polycystin-2 to conduct calcium currents in multiple organelles, and how misregulation of PACS-1 and PACS-2 expression contributes to the cystogenesis and excess apoptosis found in ADPKD.

- **Project Title: SHARED SPINNING DISK CONFOCAL MICROSCOPE SYSTEM**

  Principal Investigator & Institution: Doxsey, Stephen J.; Associate Professor; Molecular Medicine; Univ of Massachusetts Med Sch Worcester Medical School Worcester, Ma 01655

  Timing: Fiscal Year 2006; Project Start 01-APR-2006; Project End 31-MAR-2007

  Summary: (provided by applicant): The Digital Imaging Core Facility (DICF) of the University of Massachusetts (UMass) Medical School and a group of seven NIH funded principal investigators request funds to purchase a spinning disk confocal microscope system for live cell imaging. The Digital Imaging Core Facility was established by the UMass Medical School Office of Research and Scientific Council to provide multimode digital imaging microscopy facilities and digital deconvolution to the UMass research community. The requested instrument will be integrated into this campus wide research resource and would be available to the entire UMass Medical School research community when it is not being used by the major and minor users. There is a great need by many NIH funded UMass Medical School researchers for a confocal microscope system designed for live cell imaging in order to accomplish the objectives of their NIH funded research. All of the researchers requesting this instrument are involved in qualitative and quantitative studies of dynamic cellular processes, and four are members of the UMass Cellular Dynamics Program. There is currently no spinning disk confocal microscope system for live cell imaging at UMass Medical School available for general use as part of a core facility. This spinning disk confocal microscope system will allow UMass researchers to expand their research in new directions and advance their biomedical research programs. The requested spinning disk confocal microscope system will be used to conduct basic research in cancer cell biology, cell signaling, developmental biology and cancer, cell cycle regulation, intraflagellar transport as related to **polycystic kidney disease** and retinitis pigmentosa, Bardet-Biedl syndrome and Senior-Loken syndrome, molecular motor proteins, sensory transduction and immunology. The Digital Imaging Light Microscopy Core Facility of the University of Massachusetts (UMass) Medical School and a group of seven UMass faculty members request funds to purchase a spinning disk confocal microscope system to advance their NIH funded biomedical research. The requested instrument will be used to conduct basic research in cancer cell biology, cell signaling, developmental biology and cancer, cell cycle regulation and intraflagellar transport as related to **polycystic kidney disease** and other diseases.

- **Project Title: SINGLE MOLECULE STUDIES OF POLYCYSTIN-1**

  Principal Investigator & Institution: Oberhauser, Andres; Associate Professor; Neuroscience and Cell Biology; University of Texas Medical Br Galveston 301 University Blvd Galveston, Tx 77555

  Timing: Fiscal Year 2005; Project Start 01-APR-2004; Project End 31-MAR-2007

  Summary: (provided by applicant): Autosomal dominant **polycystic kidney disease** (ADPKD) is one of the most common life-threatening genetic diseases, and is a leading cause of renal failure. The majority of cases are caused by mutations in the PKD1 gene, which codes for polycystin-1, PC1, a protein predicted to function as a cell adhesion protein mediating cell-cell and cell matrix interactions. This large multi-modular protein contains 16 copies of a novel immunoglobulin (Ig)-like fold, the **polycystic kidney disease** (PKD) domain. Tandem repeats of Ig-like domains are a common feature of proteins with structural and mechanical roles, such as titin (an elastomeric protein of muscle), fibronectin (an elastic extracellular matrix protein component) or cadherin (a mechano-chemical cell adhesion protein). Recent single molecule experiments have shown that such proteins are highly extensible and elastic. We propose that PC1 functions mechanically by providing a flexible and elastic linkage between cells. The mechanical properties of PC1 may be vital for maintaining the architectural integrity of the kidney. Mutations may alter PC1's cell adhesion and mechanical properties and lead to the alterations in cell-cell interactions and abnormal tissue development which are characteristic of ADPKD. However, there is very little information about the structural organization of the extracellular domain of PC1, or how mechanical forces may affect its structural features. Neither is it known how mutations might alter PC1's structure and mechanical properties. In this R21 project we plan to use a novel combination of single molecule and protein engineering tools to test whether PC1 is a highly elastic and extensible molecule, as predicted from its structure. In Aim 1 we will use single molecule force spectroscopy to examine the stability and mechanical properties of the diverse protein domains found in PC1. In Aim 2 we will examine the effects of naturally occurring mutations on the mechanical stability and unfolding kinetics of PC1's PKD domains. The long-term goal of our research is to gain a better understanding of the function of normal and mutant forms of PC1 and lay the foundation for therapeutic approaches to the currently untreatable ADPKD.

- **Project Title: SPROUTY, A WT1 TARGET FOR GROWTH AND DEVELOPMENT**

  Principal Investigator & Institution: Licht, Jonathan D.; Professor and Chief; Oncological Sciences; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 100296574

  Timing: Fiscal Year 2005; Project Start 01-JAN-1994; Project End 31-DEC-2005

  Summary: (Adapted from the applicant's abstract) In this proposal we will characterize the expression of sprouty in renal development, murine development in general and in Wilm's tumors. We will characterize the mechanism of action of sprouty. Hence we will determine if sprouty is a growth inhibitor which may mediate some of the effects of WT1. We will determine at which steo in signaling through receptor tyrosine kinase sprouty acts. We then isolate partner proteins of spry which will lead to better idea of the molecular mechanism of sprouty. In order to determine the role of spry in normal and aberrant development we will determine in cell culture models and transgenic animals if engineered expression of spry interferes with normal renal morphogenesis. Finally to provide a critical role of sprouty as a target of WT1 important for renal development we will create knockout animals for sprouty one using conditiona cre-lox technology. Through these studies we will characterize an exciting molecule involved

isgnal transduction and development. Spry may present a target for future strategies against Wilm's tumor, other malignancies and renal disorder such as **polycystic kidney disease.**

- **Project Title: THE EXOCYST IN SYNTHESIS, CYSTOGENESIS AND TUBULOGENESIS**

  Principal Investigator & Institution: Lipschutz, Joshua H.; Assistant Professor; Medicine; University of Pennsylvania Office of Research Services Philadelphia, Pa 19104

  Timing: Fiscal Year 2005; Project Start 15-SEP-2005; Project End 31-MAY-2010

  Summary: (provided by applicant): Cysts and tubules are basic "building blocks" for epithelial organs such as the kidney, and defects in cyst and tubule formation are implicated in disorders such as autosomal dominant **polycystic kidney disease.** Our goal is to understand the biology of cystogenesis and tubulogenesis as it relates to development and disease. Using a well-described in vitro collagen gel system, we have shown that a central factor in cystogenesis and tubulogenesis is the exocyst, an evolutionarily conserved eight-protein complex involved in the secretory pathway. The secretory pathway is essential for proper cellular function, and the exocyst is known for mediating the targeting and docking of vesicles carrying secretory and basolateral proteins during the final stage of this pathway. We recently showed that the exocyst, particularly the Sec10 component, also has the novel and unexpected function of specifically regulating protein synthesis, the first stage of the secretory pathway, by interacting with the Sec61 a component of the endoplasmic reticulum (ER) translocon. In mammalian cells, proteins are simultaneously translated and translocated across the rough ER via the translocon. Our proposal is directed toward the hypothesis that the central role played by the exocyst in cyst and tubule formation is a result of its specific effects on protein synthesis. Accordingly, we will build on our findings by asking the following questions: How does the exocyst/Sec61 a interaction regulate protein synthesis? What are the interacting domains between Secl0 and Sec61a? Finally, how does the exocyst/translocon, recognize and then specifically regulate basolateral, but not apical, protein synthesis? To answer these questions we will use in vitro systems, including cell-free assays, to test whether the exocyst regulates protein translation and/or translocation (Aim 1). We will then identify and map the SeclO/Sec61 a interacting domain, and determine the functional consequences of mutating this domain, with respect to protein synthesis and cyst and tubule formation (Aim 2). Lastly, we will identify sequences that direct exocyst/translocon regulation of basolateral protein synthesis. This will be done using existing basolateral proteins that traffic to the apical membrane, due to mutations in the basolateral targeting sequence, and chimeras composed of portions of apical and basolateral proteins (Aim 3). Completion of these studies will enhance the understanding of the mechanisms of protein synthesis in cyst and tubule formation at the cellular and molecular levels and lay the groundwork for the development of novel therapeutics.

- **Project Title: THE PRIMARY CILIUM OF CONECTIVE TISSUE CELLS: INCIDENCE AND ORIENTATION**

  Principal Investigator & Institution: Farnum, Cornelia Ellen.; Professor; Biomedical Sciences; Cornell University Ithaca 120 Day Hall Ithaca, Ny 14853

  Timing: Fiscal Year 2006; Project Start 01-JUL-2006; Project End 31-MAY-2008

  Summary: (provided by applicant): It is now well established that on most cells of the body there exists a modified, non-motile primary cilium that acts as an antenna sensing the extracellular environment, be it the lumen of a tubular organ or the extracellular

matrix of connective tissues. The primary cilium ultimately transduces stimuli that result in gene expression controlling fundamental biological responses of the cell. In the past five years there has been a significant increase in the understanding to the role of the primary cilium as a sensory organelle in epithelial cells throughout the body, with the greatest breakthroughs coming from discovering certain abnormalities of the primary cilium that are linked to specific diseases, such as **polycystic kidney disease** in young children. For parallel advancements to be made in understanding the functional role of the primary cilium in cells of connective tissues, methodology must be developed that allows easy detection of primary ciliary incidence and orientation, in vitro and in vivo. In epithelia, the primary cilium of each cell projects into the lumen of the organ or to the surface of a monolayer culture. In this superficial position its presence and orientation can be analyzed by light microscopical techniques following experimental manipulation. Primary cilia have been described as present in chondrocytes, tenocytes, and other connective tissue cells, but experimental analysis of their function remains a significant challenge because 1) the cilium projects into the extracellular matrix, and 2) many connective tissue cells do not maintain phenotypic stability in long-term monolayer culture. The goal of this proposal is to develop rapid versatile analytical methods based on imaging using multiphoton microscopy to examine the incidence, orientation and molecular structure of the primary cilium in articular cartilage, growth plate, tendon and intervertebral disc. This methodology will put the exploration of the function of the primary cilium in connective tissues on par with that of its counterpart in epithelial tissues. Establishment of this methodology will open the potential for exploring the function of the primary cilium of connective tissue cells in vivo through analysis of the cilium 1) in mouse models with chondrodysplasias thought to be linked to abnormalities in development of cellular polarity and tissue organization; 2) during development when anisotropy of cell and matrix organization of connective tissues is being established; and 3) in experiments in living animals involving manipulation of the biomechanical environment associated with a specific joint. An ability to assess rapidly the incidence and orientation of the primary cilium will provide a methodology that currently is missing for analysis of results from in vitro experimentation at the molecular level to test the hypothesis that the primary cilium of connective tissue cells functions as a mechanosensor.

- **Project Title: THE PROTEOLYTIC CLEAVAGE OF POLYCYSTIN-1: HOW AND WHY**

  Principal Investigator & Institution: Qian, Feng; Assistant Professor of Medicine; Medicine; Johns Hopkins University W400 Wyman Park Building Baltimore, Md 212182680

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

  Summary: (provided by applicant): Autosomal dominant **polycystic kidney disease** (ADPKD) is one of the most common Mendelian disorders in humans affecting 1/1000 worldwide. The hallmark of the disease is the development of multiple cysts from renal tubules in both kidneys, resulting in end-stage renal failure in 50% of the patients. ADPKD is a systemic disease with many ex-renal manifestations. Since the PKD1 gene was identified in 1995, significant efforts have been made in understanding of the biology underlying the disease. But the normal function its gene product, polycystin-1, is still poorly understood. The question of how a mutation in the single PKD1 gene leads to a vast array of defects is also unresolved. The long-term goal of our research is to understand the normal biological function of polycystin-1 during the development and its role in the maintenance of adult organs, and the mechanisms by which PKD1 mutations cause the disease. Post-translational modifications of the protein are known

to play a critical role for its activity and such processes have been implicated for the function of polycystin-1. We have found that polycystin-1 undergoes proteolyctic cleavage in vivo. Our preliminary results have indicated that this type of the post-translational processes is likely important for the functionality of polycystin-1. In the grant application, we propose to investigate the role of the proteolytic cleavage of polycystin-1 using a combination of chemical, biochemical, genetic and cell biological approaches. We plan to examine the functional significance of this process in the cell culture system and in the mouse. Furthermore, we propose to characterize the mechanism of regulation of the cleavage reaction and analyze the cellular machinery of the process. This scientific query will likely provide important insights into the functions and novel mechanism of the regulation of potycystin-1. Our investigation will also likely provide clues of the mechanisms by which PKD1 mutations cause the disease. The information from our studies will likely open new avenues in the research of ADPKD and establish the foundation for developing causative and effective therapies of the disease.

- **Project Title: THE ROLE OF TGF-ALPHA IN THE PATHOGENESIS OF ARPKD**

  Principal Investigator & Institution: Dell, Katherine M.; Pediatrics; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

  Timing: Fiscal Year 2005; Project Start 01-JUL-2001; Project End 30-JUN-2007

  Summary: (adapted from the application) Autosomal recessive **polycystic kidney disease** (ARPKD) is an inherited kidney disorder characterized by massive kidney enlargement and hepatic fibrosis. Progression to end-stage renal disease is usually inevitable, often in the first years of life. A growing body of literature has established a key role for the epidermal growth factor receptor (EGFR) in the pathogenesis of abnormal cell proliferation and cyst expansion. In contrast, the expression, regulation, and function of the EGFR ligands have not been studied systematically in these diseases. Published data demonstrate that the EGFR ligand, transforming growth factor-alpha (TGF-alpha), is overexpressed in cystic tissues and cells and transgenic mice that overexpress TGF-alpha develop renal cysts. Using TGF-alpha as a paradigm, the proposed research will examine the physiologic effects of ligand upregulation and identify factors that contribute to EGFR ligand overexpression in ARPKD. The central hypothesis is that aberrant EGFR ligand expression is a common feature modulating the cellular pathophysiology of PKD. The specific aims of the project are: 1. To examine the physiologic effects of TGF-alpha upregulation in cyst formation and enlargement and to identify specific factors mediating TGF-alpha upregulation. Specific hypothesis to be tested include: a) TGF-alpha upregulation results in increased production of itself (auto-induction) and other EGFR ligands (cross-induction); b) secreted, not membrane-bound TGF-alpha, is the more important biologically-active moiety in ARPKD; c) TGF-alpha regulates EGFR expression by direct effects on EGFR mRNA transcription and stability; and d) abnormal expression of AP-2 and VHL, factors known to regulate TGF-alpha expression, mediate increased TGF-alpha expression in ARPKD. Primary and immortalized collecting tubule (CT) cell lines derived from cystic bpk mice (a murine model of ARPKD) and noncystic littermates will be used to assess the in vitro effects of exogenous TGF-alpha administration, TGF-alpha overexpression, and TGF-alpha/EGFR interactions. AP-2 and VHL protein and mRNA expression in cystic and control tissues and cells will be determined, and the role of each protein in TGF-alpha regulation assessed. 2. To determine the in vivo effects of blocking TGF-alpha production on disease progression in ARPKD. The hypothesis to be tested is that TGF-alpha has a key role in the pathogenesis of ARPKD. This will be tested by breeding the bpk mouse with a TGF-alpha knockout mouse and assessing the impact on disease progression and

expression of EGFR and other EGFR ligands. These studies will provide new insights into the biology of EGFR ligands in ARPKD. Although the proposed research focuses on ARPKD, insights provided by these studies may contribute to a broader understanding of autosomal dominant **polycystic kidney disease** (ADPKD) as well.

- **Project Title: TIGHT JUNCTION PROTEINS AND EPITHELIAL POLARITY**

  Principal Investigator & Institution: Margolis, Benjamin L.; Professor; Internal Medicine; University of Michigan at Ann Arbor 3003 South State Street, Room 1040 Ann Arbor, Mi 481091274

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

  Summary: (provided by applicant): Proper apico-basal epithelial polarity is crucial for normal kidney function and is perturbed in kidney diseases such as acute tubular necrosis and **polycystic kidney disease.** Recent advances by our group and others have provided new insights into the role of multi-protein complexes in epithelial cell polarization and protein targeting. In the current funding period our laboratory identified scaffolding proteins that localize to the tight junction and are crucial for cell polarization. Our work has focused on proteins associated with the small PDZ domain protein, mLin-7. We demonstrated that one of these mLin-7 binding partners called Protein Associated with Lin Seven 1 (PALS1) localizes to tight junctions and complexes with PALS1 Associated Tight Junction Protein (PATJ) and CrumbsS. PALS1 and PATJ are scaffolding proteins that contain PDZ and L27 domains while CrumbsS is a small apical transmembrane protein. Using siRNA and dominant negative proteins we have demonstrated that PALS1 and PATJ are crucial for epithelial cell polarity. We have also found that PALS1 directly interacts with a common polarity cassette consisting of three proteins Par3/Par6/atypical Protein Kinase C. The goal of our research is to understand how PALS1 and PATJ control the initial steps in epithelial cell polarization. We hypothesize that the scaffolding proteins, PALS1 and PATJ move from an intracellular location to mark a spot in polarizing epithelial cells that directs tight junction localization and the transition from apical to basolateral membrane surfaces. The goals of this proposal are to understand how these proteins come to identify this spot in polarizing epithelial cells and how they proceed to recruit other proteins involved in cell polarization. To achieve these goals we will examine the domains of PALS1 AND PATJ that control their movement within MDCK cells. We will also examine which domains of these proteins are important in localization, trafficking, tight junction formation and cell polarization. In addition, we will examine the signal transduction processes that control these events. These studies will shed new light on the processes necessary for early epithelial polarization and have important implication for renal epithelial function in health and disease.

- **Project Title: TRAINING CELL STRUCTURE AND FUNCTION IN NEPHROLOGY**

  Principal Investigator & Institution: Arnaout, M. Amin; Professor and Chief; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2006; Project Start 01-JUL-1986; Project End 30-JUN-2011

  Summary: (provided by applicant): The overall objective of the Nephrology Training Program at Massachusetts General Hospital is to develop individuals committed to a research career in nephrology to become independent scientists who will use novel interdisciplinary approaches to address complex biomedical problems pertaining to the kidney and the vascular system. It continues to build on its past experiences in developing productive scientists and academic nephrologists. The major components of this program include comprehensive research training under supervision of a

committed mentor that incorporates a multidisciplinary approach to biomedical investigation, a dedicated and well-equipped research environment, protection from distracting responsibilities, and comprehensive programs of formal didactic instruction and enrichment activities. (A) Research Areas and Disciplines: A major strength of this training program is its multidisciplinary nature and the active collaborations among its participating faculty. This provides ample opportunities of training across disciplines, permitting novel approaches to be applied to complex biomedical problems. Training is offered in cell and molecular biology, structural biology, photobiology, stem cell biology, genetics, genomics and proteomics, innate immunity and transplantation biology, and translational research. These disciplines are applied to nine research themes that are relevant to diseases such as diabetes, hypertension, nephritis, vasculitis and **polycystic kidney disease.** For those trainees opting for clinical research, a rigorous program in the relevant quantitative sciences is provided. All research trainees are required to participate in an annual course in the responsible conduct of research. (B) Level of Training, Background and Numbers of Trainees. In this renewal, we request ten postdoctoral positions, offered to MDs, MD-PhDs or PhDs. Five postdoctoral fellows will begin training each year and remain in research training for at least two years supported by this award. In addition, one new pre-doctoral position is requested each year to support a minority student completing an undergraduate degree or enrolled in graduate or medical school for a 1-2 year period. (C) Training Facilities. Research training takes places in the existing laboratories of the research mentors, a multidisciplinary group of established investigators with strong collaborative interactions. The research laboratories are located at MGH, a large general hospital with~900, 000 sq. ft of space dedicated to research. In addition, trainees can also access laboratories elsewhere at Harvard and MIT. Didactic formal courses are offered at MGH as well as at Harvard Medical School, Harvard School of Public Health, Harvard University and MIT.

- **Project Title: TRP CHANNEL FUNCTION AND REGULATION**

  Principal Investigator & Institution: Xu, X. Z. Shawn.; Molecular and Integrative Physiology; University of Michigan at Ann Arbor 3003 South State Street, Room 1040 Ann Arbor, Mi 481091274

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

  Summary: (provided by applicant): The long-term goal of our research is to understand the mechanisms by which ion channel-mediated calcium influx regulates cellular physiology. Currently, we focus on the role of TRP (transient receptor potential) channels, a superfamily of cation channels that are conserved from worms to humans and have been implicated in a number of human diseases. Our current understanding of the function and regulation of TRP channels primarily derives from in vitro studies performed in various cell culture systems; however, the roles of these channels in regulating cellular physiology in vivo, particularly in the context of whole organisms, have not been well evaluated. Here we propose to characterize the in vivo function and regulation of TRP channels in C. elegans, a genetically tractable model organism whose genome encodes all the seven TRP subfamilies, all of which are highly homologous to their vertebrate counterparts. We will focus on two groups of calcium-permeable TRP channels, TRPC and TRPN. As a first step, we have isolated genetic mutants of all the members in these two TRP subfamilies. We will characterize the defects of these trp mutants, and design a series of experiments aimed at elucidating the mechanisms by which these TRP channels regulate calcium signaling at the cellular and organismal level. We will also test some hypotheses with respect to the role of these TRP channels in regulating general calcium signaling. To do so, we will apply a multidisciplinary

approach involving molecular genetics, cell biology, cellular imaging, electrophysiology and biochemistry. Given the high conservation of TRP family channels throughout phylogeny and the fact that mutations in TRP family channels lead to a number of human diseases such as **polycystic kidney disease,** familial focal segmental glomerulosclerosis and hypomagnesemia, the proposed studies may provide novel insights into our understanding of the role of TRP family channels in cellular physiology and disease.

- **Project Title: TUBE-SIZE CONTROL BY THE NA K ATPASE & SEPTATE JUNCTIONS**

  Principal Investigator & Institution: Beitel, Greg J.; Biochemistry, Molecular Biology and Cell Biology; Northwestern University Evanston, Il 602081110

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

  Summary: (provided by applicant): The functions of the human vascular system, lung and kidney are critically dependent on epithelial and endothelial cells forming tubes of the correct diameters and lengths. However, the mechanisms controlling long-term tube size are poorly understood. This lack of understanding is reflected in the lack of effective treatments for many human diseases in which tube-size control is defective, such as **polycystic kidney disease** and vascular malformations, and our inability to control tube size to treat diseases not directly due to tube-size defects. For example, drugs that increase vascular tube diameter could potentially be used to treat ischemia, while drugs that block vascular tube size increases could be used as anti-angiogenic drugs to block solid tumor growth. The Drosophila tracheal system, a ramifying network of epithelial tubes that functions as a combined pulmonary/vascular system, provides an excellent system for using molecular genetic approaches to investigate the basic mechanisms of tube-size control. Preliminary work shows that the NaK ATPase 13subunit nrv2 is specifically required for tracheal tube-size control and for assembling septate junctions, the Drosophila equivalent of vertebrate tight junctions. The human NaK ATPase is mislocalized in **polycystic kidney disease** (PKD), which affects 1 in 800 people and is characterized by abnormal tube enlargement. It is unclear whether NaK ATPase mislocalization is part of the cause of, or the result of, PKD, but the preliminary studies suggest that a previously unidentified cell junctional function of the NaK ATPase could play a critical role in controlling tube size in the kidney and other tubular organs. The first specific aim of this proposal will be to investigate the role of septate junction complexes in tube-size control by determining whether several of their components act cell-autonomously and whether a known cell polarity function of several septate junction components mediates tracheal tube-size control. The second aim is to perform detailed molecular and genetic investigations of the roles of the nrv2 NaK ATPase and two Drosophila claudins, sinuous and megatrachea in tracheal tube-size control. The third aim is to clone and begin analyzing another gene that appears to define a distinct class of tube-size control gene than currently analyzed genes.

- **Project Title: XENOPUS BICAUDAL-C A MODEL FOR POLYCYSTIC KIDNEY DISEASE**

  Principal Investigator & Institution: Wessely, Oliver; Assistant Professor; Cell Biology and Anatomy; Louisiana State Univ Hsc New Orleans 433 Bolivar St New Orleans, La 70112

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

  Summary: (provided by applicant): Polycystic Kidney Diseases (PKD) are the leading cause of end-stage renal failure and require extensive treatments, such as dialysis and

kidney transplantation. Only limited forms of therapy for PKD exist, since the molecular mechanism underlying the formation of renal cysts is still poorly understood. Over the years considerable progress has been made in identifying genes mutated in human forms of PKD and in the development of animal models to study the pathogenesis of these detrimental diseases. Besides the analysis of mouse and rat PKD models, the study of the more primitive pronephric kidney has emerged as an alternative to studying PKD. The simplicity and the rapid development of the pronephros is a very attractive model to study the molecular mechanism underlying the epithelial malformations causing PKD. Loss-of-function studies using morpholino antisense oligomers provide a fast and easy way to analyze gene function within weeks instead of the rather slow genetic manipulations in mouse. This facilitates a more exploratory approach towards kidney development and its perturbation during PKD. This proposal studies Bicaudal-C, a gene mutated in the bpk and jcpk mouse models of PKD. In a previous study, the function of the Xenopus homologue of Bicaudal-C during germ layer patterning was analyzed. Here, we propose to study the role of Bicaudal-C during pronephros development in the amphibian, Xenopus laevis, by eliminating the protein in the pronephros using antisense morpholino oligomers. We will test the hypothesis that loss-of-Bicaudal-C in the pronephros induces epithelial abnormalities similar to those described in human and mouse PKD. Molecular markers will be used to characterize the onset and the progression of the phenotype. The study will also test whether elimination of Bicaudal-C leads to defects in the function of the primary cilia present on renal epithelial cells. The results will provide novel insights into PKD and will be directly applicable to mammalian studies of PKD. Furthermore, this study will provide the basis for future studies of PKD in Xenopus, using the fast developing amphibian model system to characterize the underlying biological and biochemical pathways leading to PKD.

- **Project Title: YALE CENTER FOR THE STUDY OF POLYCYSTIC KIDNEY DISEASE**

  Principal Investigator & Institution: Somlo, Stefan; Associate Professor; Internal Medicine; Yale University 47 College Street, Suite 203 New Haven, Ct 065208047

  Timing: Fiscal Year 2005; Project Start 30-SEP-1999; Project End 31-AUG-2010

  Summary: OF OVERALL CENTER (provided by applicant): The overall goal of the Yale Interdisciplinary Center for **Polycystic Kidney Disease** Research is to elucidate the mechanisms by which defects in the polycystin genes result in autosomal dominant **polycystic kidney disease** (ADPKD) and to understand the factors that modify the expression of the disease phenotype. Studies performed during the first 5 years of this Center Grant have provided the foundation for our present understanding of the importance of PC-1/PC-2 interactions in suppressing cyst formation, established a central role of the cilia in multiple forms of cystic disease, and have promoted novel concepts about how polycystins are processed and traffic in the cell. In the renewal of this award, these results have been utilized to focus the research on the areas of regulated post-translational modification and trafficking of polycystins, as well as their role in ciliary function and signaling. To investigate this hypothesis, Project by Somlo will define how PC-1 and PC-2 traffic to cilia, and will identify the domains within these proteins that mediate trafficking and determine whether graded interruption of this process can directly promote cystogenesis in animal models. Project by Caplan will explore the role of signaling by the cleaved C-terminal domain of PC-1, and how this is regulated by PC-2. Project by Sun has utilized the power of zebrafish genetic screening to identify a unique ciliary protein that mimics many of the aspects of PKD in the zebrafish model and will explore the role of this protein in normal ciliary function. Project by Cantley will investigate the role of polycystin signaling in regulating the

morphogenic events that mediate tubule formation, and will explore the ability of Ngal to modify these signals and thereby suppress cyst formation in vivo. Project by Ehrlich will utilize expertise in calcium channel signaling to define how PC-2 calcium channel activity is regulated in the cilia. These efforts will be supported by the Mouse and Cell Line Core that has an exceptional array of in vivo animal and cell-based models of polycystin function and ADPKD. We believe that these projects, by addressing the central hypothesis from different directions focused by the expertise of each investigator, will lead to substantial progress in understanding the pathogenesis of cyst formation in ADPKD, and will lay the groundwork for the establishment of clinical trials for suppressing cyst progression in patients with this disease.

- **Project Title: ZEBRAFISH APPLICATIONS IN THE STUDY OF ADPKD**

  Principal Investigator & Institution: Parikh, Samir M.; Beth Israel Deaconess Medical Center 330 Brookline Avenue, Br 264 Boston, Ma 02215

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

  Summary: (provided by applicant): Autosomal dominant **polycystic kidney disease** (ADPKD) accounts for approximately 2% of end-stage renal disease. Recent advances in characterization of the PKD1 and PKD2 genes, particularly through cell culture studies, have suggested multiple potential mechanisms for cyst formation. What is needed now is an ADPKD model that can be easily manipulated to test the importance of these pathways. The zebrafish may bridge the gap between the limits of in vitro studies and the difficulties inherent to studying rodent models. The sequencing of the zebrafish genome and the ease of performing genetic manipulations through embryo microinjection have made this organism a powerful tool for studying vertebrate genetics. We have cloned a zebrafish ortholog to PKD2. Blockade of its expression produces bilateral renal cysts. In Aim 1, we will perform an in vivo structure-function analysis of ADPKD gene products via transient knock-in/knock-down techniques to examine (a) the functional role of well-described in vitro PKD2 interactions and (b) the cystpromoting activity of the PKD1 cytoplasmic domain. In Aim 2, we will assess the contributions of two downstream pathways to cyst formation combining genetic and pharmacologic methods: cAMP/EGFR signaling and angiogenesis. We hope to capitalize on this high through-put model to elucidate in vivo functions of ADPKD gene products, identify novel in vivo targets that modify cyst formation, and show that the zebrafish is a useful pre-rodent drug-screening tool for this important disease. This work will be performed at Harvard Medical School and Beth Israel Deaconess Medical Center, in the laboratory of Vikas P. Sukhatme, M.D., Ph.D. New skills the applicant will learn include development of a disease model, structure-function analysis, and signal transduction work in vivo. The applicant has spent the last year generating the data presented herein and expects to publish papers shortly on zebrafish models of cystic and proteinuric diseases. He is committed to a career centered on basic research in an academic renal division. The expertise of the mentor and the environment of Harvard Medical School--along with the applicant's prior research, the complexity of the proposed project, and his ongoing commitment to learn and apply molecular biology to understand human disease-provide a unique opportunity for the applicant to achieve the goals of the K award and launch an independent research career.

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

- **A case of amelogenesis imperfecta, cleft lip and palate and polycystic kidney disease.**
  Author(s): Suda N, Kitahara Y, Ohyama K.
  Source: Orthodontics & Craniofacial Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16420275&query_hl=3&itool=pubmed_docsum

- **A comparative study of three kidney biomarker tests in autosomal-dominant polycystic kidney disease.**
  Author(s): Casal JA, Hermida J, Lens XM, Tutor JC.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16105025&query_hl=3&itool=pubmed_docsum

- **A novel approach to bilateral hand-assisted laparoscopic nephrectomy for autosomal dominant polycystic kidney disease.**
  Author(s): Whitten MG, Van der Werf W, Belnap L.
  Source: Surgical Endoscopy.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16432653&query_hl=3&itool=pubmed_docsum

- **A truncated polycystin-2 protein causes polycystic kidney disease and retinal degeneration in transgenic rats.**
  Author(s): Gallagher AR, Hoffmann S, Brown N, Cedzich A, Meruvu S, Podlich D, Feng Y, Konecke V, de Vries U, Hammes HP, Gretz N, Witzgall R.
  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=16943309&query_hl=3&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.

- **Analysis of missense variants in the PKHD1-gene in patients with autosomal recessive polycystic kidney disease (ARPKD).**
  Author(s): Losekoot M, Haarloo C, Ruivenkamp C, White SJ, Breuning MH, Peters DJ.
  Source: Human Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16133180&query_hl=3&itool=pubmed_docsum

- **Autosomal dominant polycystic kidney disease - clinical and genetic aspects.**
  Author(s): Bogdanova N, Markoff A, Horst J.
  Source: Kidney & Blood Pressure Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12435872&query_hl=3&itool=pubmed_docsum

- **Autosomal dominant polycystic kidney disease coexisting with cystic fibrosis.**
  Author(s): Xu N, Glockner JF, Rossetti S, Babovich-Vuksanovic D, Harris PC, Torres VE.
  Source: Journal of Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17048214&query_hl=3&itool=pubmed_docsum

- **Autosomal dominant polycystic kidney disease in pregnancy complicated by twin gestation and severe preeclampsia: a case report.**
  Author(s): Loeffler CL, Macri CJ, Bathgate SL, Freese L, Larsen JW.
  Source: J Reprod Med.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15971488&query_hl=3&itool=pubmed_docsum

- **Autosomal dominant polycystic kidney disease presenting as subarachnoid hemorrhage.**
  Author(s): Kanne JP, Talner LB.
  Source: Emerg Radiol.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15801061&query_hl=3&itool=pubmed_docsum

- **Autosomal dominant polycystic kidney disease reduces the risk of diabetes mellitus.**
  Author(s): Pietrzak-Nowacka M, Rozanski J, Safranow K, Kedzierska K, Dutkiewicz G, Ciechanowski K.
  Source: Archives of Medical Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16513485&query_hl=3&itool=pubmed_docsum

- **Autosomal dominant polycystic kidney disease showing rupture of a lateral ventral hernia following paralytic ileus.**
  Author(s): Kato T, Ubara Y, Tagami T, Sawa N, Hoshino J, Suwabe T, Yamagata T, Katori H, Takemoto F, Hara S, Matoba S, Takaichi K.
  Source: Intern Med.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15897642&query_hl=3&itool=pubmed_docsum

- **Autosomal dominant polycystic kidney disease.**
  Author(s): Ishikura K, Kamimaki I, Hamasaki Y, Hataya H, Ikeda M, Honda M.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16739257&query_hl=3&itool=pubmed_docsum

- **Autosomal dominant polycystic kidney disease: molecular genetics and pathophysiology.**
  Author(s): Sutters M, Germino GG.
  Source: The Journal of Laboratory and Clinical Medicine.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12577044&query_hl=3&itool=pubmed_docsum

- **Autosomal dominant polycystic kidney disease: role of the renin-angiotensin system in raised blood pressure in progression of renal and cardiovascular disease.**
  Author(s): Lawson CR, Doulton TW, MacGregor GA.
  Source: J Renin Angiotensin Aldosterone Syst.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17094050&query_hl=3&itool=pubmed_docsum

- **Autosomal dominant polycystic liver disease in a family without polycystic kidney disease associated with a novel missense protein kinase C substrate 80K-H mutation.**
  Author(s): Peces R, Drenth JP, Te Morsche RH, Gonzalez P, Peces C.
  Source: World Journal of Gastroenterology : Wjg.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16437702&query_hl=3&itool=pubmed_docsum

- **Autosomal recessive polycystic kidney disease (ARPKD): new insights from the identification of the ARPKD gene, PKHD1.**
  Author(s): Guay-Woodford LM.
  Source: Pediatric Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12438655&query_hl=3&itool=pubmed_docsum

- **Autosomal recessive polycystic kidney disease and congenital hepatic fibrosis: summary statement of a first National Institutes of Health/Office of Rare Diseases conference.**
  Author(s): Gunay-Aygun M, Avner ED, Bacallao RL, Choyke PL, Flynn JT, Germino GG, Guay-Woodford L, Harris P, Heller T, Ingelfinger J, Kaskel F, Kleta R, LaRusso NF, Mohan P, Pazour GJ, Shneider BL, Torres VE, Wilson P, Zak C, Zhou J, Gahl WA.
  Source: The Journal of Pediatrics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16887426&query_hl=3&itool=pubmed_docsum

- **Autosomal recessive polycystic kidney disease: appearance on fetal MRI.**
  Author(s): Liu YP, Cheng SJ, Shih SL, Huang JK.
  Source: Pediatric Radiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16283284&query_hl=3&itool=pubmed_docsum

- **Autosomal recessive polycystic kidney disease: outcomes from a single-center experience.**
  Author(s): Capisonda R, Phan V, Traubuci J, Daneman A, Balfe JW, Guay-Woodford LM.
  Source: Pediatric Nephrology (Berlin, Germany).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12579400&query_hl=3&itool=pubmed_docsum

- **Autosomal-dominant polycystic kidney disease in infancy and childhood: progression and outcome.**
  Author(s): Abdollah Shamshirsaz A, Reza Bekheirnia M, Kamgar M, Johnson AM, McFann K, Cadnapaphornchai M, Nobakhthaghighi N, Schrier RW.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16221221&query_hl=3&itool=pubmed_docsum

- **Basolateral chloride transporters in autosomal dominant polycystic kidney disease.**
  Author(s): Lebeau C, Hanaoka K, Moore-Hoon ML, Guggino WB, Beauwens R, Devuyst O.
  Source: Pflugers Archiv : European Journal of Physiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12355171&query_hl=3&itool=pubmed_docsum

- **Beta4 integrin and laminin 5 are aberrantly expressed in polycystic kidney disease: role in increased cell adhesion and migration.**
  Author(s): Joly D, Morel V, Hummel A, Ruello A, Nusbaum P, Patey N, Noel LH, Rousselle P, Knebelmann B.
  Source: American Journal of Pathology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14578180&query_hl=3&itool=pubmed_docsum

- **Bilateral emphysematous pyelonephritis with autosomal dominant polycystic kidney disease.**
  Author(s): Schenkman E, Auriemma P.
  Source: The Journal of Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9554369&query_hl=3&itool=pubmed_docsum

- **Bilateral emphysematous pyelonephritis with autosomal-dominant polycystic kidney disease successfully treated by conservative method.**
  Author(s): Shimizu H, Hariu K, Kamiyama Y, Tomomasa H, Iizumi T, Yazaki T, Umeda T.
  Source: Urologia Internationalis.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10743706&query_hl=3&itool=pubmed_docsum

- **Bilateral hand-assisted laparoscopic nephrectomy for autosomal dominant polycystic kidney disease using a single midline HandPort incision.**
  Author(s): Jenkins MA, Crane JJ, Munch LC.
  Source: Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11796276&query_hl=3&itool=pubmed_docsum

- **Bilateral nephrectomy with concomitant renal graft transplantation for autosomal dominant polycystic kidney disease.**
  Author(s): Glassman DT, Nipkow L, Bartlett ST, Jacobs SC.
  Source: The Journal of Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10953121&query_hl=3&itool=pubmed_docsum

- **Bilateral nephrectomy, peritoneal dialysis and subsequent cadaveric renal transplantation for treatment of renal failure due to polycystic kidney disease requiring continuous ventilation.**
  Author(s): Spechtenhauser B, Hochleitner BW, Ellemunter H, Simma B, Hormann C, Konigsrainer A, Margreiter R.
  Source: Pediatric Transplantation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10487288&query_hl=3&itool=pubmed_docsum

- **Bilateral open transperitoneal cyst reduction surgery for autosomal dominant polycystic kidney disease.**
  Author(s): Fleming TW, Barry JM.
  Source: The Journal of Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9400433&query_hl=3&itool=pubmed_docsum

- **Bilateral popliteal aneurysms complicating adult polycystic kidney disease in a patient with a marfanoid habitus.**
  Author(s): Al-Hakim W, Goldsmith DJ.
  Source: Postgraduate Medical Journal.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12954963&query_hl=3&itool=pubmed_docsum

- **Bilateral renal cell carcinoma in autosomal dominant polycystic kidney disease. A case report and literature review.**
  Author(s): Soderdahl DW, Thrasher JB, Hansberry KL.
  Source: American Journal of Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9057961&query_hl=3&itool=pubmed_docsum

- **Bile duct cysts in a patient with autosomal dominant polycystic kidney disease.**
  Author(s): Kolodziejski TR, Safadi BY, Nakanuma Y, Milkes DE, Soetikno RM.
  Source: Gastrointestinal Endoscopy.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14722571&query_hl=3&itool=pubmed_docsum

- **Biliary dysgenesis in the PCK rat, an orthologous model of autosomal recessive polycystic kidney disease.**
  Author(s): Masyuk TV, Huang BQ, Masyuk AI, Ritman EL, Torres VE, Wang X, Harris PC, Larusso NF.
  Source: American Journal of Pathology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15509540&query_hl=3&itool=pubmed_docsum

- **Bilineal disease and trans-heterozygotes in autosomal dominant polycystic kidney disease.**
  Author(s): Pei Y, Paterson AD, Wang KR, He N, Hefferton D, Watnick T, Germino GG, Parfrey P, Somlo S, St George-Hyslop P.
  Source: American Journal of Human Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11156533&query_hl=3&itool=pubmed_docsum

- **Biochemical validation of a rat model for polycystic kidney disease: comparison of guanidino compound profile with the human condition.**
  Author(s): Torremans A, Marescau B, Kranzlin B, Gretz N, Billiouw JM, Vanholder R, De Smet R, Bouwman K, Brouns R, De Deyn PP.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16641922&query_hl=3&itool=pubmed_docsum

- **Biology of polycystic kidney disease.**
  Author(s): Carone FA, Bacallao R, Kanwar YS.
  Source: Laboratory Investigation; a Journal of Technical Methods and Pathology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8176884&query_hl=3&itool=pubmed_docsum

- **Biventricular diastolic dysfunction in patients with autosomal-dominant polycystic kidney disease.**
  Author(s): Oflaz H, Alisir S, Buyukaydin B, Kocaman O, Turgut F, Namli S, Pamukcu B, Oncul A, Ecder T.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16221225&query_hl=3&itool=pubmed_docsum

- **Blood pressure and renal function in autosomal dominant polycystic kidney disease.**
  Author(s): Seeman T, Sikut M, Konrad M, Vondrichova H, Janda J, Scharer K.
  Source: Pediatric Nephrology (Berlin, Germany).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9323285&query_hl=3&itool=pubmed_docsum

- **Body growth in children with polycystic kidney disease. Arbeitsgemeinschaft fur Padiatrische Nephrologie.**
  Author(s): Konrad M, Zerres K, Wuhl E, Rudnik-Schoneborn S, Holtkamp U, Scharer K.
  Source: Acta Paediatrica (Oslo, Norway : 1992).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8580616&query_hl=3&itool=pubmed_docsum

- **Budd-Chiari syndrome following pretransplant mononephrectomy in an autosomal dominant polycystic kidney disease patient with liver cysts.**
  Author(s): Dionisio P, Sessa A, Conte F, Bergia R, Stramignoni E, Cravero R, Caramello E, Bajardi P.
  Source: Nephron.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9031284&query_hl=3&itool=pubmed_docsum

- **Bullous eruption in a 36-year old man with polycystic kidney disease.**
  Author(s): Viernes JL, Grimwood R.
  Source: Archives of Dermatology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9935387&query_hl=3&itool=pubmed_docsum

- **Calcium channel blocker versus angiotensin II receptor blocker in autosomal dominant polycystic kidney disease.**
  Author(s): Nutahara K, Higashihara E, Horie S, Kamura K, Tsuchiya K, Mochizuki T, Hosoya T, Nakayama T, Yamamoto N, Higaki Y, Shimizu T.
  Source: Nephron. Clinical Practice [electronic Resource].
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15637459&query_hl=3&itool=pubmed_docsum

- **Calcium restores a normal proliferation phenotype in human polycystic kidney disease epithelial cells.**
  Author(s): Yamaguchi T, Hempson SJ, Reif GA, Hedge AM, Wallace DP.
  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=16319189&query_hl=3&itool=pubmed_docsum

- **Candesartan reduces urinary fatty acid-binding protein excretion in patients with autosomal dominant polycystic kidney disease.**
  Author(s): Nakamura T, Sugaya T, Kawagoe Y, Ueda Y, Osada S, Koide H.
  Source: The American Journal of the Medical Sciences.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16234607&query_hl=3&itool=pubmed_docsum

- **Cardiovascular polycystins: insights from autosomal dominant polycystic kidney disease and transgenic animal models.**
  Author(s): Bichet D, Peters D, Patel AJ, Delmas P, Honore E.
  Source: Trends in Cardiovascular Medicine.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17055386&query_hl=3&itool=pubmed_docsum

- **Caroli's syndrome with autosomal recessive polycystic kidney disease in a two month old infant.**
  Author(s): Kim JT, Hur YJ, Park JM, Kim MJ, Park YN, Lee JS.
  Source: Yonsei Medical Journal.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16502495&query_hl=3&itool=pubmed_docsum

- **Characteristics of hypertension in young adults with autosomal dominant polycystic kidney disease compared with the general U.S. population.**
  Author(s): Kelleher CL, McFann KK, Johnson AM, Schrier RW.
  Source: American Journal of Hypertension : Journal of the American Society of Hypertension.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15533729&query_hl=3&itool=pubmed_docsum

- **Chronic subdural haematoma and arachnoid cyst in autosomal dominant polycystic kidney disease (ADPKD).**
  Author(s): Leung GK, Fan YW.
  Source: Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16150597&query_hl=3&itool=pubmed_docsum

- **Chronic subdural haematoma and autosomal polycystic kidney disease: report of two new cases.**
  Author(s): Abderrahim E, Hedri H, Laabidi J, Raies L, Kheder A, Abdallah TB, Moussa FB, Maiz HB.
  Source: Nephrology (Carlton).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15504148&query_hl=3&itool=pubmed_docsum

- **Chymase-like angiotensin II-generating activity in end-stage human autosomal dominant polycystic kidney disease.**
  Author(s): McPherson EA, Luo Z, Brown RA, LeBard LS, Corless CC, Speth RC, Bagby SP.
  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=14747398&query_hl=3&itool=pubmed_docsum

- **Cleavage of polycystin-1 requires the receptor for egg jelly domain and is disrupted by human autosomal-dominant polycystic kidney disease 1-associated mutations.**
  Author(s): Qian F, Boletta A, Bhunia AK, Xu H, Liu L, Ahrabi AK, Watnick TJ, Zhou F, Germino GG.
  Source: Proceedings of the National Academy of Sciences of the United States of America.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12482949&query_hl=3&itool=pubmed_docsum

- **Clinical and molecular characterization defines a broadened spectrum of autosomal recessive polycystic kidney disease (ARPKD).**
  Author(s): Adeva M, El-Youssef M, Rossetti S, Kamath PS, Kubly V, Consugar MB, Milliner DM, King BF, Torres VE, Harris PC.
  Source: Medicine; Analytical Reviews of General Medicine, Neurology, Psychiatry, Dermatology, and Pediatrics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16523049&query_hl=3&itool=pubmed_docsum

- **Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD).**
  Author(s): Bergmann C, Senderek J, Windelen E, Kupper F, Middeldorf I, Schneider F, Dornia C, Rudnik-Schoneborn S, Konrad M, Schmitt CP, Seeman T, Neuhaus TJ, Vester U, Kirfel J, Buttner R, Zerres K; APN (Arbeitsgemeinschaft fur Padiatrische Nephrologie).
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15698423&query_hl=3&itool=pubmed_docsum

- **Clinical management of polycystic kidney disease.**
  Author(s): Hateboer N.
  Source: Clinical Medicine (London, England).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14703027&query_hl=3&itool=pubmed_docsum

- **Collecting duct carcinoma exhibiting diastase-resistant PAS-positive globular cytoplasmic inclusions and rhabdoid features arising in adult polycystic kidney disease: a case report.**
  Author(s): Kuroda N, Satake H, Miyazaki E, Hayashi Y, Hiroi M, Enzan H.
  Source: International Journal of Surgical Pathology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15173927&query_hl=3&itool=pubmed_docsum

- **Combined presence of coronary artery ectasia and descending aortic dissection in polycystic kidney disease presenting as acute coronary syndrome.**
  Author(s): Oomman A, Ramachandran P, Kumar NS.
  Source: Indian Heart J.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14989519&query_hl=3&itool=pubmed_docsum

- **Common regulatory elements in the polycystic kidney disease 1 and 2 promoter regions.**
  Author(s): Lantinga-van Leeuwen IS, Leonhard WN, Dauwerse H, Baelde HJ, van Oost BA, Breuning MH, Peters DJ.
  Source: European Journal of Human Genetics : Ejhg.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15770226&query_hl=3&itool=pubmed_docsum

- **Comparison of methods for determining renal function decline in early autosomal dominant polycystic kidney disease: the consortium of radiologic imaging studies of polycystic kidney disease cohort.**
  Author(s): Rule AD, Torres VE, Chapman AB, Grantham JJ, Guay-Woodford LM, Bae KT, Klahr S, Bennett WM, Meyers CM, Thompson PA, Miller JP; CRISP Consortium.
  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=16452494&query_hl=3&itool=pubmed_docsum

- **Concomitant nephrectomy of massively enlarged kidneys and renal transplantation in autosomal dominant polycystic kidney disease.**
  Author(s): Tabibi A, Simforoosh N, Abadpour P, Gholamrezaie HR, Nafar M.
  Source: Transplantation Proceedings.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16213267&query_hl=3&itool=pubmed_docsum

- **Congenital hypothyroidism in association with Caroli's disease and autosomal recessive polycystic kidney disease: patient report.**
  Author(s): Jeha GS, Tatevian N, Heptulla RA.
  Source: J Pediatr Endocrinol Metab.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15813611&query_hl=3&itool=pubmed_docsum

- **Cyst fluid composition in human autosomal recessive polycystic kidney disease.**
  Author(s): Rohatgi R, Zavilowitz B, Vergara M, Woda C, Kim P, Satlin LM.
  Source: Pediatric Nephrology (Berlin, Germany).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15622499&query_hl=3&itool=pubmed_docsum

- **Design and baseline characteristics of participants in the study of antihypertensive therapy in children and adolescents with autosomal dominant polycystic kidney disease (ADPKD).**
  Author(s): Cadnapaphornchai MA, Fick-Brosnahan GM, Duley I, Johnson AM, Strain JD, DeGroff CG, Schrier RW.
  Source: Contemp Clin Trials.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15837441&query_hl=3&itool=pubmed_docsum

- **Detection of a novel nonsense mutation and an intragenic polymorphism in the PKD1 gene of a Cypriot family with autosomal dominant polycystic kidney disease.**
  Author(s): Neophytou P, Constantinides R, Lazarou A, Pierides A, Deltas CC.
  Source: Human Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8792818&query_hl=3&itool=pubmed_docsum

- **Development of polycystic kidney disease in juvenile cystic kidney mice: insights into pathogenesis, ciliary abnormalities, and common features with human disease.**
  Author(s): Smith LA, Bukanov NO, Husson H, Russo RJ, Barry TC, Taylor AL, Beier DR, Ibraghimov-Beskrovnaya O.
  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=16928806&query_hl=3&itool=pubmed_docsum

- **Diagnosis and treatment of a solitary infected hepatic cyst in two patients with adult polycystic kidney disease.**
  Author(s): Gladziwa U, Bohm R, Malms J, Keulers P, Haase G, Sieberth HG.
  Source: Clinical Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8261676&query_hl=3&itool=pubmed_docsum

- **Diagnosis of adult polycystic kidney disease by genetic markers and ultrasonographic imaging in a voluntary family register.**
  Author(s): Elles RG, Hodgkinson KA, Mallick NP, O'Donoghue DJ, Read AP, Rimmer S, Watters EA, Harris R.
  Source: Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8182715&query_hl=3&itool=pubmed_docsum

- **Diagnosis of renal and hepatic cyst infections by 18-F-fluorodeoxyglucose positron emission tomography in autosomal dominant polycystic kidney disease.**
  Author(s): Bleeker-Rovers CP, de Sevaux RG, van Hamersvelt HW, Corstens FH, Oyen WJ.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12776306&query_hl=3&itool=pubmed_docsum

- **Diagnosis of tuberous sclerosis in a patient who presented with polycystic kidney disease.**
  Author(s): Diskin CJ, Stokes TJ, Dansby LM, Carter TB, Radcliff L, Monteil D.
  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=10727553&query_hl=3&itool=pubmed_docsum

- **Dialysis-associated acquired cystic kidney disease imitating autosomal dominant polycystic kidney disease in a patient receiving long-term peritoneal dialysis.**
  Author(s): Neureiter D, Frank H, Kunzendorf U, Waldherr R, Amann K.
  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=11865101&query_hl=3&itool=pubmed_docsum

- **Dialysis-associated renal cystic disease resembling autosomal dominant polycystic kidney disease: a report of two cases.**
  Author(s): Bakir AA, Hasnain M, Young S, Dunea G.
  Source: American Journal of Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10460946&query_hl=3&itool=pubmed_docsum

- **Diaphragmatic hernia associated with adult polycystic kidney disease.**
  Author(s): Little DM, Streeter E, Gleeson FV, Dyar O, Preston JM, Cranston DW.
  Source: The Journal of Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10569575&query_hl=3&itool=pubmed_docsum

- **Dietary sucrose does not increase twenty-four-hour ambulatory blood pressure in patients with either essential hypertension or polycystic kidney disease.**
  Author(s): Van der Schaaf MR, Koomans HA, Joles JA.
  Source: Journal of Hypertension.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10100085&query_hl=3&itool=pubmed_docsum

- **Dimensions of arteriovenous fistulas in patients with autosomal dominant polycystic kidney disease.**
  Author(s): Hadimeri H, Hadimeri U, Attman PO, Nyberg G.
  Source: Nephron.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10773755&query_hl=3&itool=pubmed_docsum

- **Dissection of the thoracic aorta in renal transplant patients with polycystic kidney disease.**
  Author(s): Robertson AJ, Morris PJ.
  Source: The Australian and New Zealand Journal of Surgery.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10327130&query_hl=3&itool=pubmed_docsum

- **Diuretics versus angiotensin-converting enzyme inhibitors in autosomal dominant polycystic kidney disease.**
  Author(s): Ecder T, Edelstein CL, Fick-Brosnahan GM, Johnson AM, Chapman AB, Gabow PA, Schrier RW.
  Source: American Journal of Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11359016&query_hl=3&itool=pubmed_docsum

- **Diverticulitis and polycystic kidney disease.**
  Author(s): Lederman ED, McCoy G, Conti DJ, Lee EC.
  Source: The American Surgeon.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10695753&query_hl=3&itool=pubmed_docsum

- **DNA diagnosis and clinical manifestations of autosomal dominant polycystic kidney disease.**
  Author(s): Merta M, Stekrova J, Zidovska J, Vorsilkova M, Walterova J, Kapras J, Alanova M, Raskova D, Gaillyova R, Archmanova E, Rysava R.
  Source: Folia Biol (Praha).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9595261&query_hl=3&itool=pubmed_docsum

- **Does extended-release somatostatin slow the growth of renal cysts in autosomal-dominant polycystic kidney disease?**
  Author(s): Grantham JJ.
  Source: Nat Clin Pract Nephrol.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16932392&query_hl=3&itool=pubmed_docsum

- **Does type 2 diabetes mellitus delay renal failure in autosomal dominant polycystic kidney disease?**
  Author(s): Backenroth R, Popovtzer MM.
  Source: Renal Failure.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12472202&query_hl=3&itool=pubmed_docsum

- **Duodenal obstruction in polycystic kidney disease. Case report and review of the literature.**
  Author(s): Fried LF, Palevsky PM, Johnston JR.
  Source: American Journal of Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9653836&query_hl=3&itool=pubmed_docsum

- **Dysregulation of cellular proliferation and apoptosis mediates human autosomal dominant polycystic kidney disease (ADPKD).**
  Author(s): Lanoix J, D'Agati V, Szabolcs M, Trudel M.
  Source: Oncogene.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8808689&query_hl=3&itool=pubmed_docsum

- **Earlier diagnosis of autosomal dominant polycystic kidney disease: importance of family history and implications for cardiovascular and renal complications.**
  Author(s): Taylor M, Johnson AM, Tison M, Fain P, Schrier RW.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16129202&query_hl=3&itool=pubmed_docsum

- **Early onset polycystic kidney disease: how early is early?**
  Author(s): Birewar S, Zawada ET Jr.
  Source: S D J Med.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14650760&query_hl=3&itool=pubmed_docsum

- **Effect of simvastatin on renal function in autosomal dominant polycystic kidney disease.**
  Author(s): van Dijk MA, Kamper AM, van Veen S, Souverijn JH, Blauw GJ.
  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=11682660&query_hl=3&itool=pubmed_docsum

- **Emerging therapies for polycystic kidney disease.**
  Author(s): Gattone VH 2nd.
  Source: Current Opinion in Pharmacology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16085462&query_hl=3&itool=pubmed_docsum

- **End stage polycystic kidney disease: indications and timing of native nephrectomy relative to kidney transplantation.**
  Author(s): Fuller TF, Brennan TV, Feng S, Kang SM, Stock PG, Freise CE.
  Source: The Journal of Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16280813&query_hl=3&itool=pubmed_docsum

- **Endothelial dysfunction and increased carotid intima-media thickness in patients with autosomal dominant polycystic kidney disease.**
  Author(s): Kocaman O, Oflaz H, Yekeler E, Dursun M, Erdogan D, Demirel S, Alisir S, Turgut F, Mercanoglu F, Ecder T.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15112176&query_hl=3&itool=pubmed_docsum

- **Endothelial dysfunction and reduced nitric oxide in resistance arteries in autosomal-dominant polycystic kidney disease.**
  Author(s): Wang D, Iversen J, Wilcox CS, Strandgaard S.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12969157&query_hl=3&itool=pubmed_docsum

- **Endothelial nitric oxide synthase affects the progression of autosomal dominant polycystic kidney disease.**
  Author(s): Reiterova J, Merta M, Tesar V, Stekrova J.
  Source: Kidney & Blood Pressure Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12077489&query_hl=3&itool=pubmed_docsum

- **Enos polymorphism and renal disease progression in autosomal dominant polycystic kidney disease.**
  Author(s): Devuyst O, Persu A, Stoenoiu MS, Pirson Y, Lens XM, Chauveau D.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12722053&query_hl=3&itool=pubmed_docsum

- **Epidemiological study of kidney survival in autosomal dominant polycystic kidney disease.**
  Author(s): Schrier RW, McFann KK, Johnson AM.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12631134&query_hl=3&itool=pubmed_docsum

- **Epidermal growth factor receptor polymorphism and autosomal dominant polycystic kidney disease.**
  Author(s): Magistroni R, Manfredini P, Furci L, Ligabue G, Martino C, Leonelli M, Scapoli C, Albertazzi A.
  Source: Journal of Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12653106&query_hl=3&itool=pubmed_docsum

- **Erythropoietin-producing renal cell carcinoma arising from autosomal dominant polycystic kidney disease.**
  Author(s): Hama Y, Kaji T, Ito K, Hayakawa M, Tobe M, Kosuda S.
  Source: The British Journal of Radiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15730996&query_hl=3&itool=pubmed_docsum

- **Estimating locus heterogeneity in autosomal dominant polycystic kidney disease (ADPKD) in the Spanish population.**
  Author(s): Peral B, San Millan JL, Hernandez C, Valero A, Lathrop GM, Beckmann JS, Moreno F.
  Source: Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7905535&query_hl=3&itool=pubmed_docsum

- **Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1.**
  Author(s): Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P, Danks DM.
  Source: Lancet.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7908078&query_hl=3&itool=pubmed_docsum

- **Evidence of angiogenesis and microvascular regression in autosomal-dominant polycystic kidney disease kidneys: a corrosion cast study.**
  Author(s): Wei W, Popov V, Walocha JA, Wen J, Bello-Reuss E.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16883324&query_hl=3&itool=pubmed_docsum

- **Evidence of linkage disequilibrium in the Spanish polycystic kidney disease I population.**
  Author(s): Peral B, Ward CJ, San Millan JL, Thomas S, Stallings RL, Moreno F, Harris PC.
  Source: American Journal of Human Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7909986&query_hl=3&itool=pubmed_docsum

- **Exercise blood pressure, cardiac structure, and diastolic function in young normotensive patients with polycystic kidney disease: a prehypertensive state.**
  Author(s): Martinez-Vea A, Bardaj A, Gutierrez C, Garca C, Peralta C, Marcas L, Oliver JA.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15264179&query_hl=3&itool=pubmed_docsum

- **Expression and cellular localisation of renal endothelin-1 and endothelin receptor subtypes in autosomal-dominant polycystic kidney disease.**
  Author(s): Ong AC, Newby LJ, Dashwood MR.
  Source: Nephron. Experimental Nephrology [electronic Resource].
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12629276&query_hl=3&itool=pubmed_docsum

- **Expression of components of the renin-angiotensin system in autosomal recessive polycystic kidney disease.**
  Author(s): Loghman-Adham M, Soto CE, Inagami T, Sotelo-Avila C.
  Source: The Journal of Histochemistry and Cytochemistry : Official Journal of the Histochemistry Society.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15879580&query_hl=3&itool=pubmed_docsum

- **Ezrin distribution is abnormal in principal cells from a murine model of autosomal recessive polycystic kidney disease.**
  Author(s): Orellana SA, Quinones AM, Mandapat ML.
  Source: Pediatric Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12840161&query_hl=3&itool=pubmed_docsum

- **Factors influencing progression of renal failure in autosomal dominant polycystic kidney disease.**
  Author(s): Grunfeld JP.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9820437&query_hl=3&itool=pubmed_docsum

- **Factors relating to urinary protein excretion in children with autosomal dominant polycystic kidney disease.**
  Author(s): Sharp C, Johnson A, Gabow P.
  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=9773792&query_hl=3&itool=pubmed_docsum

- **Familial arachnoid cysts in association with autosomal dominant polycystic kidney disease.**
  Author(s): Alehan FK, Gurakan B, Agildere M.
  Source: Pediatrics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12093994&query_hl=3&itool=pubmed_docsum

- **Familial clustering of ruptured intracranial aneurysms in autosomal dominant polycystic kidney disease.**
  Author(s): Belz MM, Hughes RL, Kaehny WD, Johnson AM, Fick-Brosnahan GM, Earnest MP, Gabow PA.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11576880&query_hl=3&itool=pubmed_docsum

- **Familial hypertensive intracerebral hemorrhage and autosomal dominant polycystic kidney disease.**
  Author(s): Lin TJ, Hwang FC, Chen CJ, Chiu WT, Chang CK.
  Source: Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15925788&query_hl=3&itool=pubmed_docsum

- **Familial polycystic kidney disease in Nigeria: a report of two cases.**
  Author(s): Okeahialam BN, Pam SD, Ekedigwe JE, Ekwempu CC.
  Source: West Afr J Med.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17191430&query_hl=3&itool=pubmed_docsum

- **Familiar clustering of aortic dissection in polycystic kidney disease.**
  Author(s): Biagini A, Maffei S, Baroni M, Piacenti M, Terrazzi M, Paoli F, Trianni G, Picano E, Salvatore L.
  Source: The American Journal of Cardiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8249856&query_hl=3&itool=pubmed_docsum

- **Favorable graft survival in renal transplant recipients with polycystic kidney disease.**
  Author(s): Johnston O, O'Kelly P, Donohue J, Walshe JJ, Little DM, Hickey D, Conlon PJ.
  Source: Renal Failure.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15957548&query_hl=3&itool=pubmed_docsum

- **Fetal polycystic kidney disease in oro-facio-digital syndrome type I.**
  Author(s): Nishimura G, Kuwashima S, Kohno T, Teramoto C, Watanabe H, Kubota T.
  Source: Pediatric Radiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10398784&query_hl=3&itool=pubmed_docsum

- **Fine mapping of the autosomal recessive polycystic kidney disease locus (PKHD1) and the genes MUT, RDS, CSNK2 beta, and GSTA1 at 6p21.1-p12.**
  Author(s): Mucher G, Becker J, Knapp M, Buttner R, Moser M, Rudnik-Schoneborn S, Somlo S, Germino G, Onuchic L, Avner E, Guay-Woodford L, Zerres K.
  Source: Genomics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9503014&query_hl=3&itool=pubmed_docsum

- **Fine needle aspiration cytology of a pancreatic cyst in a patient with autosomal dominant polycystic kidney disease. A case report.**
  Author(s): Silverman JF, Prichard J, Regueiro MD.
  Source: Acta Cytol.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11393077&query_hl=3&itool=pubmed_docsum

- **Flow-associated dilatory capacity of the brachial artery is intact in early autosomal dominant polycystic kidney disease.**
  Author(s): Clausen P, Feldt-Rasmussen B, Iversen J, Lange M, Eidemak I, Strandgaard S.
  Source: American Journal of Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16825759&query_hl=3&itool=pubmed_docsum

- **Follow-up of intracranial aneurysms in autosomal dominant polycystic kidney disease by magnetic resonance angiography.**
  Author(s): Huston J 3rd, Torres VE, Wiebers DO, Schievink WI.
  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=8915973&query_hl=3&itool=pubmed_docsum

- **Follow-up of intracranial aneurysms in autosomal-dominant polycystic kidney disease.**
  Author(s): Gibbs GF, Huston J 3rd, Qian Q, Kubly V, Harris PC, Brown RD Jr, Torres VE.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15086900&query_hl=3&itool=pubmed_docsum

- **Four novel mutations of the PKD2 gene in Czech families with autosomal dominant polycystic kidney disease.**
  Author(s): Reiterova J, Stekrova J, Peters DJ, Kapras J, Kohoutova M, Merta M, Zidovska J.
  Source: Human Mutation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11968093&query_hl=3&itool=pubmed_docsum

- **Frequency and impact of autosomal dominant polycystic kidney disease in the Seychelles (Indian Ocean).**
  Author(s): Yersin C, Bovet P, Wauters JP, Schorderet DF, Pescia G, Paccaud F.
  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=9351067&query_hl=3&itool=pubmed_docsum

- **Frequency of ovarian cysts in patients with autosomal dominant polycystic kidney disease.**
  Author(s): Stamm ER, Townsend RR, Johnson AM, Garg K, Manco-Johnson M, Gabow PA.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10401025&query_hl=3&itool=pubmed_docsum

- **Functional activity of epidermal growth factor receptors in autosomal recessive polycystic kidney disease.**
  Author(s): Sweeney WE Jr, Avner ED.
  Source: The American Journal of Physiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9729511&query_hl=3&itool=pubmed_docsum

- **Functional analysis of PKHD1 splicing in autosomal recessive polycystic kidney disease.**
  Author(s): Bergmann C, Frank V, Kupper F, Schmidt C, Senderek J, Zerres K.
  Source: Journal of Human Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16897190&query_hl=3&itool=pubmed_docsum

- **Functional defects in lysosomal enzymes in autosomal dominant polycystic kidney disease (ADPKD): abnormalities in synthesis, molecular processing, polarity, and secretion.**
  Author(s): Hartz PA, Wilson PD.
  Source: Biochemical and Molecular Medicine.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9066978&query_hl=3&itool=pubmed_docsum

- **Gas-forming infection from Clostridium perfringens in a renal cyst of a patient with autosomal dominant polycystic kidney disease.**
  Author(s): Van Zijl PS, Chai TC.
  Source: Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15183978&query_hl=3&itool=pubmed_docsum

- **Gas-forming infection in a renal cyst of a patient with autosomal dominant polycystic kidney disease.**
  Author(s): Erkoc R, Sayarlioglu H, Ceylan K, Dogan E, Kara PS.
  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=16249206&query_hl=3&itool=pubmed_docsum

- **Gender difference in the mean age at the induction of hemodialysis in patients with autosomal dominant polycystic kidney disease.**
  Author(s): Ishikawa I, Maeda K, Nakai S, Kawaguchi Y.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10845819&query_hl=3&itool=pubmed_docsum

- **Generation of a transcriptional map for a 700-kb region surrounding the polycystic kidney disease type 1 (PKD1) and tuberous sclerosis type 2 (TSC2) disease genes on human chromosome 16p3.3.**
  Author(s): Burn TC, Connors TD, Van Raay TJ, Dackowski WR, Millholland JM, Klinger KW, Landes GM.
  Source: Genome Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8828041&query_hl=3&itool=pubmed_docsum

- **Genes and geneticization? The social construction of autosomal dominant polycystic kidney disease.**
  Author(s): Cox SM, Starzomski RC.
  Source: New Genet Soc.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15460614&query_hl=3&itool=pubmed_docsum

- **Genes homologous to the autosomal dominant polycystic kidney disease genes (PKD1 and PKD2).**
  Author(s): Veldhuisen B, Spruit L, Dauwerse HG, Breuning MH, Peters DJ.
  Source: European Journal of Human Genetics : Ejhg.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10602361&query_hl=3&itool=pubmed_docsum

- **Genesis and significance of hypertension in autosomal dominant polycystic kidney disease.**
  Author(s): Zeier M, Ritz E, Geberth S, Gonzalo A.
  Source: Nephron.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7830851&query_hl=3&itool=pubmed_docsum

- **Genetic evidence for a trans-heterozygous model for cystogenesis in autosomal dominant polycystic kidney disease.**
  Author(s): Koptides M, Mean R, Demetriou K, Pierides A, Deltas CC.
  Source: Human Molecular Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10655555&query_hl=3&itool=pubmed_docsum

- **Genetic heterogeneity in Korean families with autosomal-dominant polycystic kidney disease (ADPKD): the first Asian report.**
  Author(s): Lee JG, Lee KB, Kim UK, Ahn C, Hwang DY, Hwang YH, Eo HS, Lee EJ, Kim YS, Han JS, Kim S, Lee JS.
  Source: Clinical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11553048&query_hl=3&itool=pubmed_docsum

- **Genetic heterogeneity of autosomal dominant polycystic kidney disease in Argentina.**
  Author(s): Iglesias DM, Martin RS, Fraga A, Virginillo M, Kornblihtt AR, Arrizurieta E, Viribay M, San Millan JL, Herrera M, Bernath V.
  Source: Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9350815&query_hl=3&itool=pubmed_docsum

- **Genetic modifiers of polycystic kidney disease in intersubspecific KAT2J mutants.**
  Author(s): Upadhya P, Churchill G, Birkenmeier EH, Barker JE, Frankel WN.
  Source: Genomics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10366444&query_hl=3&itool=pubmed_docsum

- **Genetic studies in a black family with autosomal dominant polycystic kidney disease and sickle-cell trait.**
  Author(s): Kimberling WJ, Yium JJ, Johnson AM, Gabow PA, Martinez-Maldonado M.
  Source: Nephron.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8730427&query_hl=3&itool=pubmed_docsum

- **Genetics and pathogenesis of polycystic kidney disease.**
  Author(s): Igarashi P, Somlo S.
  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=12191984&query_hl=3&itool=pubmed_docsum

- **Genetics and phenotypic characteristics of autosomal dominant polycystic kidney disease in Finns.**
  Author(s): Peltola P, Lumiaho A, Miettinen R, Pihlajamaki J, Sandford R, Laakso M.
  Source: Journal of Molecular Medicine (Berlin, Germany).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15772804&query_hl=3&itool=pubmed_docsum

- **Genetics in adult polycystic kidney disease: how far can we go?**
  Author(s): Mallat SG, el Imad Z, Kabalan S, Khabbouth J.
  Source: J Med Liban.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10887528&query_hl=3&itool=pubmed_docsum

- **Genomic structure of the gene for the human P1 protein (MCM3) and its exclusion as a candidate for autosomal recessive polycystic kidney disease.**
  Author(s): Hofmann Y, Becker J, Wright F, Avner ED, Mrug M, Guay-Woodford LM, Somlo S, Zerres K, Germino GG, Onuchic LF.
  Source: European Journal of Human Genetics : Ejhg.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10780780&query_hl=3&itool=pubmed_docsum

- **Genotype-renal function correlation in type 2 autosomal dominant polycystic kidney disease.**
  Author(s): Magistroni R, He N, Wang K, Andrew R, Johnson A, Gabow P, Dicks E, Parfrey P, Torra R, San-Millan JL, Coto E, Van Dijk M, Breuning M, Peters D, Bogdanova N, Ligabue G, Albertazzi A, Hateboer N, Demetriou K, Pierides A, Deltas C, St George-Hyslop P, Ravine D, Pei Y.
  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=12707387&query_hl=3&itool=pubmed_docsum

- **Genotypes of autosomal dominant polycystic kidney disease in Japanese.**
  Author(s): Mizoguchi M, Tamura T, Yamaki A, Higashihara E, Shimizu Y.
  Source: Journal of Human Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11829141&query_hl=3&itool=pubmed_docsum

- **Germinal and somatic mutations in the PKD2 gene of renal cysts in autosomal dominant polycystic kidney disease.**
  Author(s): Koptides M, Hadjimichael C, Koupepidou P, Pierides A, Constantinou Deltas C.
  Source: Human Molecular Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9949210&query_hl=3&itool=pubmed_docsum

- **Gross hematuria rapidly deteriorated renal function in a patient with polycystic kidney disease and Klippel-Trenaunay-Weber syndrome.**
  Author(s): Kurebayashi S, Hashimoto K, Maki F, Shiotsuka Y, Kokado Y, Koga M.
  Source: Intern Med.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12521207&query_hl=3&itool=pubmed_docsum

- **Hand-assisted bilateral nephrectomy in a patient with adult polycystic kidney disease.**
  Author(s): Pinto MA, Juliano RV, Tobias-Machado M, Borrelli M, Wroclawski ER.
  Source: Sao Paulo Medical Journal = Revista Paulista De Medicina.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12563427&query_hl=3&itool=pubmed_docsum

- **Hand-assisted laparoscopic nephrectomy in autosomal dominant polycystic kidney disease.**
  Author(s): Lee DI, Clayman RV.
  Source: Journal of Endourology / Endourological Society.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15253790&query_hl=3&itool=pubmed_docsum

- **Haplotype analysis improves molecular diagnostics of autosomal recessive polycystic kidney disease.**
  Author(s): Consugar MB, Anderson SA, Rossetti S, Pankratz VS, Ward CJ, Torra R, Coto E, El-Youssef M, Kantarci S, Utsch B, Hildebrandt F, Sweeney WE, Avner ED, Torres VE, Cunningham JM, Harris PC.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15696446&query_hl=3&itool=pubmed_docsum

- **Hemorheological investigations in patients with polycystic kidney disease.**
  Author(s): Shand BI.
  Source: Clinical Hemorheology and Microcirculation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12237486&query_hl=3&itool=pubmed_docsum

- **Hepatic cysts in adult polycystic kidney disease.**
  Author(s): Kumar VS, Babu SK, Agarwal R, Kumar BS, Lakshmi AY, Reddy CK.
  Source: Indian Journal of Medical Sciences.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9355697&query_hl=3&itool=pubmed_docsum

- **Hepatic cysts in autosomal dominant polycystic kidney disease.**
  Author(s): Everson GT.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8213790&query_hl=3&itool=pubmed_docsum

- **Hereditary error in epidermal growth factor prohormone metabolism in a rat model of autosomal dominant polycystic kidney disease.**
  Author(s): Lakshmanan J, Eysselein V.
  Source: Biochemical and Biophysical Research Communications.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8280123&query_hl=3&itool=pubmed_docsum

- **High-resolution renal sonography in children with autosomal recessive polycystic kidney disease.**
  Author(s): Traubici J, Daneman A.
  Source: Ajr. American Journal of Roentgenology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15855129&query_hl=3&itool=pubmed_docsum

- **Homologues to the first gene for autosomal dominant polycystic kidney disease are pseudogenes.**
  Author(s): Bogdanova N, Markoff A, Gerke V, McCluskey M, Horst J, Dworniczak B.
  Source: Genomics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11414761&query_hl=3&itool=pubmed_docsum

- **Human adolescent nephronophthisis: gene locus synteny with polycystic kidney disease in pcy mice.**
  Author(s): Omran H, Haffner K, Burth S, Fernandez C, Fargier B, Villaquiran A, Nothwang HG, Schnittger S, Lehrach H, Woo D, Brandis M, Sudbrak R, Hildebrandt F.
  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=11134256&query_hl=3&itool=pubmed_docsum

- **Human cilia proteome contains homolog of zebrafish polycystic kidney disease gene qilin.**
  Author(s): Marshall WF.
  Source: Current Biology : Cb.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15530380&query_hl=3&itool=pubmed_docsum

- **Human disease: calcium signaling in polycystic kidney disease.**
  Author(s): Somlo S, Ehrlich B.
  Source: Current Biology : Cb.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11369247&query_hl=3&itool=pubmed_docsum

- **Human gene mutations. Gene symbol: PKD1. Disease: Polycystic kidney disease.**
  Author(s): Daniells C, Maheshwar M, Lazarou L, Davies F, Coles G, Ravine D.
  Source: Human Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9490292&query_hl=3&itool=pubmed_docsum

- **Hypertension and left ventricular hypertrophy in autosomal dominant polycystic kidney disease.**
  Author(s): Ecder T, Schrier RW.
  Source: Expert Rev Cardiovasc Ther.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15151483&query_hl=3&itool=pubmed_docsum

- **Hypertension in autosomal dominant polycystic kidney disease.**
  Author(s): Chapman AB, Gabow PA.
  Source: Kidney International. Supplement.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9328971&query_hl=3&itool=pubmed_docsum

- **Hypertension in autosomal dominant polycystic kidney disease: is renin acquitted as a culprit?**
  Author(s): Ritz E.
  Source: Journal of Hypertension.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16685200&query_hl=3&itool=pubmed_docsum

- **Hypertension in autosomal-dominant polycystic kidney disease: early occurrence and unique aspects.**
  Author(s): Ecder T, Schrier RW.
  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=11134267&query_hl=3&itool=pubmed_docsum

- **Hypertension in individuals at risk for autosomal dominant polycystic kidney disease: to screen or not to screen?**
  Author(s): Perrone RD, Miskulin DC.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16129219&query_hl=3&itool=pubmed_docsum

- **Hypertension, lipid abnormalities and cardiovascular changes in autosomal dominant polycystic kidney disease.**
  Author(s): Polat H, Karayaylali I, Niyazova Z, Seyrek N, Paydas S, Sagliker Y.
  Source: Nephron.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9546713&query_hl=3&itool=pubmed_docsum

- **Hypertension, proteinuria, and progression of autosomal dominant polycystic kidney disease: where do we go from here?**
  Author(s): Torres VE.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10692286&query_hl=3&itool=pubmed_docsum

- **Identification of a novel PKD1 mutation in an Irish autosomal dominant polycystic kidney disease kindred.**
  Author(s): Tighe O, Carmody M, Croke DT.
  Source: Biochemical Society Transactions.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9765984&query_hl=3&itool=pubmed_docsum

- **Identification of PKDL, a novel polycystic kidney disease 2-like gene whose murine homologue is deleted in mice with kidney and retinal defects.**
  Author(s): Nomura H, Turco AE, Pei Y, Kalaydjieva L, Schiavello T, Weremowicz S, Ji W, Morton CC, Meisler M, Reeders ST, Zhou J.
  Source: The Journal of Biological Chemistry.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9748274&query_hl=3&itool=pubmed_docsum

- **Identification of two novel polycystic kidney disease-1-like genes in human and mouse genomes.**
  Author(s): Li A, Tian X, Sung SW, Somlo S.
  Source: Genomics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12782129&query_hl=3&itool=pubmed_docsum

- **Imaging progression in polycystic kidney disease.**
  Author(s): Perrone R.
  Source: The New England Journal of Medicine.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16707757&query_hl=3&itool=pubmed_docsum

- **Impact of liver transplantation on renal function of patients with congenital hepatic fibrosis associated with autosomal recessive polycystic kidney disease.**
  Author(s): Arikan C, Ozgenc F, Akman SA, Kilic M, Tokat Y, Yagci RV, Aydogdu S.
  Source: Pediatric Transplantation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15598323&query_hl=3&itool=pubmed_docsum

- **Increased activity of activator protein-1 transcription factor components ATF2, c-Jun, and c-Fos in human and mouse autosomal dominant polycystic kidney disease.**
  Author(s): Le NH, van der Wal A, van der Bent P, Lantinga-van Leeuwen IS, Breuning MH, van Dam H, de Heer E, Peters DJ.
  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=16049073&query_hl=3&itool=pubmed_docsum

- **Increased activity of the renal kallikrein-kinin system in autosomal dominant polycystic kidney disease in rats, but not in humans.**
  Author(s): Braun C, Kleemann T, Birck R, Hilgenfeldt U, Riester U, Tschope C, van der Woude FJ, Rohmeiss P.
  Source: International Immunopharmacology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12489808&query_hl=3&itool=pubmed_docsum

- **Infertility in adults with polycystic kidney disease.**
  Author(s): Li Vecchi M, Cianfrone P, Damiano R, Fuiano G.
  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=12480981&query_hl=3&itool=pubmed_docsum

- **Influence of ACE (I/D) and G460W polymorphism of alpha-adducin in autosomal dominant polycystic kidney disease.**
  Author(s): Persu A, El-Khattabi O, Messiaen T, Pirson Y, Chauveau D, Devuyst O.
  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=13679477&query_hl=3&itool=pubmed_docsum

- **Influence of ACE I/D gene polymorphism in the progression of renal failure in autosomal dominant polycystic kidney disease: a meta-analysis.**
  Author(s): Pereira TV, Nunes AC, Rudnicki M, Magistroni R, Albertazzi A, Pereira AC, Krieger JE.
  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=16935894&query_hl=3&itool=pubmed_docsum

- **Influence of endothelin-1 gene polymorphisms on the progression of autosomal dominant polycystic kidney disease.**
  Author(s): Reiterova J, Merta M, Stekrova J, Cabartova Z, Cibulka R, Maixnerova D, Rysava R, Rihova Z, Tesar V, Motan J.
  Source: Kidney & Blood Pressure Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16943682&query_hl=3&itool=pubmed_docsum

- **Influence of the alpha-adducin and ACE gene polymorphism on the progression of autosomal-dominant polycystic kidney disease.**
  Author(s): Merta M, Reiterova J, Stekrova J, Rysava R, Rihova Z, Tesar V, Viklicky O, Kmentova D.
  Source: Kidney & Blood Pressure Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12697976&query_hl=3&itool=pubmed_docsum

- **Information from your family doctor. Polycystic kidney disease (PKD).**
  Author(s): American Academy of Family Physicians.
  Source: American Family Physician.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15663038&query_hl=3&itool=pubmed_docsum

- **Inherited autosomal dominant polycystic kidney disease--genetic polymorphism.**
  Author(s): Karnolski IN.
  Source: Folia Med (Plovdiv).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12751680&query_hl=3&itool=pubmed_docsum

- **Inhibition of HER-2(neu/ErbB2) restores normal function and structure to polycystic kidney disease (PKD) epithelia.**
  Author(s): Wilson SJ, Amsler K, Hyink DP, Li X, Lu W, Zhou J, Burrow CR, Wilson PD.
  Source: Biochimica Et Biophysica Acta.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16797938&query_hl=3&itool=pubmed_docsum

- **Injury and development in polycystic kidney disease.**
  Author(s): Calvet JP.
  Source: Current Opinion in Nephrology and Hypertension.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7922262&query_hl=3&itool=pubmed_docsum

- **Insulin resistance is related to left ventricular hypertrophy in patients with polycystic kidney disease type 1.**
  Author(s): Lumiaho A, Pihlajamaki J, Hartikainen J, Ikaheimo R, Miettinen R, Niemitukia L, Lampainen E, Laakso M.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12776274&query_hl=3&itool=pubmed_docsum

- **Intraductal papillary mucinous tumor of the pancreas associated with autosomal dominant polycystic kidney disease.**
  Author(s): Naitoh H, Shoji H, Ishikawa I, Watanabe R, Furuta Y, Tomozawa S, Igarashi H, Shinozaki S, Katsura H, Onozato R, Kudoh M.
  Source: Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15985242&query_hl=3&itool=pubmed_docsum

- **Intraflagellar transport and cilia-dependent renal disease: the ciliary hypothesis of polycystic kidney disease.**
  Author(s): Pazour GJ.
  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=15466257&query_hl=3&itool=pubmed_docsum

- **Intra-operative inferior vena cava syndrome in a patient with autosomal dominant polycystic kidney disease.**
  Author(s): Pierre SA, Jaeger MT, Siemens DR.
  Source: World Journal of Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16435147&query_hl=3&itool=pubmed_docsum

- **Kidney transplantation in the recipient with autosomal-dominant polycystic kidney disease: a single center experience.**
  Author(s): Shiroyanagi Y, Tanabe K, Hashimoto Y, Okuda H, Oshima T, Tokumoto T, Ishikawa N, Tomq H.
  Source: Transplantation Proceedings.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11119964&query_hl=3&itool=pubmed_docsum

- **Knowledge of nephrologists and patients about autosomal dominant polycystic kidney disease (ADPKD).**
  Author(s): Rosenberg EE, Tannenbaum TN, Miller SD, Lamothe EM, Rosenblatt DS.
  Source: Clinical and Investigative Medicine. Medecine Clinique Et Experimentale.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1458717&query_hl=3&itool=pubmed_docsum

- **Lack of association of ACE/angiotensinogen genotype with renal function in autosomal dominant polycystic kidney disease.**
  Author(s): Saggar-Malik AK, Afzal AR, Swissman JS, Bland M, Sagnella GA, Eastwood JB, MacGregor GA, Jeffery S.
  Source: Genetic Testing.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11142763&query_hl=3&itool=pubmed_docsum

- **Laparoscopic bilateral hand assisted nephrectomy for autosomal dominant polycystic kidney disease: initial experience.**
  Author(s): Rehman J, Landman J, Andreoni C, McDougall EM, Clayman RV.
  Source: The Journal of Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11435819&query_hl=3&itool=pubmed_docsum

- **Laparoscopic bilateral synchronous nephrectomy for autosomal dominant polycystic kidney disease: the initial experience.**
  Author(s): Gill IS, Kaouk JH, Hobart MG, Sung GT, Schweizer DK, Braun WE.
  Source: The Journal of Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11257645&query_hl=3&itool=pubmed_docsum

- **Laparoscopic cyst decortication in autosomal dominant polycystic kidney disease: impact on pain, hypertension, and renal function.**
  Author(s): Lee DI, Andreoni CR, Rehman J, Landman J, Ragab M, Yan Y, Chen C, Shindel A, Middleton W, Shalhav A, McDougall EM, Clayman RV.
  Source: Journal of Endourology / Endourological Society.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12965058&query_hl=3&itool=pubmed_docsum

- **Laparoscopic cyst decortication using the harmonic scalpel for symptomatic autosomal dominant polycystic kidney disease.**
  Author(s): McNally ML, Erturk E, Oleyourryk G, Schoeniger L.
  Source: Journal of Endourology / Endourological Society.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11552783&query_hl=3&itool=pubmed_docsum

- **Laparoscopic cyst marsupialization in patients with autosomal dominant polycystic kidney disease.**
  Author(s): Dunn MD, Portis AJ, Naughton C, Shalhav A, McDougall EM, Clayman RV.
  Source: The Journal of Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11371874&query_hl=3&itool=pubmed_docsum

- **Laparoscopic hand-assisted nephrectomy for crossed fused ectopia with polycystic kidney disease.**
  Author(s): Pietrow PK, Bass RA, Porter HJ 2nd.
  Source: Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15708066&query_hl=3&itool=pubmed_docsum

- **Laparoscopic nephrectomy for autosomal dominant polycystic kidney disease.**
  Author(s): Bendavid Y, Moloo H, Klein L, Burpee S, Schlachta CM, Poulin EC, Mamazza J.
  Source: Surgical Endoscopy.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15026905&query_hl=3&itool=pubmed_docsum

- **Laparoscopic renal denervation and nephropexy for autosomal dominant polycystic kidney disease related pain in adolescents.**
  Author(s): Resnick M, Chang AY, Casale P.
  Source: The Journal of Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16697853&query_hl=3&itool=pubmed_docsum

- **Large deletions in the polycystic kidney disease 1 (PKD1) gene.**
  Author(s): Ariyurek Y, Lantinga-van Leeuwen I, Spruit L, Ravine D, Breuning MH, Peters DJ.
  Source: Human Mutation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14695542&query_hl=3&itool=pubmed_docsum

- **Lesson of the week: Causes of haematuria in adult polycystic kidney disease.**
  Author(s): Dedi R, Bhandari S, Turney JH, Brownjohn AM, Eardley I.
  Source: Bmj (Clinical Research Ed.).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11509433&query_hl=3&itool=pubmed_docsum

- **Leucopenia in adult polycystic kidney disease patients on haemodialysis.**
  Author(s): Banerjee A, Chandna S, Jayasena D, Farrington K.
  Source: Nephron.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12021540&query_hl=3&itool=pubmed_docsum

- **Levofloxacin penetration into a renal cyst in a patient with autosomal dominant polycystic kidney disease.**
  Author(s): Hiyama L, Tang A, Miller LG.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16377378&query_hl=3&itool=pubmed_docsum

- **Lillian Jean Kaplan International Prize for advancement in the understanding of polycystic kidney disease. Understanding polycystic kidney disease: a systems biology approach.**
  Author(s): Grantham JJ.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12969132&query_hl=3&itool=pubmed_docsum

- **Liver cysts in Congolese patients with autosomal dominant polycystic kidney disease follow a family pattern.**
  Author(s): Assounga AG, Yacoubou Y, Makosso E, Ibara JR, Gombet T.
  Source: South African Medical Journal. Suid-Afrikaanse Tydskrif Vir Geneeskunde.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12939930&query_hl=3&itool=pubmed_docsum

- **Liver cysts in patients with autosomal dominant polycystic kidney disease.**
  Author(s): Gandhi RM, Patil RA, Mehta NP, Thomas C.
  Source: J Assoc Physicians India.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8307917&query_hl=3&itool=pubmed_docsum

- **Liver disease in autosomal recessive polycystic kidney disease.**
  Author(s): Shneider BL, Magid MS.
  Source: Pediatric Transplantation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16176423&query_hl=3&itool=pubmed_docsum

- **Liver involvement in autosomal-dominant polycystic kidney disease: therapeutic dilemma.**
  Author(s): Chauveau D, Fakhouri F, Grunfeld JP.
  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=10966503&query_hl=3&itool=pubmed_docsum

- **Long-term cardiovascular morbidity and mortality in autosomal dominant polycystic kidney disease patients after renal transplantation.**
  Author(s): Florijn KW, Chang PC, van der Woude FJ, van Bockel JH, van Saase JL.
  Source: Transplantation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8291117&query_hl=3&itool=pubmed_docsum

- **Lowering of Pkd1 expression is sufficient to cause polycystic kidney disease.**
  Author(s): Lantinga-van Leeuwen IS, Dauwerse JG, Baelde HJ, Leonhard WN, van de Wal A, Ward CJ, Verbeek S, Deruiter MC, Breuning MH, de Heer E, Peters DJ.
  Source: Human Molecular Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15496422&query_hl=3&itool=pubmed_docsum

- **Magnetic resonance measurements of renal blood flow as a marker of disease severity in autosomal-dominant polycystic kidney disease.**
  Author(s): King BF, Torres VE, Brummer ME, Chapman AB, Bae KT, Glockner JF, Arya K, Felmlee JP, Grantham JJ, Guay-Woodford LM, Bennett WM, Klahr S, Hirschman GH, Kimmel PL, Thompson PA, Miller JP; Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP).
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14633145&query_hl=3&itool=pubmed_docsum

- **Male infertility and adult polycystic kidney disease are associated with necrospermia.**
  Author(s): Fang S, Baker HW.
  Source: Fertility and Sterility.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12620459&query_hl=3&itool=pubmed_docsum

- **Management of unruptured cerebral aneurysms in patients with polycystic kidney disease.**
  Author(s): Yanaka K, Nagase S, Asakawa H, Matsumaru Y, Koyama A, Nose T.
  Source: Surgical Neurology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15576125&query_hl=3&itool=pubmed_docsum

- **Matrix metalloproteinases synthesized in autosomal dominant polycystic kidney disease play a role in development of a concurrent abdominal aortic aneurysm.**
  Author(s): Takagi H, Umemoto T.
  Source: Medical Hypotheses.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15694696&query_hl=3&itool=pubmed_docsum

- **MEK inhibition holds promise for polycystic kidney disease.**
  Author(s): Calvet JP.
  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=16687624&query_hl=3&itool=pubmed_docsum

- **Metastatic intracranial subdural empyema from renal cyst infection in autosomal dominant polycystic kidney disease.**
  Author(s): Nishi H, Shibagaki Y, Hatakeyama S, Ito T, Nagata T, Ohno M, Tojo A, Nangaku M, Fujita T.
  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=16221706&query_hl=3&itool=pubmed_docsum

- **Mispolarization of desmosomal proteins and altered intercellular adhesion in autosomal dominant polycystic kidney disease.**
  Author(s): Silberberg M, Charron AJ, Bacallao R, Wandinger-Ness A.
  Source: American Journal of Physiology. Renal Physiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15701820&query_hl=3&itool=pubmed_docsum

- **Molecular basis of autosomal dominant polycystic kidney disease.**
  Author(s): Al-Bhalal L, Akhtar M.
  Source: Advances in Anatomic Pathology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15900113&query_hl=3&itool=pubmed_docsum

- **Molecular cytogenetic aberrations in autosomal dominant polycystic kidney disease tissue.**
  Author(s): Gogusev J, Murakami I, Doussau M, Telvi L, Stojkoski A, Lesavre P, Droz D.
  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=12538736&query_hl=3&itool=pubmed_docsum

- **Molecular genetics of autosomal recessive polycystic kidney disease.**
  Author(s): Harris PC, Rossetti S.
  Source: Molecular Genetics and Metabolism.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14741187&query_hl=3&itool=pubmed_docsum

- **mTOR is out of control in polycystic kidney disease.**
  Author(s): Mostov KE.
  Source: Proceedings of the National Academy of Sciences of the United States of America.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16567652&query_hl=3&itool=pubmed_docsum

- **Multi-exon deletions of the PKHD1 gene cause autosomal recessive polycystic kidney disease (ARPKD).**
  Author(s): Bergmann C, Kupper F, Schmitt CP, Vester U, Neuhaus TJ, Senderek J, Zerres K.
  Source: Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16199545&query_hl=3&itool=pubmed_docsum

- **Multiple thoracic paraspinal meningeal cysts in autosomal dominant polycystic kidney disease.**
  Author(s): Coche E, Persu A, Cosnard G, Quoidbach A, Pirson Y.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12552486&query_hl=3&itool=pubmed_docsum

- **Mutation analysis of autosomal dominant polycystic kidney disease genes in Han Chinese.**
  Author(s): Zhang S, Mei C, Zhang D, Dai B, Tang B, Sun T, Zhao H, Zhou Y, Li L, Wu Y, Wang W, Shen X, Song J.
  Source: Nephron. Experimental Nephrology [electronic Resource].
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15775720&query_hl=3&itool=pubmed_docsum

- **Mutations of the PKD2 gene in Taiwanese patients with autosomal dominant polycystic kidney disease.**
  Author(s): Chang MY, Fang JT, Huang CC, Wu IW, Wu Chou YH.
  Source: Renal Failure.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15717641&query_hl=3&itool=pubmed_docsum

- **Myths and facts.about polycystic kidney disease.**
  Author(s): Munson BL.
  Source: Nursing.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15180011&query_hl=3&itool=pubmed_docsum

- **Na transport in autosomal recessive polycystic kidney disease (ARPKD) cyst lining epithelial cells.**
  Author(s): Rohatgi R, Greenberg A, Burrow CR, Wilson PD, Satlin LM.
  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=12660316&query_hl=3&itool=pubmed_docsum

- **Natural history of autosomal dominant polycystic kidney disease.**
  Author(s): Fick GM, Gabow PA.
  Source: Annual Review of Medicine.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8198379&query_hl=3&itool=pubmed_docsum

- **Nature and nurture on phenotypic variability of autosomal dominant polycystic kidney disease.**
  Author(s): Pei Y.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15780121&query_hl=3&itool=pubmed_docsum

- **Nephrectomy for end-stage polycystic kidney disease can be performed safely at the time of transplantation.**
  Author(s): Davis CL.
  Source: Nat Clin Pract Nephrol.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16932464&query_hl=3&itool=pubmed_docsum

- **Nephrotic syndrome and IgA nephropathy in polycystic kidney disease.**
  Author(s): Hiura T, Yamazaki H, Saeki T, Kawabe S, Ueno M, Nishi S, Miyamura S, Gejyo F.
  Source: Clinical and Experimental Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16791401&query_hl=3&itool=pubmed_docsum

- **New options for prenatal diagnosis in autosomal recessive polycystic kidney disease by mutation analysis of the PKHD1 gene.**
  Author(s): Zerres K, Senderek J, Rudnik-Schoneborn S, Eggermann T, Kunze J, Mononen T, Kaariainen H, Kirfel J, Moser M, Buettner R, Bergmann C.
  Source: Clinical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15200508&query_hl=3&itool=pubmed_docsum

- **New therapeutic option for autosomal dominant polycystic kidney disease patients with enlarged kidney and liver.**
  Author(s): Ubara Y.
  Source: Ther Apher Dial.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16911186&query_hl=3&itool=pubmed_docsum

- **No association of the TGF-beta1 gene polymorphisms with the renal progression in autosomal dominant polycystic kidney disease (ADPKD) patients.**
  Author(s): Lee JG, Ahn C, Yoon SC, Park JH, Eo HS, No JJ, Kim KH, Lee EJ, Hwang YH, Hwang DY, Kim YS, Han JS, Kim S, Lee JS, Kim SH.
  Source: Clinical Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12572925&query_hl=3&itool=pubmed_docsum

- **No effect of angiotensin-converting enzyme gene polymorphism on disease progression and left ventricular hypertrophy in autosomal dominant polycystic kidney disease.**
  Author(s): Ecder T, McFann KK, Raynolds MV, Schrier RW.
  Source: American Journal of Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14600431&query_hl=3&itool=pubmed_docsum

- **No effect of enalapril on progression in autosomal dominant polycystic kidney disease.**
  Author(s): van Dijk MA, Breuning MH, Duiser R, van Es LA, Westendorp RG.
  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=14551359&query_hl=3&itool=pubmed_docsum

- **Occult intracranial aneurysms in polycystic kidney disease: screening with MR angiography.**
  Author(s): Ruggieri PM, Poulos N, Masaryk TJ, Ross JS, Obuchowski NA, Awad IA, Braun WE, Nally J, Lewin JS, Modic MT.
  Source: Radiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8134594&query_hl=3&itool=pubmed_docsum

- **On new hypotheses about autosomal dominant polycystic kidney disease type 1.**
  Author(s): Bersani E, De Fonzo V, Aluffi-Pentini F, Parisi V.
  Source: Medical Hypotheses.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11918441&query_hl=3&itool=pubmed_docsum

- **Optimal care of autosomal dominant polycystic kidney disease patients.**
  Author(s): Schrier RW.
  Source: Nephrology (Carlton).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16669974&query_hl=3&itool=pubmed_docsum

- **Oral-facial-digital syndrome type 1 coexisting with polycystic kidney disease.**
  Author(s): Scolari F, Valzorio B, Carli O, Vizzardi V, Grazioli L, Bondioni MP, Maiorca R.
  Source: Contrib Nephrol.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9399040&query_hl=3&itool=pubmed_docsum

- **Oral-facial-digital syndrome type 1 is another dominant polycystic kidney disease: clinical, radiological and histopathological features of a new kindred.**
  Author(s): Feather SA, Winyard PJ, Dodd S, Woolf AS.
  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=9249769&query_hl=3&itool=pubmed_docsum

- **Organic anion secretion in polycystic kidney disease.**
  Author(s): Tanner GA, Gretz N, Shao Y, Evan AP, Steinhausen M.
  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=9259348&query_hl=3&itool=pubmed_docsum

- **Orpk mouse model of polycystic kidney disease reveals essential role of primary cilia in pancreatic tissue organization.**
  Author(s): Cano DA, Murcia NS, Pazour GJ, Hebrok M.
  Source: Development (Cambridge, England).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15226261&query_hl=3&itool=pubmed_docsum

- **Orthostatic hypoxaemia in dialysed adult polycystic kidney disease patients.**
  Author(s): Korzets Z, Golan E, Ben-Chitrit S, Smorjik Y, Os P, Bernheim J.
  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=9141003&query_hl=3&itool=pubmed_docsum

- **Ovarian manifestations in women with autosomal dominant polycystic kidney disease.**
  Author(s): Heinonen PK, Vuento M, Maunola M, Ala-Houhala I.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12200801&query_hl=3&itool=pubmed_docsum

- **Overexpression of PKD1 causes polycystic kidney disease.**
  Author(s): Thivierge C, Kurbegovic A, Couillard M, Guillaume R, Cote O, Trudel M.
  Source: Molecular and Cellular Biology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16449663&query_hl=3&itool=pubmed_docsum

- **PKD1 and PKD2 mutations in Slovenian families with autosomal dominant polycystic kidney disease.**
  Author(s): Vouk K, Strmecki L, Stekrova J, Reiterova J, Bidovec M, Hudler P, Kenig A, Jereb S, Zupanic-Pajnic I, Balazic J, Haarpaintner G, Leskovar B, Adamlje A, Skoflic A, Dovc R, Hojs R, Komel R.
  Source: Bmc Medical Genetics [electronic Resource].
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16430766&query_hl=3&itool=pubmed_docsum

- **PKD2 gene mutation analysis in Korean autosomal dominant polycystic kidney disease patients using two-dimensional gene scanning.**
  Author(s): Chung W, Kim H, Hwang YH, Kim SY, Ko AR, Ro H, Lee KB, Lee JS, Oh KH, Ahn C.
  Source: Clinical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17100995&query_hl=3&itool=pubmed_docsum

- **PKHDL1, a homolog of the autosomal recessive polycystic kidney disease gene, encodes a receptor with inducible T lymphocyte expression.**
  Author(s): Hogan MC, Griffin MD, Rossetti S, Torres VE, Ward CJ, Harris PC.
  Source: Human Molecular Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12620974&query_hl=3&itool=pubmed_docsum

- **Polycystic kidney disease as a result of loss of the tuberous sclerosis 2 tumor suppressor gene during development.**
  Author(s): Cai S, Everitt JI, Kugo H, Cook J, Kleymenova E, Walker CL.
  Source: American Journal of Pathology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12547704&query_hl=3&itool=pubmed_docsum

- **Polycystic kidney disease associated with cervical arteriovenous shunt and bilateral jugular vein occlusion.**
  Author(s): Nishida T, Ishihara S, Kaji T, Tajima S, Tanabe H, Motoyoshi K, Kamakura K.
  Source: Intern Med.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12487186&query_hl=3&itool=pubmed_docsum

- **Polycystic kidney disease: cell division without a c(l)ue?**
  Author(s): Simons M, Walz G.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16816842&query_hl=3&itool=pubmed_docsum

- **Polycystic kidney disease--the ciliary connection.**
  Author(s): Ong AC, Wheatley DN.
  Source: Lancet.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12620752&query_hl=3&itool=pubmed_docsum

- **Predominant extrahepatic biliary disease in autosomal recessive polycystic kidney disease: a new association.**
  Author(s): Goilav B, Norton KI, Satlin LM, Guay-Woodford L, Chen F, Magid MS, Emre S, Shneider BL.
  Source: Pediatric Transplantation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16677351&query_hl=3&itool=pubmed_docsum

- **Prenatal diagnosis of autosomal recessive polycystic kidney disease (ARPKD) without DNA from an index patient in a current pregnancy.**
  Author(s): Gaspar H, Michel-Calemard L, Morel Y, Wisser J, Stallmach T, Schinzel A.
  Source: Prenatal Diagnosis.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16566041&query_hl=3&itool=pubmed_docsum

- **Primary cilia and regulation of renal Na+ transport. Focus on "Heightened epithelial Na+ channel-mediated Na+ absorption in a murine polycystic kidney disease model epithelium lacking apical monocilia".**
  Author(s): Gray MA.
  Source: American Journal of Physiology. Cell Physiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16531571&query_hl=3&itool=pubmed_docsum

- **Quantification and longitudinal trends of kidney, renal cyst, and renal parenchyma volumes in autosomal dominant polycystic kidney disease.**
  Author(s): King BF, Reed JE, Bergstralh EJ, Sheedy PF 2nd, Torres VE.
  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=10906164&query_hl=3&itool=pubmed_docsum

- **Quantitative analysis of digital subtraction renal vasography in patients with autosomal dominant polycystic kidney disease correlated with clinical and paraclinical data.**
  Author(s): Velkova K, Dimitrakov D.
  Source: Folia Med (Plovdiv).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8698284&query_hl=3&itool=pubmed_docsum

- **Re: Angiography-related transient cortical blindness in patients with adult polycystic kidney disease.**
  Author(s): Yilmaz S, Sindel T, Luleci E.
  Source: Australasian Radiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12581069&query_hl=3&itool=pubmed_docsum

- **Recombinant human growth hormone therapy in autosomal recessive polycystic kidney disease.**
  Author(s): Lilova M, Kaplan BS, Meyers KE.
  Source: Pediatric Nephrology (Berlin, Germany).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12488992&query_hl=3&itool=pubmed_docsum

- **Recurrence of intracranial aneurysms in autosomal-dominant polycystic kidney disease.**
  Author(s): Belz MM, Fick-Brosnahan GM, Hughes RL, Rubinstein D, Chapman AB, Johnson AM, McFann KK, Kaehny WD, Gabow PA.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12675859&query_hl=3&itool=pubmed_docsum

- **Recurrent pancreatitis in a patient with autosomal-dominant polycystic kidney disease.**
  Author(s): Basar O, Ibis M, Ucar E, Ertugrul I, Yolcu OF, Koklu S, Parlak E, Ulker A.
  Source: Pancreatology : Official Journal of the International Association of Pancreatology (Iap). [et Al.].
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16354965&query_hl=3&itool=pubmed_docsum

- **Reliability of magnetic resonance imaging for measuring the volumetric indices in autosomal-dominant polycystic kidney disease: correlation with hypertension and renal function.**
  Author(s): Lee YR, Lee KB.
  Source: Nephron. Clinical Practice [electronic Resource].
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16636585&query_hl=3&itool=pubmed_docsum

- **Renal cyst ablation with n-butyl cyanoacrylate and iodized oil in symptomatic patients with autosomal dominant polycystic kidney disease: preliminary report.**
  Author(s): Kim SH, Moon MW, Lee HJ, Sim JS, Kim SH, Ahn C.
  Source: Radiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12563157&query_hl=3&itool=pubmed_docsum

- **Renal transcatheter arterial embolization for autosomal dominant polycystic kidney disease: report of two cases.**
  Author(s): Masue N, Katoh S, Itoh S, Ehara H, Takahashi Y, Ishihara S, Deguchi T.
  Source: Hinyokika Kiyo.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16363706&query_hl=3&itool=pubmed_docsum

- **Research on autosomal dominant polycystic kidney disease in China.**
  Author(s): Dai B, Mei CL.
  Source: Chinese Medical Journal.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17134592&query_hl=3&itool=pubmed_docsum

- **Role of keratinocyte growth factor in the pathogenesis of autosomal dominant polycystic kidney disease.**
  Author(s): Mei C, Mao Z, Shen X, Wang W, Dai B, Tang B, Wu Y, Cao Y, Zhang S, Zhao H, Sun T.
  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=16141466&query_hl=3&itool=pubmed_docsum

- **Ruptured giant liver cyst: a rare cause of acute abdomen in a haemodialysis patient with autosomal dominant polycystic kidney disease.**
  Author(s): Carels RA, van Bommel EF.
  Source: The Netherlands Journal of Medicine.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12572709&query_hl=3&itool=pubmed_docsum

- **Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease.**
  Author(s): Ruggenenti P, Remuzzi A, Ondei P, Fasolini G, Antiga L, Ene-Iordache B, Remuzzi G, Epstein FH.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15954910&query_hl=3&itool=pubmed_docsum

- **Secretion of cytokines and growth factors into autosomal dominant polycystic kidney disease liver cyst fluid.**
  Author(s): Nichols MT, Gidey E, Matzakos T, Dahl R, Stiegmann G, Shah RJ, Grantham JJ, Fitz JG, Doctor RB.
  Source: Hepatology (Baltimore, Md.).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15382115&query_hl=3&itool=pubmed_docsum

- **Selective ablation of symptomatic dominant renal cysts using 99% ethanol in adult polycystic kidney disease.**
  Author(s): Singh I, Mehrotra G.
  Source: Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17010722&query_hl=3&itool=pubmed_docsum

- **Sonographic assessment of the severity and progression of autosomal dominant polycystic kidney disease: the Consortium of Renal Imaging Studies in Polycystic Kidney Disease (CRISP).**
  Author(s): O'Neill WC, Robbin ML, Bae KT, Grantham JJ, Chapman AB, Guay-Woodford LM, Torres VE, King BF, Wetzel LH, Thompson PA, Miller JP.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16310571&query_hl=3&itool=pubmed_docsum

- **Sonography of macrocysts in infantile polycystic kidney disease.**
  Author(s): Stein-Wexler R, Jain K.
  Source: Journal of Ultrasound in Medicine : Official Journal of the American Institute of Ultrasound in Medicine.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12523616&query_hl=3&itool=pubmed_docsum

- **Spectrum of mutations in the gene for autosomal recessive polycystic kidney disease (ARPKD/PKHD1).**
  Author(s): Bergmann C, Senderek J, Sedlacek B, Pegiazoglou I, Puglia P, Eggermann T, Rudnik-Schoneborn S, Furu L, Onuchic LF, De Baca M, Germino GG, Guay-Woodford L, Somlo S, Moser M, Buttner R, Zerres K.
  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=12506140&query_hl=3&itool=pubmed_docsum

- **Spontaneous rupture of a left gastroepiploic artery aneurysm in a patient with autosomal-dominant polycystic kidney disease.**
  Author(s): Nagaba Y, Nishimaki H, Ichinoe M, Okuwaki Y, Hamura M, Makino T, Sano T, Higashihara M, Kamata K, Soma K.
  Source: Clinical Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15730059&query_hl=3&itool=pubmed_docsum

- **Structure-function relationships of the extracellular domain of the autosomal dominant polycystic kidney disease-associated protein, polycystin-1.**
  Author(s): Weston BS, Malhas AN, Price RG.
  Source: Febs Letters.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12633844&query_hl=3&itool=pubmed_docsum

- **Successful transplantation in a child with rapid progression of autosomal recessive polycystic kidney disease associated with a novel mutation.**
  Author(s): Prelog M, Bergmann C, Ausserlechner MJ, Fischer H, Margreiter R, Gassner I, Brunner A, Jungraithmayr TC, Zerres K, Sergi EC, Zimmerhackl LB.
  Source: Pediatric Transplantation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16677362&query_hl=3&itool=pubmed_docsum

- **Sudden death caused by dissecting thoracic aortic aneurysm in a patient with autosomal dominant polycystic kidney disease.**
  Author(s): Lee CC, Chang WT, Fang CC, Tsai IL, Chen WJ.
  Source: Resuscitation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15451591&query_hl=3&itool=pubmed_docsum

- **The effect of sodium and angiotensin-converting enzyme inhibition on the classic circulating renin-angiotensin system in autosomal-dominant polycystic kidney disease patients.**
  Author(s): Doulton TW, Saggar-Malik AK, He FJ, Carney C, Markandu ND, Sagnella GA, MacGregor GA.
  Source: Journal of Hypertension.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16612257&query_hl=3&itool=pubmed_docsum

- **The ENOS polymorphism is not associated with severity of renal disease in polycystic kidney disease 1.**
  Author(s): Walker D, Consugar M, Slezak J, Rossetti S, Torres VE, Winearls CG, Harris PC.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12500225&query_hl=3&itool=pubmed_docsum

- **The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease.**
  Author(s): Shillingford JM, Murcia NS, Larson CH, Low SH, Hedgepeth R, Brown N, Flask CA, Novick AC, Goldfarb DA, Kramer-Zucker A, Walz G, Piontek KB, Germino GG, Weimbs T.
  Source: Proceedings of the National Academy of Sciences of the United States of America.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16567633&query_hl=3&itool=pubmed_docsum

- **The pathogenesis of autosomal dominant polycystic kidney disease.**
  Author(s): Sutters M.
  Source: Nephron. Experimental Nephrology [electronic Resource].
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16691033&query_hl=3&itool=pubmed_docsum

- **The reproducibility of the circadian BP rhythm in treated hypertensive patients with polycystic kidney disease and mild chronic renal impairment--a prospective ABPM study.**
  Author(s): Covic A, Mititiuc I, Gusbeth-Tatomir P, Goldsmith DJ.
  Source: Journal of Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12455715&query_hl=3&itool=pubmed_docsum

- **Therapeutic approaches in autosomal dominant polycystic kidney disease (ADPKD): is there light at the end of the tunnel?**
  Author(s): Walz G.
  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=16705023&query_hl=3&itool=pubmed_docsum

- **Tissue Doppler imaging in the evaluation of left ventricular function in young adults with autosomal dominant polycystic kidney disease.**
  Author(s): Almeida EA, Oliveira EI, Lopes JA, Almeida AG, Prata MM.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16564936&query_hl=3&itool=pubmed_docsum

- **Trichosporon loubieri infection in a patient with adult polycystic kidney disease.**
  Author(s): Padhye AA, Verghese S, Ravichandran P, Balamurugan G, Hall L, Padmaja P, Fernandez MC.
  Source: Journal of Clinical Microbiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12517900&query_hl=3&itool=pubmed_docsum

- **Tuberous sclerosis complex and polycystic kidney disease together: an exception to the contiguous gene syndrome.**
  Author(s): Woerner AC, Au KS, Williams AT, Harris PC, Northrup H.
  Source: Genetics in Medicine : Official Journal of the American College of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16540757&query_hl=3&itool=pubmed_docsum

- **Type identification of autosomal dominant polycystic kidney disease by analysis of fluorescent short tandem repeat markers.**
  Author(s): Lin WD, Wu JY, Tsai FJ, Gau MT, Lee CC.
  Source: J Formos Med Assoc.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12440087&query_hl=3&itool=pubmed_docsum

- **Ultrasonographic study of pancreatic cysts in autosomal dominant polycystic kidney disease.**
  Author(s): Torra R, Nicolau C, Badenas C, Navarro S, Perez L, Estivill X, Darnell A.
  Source: Clinical Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9021236&query_hl=3&itool=pubmed_docsum

- **Understanding pathogenic mechanisms in polycystic kidney disease provides clues for therapy.**
  Author(s): Harris PC, Torres VE.
  Source: Current Opinion in Nephrology and Hypertension.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16775462&query_hl=3&itool=pubmed_docsum

- **Unilateral and segmental localised polycystic kidney disease.**
  Author(s): Gouldesbrough DR, Fleming S.
  Source: Journal of Clinical Pathology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9930078&query_hl=3&itool=pubmed_docsum

- **Unilateral autosomal dominant polycystic kidney disease with contralateral renal agenesis: a case report.**
  Author(s): Jeong GH, Park BS, Jeong TK, Ma SK, Yeum CH, Kim SW, Kim NH, Choi KC.
  Source: Journal of Korean Medical Science.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12692431&query_hl=3&itool=pubmed_docsum

- **Unilateral form of polycystic kidney disease.**
  Author(s): Branger B.
  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=10534533&query_hl=3&itool=pubmed_docsum

- **Unilateral nephrectomy as palliative therapy in an infant with autosomal recessive polycystic kidney disease.**
  Author(s): Shukla AR, Kiddoo DA, Canning DA.
  Source: The Journal of Urology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15540776&query_hl=3&itool=pubmed_docsum

- **Unsuspected atherosclerotic renal artery stenosis causing renal failure in a patient with adult polycystic kidney disease.**
  Author(s): Makanjuola D, Reidy J, Scoble JE.
  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=9075150&query_hl=3&itool=pubmed_docsum

- **Urate homeostasis in polycystic kidney disease: comparison with chronic glomerulonephritic kidney.**
  Author(s): Mavromatidis K, Magoula I, Tsapas G.
  Source: Renal Failure.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12212824&query_hl=3&itool=pubmed_docsum

- **Urinary excretion of monocyte chemoattractant protein-1 in autosomal dominant polycystic kidney disease.**
  Author(s): Zheng D, Wolfe M, Cowley BD Jr, Wallace DP, Yamaguchi T, Grantham JJ.
  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=14514736&query_hl=3&itool=pubmed_docsum

- **Urinary tract infections, VUR, and autosomal dominant polycystic kidney disease.**
  Author(s): Koslowe O, Frank R, Gauthier B, Vergara M, Trachtman H.
  Source: Pediatric Nephrology (Berlin, Germany).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12811648&query_hl=3&itool=pubmed_docsum

- **Vancomycin concentrations in autosomal dominant polycystic kidney disease.**
  Author(s): Chow KM, Chan CY, Leung CB, Cheung SW, Szeto CC.
  Source: Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15614718&query_hl=3&itool=pubmed_docsum

- **Variable renal disease progression in autosomal dominant polycystic kidney disease: a role for nitric oxide?**
  Author(s): Devuyst O.
  Source: Journal of Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12832751&query_hl=3&itool=pubmed_docsum

- **Vascular abnormalities in patients with autosomal dominant polycystic kidney disease--the influence on arteriovenous fistula creation.**
  Author(s): Weyde W, Krajewska M, Penar J, Bartosik H, Klinger M.
  Source: Clinical Nephrology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15182129&query_hl=3&itool=pubmed_docsum

- **Vasopressin antagonists in polycystic kidney disease.**
  Author(s): Torres VE.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16221255&query_hl=3&itool=pubmed_docsum

- **Volume progression in polycystic kidney disease.**
  Author(s): Brosnahan GM.
  Source: The New England Journal of Medicine.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16914712&query_hl=3&itool=pubmed_docsum

- **Volume progression in polycystic kidney disease.**
  Author(s): Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King BF Jr, Wetzel LH, Baumgarten DA, Kenney PJ, Harris PC, Klahr S, Bennett WM, Hirschman GN, Meyers CM, Zhang X, Zhu F, Miller JP; CRISP Investigators.
  Source: The New England Journal of Medicine.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16707749&query_hl=3&itool=pubmed_docsum

- **Volumetric determination of progression in autosomal dominant polycystic kidney disease by computed tomography.**
  Author(s): Sise C, Kusaka M, Wetzel LH, Winklhofer F, Cowley BD, Cook LT, Gordon M, Grantham JJ.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11115083&query_hl=3&itool=pubmed_docsum

- **Volumetric measurement of renal cysts and parenchyma using MRI: phantoms and patients with polycystic kidney disease.**
  Author(s): Bae KT, Commean PK, Lee J.
  Source: Journal of Computer Assisted Tomography.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10966197&query_hl=3&itool=pubmed_docsum

- **Von Hippel-Lindau disease masquerading as autosomal dominant polycystic kidney disease.**
  Author(s): Chatha RK, Johnson AM, Rothberg PG, Townsend RR, Neumann HP, Gabow PA.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11273887&query_hl=3&itool=pubmed_docsum

- **Von Hippel-Lindau disease: an important differential diagnosis of polycystic kidney disease.**
  Author(s): Browne G, Jefferson JA, Wright GD, Hughes AE, Doherty CC, Nevin NC, Keogh JA.
  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=9198040&query_hl=3&itool=pubmed_docsum

CHAPTER 2. ALTERNATIVE MEDICINE AND POLYCYSTIC KIDNEY DISEASE

Overview

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

National Center for Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (**http://nccam.nih.gov/**) has created a link to the National Library of Medicine's databases to facilitate research for articles that specifically relate to polycystic kidney disease and complementary medicine. To search the database, go to the following Web site: **http://www.nlm.nih.gov/nccam/camonpubmed.html**. Select **CAM on PubMed**. Enter **polycystic kidney disease** (or synonyms) into the search box. Click **Go**. The following references provide information on particular aspects of complementary and alternative medicine that are related to polycystic kidney disease:

- **Abnormal lipid and fatty acid compositions of kidneys from mice with polycystic kidney disease.**
  Author(s): Aukema HM, Yamaguchi T, Takahashi H, Celi B, Holub BJ.
  Source: Lipids.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1385849&query_hl=1&itool=pubmed_docsum

- **Acetaminophen-induced anion gap metabolic acidosis and 5-oxoprolinuria (pyroglutamic aciduria) acquired in hospital.**
  Author(s): Humphreys BD, Forman JP, Zandi-Nejad K, Bazari H, Seifter J, Magee CC.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15983968&query_hl=1&itool=pubmed_docsum

- **cAMP stimulates the in vitro proliferation of renal cyst epithelial cells by activating the extracellular signal-regulated kinase pathway.**
  Author(s): Yamaguchi T, Pelling JC, Ramaswamy NT, Eppler JW, Wallace DP, Nagao S, Rome LA, Sullivan LP, Grantham JJ.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10760082&query_hl=1&itool=pubmed_docsum

- **Cell polarity in human renal cystic disease.**
  Author(s): Carone FA, Nakamura S, Caputo M, Bacallao R, Nelson WJ, Kanwar YS.
  Source: Laboratory Investigation; a Journal of Technical Methods and Pathology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8196361&query_hl=1&itool=pubmed_docsum

- **Conservative long-term treatment of chronic renal failure with keto acid and amino acid supplementation.**
  Author(s): Schmicker R, Vetter K, Lindenau K, Frohling PT, Kokot F.
  Source: Infusionsther Klin Ernahr.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=3125108&query_hl=1&itool=pubmed_docsum

- **Cures for polycystic kidney diseases?**
  Author(s): Woolf AS.
  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=7816242&query_hl=1&itool=pubmed_docsum

- **Detrimental effects of a high fat diet in early renal injury are ameliorated by fish oil in Han:SPRD-cy rats.**
  Author(s): Lu J, Bankovic-Calic N, Ogborn M, Saboorian MH, Aukema HM.
  Source: The Journal of Nutrition.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12514287&query_hl=1&itool=pubmed_docsum

- **Diagnostic aspects, functional significance and therapy of simple renal cysts. A clinical, radiologic and experimental study.**
  Author(s): Holmberg G.
  Source: Scand J Urol Nephrol Suppl.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1292068&query_hl=1&itool=pubmed_docsum

- **Diet and disease alter phosphoinositide composition and metabolism in murine polycystic kidneys.**
  Author(s): Aukema HM, Yamaguchi T, Tomobe K, Philbrick DJ, Chapkin RS, Takahashi H, Holub BJ.

Source: The Journal of Nutrition.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7738678&query_hl=1&itool=pubmed_docsum

- **Dietary betaine modifies hepatic metabolism but not renal injury in rat polycystic kidney disease.**
  Author(s): Ogborn MR, Nitschmann E, Bankovic-Calic N, Buist R, Peeling J.
  Source: American Journal of Physiology. Gastrointestinal and Liver Physiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11093938&query_hl=1&itool=pubmed_docsum

- **Dietary flax oil reduces renal injury, oxidized LDL content, and tissue n-6/n-3 FA ratio in experimental polycystic kidney disease.**
  Author(s): Ogborn MR, Nitschmann E, Bankovic-Calic N, Weiler HA, Aukema H.
  Source: Lipids.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12558056&query_hl=1&itool=pubmed_docsum

- **Dietary modulation of p-nonylphenol-induced polycystic kidneys in male Sprague-Dawley rats.**
  Author(s): Cooper S, Latendresse JR, Doerge DR, Twaddle NC, Fu X, Delclos KB.
  Source: Toxicological Sciences : an Official Journal of the Society of Toxicology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16554316&query_hl=1&itool=pubmed_docsum

- **Does a low protein diet really slow down the rate of progression of chronic renal failure?**
  Author(s): Gretz N, Meisinger E, Strauch M.
  Source: Blood Purification.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=2645923&query_hl=1&itool=pubmed_docsum

- **Dynamics of erythropoiesis following renal transplantation.**
  Author(s): Besarab A, Caro J, Jarrell BE, Francos G, Erslev AJ.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=3323595&query_hl=1&itool=pubmed_docsum

- **Effect of dietary soy protein and genistein on disease progression in mice with polycystic kidney disease.**
  Author(s): Tomobe K, Philbrick DJ, Ogborn MR, Takahashi H, Holub BJ.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9428452&query_hl=1&itool=pubmed_docsum

- **Effects of dietary protein restriction and oil type on the early progression of murine polycystic kidney disease.**
  Author(s): Aukema HM, Ogborn MR, Tomobe K, Takahashi H, Hibino T, Holub BJ.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1453579&query_hl=1&itool=pubmed_docsum

- **Effects of dietary supplementation with n-3 fatty acids on kidney morphology and the fatty acid composition of phospholipids and triglycerides from mice with polycystic kidney disease.**
  Author(s): Yamaguchi T, Valli VE, Philbrick D, Holub B, Yoshida K, Takahashi H.
  Source: Res Commun Chem Pathol Pharmacol.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=2236900&query_hl=1&itool=pubmed_docsum

- **Efficacy of taxol in the orpk mouse model of polycystic kidney disease.**
  Author(s): Sommardahl CS, Woychik RP, Sweeney WE, Avner ED, Wilkinson JE.
  Source: Pediatric Nephrology (Berlin, Germany).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9438653&query_hl=1&itool=pubmed_docsum

- **Elevated bone turnover in rat polycystic kidney disease is not due to prostaglandin E2.**
  Author(s): Weiler H, Kovacs H, Nitschmann E, Fitzpatrick Wong S, Bankovic-Calic N, Ogborn M.
  Source: Pediatric Nephrology (Berlin, Germany).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12376805&query_hl=1&itool=pubmed_docsum

- **Evidence that soyasaponin Bb retards disease progression in a murine model of polycystic kidney disease.**
  Author(s): Philbrick DJ, Bureau DP, Collins FW, Holub BJ.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12631339&query_hl=1&itool=pubmed_docsum

- **Flaxseed ameliorates interstitial nephritis in rat polycystic kidney disease.**
  Author(s): Ogborn MR, Nitschmann E, Weiler H, Leswick D, Bankovic-Calic N.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9987066&query_hl=1&itool=pubmed_docsum

- **Galectin-3 associates with the primary cilium and modulates cyst growth in congenital polycystic kidney disease.**
  Author(s): Chiu MG, Johnson TM, Woolf AS, Dahm-Vicker EM, Long DA, Guay-Woodford L, Hillman KA, Bawumia S, Venner K, Hughes RC, Poirier F, Winyard PJ.

Source: American Journal of Pathology.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17148658&query_hl=1&itool=pubmed_docsum

- **High dosage metolazone in chronic renal failure.**
Author(s): Dargie HJ, Allison ME, Kennedy AC, Gray MJ.
Source: British Medical Journal.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=5082545&query_hl=1&itool=pubmed_docsum

- **In vitro formation of cysts derived from a rat model of autosomal dominant polycystic kidney disease.**
Author(s): Pey R, Hafner M, Schieren G, Bach J, Gretz N.
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=9044330&query_hl=1&itool=pubmed_docsum

- **Infusion of total dose iron versus oral iron supplementation in ambulatory peritoneal dialysis patients: a prospective, cross-over trial.**
Author(s): Ahsan N.
Source: Adv Perit Dial.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11045266&query_hl=1&itool=pubmed_docsum

- **Inhibition of polycystin-L channel by the Chinese herb Sparganum stoloniferum Buch.-Ham.**
Author(s): Li F, Dai XQ, Li Q, Wu Y, Chen XZ.
Source: Canadian Journal of Physiology and Pharmacology.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17111037&query_hl=1&itool=pubmed_docsum

- **Initial effect of enalapril on kidney function in patients with moderate to severe chronic nephropathy.**
Author(s): Kamper AL, Thomsen HS, Nielsen SL, Strandgaard S.
Source: Scandinavian Journal of Urology and Nephrology.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=2157277&query_hl=1&itool=pubmed_docsum

- **Massive bilateral nephroblastomatosis in a 13-year-old-girl.**
Author(s): Pichler E, Jurgenssen OA, Balzar E, Pinggera WF, Wolf A, Wagner O, Reinartz G, Czembirek H, Syre G.
Source: European Journal of Pediatrics.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=6288384&query_hl=1&itool=pubmed_docsum

- **Matrix metalloproteinases and TIMPS in cultured C57BL/6J-cpk kidney tubules.**
Author(s): Rankin CA, Suzuki K, Itoh Y, Ziemer DM, Grantham JJ, Calvet JP, Nagase H.

Source: Kidney International.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8872958&query_hl=1&itool=pubmed_docsum

- **Microtubule active taxanes inhibit polycystic kidney disease progression in cpk mice.**
Author(s): Woo DD, Tabancay AP Jr, Wang CJ.
Source: Kidney International.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9150481&query_hl=1&itool=pubmed_docsum

- **Modification of polycystic kidney disease and fatty acid status by soy protein diet.**
Author(s): Ogborn MR, Nitschmann E, Weiler HA, Bankovic-Calic N.
Source: Kidney International.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10620197&query_hl=1&itool=pubmed_docsum

- **Modulation of renal injury in pcy mice by dietary fat containing n-3 fatty acids depends on the level and type of fat.**
Author(s): Sankaran D, Lu J, Bankovic-Calic N, Ogborn MR, Aukema HM.
Source: Lipids.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15233398&query_hl=1&itool=pubmed_docsum

- **Morphology of cystic renal lesions. Lectin and immuno-histochemical study.**
Author(s): Kovacs J, Zilahy M, Gomba S.
Source: Acta Chir Hung.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9408336&query_hl=1&itool=pubmed_docsum

- **Observations in a Saudi-Arabian dialysis population over a 13-year period.**
Author(s): Hussein MM, Mooij JM, Roujouleh H, el-Sayed H.
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=7800203&query_hl=1&itool=pubmed_docsum

- **Pain management in polycystic kidney disease.**
Author(s): Bajwa ZH, Gupta S, Warfield CA, Steinman TI.
Source: Kidney International.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11703580&query_hl=1&itool=pubmed_docsum

- **Periodic dialysis in terminal uremia.**
Author(s): Abella R, Blondeel NJ, Roguska J, Walker C, Simon NM, Del Greco F.
Source: Jama : the Journal of the American Medical Association.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=4289324&query_hl=1&itool=pubmed_docsum

- **Polycystic kidney disease induced in F(1) Sprague-Dawley rats fed para-nonylphenol in a soy-free, casein-containing diet.**
  Author(s): Latendresse JR, Newbold RR, Weis CC, Delclos KB.
  Source: Toxicological Sciences : an Official Journal of the Society of Toxicology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11399801&query_hl=1&itool=pubmed_docsum

- **Polycystin-2 cation channel function is under the control of microtubular structures in primary cilia of renal epithelial cells.**
  Author(s): Li Q, Montalbetti N, Wu Y, Ramos A, Raychowdhury MK, Chen XZ, Cantiello HF.
  Source: The Journal of Biological Chemistry.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16950792&query_hl=1&itool=pubmed_docsum

- **Predictors of renal function in diabetic and non-diabetic renal disease.**
  Author(s): Feehally J, Taverner D, Burden AC, Walls J.
  Source: Clinica Chimica Acta; International Journal of Clinical Chemistry.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=6354517&query_hl=1&itool=pubmed_docsum

- **Racial origin and primary renal diagnosis in 771 patients with end-stage renal disease.**
  Author(s): Pazianas M, Eastwood JB, MacRae KD, Phillips ME.
  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=1798591&query_hl=1&itool=pubmed_docsum

- **Rate of functional deterioration in polycystic kidney disease.**
  Author(s): Franz KA, Reubi FC.
  Source: Kidney International.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=6405076&query_hl=1&itool=pubmed_docsum

- **Relationship of renal function to homocysteine and lipoprotein(a) levels: the frequency of the combination of both risk factors in chronic renal impairment.**
  Author(s): Parsons DS, Reaveley DA, Pavitt DV, Brown EA.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12407635&query_hl=1&itool=pubmed_docsum

- **Serum levels of the soluble interleukin-2 receptor are dependent on the kidney function.**
  Author(s): Nassberger L, Sturfelt G, Thysell H.

Source: American Journal of Nephrology.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1292338&query_hl=1&itool=pubmed_docsum

- **Taxol inhibits progression of congenital polycystic kidney disease.**
  Author(s): Woo DD, Miao SY, Pelayo JC, Woolf AS.
  Source: Nature.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7908721&query_hl=1&itool=pubmed_docsum

- **The effect of dietary flaxseed supplementation on organic anion and osmolyte content and excretion in rat polycystic kidney disease.**
  Author(s): Ogborn MR, Nitschmann E, Bankovic-Calic N, Buist R, Peeling J.
  Source: Biochemistry and Cell Biology = Biochimie Et Biologie Cellulaire.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9923725&query_hl=1&itool=pubmed_docsum

- **The effect of paclitaxel on the progression of polycystic kidney disease in rodents.**
  Author(s): Martinez JR, Cowley BD, Gattone VH 2nd, Nagao S, Yamaguchi T, Kaneta S, Takahashi H, Grantham JJ.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9041221&query_hl=1&itool=pubmed_docsum

- **Transforming growth factor alpha and epidermal growth factor expression in experimental murine polycystic kidney disease.**
  Author(s): Ogborn MR, Sareen S.
  Source: Pediatric Nephrology (Berlin, Germany).
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8703707&query_hl=1&itool=pubmed_docsum

Additional Web Resources

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

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

- Yahoo.com: **http://dir.yahoo.com/Health/Alternative_Medicine/**

General References

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

CHAPTER 3. BOOKS ON POLYCYSTIC KIDNEY DISEASE

Overview

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

Book Summaries: Online Booksellers

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

- **ADPKD patients manual: Understanding and living with autosomal dominant polycystic kidney disease** Irene T Duley (1995); ISBN: 0961456744; http://www.amazon.com/exec/obidos/ASIN/0961456744/icongroupinterna
- **Autosomal Dominant Adult: Polycystic Kidney Disease: An article from: Synergy** Aurora Costea (2005); ISBN: B000BGATJ0; http://www.amazon.com/exec/obidos/ASIN/B000BGATJ0/icongroupinterna
- **Autosomal Dominant Polycystic Kidney Desease: Seminar on Autosomal Dominant Polycystic Kidney Disease, Vimercate, June 18, 1994 (Contributions to Nephrology)** Seminar on Autosomal Dominant Polycystic Kidney Disease, A. Sessa, F. Conte, and P. Serbelloni (1995); ISBN: 3805560907; http://www.amazon.com/exec/obidos/ASIN/3805560907/icongroupinterna

- **Cilia function in left-right patterning and polycystic kidney disease: (Dissertation)** Felix A. Olale (2006); ISBN: B000JVRLHK; http://www.amazon.com/exec/obidos/ASIN/B000JVRLHK/icongroupinterna
- **Gale Encyclopedia of Medicine: Polycystic kidney disease** Paul A. Johnson Ed.M. (2004); ISBN: B00075V21O; http://www.amazon.com/exec/obidos/ASIN/B00075V21O/icongroupinterna
- **Health tips for living with polycystic kidney disease** Arlene B Chapman (2001); ISBN: 0931365155; http://www.amazon.com/exec/obidos/ASIN/0931365155/icongroupinterna
- **Novel involvement of nuclear hormone receptors in autosomal dominant polycystic kidney disease: (Dissertation)** Erica Lynn Allen (2006); ISBN: B000GQM1EG; http://www.amazon.com/exec/obidos/ASIN/B000GQM1EG/icongroupinterna
- **PKD patient's manual: Understanding & living with autosomal dominant polycystic kidney disease** Irene Duley (1989); ISBN: B00072BTKQ; http://www.amazon.com/exec/obidos/ASIN/B00072BTKQ/icongroupinterna
- **Polycystic Kidney Disease (Contributions to Nephrology)** M. H. Breuning, M. Devoto, and G. Romeo (1992); ISBN: 3805555865; http://www.amazon.com/exec/obidos/ASIN/3805555865/icongroupinterna
- **Polycystic Kidney Disease (Oxford Clinical Nephrology Series)** Michael L. Watson and Vicente E. Torres (1996); ISBN: 0192625780; http://www.amazon.com/exec/obidos/ASIN/0192625780/icongroupinterna
- **Polycystin-1 regulates von Hippel Lindau partner Jade-1: A potential role for Jade-1 in autosomal dominant polycystic kidney disease : (Dissertation)** Rebecca Louise Foy (2006); ISBN: B000FIGA1A; http://www.amazon.com/exec/obidos/ASIN/B000FIGA1A/icongroupinterna
- **Problems in diagnosis and management of polycystic kidney disease: Proceedings of the First International Workshop on Polycystic Kidney Disease** (1985); ISBN: 0961456701; http://www.amazon.com/exec/obidos/ASIN/0961456701/icongroupinterna
- **Proceedings of the Fifth International Workshop on Polycystic Kidney Disease** Patricia A. Gabow and Jared J.Grantham (1993); ISBN: 096145671X; http://www.amazon.com/exec/obidos/ASIN/096145671X/icongroupinterna
- **Q&A on PKD: PKD Foundation's scientific advisors answer patient questions about dealing with polycystic kidney disease today** M.D., Jared J. Grantham, M.D. Patricia A. Gabow (2002); ISBN: 0961456795; http://www.amazon.com/exec/obidos/ASIN/0961456795/icongroupinterna
- **The Official Patient's Sourcebook on Polycystic Kidney Disease** James N. Parker and Philip M. Parker (2002); ISBN: 0597832277; http://www.amazon.com/exec/obidos/ASIN/0597832277/icongroupinterna
- **Your child, your family, and autosomal recessive polycystic kidney disease** Lisa M Guay-Woodford (1996); ISBN: B0006RGQIC; http://www.amazon.com/exec/obidos/ASIN/B0006RGQIC/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 **polycystic kidney disease** (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]:

- **Adult polycystic kidney diseases** Author: Martinez-Maldonado, Manuel.; Year: 1976; Foundation, 1976
- **Polycystic kidney disease** Author: Watson, Michael L. (Leonard); Year: 1996; Oxford; New York: Oxford University Press, 1996; ISBN: 9780192625 http://www.amazon.com/exec/obidos/ASIN/9780192625/icongroupinterna
- **Polycystic kidney disease: hereditary and acquired** Author: Grantham, Jared J.,; Year: 1984; Foundation, c1984
- **Polycystic kidney disease in children.** Author: Uhler, Walter Miller,; Year: 1951; Minneapolis] 1951
- **Problems in diagnosis and management of polycystic kidney disease: proceedings of the First International Workshop on Polycystic Kidney Disease** Author: Grantham, Jared J.,; Year: 1985; Kansas City [Mo.]: PKR Foundation, c1985; ISBN: 9780961456 http://www.amazon.com/exec/obidos/ASIN/9780961456/icongroupinterna
- **Psychosocial effects of genetic testing in adult polycystic kidney disease: final report** Author: Rosenberg, Ellen,; Year: 1991; Quel bec]: Conseil quel bel cois de la recherche sociale, [1991]

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

CHAPTER 4. MULTIMEDIA ON POLYCYSTIC KIDNEY DISEASE

Overview

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

Bibliography: Multimedia on Polycystic Kidney Disease

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

- **Hand-assisted laparoscopic splenectomy for splenomegaly [videorecording]: laparoscopic retroperiton[e]al symphathectomy [i.e. sympathectomy]; Laparoscopic unroofing of symptomatic polycystic kidney disease** Source: Society American Gastrointestinal Endoscopic; Year: 1999; Format: Videorecording; Woodbury, CT: Distributed by Cineì -Med, [1999]
- **Polycystic kidney disease and other cystic disorders [slide]** Source: Alexander C. Chester, George E. Schreiner, Harry G. Preuss; Format: Slide; New York]: Medcom, c1978-

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.

---

[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.

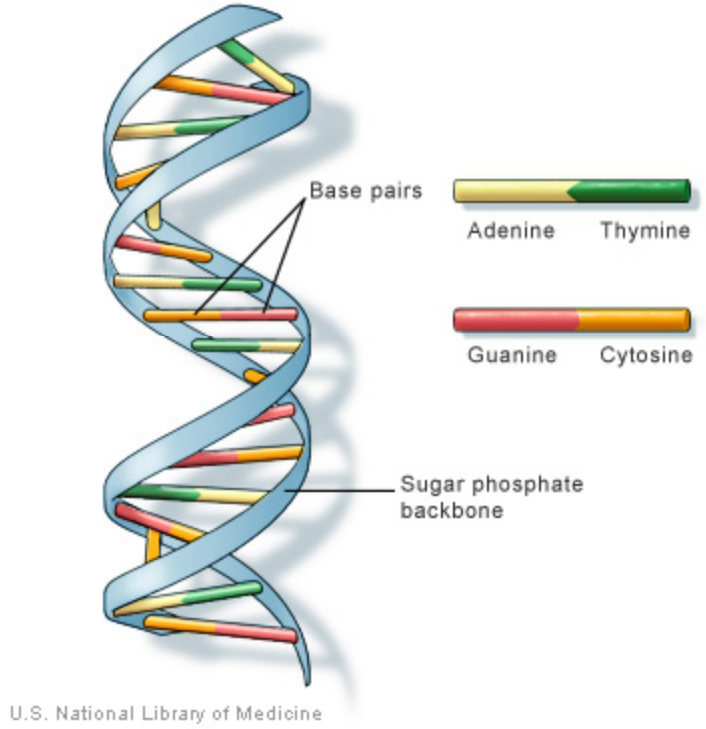
What Is DNA?

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).

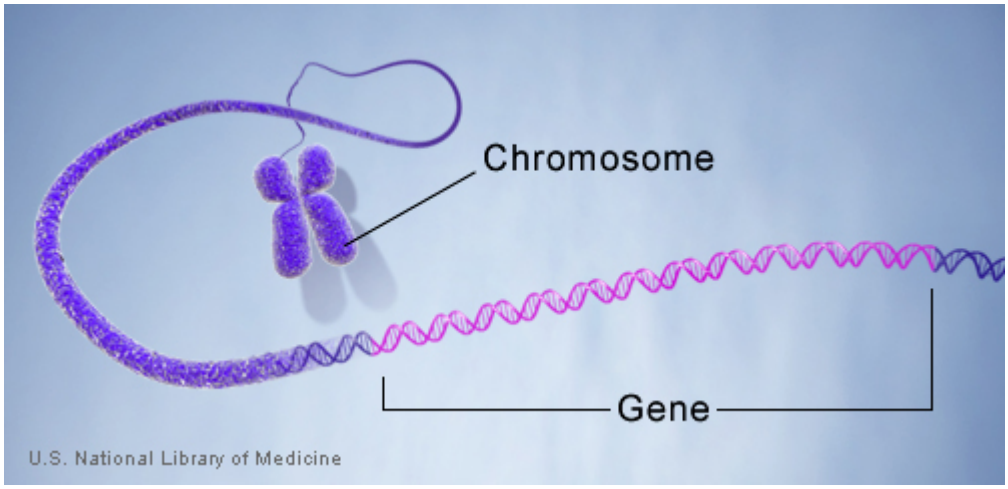
Mitochondrial DNA contains 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation. The remaining genes provide instructions for making molecules called transfer RNAs (tRNAs) and ribosomal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



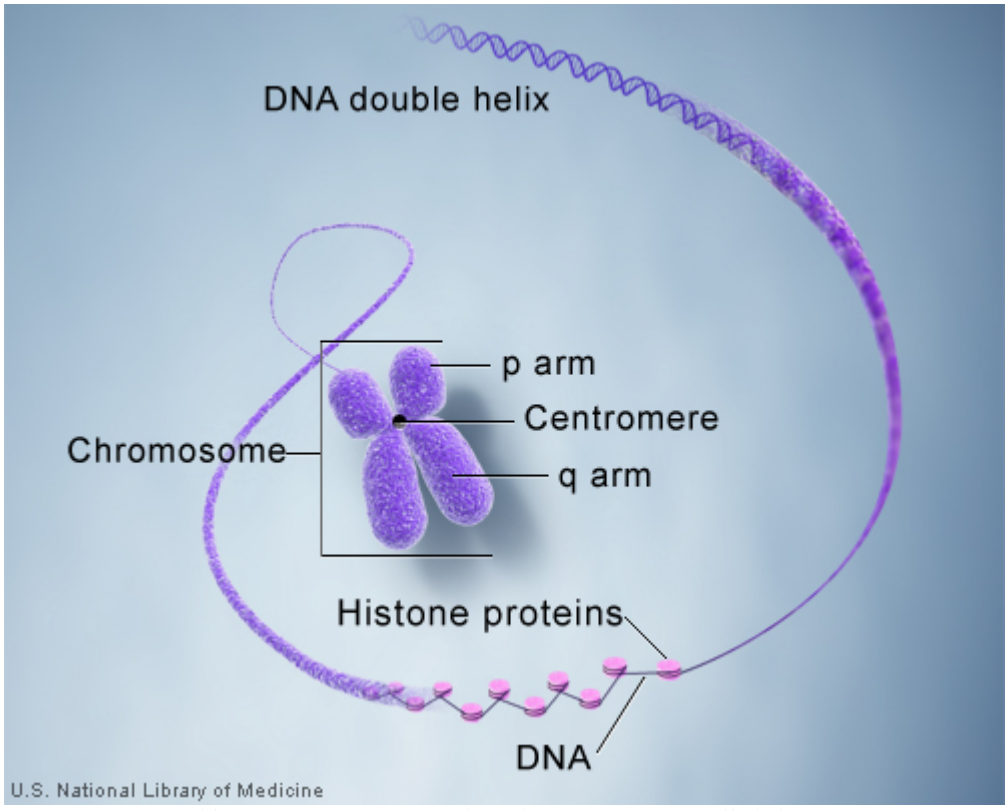
Genes are made up of DNA. Each chromosome contains many genes.

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.

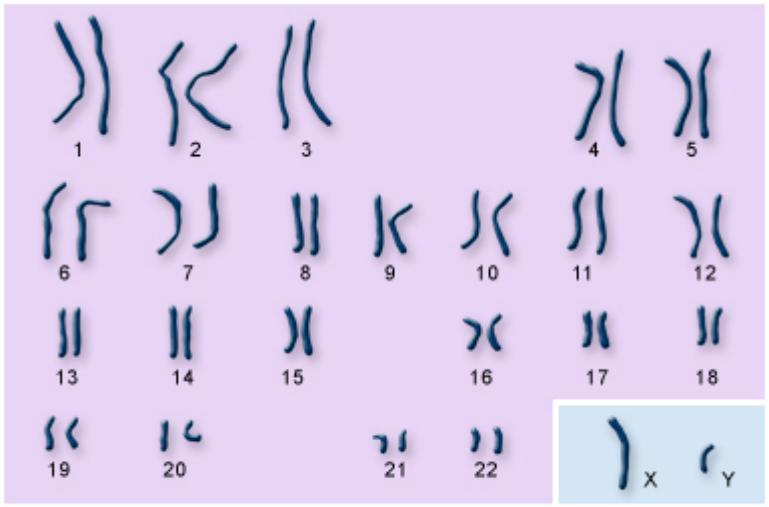
Each chromosome has a constriction point called the centromere, which divides the chromosome into two sections, or "arms." The short arm of the chromosome is labeled the "p arm." The long arm of the chromosome is labeled the "q arm." The location of the centromere on each chromosome gives the chromosome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

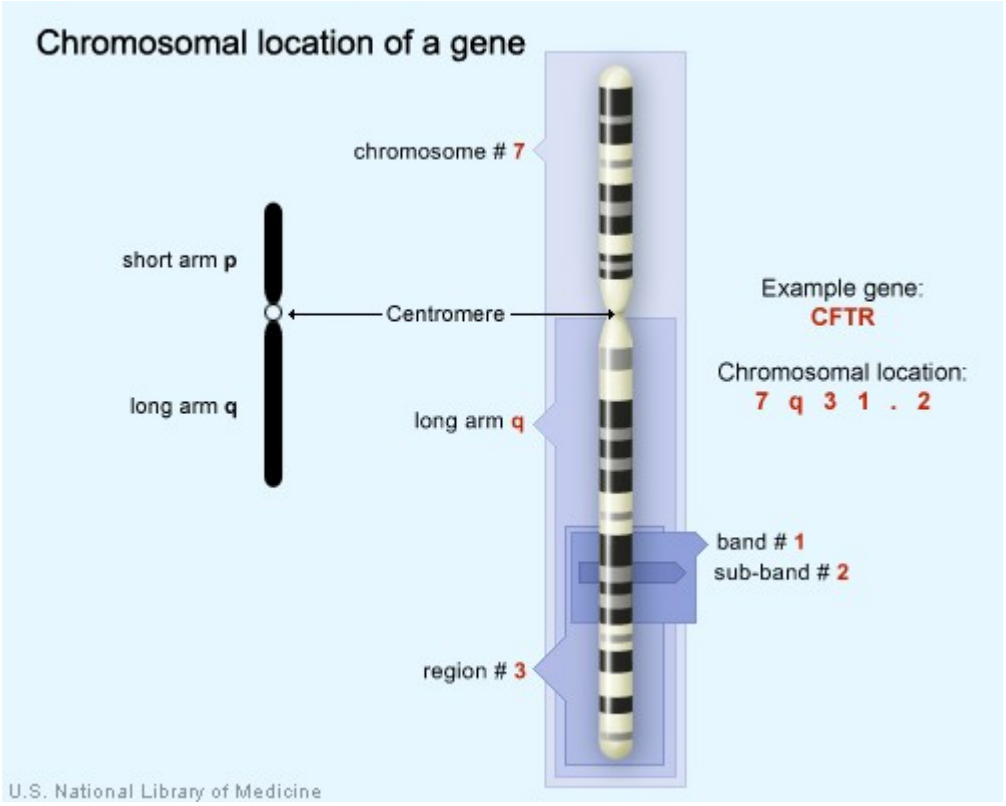
17q12-q21

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?

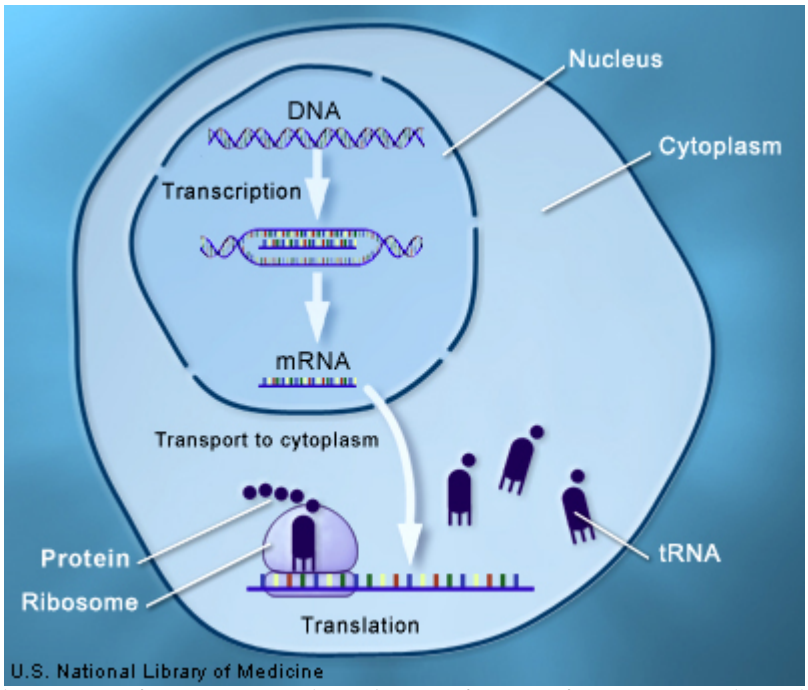
Most genes contain the information needed to make functional molecules called proteins. (A few genes produce other molecules that help the cell assemble proteins.) The journey from gene to protein is complex and tightly controlled within each cell. It consists of two major steps: transcription and translation.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

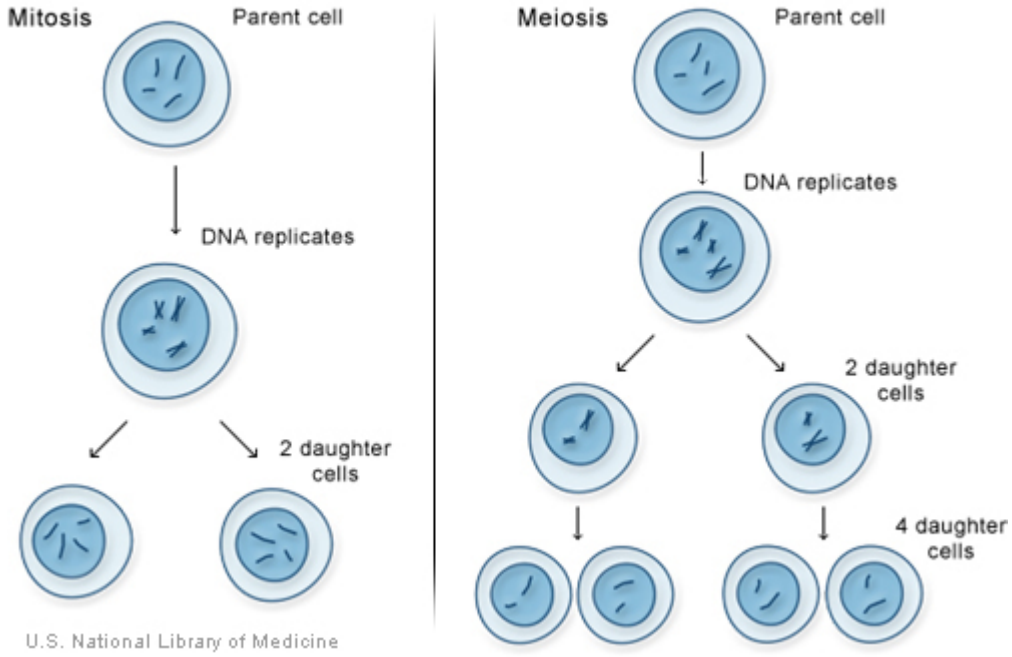
Gene regulation can occur at any point during gene expression, but most commonly occurs at the level of transcription (when the information in a gene's DNA is transferred to mRNA). Signals from the environment or from other cells activate proteins called transcription factors. These proteins bind to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

[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).

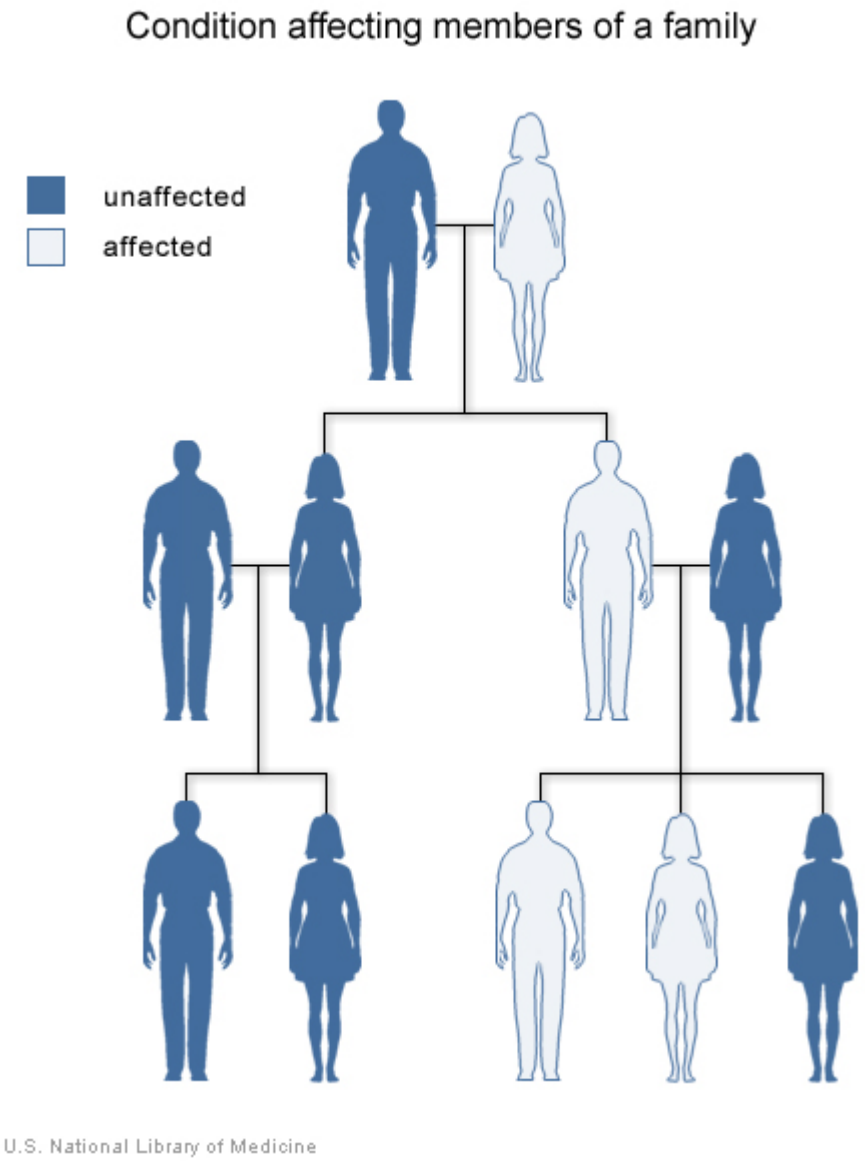
Inheriting Genetic Conditions

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.

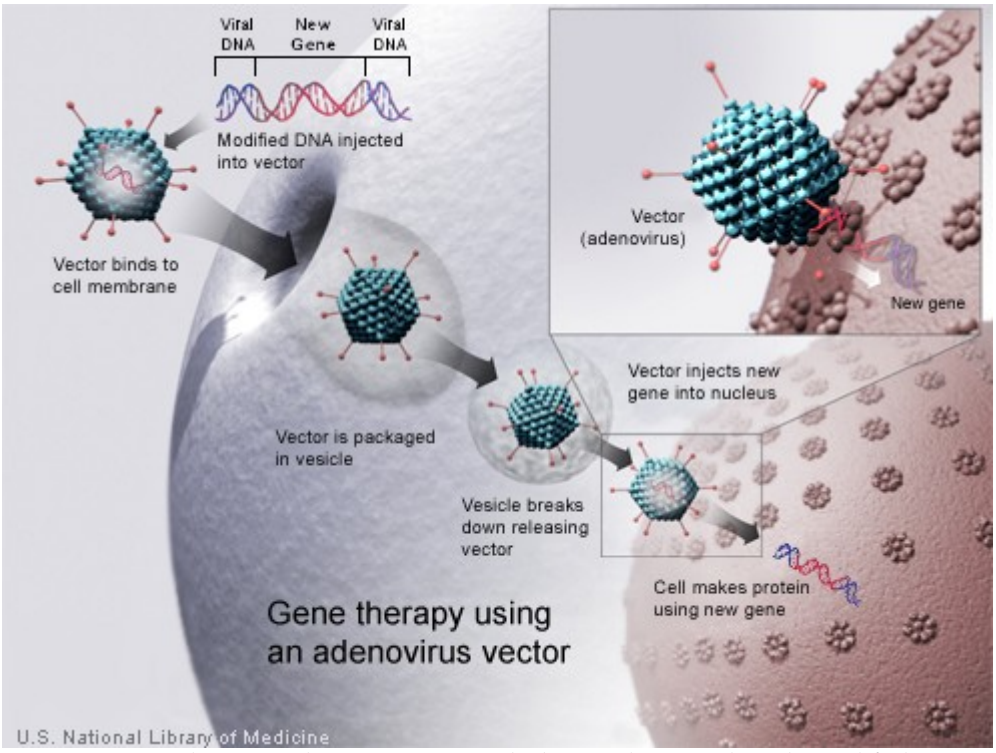
How Does Gene Therapy Work?

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/**

---

[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 **polycystic kidney disease** (or synonyms) into the search box and click **Search**. The results will be presented in a tabular form, indicating the number of references in each database category.

Results Summary

Category	Items Found
Journal Articles	6733
Books / Periodicals / Audio Visual	33
Consumer Health	71
Meeting Abstracts	3
Other Collections	8
Total	6848

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 **polycystic kidney disease** (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.

---

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/**.

The Genome Project and Polycystic Kidney Disease

In the following section, we will discuss databases and references which relate to the Genome Project and polycystic kidney disease.

Online Mendelian Inheritance in Man (OMIM)

The Online Mendelian Inheritance in Man (OMIM) database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere. OMIM was developed for the World Wide Web by the National Center for Biotechnology Information (NCBI).[23] The database contains textual information, pictures, and reference information. It also contains copious links to NCBI's Entrez database of MEDLINE articles and sequence information.

To search the database, go to **http://www.ncbi.nlm.nih.gov/Omim/searchomim.html**. Type **polycystic kidney disease** (or synonyms) into the search box, and click **Go**. If too many results appear, you can narrow the search by adding the word **clinical**. Each report will

---

[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.

[23] Adapted from **http://www.ncbi.nlm.nih.gov/**. Established in 1988 as a national resource for molecular biology information, NCBI creates public databases, conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information--all for the better understanding of molecular processes affecting human health and disease.

have additional links to related research and databases. The following is an example of the results you can obtain from the OMIM for polycystic kidney disease:

- **POLYCYSTIC KIDNEY DISEASE 2; PKD2**
  Web site: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=173910
- **POLYCYSTIC KIDNEY DISEASE 3, AUTOSOMAL DOMINANT; PKD3**
  Web site: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600666
- **POLYCYSTIC KIDNEY DISEASE 1; PKD1**
  Web site: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=601313

Genes and Disease (NCBI - Map)

The Genes and Disease database is produced by the National Center for Biotechnology Information of the National Library of Medicine at the National Institutes of Health. This Web site categorizes each disorder by system of the body. Go to **http://www.ncbi.nlm.nih.gov/disease/**, and browse the system pages to have a full view of important conditions linked to human genes. Since this site is regularly updated, you may wish to revisit it from time to time. The following systems and associated disorders are addressed:

- **Cancer:** Uncontrolled cell division.
  Examples: Breast and ovarian cancer, Burkitt lymphoma, chronic myeloid leukemia, colon cancer, lung cancer, malignant melanoma, multiple endocrine neoplasia, neurofibromatosis, p53 tumor suppressor, pancreatic cancer, prostate cancer, Ras oncogene, RB: retinoblastoma, von Hippel-Lindau syndrome.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Cancer.html**
- **Immune System:** Fights invaders.
  Examples: Asthma, autoimmune polyglandular syndrome, Crohn's disease, DiGeorge syndrome, familial Mediterranean fever, immunodeficiency with Hyper-IgM, severe combined immunodeficiency.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Immune.html**
- **Metabolism:** Food and energy.
  Examples: Adreno-leukodystrophy, atherosclerosis, Best disease, Gaucher disease, glucose galactose malabsorption, gyrate atrophy, juvenile-onset diabetes, obesity, paroxysmal nocturnal hemoglobinuria, phenylketonuria, Refsum disease, Tangier disease, Tay-Sachs disease.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Metabolism.html**
- **Muscle and Bone:** Movement and growth.
  Examples: Duchenne muscular dystrophy, Ellis-van Creveld syndrome, Marfan syndrome, myotonic dystrophy, spinal muscular atrophy.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Muscle.html**
- **Nervous System:** Mind and body.
  Examples: Alzheimer disease, amyotrophic lateral sclerosis, Angelman syndrome, Charcot-Marie-Tooth disease, epilepsy, essential tremor, fragile X syndrome, Friedreich's ataxia, Huntington disease, Niemann-Pick disease, Parkinson disease, Prader-Willi syndrome, Rett syndrome, spinocerebellar atrophy, Williams syndrome.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Brain.html**

- **Signals:** Cellular messages.
  Examples: Ataxia telangiectasia, Cockayne syndrome, glaucoma, male-patterned baldness, SRY: sex determination, tuberous sclerosis, Waardenburg syndrome, Werner syndrome.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Signals.html**
- **Transporters:** Pumps and channels.
  Examples: Cystic fibrosis, deafness, diastrophic dysplasia, Hemophilia A, long-QT syndrome, Menkes syndrome, Pendred syndrome, polycystic kidney disease, sickle cell anemia, Wilson's disease, Zellweger syndrome.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Transporters.html**

Entrez

Entrez is a search and retrieval system that integrates several linked databases at the National Center for Biotechnology Information (NCBI). These databases include nucleotide sequences, protein sequences, macromolecular structures, whole genomes, and MEDLINE through PubMed. Entrez provides access to the following databases:

- **Books:** Online books,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=books**
- **Genome:** Complete genome assemblies,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Genome**
- **GEO DataSets:** Curated gene expression and molecular abundance data sets assembled from the Gene Expression Omnibus (GEO) repository,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=geo**
- **GEO Profiles:** Individual gene expression and molecular abundance profiles assembled from the Gene Expression Omnibus (GEO) repository,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=geo**
- **NCBI's Protein Sequence Information Survey Results:**
  Web site: **http://www.ncbi.nlm.nih.gov/About/proteinsurvey/**
- **Nucleotide Sequence Database (Genbank):**
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Nucleotide**
- **OMIM:** Online Mendelian Inheritance in Man,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM**
- **PopSet:** Population study data sets,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Popset**
- **Protein Sequence Database:**
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein**
- **PubMed:** Biomedical literature (PubMed),
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed**
- **Structure:** Three-dimensional macromolecular structures,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Structure**
- **Taxonomy:** Organisms in GenBank,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Taxonomy**

To access the Entrez system at the National Center for Biotechnology Information, go to **http://www.ncbi.nlm.nih.gov/gquery/gquery.fcgi**, and then select the database that you would like to search. Or, to search across databases, you can enter **polycystic kidney disease** (or synonyms) into the search box and click **Go**.

Jablonski's Multiple Congenital Anomaly/Mental Retardation (MCA/MR) Syndromes Database[24]

This online resource has been developed to facilitate the identification and differentiation of syndromic entities. Special attention is given to the type of information that is usually limited or completely omitted in existing reference sources due to space limitations of the printed form.

You can search across syndromes using an alphabetical index at **http://www.nlm.nih.gov/mesh/jablonski/syndrome_toc/toc_a.html**. Search by keywords at **http://www.nlm.nih.gov/mesh/jablonski/syndrome_db.html**.

The Genome Database[25]

Established at Johns Hopkins University in Baltimore, Maryland in 1990, the GDB Human Genome Database (GDB) is the official central repository for genomic mapping data resulting from the Human Genome Initiative. In the spring of 1999, the Bioinformatics Supercomputing Centre (BiSC) at the Hospital for Sick Children in Toronto, Ontario assumed the management of GDB. The Human Genome Initiative is a worldwide research effort focusing on structural analysis of human DNA to determine the location and sequence of the estimated 100,000 human genes. In support of this project, GDB stores and curates data generated by researchers worldwide who are engaged in the mapping effort of the Human Genome Project (HGP). GDB's mission is to provide scientists with an encyclopedia of the human genome which is continually revised and updated to reflect the current state of scientific knowledge. Although GDB has historically focused on gene mapping, its focus will broaden as the Genome Project moves from mapping to sequence, and finally, to functional analysis.

To access the GDB, simply go to the following hyperlink: **http://www.gdb.org/**. Search **All Biological Data** by **Name/GDB ID**. Type **polycystic kidney disease** (or synonyms) into the search box, and review the results. If more than one word is used in the search box, then separate each one with the word **and** or **or** (using **or** might be useful when using synonyms).

---

[24] Adapted from the National Library of Medicine: **http://www.nlm.nih.gov/mesh/jablonski/about_syndrome.html**.

[25] Adapted from the Genome Database: **http://www.gdb.org/gdb/aboutGDB.html#mission**.

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 polycystic kidney disease can appear at any moment and be published by a number of sources, the best approach to finding guidelines is to systematically scan the Internet-based services that post them.

Patient Guideline Sources

This section directs you to sources which either publish fact sheets or can help you find additional guidelines on topics related to polycystic kidney disease. Due to space limitations, these sources are listed in a concise manner. Do not hesitate to consult the following sources by either using the Internet hyperlink provided, or, in cases where the contact information is provided, contacting the publisher or author directly.

The National Institutes of Health

The NIH gateway to patients is located at **http://health.nih.gov/**. From this site, you can search across various sources and institutes, a number of which are summarized below.

Topic Pages: MEDLINEplus

The National Library of Medicine has created a vast and patient-oriented healthcare information portal called MEDLINEplus. Within this Internet-based system are **health topic pages** which list links to available materials relevant to polycystic kidney disease. To access this system, log on to **http://www.nlm.nih.gov/medlineplus/healthtopics.html**. From there you can either search using the alphabetical index or browse by broad topic areas. Recently, MEDLINEplus listed the following when searched for **polycystic kidney disease**:

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

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

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

Kidney Transplantation
http://www.nlm.nih.gov/medlineplus/kidneytransplantation.html

Urinary Tract Infections
http://www.nlm.nih.gov/medlineplus/urinarytractinfections.html

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

Healthfinder™

Healthfinder™ is sponsored by the U.S. Department of Health and Human Services and offers links to hundreds of other sites that contain healthcare information. This Web site is located at **http://www.healthfinder.gov**. Again, keyword searches can be used to find guidelines. The following was recently found in this database:

- **AKF: Kidney Disease**
  Source: www.kidneyfund.org
  http://www.kidneyfund.org/kf_disease.asp

- **Kidney & Urologic Diseases AZ List of Topics and Titles**
  Source: kidney.niddk.nih.gov
  http://kidney.niddk.nih.gov/kudiseases/a-z.asp

- **Kidney Cysts - Simple Cysts, Polycystic Kidney Disease**
  Source: www.kidneyurology.org
  http://www.kidneyurology.org/Patient_Resources/PaR_Lib_KidneyCysts.htm

- **MedlinePlus: Kidney Diseases**
  Source: www.nlm.nih.gov
  http://www.nlm.nih.gov/medlineplus/kidneydiseases.html

- **MedlinePlus: Kidneys and Urinary System Topics**
  Source: www.nlm.nih.gov
  http://www.nlm.nih.gov/medlineplus/kidneysandurinarysystem.html

- **Polycystic Kidney Disease**
  Source: kidney.niddk.nih.gov
  http://kidney.niddk.nih.gov/kudiseases/pubs/polycystic/

- **Preventing Kidney Disease**
  Source: www.kidneyurology.org
  http://www.kidneyurology.org/Patient_Resources/PaR_Lib_BKidneyDisease.htm

The NIH Search Utility

The NIH search utility allows you to search for documents on over 100 selected Web sites that comprise the NIH-WEB-SPACE. Each of these servers is "crawled" and indexed on an ongoing basis. Your search will produce a list of various documents, all of which will relate in some way to polycystic kidney disease. The drawbacks of this approach are that the information is not organized by theme and that the references are often a mix of information for professionals and patients. Nevertheless, a large number of the listed Web sites provide useful background information. We can only recommend this route, therefore, for relatively rare or specific disorders, or when using highly targeted searches. To use the NIH search utility, visit the following Web page: **http://health.nih.gov/index.asp**. Under **Search Health Topics**, type **polycystic kidney disease** (or synonyms) into the search box, and click **Search**.

Additional Web Sources

A number of Web sites are available to the public that often link to government sites. These can also point you in the direction of essential information. The following is a representative sample:

- Family Village: **http://www.familyvillage.wisc.edu/specific.htm**
- Google: **http://directory.google.com/Top/Health/Conditions_and_Diseases/**
- Med Help International: **http://www.medhelp.org/HealthTopics/A.html**
- Open Directory Project: **http://dmoz.org/Health/Conditions_and_Diseases/**
- Yahoo.com: **http://dir.yahoo.com/Health/Diseases_and_Conditions/**
- WebMD®Health: **http://www.webmd.com/diseases_and_conditions/default.htm**

Finding Associations

There are several Internet directories that provide lists of medical associations with information on or resources relating to polycystic kidney disease. By consulting all of

associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with polycystic kidney disease.

The National Health Information Center (NHIC)

The National Health Information Center (NHIC) offers a free referral service to help people find organizations that provide information about polycystic kidney disease. For more information, see the NHIC's Web site at **http://www.health.gov/NHIC/** or contact an information specialist by calling 1-800-336-4797.

Directory of Health Organizations

The Directory of Health Organizations, provided by the National Library of Medicine Specialized Information Services, is a comprehensive source of information on associations. The Directory of Health Organizations database can be accessed via the Internet at **http://sis.nlm.nih.gov/dirline.html**. It is composed of two parts: DIRLINE and Health Hotlines.

The DIRLINE database comprises some 10,000 records of organizations, research centers, and government institutes and associations that primarily focus on health and biomedicine. Simply type in **polycystic kidney disease** (or a synonym), and you will receive information on all relevant organizations listed in the database.

Health Hotlines directs you to toll-free numbers to over 300 organizations. You can access this database directly at **http://healthhotlines.nlm.nih.gov/**. On this page, you are given the option to search by keyword or by browsing the subject list. When you have received your search results, click on the name of the organization for its description and contact information.

The National Organization for Rare Disorders, Inc.

The National Organization for Rare Disorders, Inc. has prepared a Web site that provides, at no charge, lists of associations organized by health topic. You can access this database at the following Web site: **http://www.rarediseases.org/search/orgsearch.html**. Type **polycystic kidney disease** (or a synonym) into the search box, and click **Submit Query**.

Resources for Patients and Families

The following are organizations that provide support and advocacy for patient with genetic conditions and their families[26]:

- 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/**

---

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

- 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**

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 polycystic kidney disease:

- **Basic Guidelines for Polycystic Kidney Disease**

  Hypertension
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000468.htm

  Kidney stones
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000458.htm

  PCKD
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000502.htm

  Polycystic kidney disease
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000502.htm

- **Signs & Symptoms for Polycystic Kidney Disease**

  Abdominal mass
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003274.htm

Abdominal pain
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003120.htm

Abdominal tenderness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003120.htm

Anemia
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000560.htm

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

Cysts
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003240.htm

Drowsiness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003208.htm

Dysuria
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003145.htm

Enlarged liver
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003275.htm

Excessive urination at night
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003141.htm

Flank pain
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003113.htm

Headache
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003024.htm

Heart murmurs
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003266.htm

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

Hepatomegaly
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003275.htm

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

Joint pain
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003261.htm

Nail abnormalities
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003247.htm

Nocturia
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003141.htm

Painful menstruation
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003150.htm

Polyuria
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003146.htm

Stress
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003211.htm

- **Diagnostics and Tests for Polycystic Kidney Disease**

Abdominal CT scan
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003789.htm

Abdominal MRI
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003796.htm

Abdominal ultrasound
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003777.htm

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

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

CBC
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003642.htm

Cerebral angiography
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003799.htm

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

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

Cyst
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003240.htm

Cysts
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003240.htm

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

Erythropoietin
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003683.htm

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

Hemoglobin
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003645.htm

IVP
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003782.htm

MRI
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003335.htm

Ultrasound
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003336.htm

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

Urine protein
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003580.htm

- **Surgery and Procedures for Polycystic Kidney Disease**

Kidney transplant
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003005.htm

Nephrectomy
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003001.htm

Renal transplant
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003005.htm

- **Background Topics for Polycystic Kidney Disease**

Autosomal dominant
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002049.htm

Autosomal recessive
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002052.htm

Bleeding
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000045.htm

Chronic
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002312.htm

Kidney disease - support group
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002172.htm

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

Support group
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002150.htm

Systemic
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002294.htm

Testes
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002334.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

POLYCYSTIC KIDNEY DISEASE DICTIONARY

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

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

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

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

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

Ablation: The removal of an organ by surgery. [NIH]

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

Acidosis: A pathologic condition resulting from accumulation of acid or depletion of the alkaline reserve (bicarbonate content) in the blood and body tissues, and characterized by an increase in hydrogen ion concentration. [EU]

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

Acute renal: A condition in which the kidneys suddenly stop working. In most cases, kidneys can recover from almost complete loss of function. [NIH]

Acute tubular: A severe form of acute renal failure that develops in people with severe illnesses like infections or with low blood pressure. Patients may need dialysis. Kidney function often improves if the underlying disease is successfully treated. [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]

Adherens Junctions: Anchoring points where the cytoskeleton of neighboring cells are connected to each other. They are composed of specialized areas of the plasma membrane where bundles of microfilaments attach to the membrane through the transmembrane

linkers, cadherins, which in turn attach through their extracellular domains to cadherins in the neighboring cell membranes. In sheets of cells, they form into adhesion belts (zonula adherens) that go all the way around a cell. [NIH]

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

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

Adrenal Glands: Paired glands situated in the retroperitoneal tissues at the superior pole of each kidney. [NIH]

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

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

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

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

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

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

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

Airways: Tubes that carry air into and out of the lungs. [NIH]

Aldosterone: (11 beta)-11,21-Dihydroxy-3,20-dioxopregn-4-en-18-al. A hormone secreted by the adrenal cortex that functions in the regulation of electrolyte and water balance by increasing the renal retention of sodium and the excretion of potassium. [NIH]

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

Alkaline: Having the reactions of an alkali. [EU]

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

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

Allogeneic: Taken from different individuals of the same species. [NIH]

Alpha Particles: Positively charged particles composed of two protons and two neutrons, i.e., helium nuclei, emitted during disintegration of very heavy isotopes; a beam of alpha particles or an alpha ray has very strong ionizing power, but weak penetrability. [NIH]

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

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

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

Ameliorated: A changeable condition which prevents the consequence of a failure or accident from becoming as bad as it otherwise would. [NIH]

Amelogenesis Imperfecta: Either hereditary enamel hypoplasia or hypocalcification. [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]

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

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

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

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

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

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

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

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

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

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

Angiotensin-Converting Enzyme Inhibitors: A class of drugs whose main indications are the treatment of hypertension and heart failure. They exert their hemodynamic effect mainly by inhibiting the renin-angiotensin system. They also modulate sympathetic nervous system activity and increase prostaglandin synthesis. They cause mainly vasodilation and mild natriuresis without affecting heart rate and contractility. [NIH]

Angiotensinogen: An alpha-globulin of which a fragment of 14 amino acids is converted by renin to angiotensin I, the inactive precursor of angiotensin II. It is a member of the serpin superfamily. [NIH]

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

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

Anisotropy: A physical property showing different values in relation to the direction in or along which the measurement is made. The physical property may be with regard to thermal or electric conductivity or light refraction. In crystallography, it describes crystals whose index of refraction varies with the direction of the incident light. It is also called acolotropy and colotropy. The opposite of anisotropy is isotropy wherein the same values characterize the object when measured along axes in all directions. [NIH]

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

Anoikis: Apoptosis triggered by loss of contact with the extracellular matrix. [NIH]

Anomalies: Birth defects; abnormalities. [NIH]

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

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

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

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

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

Antigen: Any substance which is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibody or specifically sensitized T-lymphocytes, or both. Antigens may be soluble

substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (q.v.) combines with antibody or a specific receptor on a lymphocyte. Abbreviated Ag. [EU]

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

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

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

Anti-Inflammatory Agents: Substances that reduce or suppress inflammation. [NIH]

Antimitotic: Inhibiting or preventing mitosis. [EU]

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

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

Antiproliferative: Counteracting a process of proliferation. [EU]

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

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

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

Aortic Aneurysm: Aneurysm of the aorta. [NIH]

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

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

Aquaporins: Membrane proteins which facilitate the passage of water. They are members of the family of membrane channel proteins which includes the lens major intrinsic protein and bacterial glycerol transporters. [NIH]

Aqueous: Having to do with water. [NIH]

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

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

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

Arterial embolization: The blocking of an artery by a clot of foreign material. This can be done as treatment to block the flow of blood to a tumor. [NIH]

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

Arteriolar: Pertaining to or resembling arterioles. [EU]

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

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

Arteriovenous Fistula: An abnormal communication between an artery and a vein. [NIH]

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

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

Aseptic: Free from infection or septic material; sterile. [EU]

Aspiration: The act of inhaling. [NIH]

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

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

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

ATP: ATP an abbreviation for adenosine triphosphate, a compound which serves as a carrier of energy for cells. [NIH]

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

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

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

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

Autodigestion: Autolysis; a condition found in disease of the stomach: the stomach wall is digested by the gastric juice. [NIH]

Axillary: Pertaining to the armpit area, including the lymph nodes that are located there. [NIH]

Axillary Artery: The continuation of the subclavian artery; it distributes over the upper limb, axilla, chest and shoulder. [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]

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

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

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

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

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

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]

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]

Bile Acids: Acids made by the liver that work with bile to break down fats. [NIH]

Bile Acids and Salts: Steroid acids and salts. The primary bile acids are derived from cholesterol in the liver and usually conjugated with glycine or taurine. The secondary bile acids are further modified by bacteria in the intestine. They play an important role in the digestion and absorption of fat. They have also been used pharmacologically, especially in the treatment of gallstones. [NIH]

Bile duct: A tube through which bile passes in and out of the liver. [NIH]

Biliary: Having to do with the liver, bile ducts, and/or gallbladder. [NIH]

Biliary Tract: The gallbladder and its ducts. [NIH]

Binding Sites: The reactive parts of a macromolecule that directly participate in its specific combination with another molecule. [NIH]

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

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

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

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

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]

Biotin: Hexahydro-2-oxo-1H-thieno(3,4-d)imidazole-4-pentanoic acid. Growth factor present in minute amounts in every living cell. It occurs mainly bound to proteins or polypeptides and is abundant in liver, kidney, pancreas, yeast, and milk.The biotin content of cancerous tissue is higher than that of normal tissue. [NIH]

Bladder: The organ that stores urine. [NIH]

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

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

Blood Glucose: Glucose in blood. [NIH]

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

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

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

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

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

Brachial Artery: The continuation of the axillary artery; it branches into the radial and ulnar arteries. [NIH]

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

Brain Neoplasms: Neoplasms of the intracranial components of the central nervous system, including the cerebral hemispheres, basal ganglia, hypothalamus, thalamus, brain stem, and cerebellum. Brain neoplasms are subdivided into primary (originating from brain tissue) and secondary (i.e., metastatic) forms. Primary neoplasms are subdivided into benign and malignant forms. In general, brain tumors may also be classified by age of onset, histologic type, or presenting location in the brain. [NIH]

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

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

Cadherins: A group of functionally related glycoproteins responsible for the calcium-dependent cell-to-cell adhesion mechanism. They are divided into subclasses E-, P-, and N-cadherins, which are distinct in immunological specificity and tissue distribution. They

promote cell adhesion via a homophilic mechanism. These compounds play a role in the construction of tissues and of the whole animal body. [NIH]

Calcineurin: A calcium- and calmodulin-binding protein present in highest concentrations in the central nervous system. Calcineurin is composed of two subunits. A catalytic subunit, calcineurin A, and a regulatory subunit, calcineurin B, with molecular weights of about 60 kD and 19 kD, respectively. Calcineurin has been shown to dephosphorylate a number of phosphoproteins including histones, myosin light chain, and the regulatory subunit of cAMP-dependent protein kinase. It is involved in the regulation of signal transduction and is the target of an important class of immunophilin-immunosuppressive drug complexes in T-lymphocytes that act by inhibiting T-cell activation. EC 3.1.3.-. [NIH]

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

Calcium Channels: Voltage-dependent cell membrane glycoproteins selectively permeable to calcium ions. They are categorized as L-, T-, N-, P-, Q-, and R-types based on the activation and inactivation kinetics, ion specificity, and sensitivity to drugs and toxins. The L- and T-types are present throughout the cardiovascular and central nervous systems and the N-, P-, Q-, & R-types are located in neuronal tissue. [NIH]

Calcium Signaling: Signal transduction mechanisms whereby calcium mobilization (from outside the cell or from intracellular storage pools) to the cytoplasm is triggered by external stimuli. Calcium signals are often seen to propagate as waves, oscillations, spikes or puffs. The calcium acts as an intracellular messenger by activating calcium-responsive proteins. [NIH]

Callus: A callosity or hard, thick skin; the bone-like reparative substance that is formed round the edges and fragments of broken bone. [NIH]

Calmodulin: A heat-stable, low-molecular-weight activator protein found mainly in the brain and heart. The binding of calcium ions to this protein allows this protein to bind to cyclic nucleotide phosphodiesterases and to adenyl cyclase with subsequent activation. Thereby this protein modulates cyclic AMP and cyclic GMP levels. [NIH]

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

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

Carcinogenic: Producing carcinoma. [EU]

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

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

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

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

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

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

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]

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

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

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

Celecoxib: A drug that reduces pain. Celecoxib belongs to the family of drugs called nonsteroidal anti-inflammatory agents. It is being studied for cancer prevention. [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 Adhesion Molecules: Surface ligands, usually glycoproteins, that mediate cell-to-cell adhesion. Their functions include the assembly and interconnection of various vertebrate systems, as well as maintenance of tissue integration, wound healing, morphogenic movements, cellular migrations, and metastasis. [NIH]

Cell Aggregation: The phenomenon by which dissociated cells intermixed in vitro tend to group themselves with cells of their own type. [NIH]

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

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

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

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

Cell Lineage: The developmental history of cells as traced from the first division of the original cell or cells in the embryo. [NIH]

Cell membrane: Cell membrane = plasma membrane. The structure enveloping a cell, enclosing the cytoplasm, and forming a selective permeability barrier; it consists of lipids, proteins, and some carbohydrates, the lipids thought to form a bilayer in which integral proteins are embedded to varying degrees. [EU]

Cell Movement: The movement of cells from one location to another. [NIH]

Cell Polarity: Orientation of intracellular structures especially with respect to the apical and basolateral domains of the plasma membrane. Polarized cells must direct proteins from the Golgi apparatus to the appropriate domain since tight junctions prevent proteins from diffusing between the two domains. [NIH]

Cell proliferation: An increase in the number of cells as a result of cell growth and cell division. [NIH]

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

Cell Survival: The span of viability of a cell characterized by the capacity to perform certain functions such as metabolism, growth, reproduction, some form of responsiveness, and adaptability. [NIH]

Cellular Structures: Components of a cell. [NIH]

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

Central Nervous System Infections: Pathogenic infections of the brain, spinal cord, and meninges. DNA virus infections; RNA virus infections; bacterial infections; mycoplasma infections; Spirochaetales infections; fungal infections; protozoan infections; helminthiasis; and prion diseases may involve the central nervous system as a primary or secondary process. [NIH]

Centriole: A small body which plays a part in the cell division. It is found near the nucleus of a cell. [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]

Centrosome: The cell center, consisting of a pair of centrioles surrounded by a cloud of amorphous material called the pericentriolar region. During interphase, the centrosome nucleates microtubule outgrowth. The centrosome duplicates and, during mitosis, separates to form the two poles of the mitotic spindle (mitotic spindle apparatus). [NIH]

Cerebellar: Pertaining to the cerebellum. [EU]

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

Cerebral Angiography: Radiography of the vascular system of the brain after injection of a contrast medium. [NIH]

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

Cerebral Infarction: The formation of an area of necrosis in the cerebrum caused by an insufficiency of arterial or venous blood flow. Infarcts of the cerebrum are generally classified by hemisphere (i.e., left vs. right), lobe (e.g., frontal lobe infarction), arterial distribution (e.g., infarction, anterior cerebral artery), and etiology (e.g., embolic infarction). [NIH]

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

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

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

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

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

Cervix: The lower, narrow end of the uterus that forms a canal between the uterus and vagina. [NIH]

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

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

Chimera: An individual that contains cell populations derived from different zygotes. [NIH]

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

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

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

Chondrocytes: Polymorphic cells that form cartilage. [NIH]

Chorioretinitis: Inflammation of the choroid in which the sensory retina becomes edematous and opaque. The inflammatory cells and exudate may burst through the sensory retina to cloud the vitreous body. [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 renal: Slow and progressive loss of kidney function over several years, often resulting in end-stage renal disease. People with end-stage renal disease need dialysis or transplantation to replace the work of the kidneys. [NIH]

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

Ciliary: Inflammation or infection of the glands of the margins of the eyelids. [NIH]

Cilium: A hairlike appendage of the surface of a cell. It aids in cellular locomotion and creates currents in surrounding fluids. [NIH]

Circadian: Repeated more or less daily, i. e. on a 23- to 25-hour cycle. [NIH]

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

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

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

Clathrin: The main structural coat protein of coated vesicles which play a key role in the intracellular transport between membranous organelles. Clathrin also interacts with cytoskeletal proteins. [NIH]

Cleft Lip: Congenital defect in the upper lip where the maxillary prominence fails to merge with the merged medial nasal prominences. It is thought to be caused by faulty migration of the mesoderm in the head region. [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]

Coated Vesicles: Vesicles formed when cell-membrane coated pits invaginate and pinch off. The outer surface of these vesicles are covered with a lattice-like network of coat proteins, such as clathrin, coat protein complex proteins, or caveolins. [NIH]

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

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

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

Colchicine: A major alkaloid from Colchicum autumnale L. and found also in other Colchicum species. Its primary therapeutic use is in the treatment of gout, but it has been used also in the therapy of familial Mediterranean fever (periodic disease). [NIH]

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

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

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

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

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

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

Computational Biology: A field of biology concerned with the development of techniques for the collection and manipulation of biological data, and the use of such data to make biological discoveries or predictions. This field encompasses all computational methods and theories applicable to molecular biology and areas of computer-based techniques for solving biological problems including manipulation of models and datasets. [NIH]

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

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

tomography. [NIH]

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

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

Conception: The onset of pregnancy, marked by implantation of the blastocyst; the formation of a viable zygote. [EU]

Concomitant: Accompanying; accessory; joined with another. [EU]

Conduction: The transfer of sound waves, heat, nervous impulses, or electricity. [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]

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

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

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

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

Constriction: The act of constricting. [NIH]

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

Contractility: Capacity for becoming short in response to a suitable stimulus. [EU]

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

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

Contrast Media: Substances used in radiography that allow visualization of certain tissues. [NIH]

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

Control group: In a clinical trial, the group that does not receive the new treatment being studied. This group is compared to the group that receives the new treatment, to see if the new treatment works. [NIH]

Convulsions: A general term referring to sudden and often violent motor activity of cerebral or brainstem origin. Convulsions may also occur in the absence of an electrical cerebral discharge (e.g., in response to hypotension). [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]

Corpus: The body of the uterus. [NIH]

Corpus Callosum: Broad plate of dense myelinated fibers that reciprocally interconnect regions of the cortex in all lobes with corresponding regions of the opposite hemisphere. The corpus callosum is located deep in the longitudinal fissure. [NIH]

Corrosion: Irreversible destruction of skin tissue. [NIH]

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

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

Cortical Blindness: The inability to understand or interpret what is seen due to a disturbance in the cerebral associational areas, the retina, the sensory pathways, and the striate area being intact. [NIH]

Craniocerebral Trauma: Traumatic injuries involving the cranium and intracranial structures (i.e., brain; cranial nerves; meninges; and other structures). Injuries may be classified by whether or not the skull is penetrated (i.e., penetrating vs. nonpenetrating) or whether there is an associated hemorrhage. [NIH]

Creatinine: A compound that is excreted from the body in urine. Creatinine levels are measured to monitor kidney function. [NIH]

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

Cues: Signals for an action; that specific portion of a perceptual field or pattern of stimuli to which a subject has learned to respond. [NIH]

Culture Media: Any liquid or solid preparation made specifically for the growth, storage, or transport of microorganisms or other types of cells. The variety of media that exist allow for the culturing of specific microorganisms and cell types, such as differential media, selective media, test media, and defined media. Solid media consist of liquid media that have been solidified with an agent such as agar or gelatin. [NIH]

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

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

Cyclic: Pertaining to or occurring in a cycle or cycles; the term is applied to chemical compounds that contain a ring of atoms in the nucleus. [EU]

Cyclin: Molecule that regulates the cell cycle. [NIH]

Cyst: A sac or capsule filled with fluid. [NIH]

Cyst Fluid: Liquid material found in epithelial-lined closed cavities or sacs. [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]

Cytoskeletal Proteins: Major constituent of the cytoskeleton found in the cytoplasm of eukaryotic cells. They form a flexible framework for the cell, provide attachment points for organelles and formed bodies, and make communication between parts of the cell possible. [NIH]

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

Cytotoxic: Cell-killing. [NIH]

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

Deamination: The removal of an amino group (NH2) from a chemical compound. [NIH]

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

Decortication: Removal of part or all of the external surface of an organ. [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]

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

Denaturation: Rupture of the hydrogen bonds by heating a DNA solution and then cooling it rapidly causes the two complementary strands to separate. [NIH]

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

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

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

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

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

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

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]

Dialyzer: A part of the hemodialysis machine. (See hemodialysis under dialysis.) The dialyzer has two sections separated by a membrane. One section holds dialysate. The other holds the patient's blood. [NIH]

Diarrhea: Passage of excessively liquid or excessively frequent stools. [NIH]

Diastole: Period of relaxation of the heart, especially the ventricles. [NIH]

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

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

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

Dilation: A process by which the pupil is temporarily enlarged with special eye drops (mydriatic); allows the eye care specialist to better view the inside of the eye. [NIH]

Diploid: Having two sets of chromosomes. [NIH]

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

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

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

Disease 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]

Disinfectant: An agent that disinfects; applied particularly to agents used on inanimate objects. [EU]

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

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

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

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

Diuretic: A drug that increases the production of urine. [NIH]

DNA Topoisomerase: An enzyme catalyzing ATP-independent breakage of single-stranded DNA, followed by passage and rejoining of another single-stranded DNA. This enzyme class brings about the conversion of one topological isomer of DNA into another, e.g., the relaxation of superhelical turns in DNA, the interconversion of simple and knotted rings of single-stranded DNA, and the intertwisting of single-stranded rings of complementary sequences. (From Enzyme Nomenclature, 1992) EC 5.99.1.2. [NIH]

Dominance: In genetics, the full phenotypic expression of a gene in both heterozygotes and homozygotes. [EU]

Double-blind: Pertaining to a clinical trial or other experiment in which neither the subject nor the person administering treatment knows which treatment any particular subject is receiving. [EU]

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

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

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

Duodenum: The first part of the small intestine. [NIH]

Dynein: A transport protein that normally binds proteins to the microtubule. [NIH]

Dysgenesis: Defective development. [EU]

Dyskinesia: Impairment of the power of voluntary movement, resulting in fragmentary or incomplete movements. [EU]

Dysplasia: Cells that look abnormal under a microscope but are not cancer. [NIH]

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

Eclampsia: Onset of convulsions or coma in a previously diagnosed pre-eclamptic patient. [NIH]

Ectopic: Pertaining to or characterized by ectopia. [EU]

Edema: Excessive amount of watery fluid accumulated in the intercellular spaces, most commonly present in subcutaneous tissue. [NIH]

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

Efficacy: The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions. Ideally, the determination of efficacy is based on the results of a randomized control trial. [NIH]

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

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

Elective: Subject to the choice or decision of the patient or physician; applied to procedures that are advantageous to the patient but not urgent. [EU]

Electric Conductivity: The ability of a substrate to allow the passage of electrons. [NIH]

Electrolysis: Destruction by passage of a galvanic electric current, as in disintegration of a chemical compound in solution. [NIH]

Electrolyte: A substance that dissociates into ions when fused or in solution, and thus becomes capable of conducting electricity; an ionic solute. [EU]

Electrons: Stable elementary particles having the smallest known negative charge, present in all elements; also called negatrons. Positively charged electrons are called positrons. The numbers, energies and arrangement of electrons around atomic nuclei determine the chemical identities of elements. Beams of electrons are called cathode rays or beta rays, the latter being a high-energy biproduct of nuclear decay. [NIH]

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

Emboli: Bit of foreign matter which enters the blood stream at one point and is carried until it is lodged or impacted in an artery and obstructs it. It may be a blood clot, an air bubble, fat or other tissue, or clumps of bacteria. [NIH]

Embolization: The blocking of an artery by a clot or foreign material. Embolization can be done as treatment to block the flow of blood to a tumor. [NIH]

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

Embryogenesis: The process of embryo or embryoid formation, whether by sexual (zygotic) or asexual means. In asexual embryogenesis embryoids arise directly from the explant or on intermediary callus tissue. In some cases they arise from individual cells (somatic cell embryoge). [NIH]

Empyema: Presence of pus in a hollow organ or body cavity. [NIH]

Emulsions: Colloids of two immiscible liquids where either phase may be either fatty or aqueous; lipid-in-water emulsions are usually liquid, like milk or lotion and water-in-lipid emulsions tend to be creams. [NIH]

Enalapril: An angiotensin-converting enzyme inhibitor that is used to treat hypertension. [NIH]

Enamel: A very hard whitish substance which covers the dentine of the anatomical crown of a tooth. [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]

Endocrine Glands: Ductless glands that secrete substances which are released directly into the circulation and which influence metabolism and other body functions. [NIH]

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

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

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

Endothelium: A layer of epithelium that lines the heart, blood vessels (endothelium, vascular), lymph vessels (endothelium, lymphatic), and the serous cavities of the body. [NIH]

Endothelium-derived: Small molecule that diffuses to the adjacent muscle layer and relaxes it. [NIH]

Endotoxic: Of, relating to, or acting as an endotoxin (= a heat-stable toxin, associated with

the outer membranes of certain gram-negative bacteria. Endotoxins are not secreted and are released only when the cells are disrupted). [EU]

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

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]

Energetic: Exhibiting energy : strenuous; operating with force, vigour, or effect. [EU]

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

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

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

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

Epidemic: Occurring suddenly in numbers clearly in excess of normal expectancy; said especially of infectious diseases but applied also to any disease, injury, or other health-related event occurring in such outbreaks. [EU]

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

Epidermal Growth Factor: A 6 kD polypeptide growth factor initially discovered in mouse submaxillary glands. Human epidermal growth factor was originally isolated from urine based on its ability to inhibit gastric secretion and called urogastrone. epidermal growth factor exerts a wide variety of biological effects including the promotion of proliferation and differentiation of mesenchymal and epithelial cells. [NIH]

Epidermal growth factor receptor: EGFR. The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also known as ErbB1 or HER1. [NIH]

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]

Epigastric: Having to do with the upper middle area of the abdomen. [NIH]

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

Epistasis: The degree of dominance exerted by one gene on the expression of a non-allelic gene. [NIH]

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

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

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

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

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

Erythropoiesis: The production of erythrocytes. [EU]

Essential Tremor: A rhythmic, involuntary, purposeless, oscillating movement resulting from the alternate contraction and relaxation of opposing groups of muscles. [NIH]

Ethanol: A clear, colorless liquid rapidly absorbed from the gastrointestinal tract and distributed throughout the body. It has bactericidal activity and is used often as a topical disinfectant. It is widely used as a solvent and preservative in pharmaceutical preparations as well as serving as the primary ingredient in alcoholic beverages. [NIH]

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

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

Evoke: The electric response recorded from the cerebral cortex after stimulation of a peripheral sense organ. [NIH]

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

Exocrine: Secreting outwardly, via a duct. [EU]

Exocytosis: Cellular release of material within membrane-limited vesicles by fusion of the vesicles with the cell membrane. [NIH]

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

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]

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]

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

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

Fat: Total lipids including phospholipids. [NIH]

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

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

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

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

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

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

Fibula: The bone of the lower leg lateral to and smaller than the tibia. In proportion to its length, it is the most slender of the long bones. [NIH]

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

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

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

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

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]

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

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

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

Gas exchange: Primary function of the lungs; transfer of oxygen from inhaled air into the blood and of carbon dioxide from the blood into the lungs. [NIH]

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

Gastrin: A hormone released after eating. Gastrin causes the stomach to produce more acid. [NIH]

Gastrointestinal: Refers to the stomach and intestines. [NIH]

Gastrointestinal tract: The stomach and intestines. [NIH]

Gels: Colloids with a solid continuous phase and liquid as the dispersed phase; gels may be unstable when, due to temperature or other cause, the solid phase liquifies; the resulting colloid is called a sol. [NIH]

Gene: The functional and physical unit of heredity passed from parent to offspring. Genes

are pieces of DNA, and most genes contain the information for making a specific protein. [NIH]

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

Gene Expression Profiling: The determination of the pattern of genes expressed i.e., transcribed, under specific circumstances or in a specific cell. [NIH]

Gene Library: A large collection of cloned DNA fragments from a given organism, tissue, organ, or cell type. It may contain complete genomic sequences (genomic library) or complementary DNA sequences, the latter being formed from messenger RNA and lacking intron sequences. [NIH]

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

Gene Silencing: Interruption or suppression of the expression of a gene at transcriptional or translational levels. [NIH]

Gene Targeting: The integration of exogenous DNA into the genome of an organism at sites where its expression can be suitably controlled. This integration occurs as a result of homologous recombination. [NIH]

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

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 Markers: A phenotypically recognizable genetic trait which can be used to identify a genetic locus, a linkage group, or a recombination event. [NIH]

Genetic Screening: Searching a population or individuals for persons possessing certain genotypes or karyotypes that: (1) are already associated with disease or predispose to disease; (2) may lead to disease in their descendants; or (3) produce other variations not known to be associated with disease. Genetic screening may be directed toward identifying phenotypic expression of genetic traits. It includes prenatal genetic screening. [NIH]

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

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

Genistein: An isoflavonoid derived from soy products. It inhibits protein-tyrosine kinase and topoisomerase-ii (dna topoisomerase (atp-hydrolysing)) activity and is used as an antineoplastic and antitumor agent. Experimentally, it has been shown to induce G2 phase arrest in human and murine cell lines. [NIH]

Genital: Pertaining to the genitalia. [EU]

Genitourinary: Pertaining to the genital and urinary organs; urogenital; urinosexual. [EU]

Genomic Library: A form of gene library containing the complete DNA sequences present in the genome of a given organism. It contrasts with a cDNA library which contains only sequences utilized in protein coding (lacking introns). [NIH]

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

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

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

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

Gestation: The period of development of the young in viviparous animals, from the time of fertilization of the ovum until birth. [EU]

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

Gliosis: The production of a dense fibrous network of neuroglia; includes astrocytosis, which is a proliferation of astrocytes in the area of a degenerative lesion. [NIH]

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

Glomeruli: Plural of glomerulus. [NIH]

Glomerulosclerosis: Scarring of the glomeruli. It may result from diabetes mellitus (diabetic glomerulosclerosis) or from deposits in parts of the glomerulus (focal segmental glomerulosclerosis). The most common signs of glomerulosclerosis are proteinuria and kidney failure. [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]

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

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

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

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

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]

Graft Rejection: An immune response with both cellular and humoral components, directed against an allogeneic transplant, whose tissue antigens are not compatible with those of the recipient. [NIH]

Graft Survival: The survival of a graft in a host, the factors responsible for the survival and the changes occurring within the graft during growth in the host. [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]

Growth factors: Substances made by the body that function to regulate cell division and cell survival. Some growth factors are also produced in the laboratory and used in biological therapy. [NIH]

Growth Plate: The area between the epiphysis and the diaphysis within which bone growth occurs. [NIH]

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

Guanine Nucleotide Exchange Factors: Protein factors that promote the exchange of GTP for GDP bound to GTP-binding proteins. [NIH]

Guanylate Cyclase: An enzyme that catalyzes the conversion of GTP to 3',5'-cyclic GMP and pyrophosphate. It also acts on ITP and dGTP. (From Enzyme Nomenclature, 1992) EC 4.6.1.2. [NIH]

Habitual: Of the nature of a habit; according to habit; established by or repeated by force of habit, customary. [EU]

Haematoma: A localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the wall of a blood vessel. [EU]

Haematuria: Blood in the urine. [EU]

Haemodialysis: The removal of certain elements from the blood by virtue of the difference in the rates of their diffusion through a semipermeable membrane, e.g., by means of a haemodialyzer. [EU]

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

Half-Life: The time it takes for a substance (drug, radioactive nuclide, or other) to lose half of its pharmacologic, physiologic, or radiologic activity. [NIH]

Haploid: An organism with one basic chromosome set, symbolized by n; the normal condition of gametes in diploids. [NIH]

Haptens: Small antigenic determinants capable of eliciting an immune response only when coupled to a carrier. Haptens bind to antibodies but by themselves cannot elicit an antibody response. [NIH]

Headache: Pain in the cranial region that may occur as an isolated and benign symptom or as a manifestation of a wide variety of conditions including subarachnoid hemorrhage; craniocerebral trauma; central nervous system infections; intracranial hypertension; and

other disorders. In general, recurrent headaches that are not associated with a primary disease process are referred to as headache disorders (e.g., migraine). [NIH]

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

Heart failure: Loss of pumping ability by the heart, often accompanied by fatigue, breathlessness, and excess fluid accumulation in body tissues. [NIH]

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]

Hemodynamics: The movements of the blood and the forces involved in systemic or regional blood circulation. [NIH]

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

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

Hemoglobinuria: The presence of free hemoglobin in the urine. [NIH]

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

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

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

Hepatic: Refers to the liver. [NIH]

Hepatobiliary: Pertaining to the liver and the bile or the biliary ducts. [EU]

Hepatocyte: A liver cell. [NIH]

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

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

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

Hernia: Protrusion of a loop or knuckle of an organ or tissue through an abnormal opening. [NIH]

Heterodimers: Zippered pair of nonidentical proteins. [NIH]

Heteroduplex Analysis: A method of detecting gene mutation by mixing PCR-amplified mutant and wild-type DNA followed by denaturation and reannealing. The resultant products are resolved by gel electrophoresis, with single base substitutions detectable under optimal electrophoretic conditions and gel formulations. Large base pair mismatches may also be analyzed by using electron microscopy to visualize heteroduplex regions. [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]

Homeobox: Distinctive sequence of DNA bases. [NIH]

Homeostasis: The processes whereby the internal environment of an organism tends to remain balanced and stable. [NIH]

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

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

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

Human growth hormone: A protein hormone, secreted by the anterior lobe of the pituitary, which promotes growth of the whole body by stimulating protein synthesis. The human gene has already been cloned and successfully expressed in bacteria. [NIH]

Humoral: Of, relating to, proceeding from, or involving a bodily humour - now often used of endocrine factors as opposed to neural or somatic. [EU]

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

Hydration: Combining with water. [NIH]

Hydrocephalus: Excessive accumulation of cerebrospinal fluid within the cranium which may be associated with dilation of cerebral ventricles, intracranial hypertension; headache; lethargy; urinary incontinence; and ataxia (and in infants macrocephaly). This condition may be caused by obstruction of cerebrospinal fluid pathways due to neurologic abnormalities, intracranial hemorrhages; central nervous system infections; brain neoplasms; craniocerebral trauma; and other conditions. Impaired resorption of cerebrospinal fluid from the arachnoid villi results in a communicating form of hydrocephalus. Hydrocephalus ex-vacuo refers to ventricular dilation that occurs as a result of brain substance loss from cerebral infarction and other conditions. [NIH]

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

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

Hydronephrosis: Abnormal enlargement of a kidney, which may be caused by blockage of the ureter (such as by a kidney stone) or chronic kidney disease that prevents urine from draining into the bladder. [NIH]

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

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]

Hyperplasia: An increase in the number of cells in a tissue or organ, not due to tumor formation. It differs from hypertrophy, which is an increase in bulk without an increase in the number of cells. [NIH]

Hypersecretion: Excessive secretion. [EU]

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

Hypertrophy: General increase in bulk of a part or organ, not due to tumor formation, nor to an increase in the number of cells. [NIH]

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

Ileus: Obstruction of the intestines. [EU]

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

Imidazole: C3H4N2. The ring is present in polybenzimidazoles. [NIH]

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

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

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

Immunochemistry: Field of chemistry that pertains to immunological phenomena and the study of chemical reactions related to antigen stimulation of tissues. It includes physicochemical interactions between antigens and antibodies. [NIH]

Immunodeficiency: The decreased ability of the body to fight infection and disease. [NIH]

Immunodiffusion: Technique involving the diffusion of antigen or antibody through a semisolid medium, usually agar or agarose gel, with the result being a precipitin reaction. [NIH]

Immunoelectrophoresis: A technique that combines protein electrophoresis and double immunodiffusion. In this procedure proteins are first separated by gel electrophoresis (usually agarose), then made visible by immunodiffusion of specific antibodies. A distinct elliptical precipitin arc results for each protein detectable by the antisera. [NIH]

Immunogenic: Producing immunity; evoking an immune response. [EU]

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

Immunology: The study of the body's immune system. [NIH]

Immunophilin: A drug for the treatment of Parkinson's disease. [NIH]

Immunosuppressive: Describes the ability to lower immune system responses. [NIH]

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

Implantation: The insertion or grafting into the body of biological, living, inert, or radioactive material. [EU]

In situ: In the natural or normal place; confined to the site of origin without invasion of neighbouring tissues. [EU]

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

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

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

Incontinence: Inability to control the flow of urine from the bladder (urinary incontinence) or the escape of stool from the rectum (fecal incontinence). [NIH]

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

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

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

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

Inferior vena cava: A large vein that empties into the heart. It carries blood from the legs and feet, and from organs in the abdomen and pelvis. [NIH]

Infertility: The diminished or absent ability to conceive or produce an offspring while sterility is the complete inability to conceive or produce an offspring. [NIH]

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

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

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

Inorganic: Pertaining to substances not of organic origin. [EU]

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

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

Insulin-dependent diabetes mellitus: A disease characterized by high levels of blood

glucose resulting from defects in insulin secretion, insulin action, or both. Autoimmune, genetic, and environmental factors are involved in the development of type I diabetes. [NIH]

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]

Interleukin-2: Chemical mediator produced by activated T lymphocytes and which regulates the proliferation of T cells, as well as playing a role in the regulation of NK cell activity. [NIH]

Intermittent: Occurring at separated intervals; having periods of cessation of activity. [EU]

Internal Medicine: A medical specialty concerned with the diagnosis and treatment of diseases of the internal organ systems of adults. [NIH]

Interphase: The interval between two successive cell divisions during which the chromosomes are not individually distinguishable and DNA replication occurs. [NIH]

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

Intervertebral: Situated between two contiguous vertebrae. [EU]

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

Intestines: The section of the alimentary canal from the stomach to the anus. It includes the large intestine and small intestine. [NIH]

Intracellular: Inside a cell. [NIH]

Intracellular Membranes: Membranes of subcellular structures. [NIH]

Intracranial Aneurysm: A saclike dilatation of the walls of a blood vessel, usually an artery. [NIH]

Intracranial Hemorrhages: Bleeding within the intracranial cavity, including hemorrhages in the brain and within the cranial epidural, subdural, and subarachnoid spaces. [NIH]

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

Intrahepatic: Within the liver. [NIH]

Intrahepatic bile ducts: The bile ducts that pass through and drain bile from the liver. [NIH]

Intraocular: Within the eye. [EU]

Intraocular pressure: Pressure of the fluid inside the eye; normal IOP varies among individuals. [NIH]

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

Introns: Non-coding, intervening sequences of DNA that are transcribed, but are removed from within the primary gene transcript and rapidly degraded during maturation of messenger RNA. Most genes in the nuclei of eukaryotes contain introns, as do mitochondrial and chloroplast genes. [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]

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

Ion Channels: Gated, ion-selective glycoproteins that traverse membranes. The stimulus for channel gating can be a membrane potential, drug, transmitter, cytoplasmic messenger, or a mechanical deformation. Ion channels which are integral parts of ionotropic neurotransmitter receptors are not included. [NIH]

Ion Transport: The movement of ions across energy-transducing cell membranes. Transport can be active or passive. Passive ion transport (facilitated diffusion) derives its energy from the concentration gradient of the ion itself and allows the transport of a single solute in one direction (uniport). Active ion transport is usually coupled to an energy-yielding chemical or photochemical reaction such as ATP hydrolysis. This form of primary active transport is called an ion pump. Secondary active transport utilizes the voltage and ion gradients produced by the primary transport to drive the cotransport of other ions or molecules. These may be transported in the same (symport) or opposite (antiport) direction. [NIH]

Ionization: 1. Any process by which a neutral atom gains or loses electrons, thus acquiring a net charge, as the dissociation of a substance in solution into ions or ion production by the passage of radioactive particles. 2. Iontophoresis. [EU]

Ionizing: Radiation comprising charged particles, e. g. electrons, protons, alpha-particles, etc., having sufficient kinetic energy to produce ionization by collision. [NIH]

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

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

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

Kallikrein-Kinin System: A system produced in the distal nephron of the kidney. Its components are kallikrein, kinins, kininase I and II, and enkephalinase. It is involved in mediation and modulation of the renin-angiotensin-aldosterone system, prostaglandins, vasopressins, and in the regulation of sodium-water balance, renal hemodynamics, and particularly blood pressure. The system participates in the control of renal functions and the physiopathology of renal diseases. [NIH]

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

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

Keratinocyte growth factor: A substance that stimulates the growth of epithelial cells that line the surface of the mouth and intestinal tract. [NIH]

Keto: It consists of 8 carbon atoms and within the endotoxins, it connects poysaccharide and lipid A. [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 Medulla: The internal portion of the kidney, consisting of striated conical masses, the renal pyramids, whose bases are adjacent to the cortex and whose apices form prominent papillae projecting into the lumen of the minor calyces. [NIH]

Kidney stone: A stone that develops from crystals that form in urine and build up on the inner surfaces of the kidney, in the renal pelvis, or in the ureters. [NIH]

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

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

Kinesin: A microtubule-associated mechanical adenosine triphosphatase, that uses the energy of ATP hydrolysis to move organelles along microtubules toward the plus end of the microtubule. The protein is found in squid axoplasm, optic lobes, and in bovine brain. Bovine kinesin is a heterotetramer composed of two heavy (120 kDa) and two light (62 kDa) chains. EC 3.6.1.-. [NIH]

Kinetic: Pertaining to or producing motion. [EU]

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

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]

Laterality: Behavioral manifestations of cerebral dominance in which there is preferential use and superior functioning of either the left or the right side, as in the preferred use of the right hand or right foot. [NIH]

Laxative: An agent that acts to promote evacuation of the bowel; a cathartic or purgative. [EU]

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]

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

Lethal: Deadly, fatal. [EU]

Lethargy: Abnormal drowsiness or stupor; a condition of indifference. [EU]

Leucine: An essential branched-chain amino acid important for hemoglobin formation. [NIH]

Leucocyte: All the white cells of the blood and their precursors (myeloid cell series, lymphoid cell series) but commonly used to indicate granulocytes exclusive of lymphocytes. [NIH]

Leukemia: Cancer of blood-forming tissue. [NIH]

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

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

Ligases: A class of enzymes that catalyze the formation of a bond between two substrate molecules, coupled with the hydrolysis of a pyrophosphate bond in ATP or a similar energy donor. (Dorland, 28th ed) EC 6. [NIH]

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

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

Lip: Either of the two fleshy, full-blooded margins of the mouth. [NIH]

Lipid: Fat. [NIH]

Lipid A: Lipid A is the biologically active component of lipopolysaccharides. It shows strong endotoxic activity and exhibits immunogenic properties. [NIH]

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

Lipopolysaccharides: Substance consisting of polysaccaride and lipid. [NIH]

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

Lipoprotein(a): A family of lipoprotein particles varying in density and size depending on the protein-lipid ratio and the protein composition. These particles consist of apolipoprotein B-100 covalently linked to apolipoprotein-a by one or two disulfide bonds. There is a correlation between high plasma levels of this lipoprotein and increased risk for atherosclerotic cardiovascular disease. [NIH]

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

Liver Transplantation: The transference of a part of or an entire liver from one human or animal to another. [NIH]

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

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

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

Locomotion: Movement or the ability to move from one place or another. It can refer to humans, vertebrate or invertebrate animals, and microorganisms. [NIH]

Loop: A wire usually of platinum bent at one end into a small loop (usually 4 mm inside diameter) and used in transferring microorganisms. [NIH]

Lovastatin: A fungal metabolite isolated from cultures of Aspergillus terreus. The compound is a potent anticholesteremic agent. It inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase (hydroxymethylglutaryl CoA reductases), which is the rate-limiting enzyme in cholesterol biosynthesis. It also stimulates the production of low-density lipoprotein receptors in the liver. [NIH]

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

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]

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

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

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

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

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

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

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

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

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

Magnetic Resonance Angiography: Non-invasive method of vascular imaging and determination of internal anatomy without injection of contrast media or radiation exposure. The technique is used especially in cerebral angiography as well as for studies of other vascular structures. [NIH]

Magnetic Resonance Imaging: Non-invasive method of demonstrating internal anatomy based on the principle that atomic nuclei in a strong magnetic field absorb pulses of radiofrequency energy and emit them as radiowaves which can be reconstructed into computerized images. The concept includes proton spin tomographic techniques. [NIH]

Malabsorption: Impaired intestinal absorption of nutrients. [EU]

Malformation: A morphologic defect resulting from an intrinsically abnormal

developmental process. [EU]

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

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

Mammography: Radiographic examination of the breast. [NIH]

Maxillary: Pertaining to the maxilla : the irregularly shaped bone that with its fellow forms the upper jaw. [EU]

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

Mediate: Indirect; accomplished by the aid of an intervening medium. [EU]

Mediator: An object or substance by which something is mediated, such as (1) a structure of the nervous system that transmits impulses eliciting a specific response; (2) a chemical substance (transmitter substance) that induces activity in an excitable tissue, such as nerve or muscle; or (3) a substance released from cells as the result of the interaction of antigen with antibody or by the action of antigen with a sensitized lymphocyte. [EU]

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

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

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

Medullary: Pertaining to the marrow or to any medulla; resembling marrow. [EU]

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

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

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

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

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

Membrane Fusion: The adherence of cell membranes, intracellular membranes, or artifical membrane models of either to each other or to viruses, parasites, or interstitial particles through a variety of chemical and physical processes. [NIH]

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

Membrane Microdomains: Detergent-insoluble cell membrane components. They are enriched in sphingolipids and cholesterol and clustered with glycosyl-phosphatidylinositol (GPI)-anchored proteins. [NIH]

Membrane Proteins: Proteins which are found in membranes including cellular and

intracellular membranes. They consist of two types, peripheral and integral proteins. They include most membrane-associated enzymes, antigenic proteins, transport proteins, and drug, hormone, and lectin receptors. [NIH]

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

Meningeal: Refers to the meninges, the tissue covering the brain and spinal cord. [NIH]

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

Menstruation: The normal physiologic discharge through the vagina of blood and mucosal tissues from the nonpregnant uterus. [NIH]

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

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

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

Mentors: Senior professionals who provide guidance, direction and support to those persons desirous of improvement in academic positions, administrative positions or other career development situations. [NIH]

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

Mesoderm: The middle germ layer of the embryo. [NIH]

Mesonephros: The excretory organ of the embryo, collective Wolffian tubules, which forms the urogenital fold from which the reproductive organs develop. The mesonephros is the permanent kidney in fish and amphibians, but atrophies in reptiles, birds, and mammals. [NIH]

Meta-Analysis: A quantitative method of combining the results of independent studies (usually drawn from the published literature) and synthesizing summaries and conclusions which may be used to evaluate therapeutic effectiveness, plan new studies, etc., with application chiefly in the areas of research and medicine. [NIH]

Metabolic acidosis: (met-ah-BOL-ik as-id-O-sis): A condition in which the blood is too acidic. It may be caused by severe illness or sepsis (bacteria in the bloodstream). [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]

Metolazone: A potent, long acting diuretic useful in chronic renal disease. It also tends to lower blood pressure and increase potassium loss. [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]

Microfilaments: The smallest of the cytoskeletal filaments. They are composed chiefly of actin. [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]

Microtubules: Slender, cylindrical filaments found in the cytoskeleton of plant and animal cells. They are composed of the protein tubulin. [NIH]

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

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

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

Mitochondrial Swelling: Increase in volume of mitochondria due to an influx of fluid; it occurs in hypotonic solutions due to osmotic pressure and in isotonic solutions as a result of altered permeability of the membranes of respiring mitochondria. [NIH]

Mitosis: A method of indirect cell division by means of which the two daughter nuclei normally receive identical complements of the number of chromosomes of the somatic cells of the species. [NIH]

Mitotic: Cell resulting from mitosis. [NIH]

Mitotic inhibitors: Drugs that kill cancer cells by interfering with cell division (mitostis). [NIH]

Mitotic Spindle Apparatus: An organelle consisting of three components: (1) the astral microtubules, which form around each centrosome and extend to the periphery; (2) the polar microtubules which extend from one spindle pole to the equator; and (3) the kinetochore microtubules, which connect the centromeres of the various chromosomes to either centrosome. [NIH]

Mobilization: The process of making a fixed part or stored substance mobile, as by separating a part from surrounding structures to make it accessible for an operative procedure or by causing release into the circulation for body use of a substance stored in the body. [EU]

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

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

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

Molecular Structure: The location of the atoms, groups or ions relative to one another in a molecule, as well as the number, type and location of covalent bonds. [NIH]

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

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

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

Monocyte: A type of white blood cell. [NIH]

Monocyte Chemoattractant Protein-1: A chemokine that is a chemoattractant for human monocytes and may also cause cellular activation of specific functions related to host

defense. It is produced by leukocytes of both monocyte and lymphocyte lineage and by fibroblasts during tissue injury. [NIH]

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

Morphogenesis: The development of the form of an organ, part of the body, or organism. [NIH]

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

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

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

Motility: The ability to move spontaneously. [EU]

Motor Activity: The physical activity of an organism as a behavioral phenomenon. [NIH]

Mucinous: Containing or resembling mucin, the main compound in mucus. [NIH]

Mucins: A secretion containing mucopolysaccharides and protein that is the chief constituent of mucus. [NIH]

Mucociliary: Pertaining to or affecting the mucus membrane and hairs (including eyelashes, nose hair, .): mucociliary clearing: the clearance of mucus by ciliary movement (particularly in the respiratory system). [EU]

Mucus: The viscous secretion of mucous membranes. It contains mucin, white blood cells, water, inorganic salts, and exfoliated cells. [NIH]

Multicenter Studies: Controlled studies which are planned and carried out by several cooperating institutions to assess certain variables and outcomes in specific patient populations, for example, a multicenter study of congenital anomalies in children. [NIH]

Multicenter study: A clinical trial that is carried out at more than one medical institution. [NIH]

Muscle Fibers: Large single cells, either cylindrical or prismatic in shape, that form the basic unit of muscle tissue. They consist of a soft contractile substance enclosed in a tubular sheath. [NIH]

Muscular Atrophy: Derangement in size and number of muscle fibers occurring with aging, reduction in blood supply, or following immobilization, prolonged weightlessness, malnutrition, and particularly in denervation. [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]

Myosin: Chief protein in muscle and the main constituent of the thick filaments of muscle fibers. In conjunction with actin, it is responsible for the contraction and relaxation of muscles. [NIH]

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

Natriuresis: The excretion of abnormal amounts of sodium in the urine. [EU]

Natural selection: A part of the evolutionary process resulting in the survival and

reproduction of the best adapted individuals. [NIH]

Nausea: An unpleasant sensation in the stomach usually accompanied by the urge to vomit. Common causes are early pregnancy, sea and motion sickness, emotional stress, intense pain, food poisoning, and various enteroviruses. [NIH]

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

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

Neoplasia: Abnormal and uncontrolled cell growth. [NIH]

Nephrectomy: Surgery to remove a kidney. Radical nephrectomy removes the kidney, the adrenal gland, nearby lymph nodes, and other surrounding tissue. Simple nephrectomy removes only the kidney. Partial nephrectomy removes the tumor but not the entire kidney. [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]

Nephrology: A subspecialty of internal medicine concerned with the anatomy, physiology, and pathology of the kidney. [NIH]

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]

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

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

Neurologic: Having to do with nerves or the nervous system. [NIH]

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

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

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

Neuroretinitis: Inflammation of the optic nerve head and adjacent retina. [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]

Neutrons: Electrically neutral elementary particles found in all atomic nuclei except light hydrogen; the mass is equal to that of the proton and electron combined and they are

unstable when isolated from the nucleus, undergoing beta decay. Slow, thermal, epithermal, and fast neutrons refer to the energy levels with which the neutrons are ejected from heavier nuclei during their decay. [NIH]

Night Blindness: Anomaly of vision in which there is a pronounced inadequacy or complete absence of dark-adaptation. [NIH]

Nitric Oxide: A free radical gas produced endogenously by a variety of mammalian cells. It is synthesized from arginine by a complex reaction, catalyzed by nitric oxide synthase. Nitric oxide is endothelium-derived relaxing factor. It is released by the vascular endothelium and mediates the relaxation induced by some vasodilators such as acetylcholine and bradykinin. It also inhibits platelet aggregation, induces disaggregation of aggregated platelets, and inhibits platelet adhesion to the vascular endothelium. Nitric oxide activates cytosolic guanylate cyclase and thus elevates intracellular levels of cyclic GMP. [NIH]

Normotensive: 1. Characterized by normal tone, tension, or pressure, as by normal blood pressure. 2. A person with normal blood pressure. [EU]

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]

Nucleates: Bacteria-inducing ice nucleation at warm temperatures (between zero and minus ten degrees C.). [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]

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

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

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

Oocytes: Female germ cells in stages between the prophase of the first maturation division and the completion of the second maturation division. [NIH]

Operon: The genetic unit consisting of a feedback system under the control of an operator gene, in which a structural gene transcribes its message in the form of mRNA upon blockade

of a repressor produced by a regulator gene. Included here is the attenuator site of bacterial operons where transcription termination is regulated. [NIH]

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]

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

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

Organogenesis: Clonal propagation which involves culturing explants from roots, leaves, or stems to form undifferentiated callus tissue; after the cells form shoots, they are separated and rooted. Alternatively, if the callus is put in liquid culture, somatic embryos form. [NIH]

Osmolarity: The concentration of osmotically active particles expressed in terms of osmoles of solute per litre of solution. [EU]

Osmoles: The standard unit of osmotic pressure. [NIH]

Osmosis: Tendency of fluids (e.g., water) to move from the less concentrated to the more concentrated side of a semipermeable membrane. [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]

Ovarian Cysts: General term for cysts and cystic diseases of the ovary. [NIH]

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

Ovary: Either of the paired glands in the female that produce the female germ cells and secrete some of the female sex hormones. [NIH]

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

Ovum: A female germ cell extruded from the ovary at ovulation. [NIH]

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

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

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

1991, pxv-xvi). [NIH]

Paclitaxel: Antineoplastic agent isolated from the bark of the Pacific yew tree, Taxus brevifolia. Paclitaxel stabilizes microtubules in their polymerized form and thus mimics the action of the proto-oncogene proteins c-mos. [NIH]

Palate: The structure that forms the roof of the mouth. It consists of the anterior hard palate and the posterior soft palate. [NIH]

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

Palliative therapy: Treatment given to relieve symptoms caused by advanced cancer. Palliative therapy does not alter the course of a disease but improves the quality of life. [NIH]

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

Pancreatic: Having to do with the pancreas. [NIH]

Pancreatic cancer: Cancer of the pancreas, a salivary gland of the abdomen. [NIH]

Pancreatitis: Acute or chronic inflammation of the pancreas, which may be asymptomatic or symptomatic, and which is due to autodigestion of a pancreatic tissue by its own enzymes. It is caused most often by alcoholism or biliary tract disease; less commonly it may be associated with hyperlipaemia, hyperparathyroidism, abdominal trauma (accidental or operative injury), vasculitis, or uraemia. [EU]

Papilla: A small nipple-shaped elevation. [NIH]

Papillary: Pertaining to or resembling papilla, or nipple. [EU]

Parathyroid: 1. Situated beside the thyroid gland. 2. One of the parathyroid glands. 3. A sterile preparation of the water-soluble principle(s) of the parathyroid glands, ad-ministered parenterally as an antihypocalcaemic, especially in the treatment of acute hypoparathyroidism with tetany. [EU]

Parathyroid Glands: Two small paired endocrine glands in the region of the thyroid gland. They secrete parathyroid hormone and are concerned with the metabolism of calcium and phosphorus. [NIH]

Parathyroid hormone: A substance made by the parathyroid gland that helps the body store and use calcium. Also called parathormone, parathyrin, or PTH. [NIH]

Parathyroidectomy: Excision of one or both of the parathyroid glands. [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]

Paroxysmal: Recurring in paroxysms (= spasms or seizures). [EU]

Particle: A tiny mass of material. [EU]

Patch: A piece of material used to cover or protect a wound, an injured part, etc.: a patch over the eye. [NIH]

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

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

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

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]

Pelvic: Pertaining to the pelvis. [EU]

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

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

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]

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

Peritoneal: Having to do with the peritoneum (the tissue that lines the abdominal wall and covers most of the organs in the abdomen). [NIH]

Peritoneal Cavity: The space enclosed by the peritoneum. It is divided into two portions, the greater sac and the lesser sac or omental bursa, which lies behind the stomach. The two sacs are connected by the foramen of Winslow, or epiploic foramen. [NIH]

Peritoneal Dialysis: Dialysis fluid being introduced into and removed from the peritoneal cavity as either a continuous or an intermittent procedure. [NIH]

Peritoneum: Endothelial lining of the abdominal cavity, the parietal peritoneum covering the inside of the abdominal wall and the visceral peritoneum covering the bowel, the mesentery, and certain of the organs. The portion that covers the bowel becomes the serosal layer of the bowel wall. [NIH]

Pharmacologic: Pertaining to pharmacology or to the properties and reactions of drugs. [EU]

Phenotype: The outward appearance of the individual. It is the product of interactions between genes and between the genotype and the environment. This includes the killer phenotype, characteristic of yeasts. [NIH]

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

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

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

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

Phosphorylate: Attached to a phosphate group. [NIH]

Phosphorylated: Attached to a phosphate group. [NIH]

Phosphorylation: The introduction of a phosphoryl group into a compound through the formation of an ester bond between the compound and a phosphorus moiety. [NIH]

Photobiology: The branch of biology dealing with the effect of light on organisms. [NIH]

Photoreceptor: Receptor capable of being activated by light stimuli, as a rod or cone cell of the eye. [NIH]

Phylogeny: The relationships of groups of organisms as reflected by their evolutionary history. [NIH]

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

Physicochemical: Pertaining to physics and chemistry. [EU]

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

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

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

Pilot Projects: Small-scale tests of methods and procedures to be used on a larger scale if the pilot study demonstrates that these methods and procedures can work. [NIH]

Pilot study: The initial study examining a new method or treatment. [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]

Plastids: Self-replicating cytoplasmic organelles of plant and algal cells that contain pigments and may synthesize and accumulate various substances. Plastids are used in phylogenetic studies. [NIH]

Platelet Activation: A series of progressive, overlapping events triggered by exposure of the platelets to subendothelial tissue. These events include shape change, adhesiveness, aggregation, and release reactions. When carried through to completion, these events lead to the formation of a stable hemostatic plug. [NIH]

Platelet Aggregation: The attachment of platelets to one another. This clumping together can be induced by a number of agents (e.g., thrombin, collagen) and is part of the mechanism leading to the formation of a thrombus. [NIH]

Platelets: A type of blood cell that helps prevent bleeding by causing blood clots to form. Also called thrombocytes. [NIH]

Pneumonia: Inflammation of the lungs. [NIH]

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]

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

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]

Popliteal: Compression of the nerve at the neck of the fibula. [NIH]

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

Postnatal: Occurring after birth, with reference to the newborn. [EU]

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

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

Potassium: An element that is in the alkali group of metals. It has an atomic symbol K, atomic number 19, and atomic weight 39.10. It is the chief cation in the intracellular fluid of muscle and other cells. Potassium ion is a strong electrolyte and it plays a significant role in the regulation of fluid volume and maintenance of the water-electrolyte balance. [NIH]

Potentiates: A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [NIH]

Potentiating: A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [NIH]

Potentiation: An overall effect of two drugs taken together which is greater than the sum of the effects of each drug taken alone. [NIH]

Practice Guidelines: Directions or principles presenting current or future rules of policy for the health care practitioner to assist him in patient care decisions regarding diagnosis, therapy, or related clinical circumstances. The guidelines may be developed by government agencies at any level, institutions, professional societies, governing boards, or by the convening of expert panels. The guidelines form a basis for the evaluation of all aspects of health care and delivery. [NIH]

Precursor: Something that precedes. In biological processes, a substance from which another, usually more active or mature substance is formed. In clinical medicine, a sign or symptom that heralds another. [EU]

Preeclampsia: A toxaemia of late pregnancy characterized by hypertension, edema, and proteinuria, when convulsions and coma are associated, it is called eclampsia. [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]

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

Primary endpoint: The main result that is measured at the end of a study to see if a given treatment worked (e.g., the number of deaths or the difference in survival between the treatment group and the control group). What the primary endpoint will be is decided before the study begins. [NIH]

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

Progression: Increase in the size of a tumor or spread of cancer in the body. [NIH]

Progressive: Advancing; going forward; going from bad to worse; increasing in scope or severity. [EU]

Progressive disease: Cancer that is increasing in scope or severity. [NIH]

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

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

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

Pronephros: The primordial kidney; an excretory structure or its rudiments developing in the embryo before the mesonephros. [NIH]

Prophase: The first phase of cell division, in which the chromosomes become visible, the nucleus starts to lose its identity, the spindle appears, and the centrioles migrate toward opposite poles. [NIH]

Prostaglandin: Any of a group of components derived from unsaturated 20-carbon fatty acids, primarily arachidonic acid, via the cyclooxygenase pathway that are extremely potent mediators of a diverse group of physiologic processes. The abbreviation for prostaglandin is PG; specific compounds are designated by adding one of the letters A through I to indicate the type of substituents found on the hydrocarbon skeleton and a subscript (1, 2 or 3) to indicate the number of double bonds in the hydrocarbon skeleton e.g., PGE2. The predominant naturally occurring prostaglandins all have two double bonds and are synthesized from arachidonic acid (5,8,11,14-eicosatetraenoic acid) by the pathway shown in the illustration. The 1 series and 3 series are produced by the same pathway with fatty acids having one fewer double bond (8,11,14-eicosatrienoic acid or one more double bond (5,8,11,14,17-eicosapentaenoic acid) than arachidonic acid. The subscript a or ß indicates the configuration at C-9 (a denotes a substituent below the plane of the ring, ß, above the plane). The naturally occurring PGF's have the a configuration, e.g., PGF2a. All of the prostaglandins act by binding to specific cell-surface receptors causing an increase in the level of the intracellular second messenger cyclic AMP (and in some cases cyclic GMP also). The effect produced by the cyclic AMP increase depends on the specific cell type. In some cases there is also a positive feedback effect. Increased cyclic AMP increases prostaglandin synthesis leading to further increases in cyclic AMP. [EU]

Prostaglandins A: (13E,15S)-15-Hydroxy-9-oxoprosta-10,13-dien-1-oic acid (PGA(1)); (5Z,13E,15S)-15-hydroxy-9-oxoprosta-5,10,13-trien-1-oic acid (PGA(2)); (5Z,13E,15S,17Z)-15-hydroxy-9-oxoprosta-5,10,13,17-tetraen-1-oic acid (PGA(3)). A group of naturally occurring secondary prostaglandins derived from PGE. PGA(1) and PGA(2) as well as their 19-hydroxy derivatives are found in many organs and tissues. [NIH]

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

Protein Binding: The process in which substances, either endogenous or exogenous, bind to proteins, peptides, enzymes, protein precursors, or allied compounds. Specific protein-binding measures are often used as assays in diagnostic assessments. [NIH]

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

Protein 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]

Protein Transport: The process of moving proteins from one cellular compartment (including extracellular) to another by various sorting and transport mechanisms such as gated transport, protein translocation, and vesicular transport. [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]

Protein-Tyrosine Kinase: An enzyme that catalyzes the phosphorylation of tyrosine residues in proteins with ATP or other nucleotides as phosphate donors. EC 2.7.1.112. [NIH]

Proteinuria: The presence of protein in the urine, indicating that the kidneys are not working properly. [NIH]

Proteoglycans: Glycoproteins which have a very high polysaccharide content. [NIH]

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

Proteome: The protein complement of an organism coded for by its genome. [NIH]

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

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

Proto-Oncogene Proteins: Products of proto-oncogenes. Normally they do not have oncogenic or transforming properties, but are involved in the regulation or differentiation of cell growth. They often have protein kinase activity. [NIH]

Proto-Oncogene Proteins c-mos: Cellular proteins encoded by the c-mos genes. They function in the cell cycle to maintain maturation promoting factor in the active state and have protein-serine/threonine kinase activity. Oncogenic transformation can take place when c-mos proteins are expressed at the wrong time. [NIH]

Protozoa: A subkingdom consisting of unicellular organisms that are the simplest in the animal kingdom. Most are free living. They range in size from submicroscopic to macroscopic. Protozoa are divided into seven phyla: Sarcomastigophora, Labyrinthomorpha, Apicomplexa, Microspora, Ascetospora, Myxozoa, and Ciliophora. [NIH]

Proximal: Nearest; closer to any point of reference; opposed to distal. [EU]

Pseudogenes: Genes bearing close resemblance to known genes at different loci, but rendered non-functional by additions or deletions in structure that prevent normal transcription or translation. When lacking introns and containing a poly-A segment near the downstream end (as a result of reverse copying from processed nuclear RNA into double-stranded DNA), they are called processed genes. [NIH]

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

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

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

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

Pulmonary: Relating to the lungs. [NIH]

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

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

Pulse: The rhythmical expansion and contraction of an artery produced by waves of pressure caused by the ejection of blood from the left ventricle of the heart as it contracts. [NIH]

Purines: A series of heterocyclic compounds that are variously substituted in nature and are known also as purine bases. They include adenine and guanine, constituents of nucleic acids, as well as many alkaloids such as caffeine and theophylline. Uric acid is the metabolic end product of purine metabolism. [NIH]

Pyelonephritis: Inflammation of the kidney and its pelvis, beginning in the interstitium and rapidly extending to involve the tubules, glomeruli, and blood vessels; due to bacterial infection. [EU]

Pyrimidines: A family of 6-membered heterocyclic compounds occurring in nature in a wide variety of forms. They include several nucleic acid constituents (cytosine, thymine, and uracil) and form the basic structure of the barbiturates. [NIH]

Quality of Life: A generic concept reflecting concern with the modification and enhancement of life attributes, e.g., physical, political, moral and social environment. [NIH]

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

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

Radiation therapy: The use of high-energy radiation from x-rays, gamma rays, neutrons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a

machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body in the area near cancer cells (internal radiation therapy, implant radiation, or brachytherapy). Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. Also called radiotherapy. [NIH]

Radioactive: Giving off radiation. [NIH]

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

Radiological: Pertaining to radiodiagnostic and radiotherapeutic procedures, and interventional radiology or other planning and guiding medical radiology. [NIH]

Radiology: A specialty concerned with the use of x-ray and other forms of radiant energy in the diagnosis and treatment of disease. [NIH]

Randomized: Describes an experiment or clinical trial in which animal or human subjects are assigned by chance to separate groups that compare different treatments. [NIH]

Randomized clinical trial: A study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best. It is the patient's choice to be in a randomized trial. [NIH]

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]

Red Nucleus: A pinkish-yellow portion of the midbrain situated in the rostral mesencephalic tegmentum. It receives a large projection from the contralateral half of the cerebellum via the superior cerebellar peduncle and a projection from the ipsilateral motor cortex. [NIH]

Reductase: Enzyme converting testosterone to dihydrotestosterone. [NIH]

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

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

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

Renal agenesis: The absence or severe malformation of one or both kidneys. [NIH]

Renal Artery: A branch of the abdominal aorta which supplies the kidneys, adrenal glands and ureters. [NIH]

Renal cell carcinoma: A type of kidney cancer. [NIH]

Renal cysts: Abnormal fluid-filled sacs in the kidney that range in size from microscopic to much larger. Many simple cysts are harmless, while other types can seriously damage the kidneys. [NIH]

Renal failure: Progressive renal insufficiency and uremia, due to irreversible and progressive renal glomerular tubular or interstitial disease. [NIH]

Renal pelvis: The area at the center of the kidney. Urine collects here and is funneled into the ureter, the tube that connects the kidney to the bladder. [NIH]

Renal tubular: A defect in the kidneys that hinders their normal excretion of acids. Failure to excrete acids can lead to weak bones, kidney stones, and poor growth in children. [NIH]

Renal tubular acidosis: A rare disorder in which structures in the kidney that filter the blood are impaired, producing using that is more acid than normal. [NIH]

Renin: An enzyme which is secreted by the kidney and is formed from prorenin in plasma and kidney. The enzyme cleaves the Leu-Leu bond in angiotensinogen to generate angiotensin I. EC 3.4.23.15. (Formerly EC 3.4.99.19). [NIH]

Renin-Angiotensin System: A system consisting of renin, angiotensin-converting enzyme, and angiotensin II. Renin, an enzyme produced in the kidney, acts on angiotensinogen, an alpha-2 globulin produced by the liver, forming angiotensin I. The converting enzyme contained in the lung acts on angiotensin I in the plasma converting it to angiotensin II, the most powerful directly pressor substance known. It causes contraction of the arteriolar smooth muscle and has other indirect actions mediated through the adrenal cortex. [NIH]

Repressor: Any of the specific allosteric protein molecules, products of regulator genes, which bind to the operator of operons and prevent RNA polymerase from proceeding into the operon to transcribe messenger RNA. [NIH]

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

Resorption: The loss of substance through physiologic or pathologic means, such as loss of dentin and cementum of a tooth, or of the alveolar process of the mandible or maxilla. [EU]

Respiration: The act of breathing with the lungs, consisting of inspiration, or the taking into the lungs of the ambient air, and of expiration, or the expelling of the modified air which contains more carbon dioxide than the air taken in (Blakiston's Gould Medical Dictionary, 4th ed.). This does not include tissue respiration (= oxygen consumption) or cell respiration (= cell respiration). [NIH]

Respiratory Physiology: Functions and activities of the respiratory tract as a whole or of any of its parts. [NIH]

Respiratory System: The tubular and cavernous organs and structures, by means of which pulmonary ventilation and gas exchange between ambient air and the blood are brought about. [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]

Retinitis: Inflammation of the retina. It is rarely limited to the retina, but is commonly

associated with diseases of the choroid (chorioretinitis) and of the optic nerve (neuroretinitis). The disease may be confined to one eye, but since it is generally dependent on a constitutional factor, it is almost always bilateral. It may be acute in course, but as a rule it lasts many weeks or even several months. [NIH]

Retinitis Pigmentosa: Hereditary, progressive degeneration of the neuroepithelium of the retina characterized by night blindness and progressive contraction of the visual field. [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]

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]

Rheumatology: A subspecialty of internal medicine concerned with the study of inflammatory or degenerative processes and metabolic derangement of connective tissue structures which pertain to a variety of musculoskeletal disorders, such as arthritis. [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]

Rickettsiae: One of a group of obligate intracellular parasitic microorganisms, once regarded as intermediate in their properties between bacteria and viruses but now classified as bacteria in the order Rickettsiales, which includes 17 genera and 3 families: Rickettsiace. [NIH]

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

Risk patient: Patient who is at risk, because of his/her behaviour or because of the type of person he/she is. [EU]

Rod: A reception for vision, located in the retina. [NIH]

Rod cells: 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]

Ryanodine: Insecticidal alkaloid isolated from Ryania speciosa; proposed as a myocardial depressant. [NIH]

Salivary: The duct that convey saliva to the mouth. [NIH]

Scalpel: A small pointed knife with a convex edge. [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]

Secretion: 1. The process of elaborating a specific product as a result of the activity of a gland; this activity may range from separating a specific substance of the blood to the elaboration of a new chemical substance. 2. Any substance produced by secretion. [EU]

Secretory: Secreting; relating to or influencing secretion or the secretions. [NIH]

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

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

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

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

Seizures: Clinical or subclinical disturbances of cortical function due to a sudden, abnormal, excessive, and disorganized discharge of brain cells. Clinical manifestations include abnormal motor, sensory and psychic phenomena. Recurrent seizures are usually referred to as epilepsy or "seizure disorder." [NIH]

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

Sensor: A device designed to respond to physical stimuli such as temperature, light, magnetism or movement and transmit resulting impulses for interpretation, recording, movement, or operating control. [NIH]

Sepsis: The presence of bacteria in the bloodstream. [NIH]

Septate: An organ or structure that is divided into compartments. [NIH]

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

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

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]

Sex Determination: The biological characteristics which distinguish human beings as female or male. [NIH]

Shunt: A surgically created diversion of fluid (e.g., blood or cerebrospinal fluid) from one area of the body to another area of the body. [NIH]

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

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

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

Simvastatin: A derivative of lovastatin and potent competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (hydroxymethylglutaryl CoA reductases), which is the rate-limiting enzyme in cholesterol biosynthesis. It may also interfere with steroid hormone production. Due to the induction of hepatic LDL receptors, it increases breakdown of LDL-cholesterol (lipoproteins, LDL cholesterol). [NIH]

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

Skeleton: The framework that supports the soft tissues of vertebrate animals and protects many of their internal organs. The skeletons of vertebrates are made of bone and/or cartilage. [NIH]

Skull: The skeleton of the head including the bones of the face and the bones enclosing the brain. [NIH]

Small intestine: The part of the digestive tract that is located between the stomach and the large intestine. [NIH]

Smooth muscle: Muscle that performs automatic tasks, such as constricting blood vessels. [NIH]

Social Work: The use of community resources, individual case work, or group work to promote the adaptive capacities of individuals in relation to their social and economic environments. It includes social service agencies. [NIH]

Sodium: An element that is a member of the alkali group of metals. It has the atomic symbol Na, atomic number 11, and atomic weight 23. With a valence of 1, it has a strong affinity for oxygen and other nonmetallic elements. Sodium provides the chief cation of the extracellular body fluids. Its salts are the most widely used in medicine. (From Dorland, 27th ed) Physiologically the sodium ion plays a major role in blood pressure regulation, maintenance of fluid volume, and electrolyte balance. [NIH]

Soft tissue: Refers to muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body. [NIH]

Solid tumor: Cancer of body tissues other than blood, bone marrow, or the lymphatic system. [NIH]

Solvent: 1. Dissolving; effecting a solution. 2. A liquid that dissolves or that is capable of dissolving; the component of a solution that is present in greater amount. [EU]

Soma: The body as distinct from the mind; all the body tissue except the germ cells; all the axial body. [NIH]

Somatic: 1. Pertaining to or characteristic of the soma or body. 2. Pertaining to the body wall in contrast to the viscera. [EU]

Somatic 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]

Spleen: An organ that is part of the lymphatic system. The spleen produces lymphocytes, filters the blood, stores blood cells, and destroys old blood cells. It is located on the left side of the abdomen near the stomach. [NIH]

Splenectomy: An operation to remove the spleen. [NIH]

Splenomegaly: Enlargement of the spleen. [NIH]

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

Stabilization: The creation of a stable state. [EU]

Steel: A tough, malleable, iron-based alloy containing up to, but no more than, two percent carbon and often other metals. It is used in medicine and dentistry in implants and instrumentation. [NIH]

Stem Cells: Relatively undifferentiated cells of the same lineage (family type) that retain the ability to divide and cycle throughout postnatal life to provide cells that can become specialized and take the place of those that die or are lost. [NIH]

Stenosis: Narrowing or stricture of a duct or canal. [EU]

Sterile: Unable to produce children. [NIH]

Sterility: 1. The inability to produce offspring, i.e., the inability to conceive (female s.) or to induce conception (male s.). 2. The state of being aseptic, or free from microorganisms. [EU]

Steroid: A group name for lipids that contain a hydrogenated

cyclopentanoperhydrophenanthrene ring system. Some of the substances included in this group are progesterone, adrenocortical hormones, the gonadal hormones, cardiac aglycones, bile acids, sterols (such as cholesterol), toad poisons, saponins, and some of the carcinogenic hydrocarbons. [EU]

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

Stimulus: That which can elicit or evoke action (response) in a muscle, nerve, gland or other excitable issue, or cause an augmenting action upon any function or metabolic process. [NIH]

Stomach: An organ of digestion situated in the left upper quadrant of the abdomen between the termination of the esophagus and the beginning of the duodenum. [NIH]

Stool: The waste matter discharged in a bowel movement; feces. [NIH]

Strand: DNA normally exists in the bacterial nucleus in a helix, in which two strands are coiled together. [NIH]

Stress: Forcibly exerted influence; pressure. Any condition or situation that causes strain or tension. Stress may be either physical or psychologic, or both. [NIH]

Striate: Recurrent branch of the anterior cerebral artery which supplies the anterior limb of the internal capsule. [NIH]

Stricture: The abnormal narrowing of a body opening. Also called stenosis. [NIH]

Stroke: Sudden loss of function of part of the brain because of loss of blood flow. Stroke may be caused by a clot (thrombosis) or rupture (hemorrhage) of a blood vessel to the brain. [NIH]

Stroma: The middle, thickest layer of tissue in the cornea. [NIH]

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

Subarachnoid: Situated or occurring between the arachnoid and the pia mater. [EU]

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

Subcutaneous: Beneath the skin. [NIH]

Submaxillary: Four to six lymph glands, located between the lower jaw and the submandibular salivary gland. [NIH]

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

Substance P: An eleven-amino acid neurotransmitter that appears in both the central and peripheral nervous systems. It is involved in transmission of pain, causes rapid contractions of the gastrointestinal smooth muscle, and modulates inflammatory and immune responses. [NIH]

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

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]

Supplementation: Adding nutrients to the diet. [NIH]

Support group: A group of people with similar disease who meet to discuss how better to cope with their cancer and treatment. [NIH]

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]

Sympathectomy: The removal or interruption of some part of the sympathetic nervous system for therapeutic or research purposes. [NIH]

Sympathetic Nervous System: The thoracolumbar division of the autonomic nervous system. Sympathetic preganglionic fibers originate in neurons of the intermediolateral column of the spinal cord and project to the paravertebral and prevertebral ganglia, which in turn project to target organs. The sympathetic nervous system mediates the body's response to stressful situations, i.e., the fight or flight reactions. It often acts reciprocally to the parasympathetic system. [NIH]

Symphysis: A secondary cartilaginous joint. [NIH]

Symptomatic: Having to do with symptoms, which are signs of a condition or disease. [NIH]

Synaptic: Pertaining to or affecting a synapse (= site of functional apposition between neurons, at which an impulse is transmitted from one neuron to another by electrical or chemical means); pertaining to synapsis (= pairing off in point-for-point association of homologous chromosomes from the male and female pronuclei during the early prophase of meiosis). [EU]

Syringomyelia: The presence in the spinal cord of elongated central fluid containing cavities surrounded by gliosis. [NIH]

Systemic: Affecting the entire body. [NIH]

Systemic disease: Disease that affects the whole body. [NIH]

Systolic: Indicating the maximum arterial pressure during contraction of the left ventricle of the heart. [EU]

Taxanes: Anticancer drugs that inhibit cancer cell growth by stopping cell division. Also called antimitotic or antimicrotubule agents or mitotic inhibitors. [NIH]

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

Temporal: One of the two irregular bones forming part of the lateral surfaces and base of the skull, and containing the organs of hearing. [NIH]

Tendon: A discrete band of connective tissue mainly composed of parallel bundles of collagenous fibers by which muscles are attached, or two muscles bellies joined. [NIH]

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

Tetany: 1. Hyperexcitability of nerves and muscles due to decrease in concentration of extracellular ionized calcium, which may be associated with such conditions as parathyroid hypofunction, vitamin D deficiency, and alkalosis or result from ingestion of alkaline salts; it is characterized by carpopedal spasm, muscular twitching and cramps, laryngospasm with inspiratory stridor, hyperreflexia and choreiform movements. 2. Tetanus. [EU]

Thalamic: Cell that reaches the lateral nucleus of amygdala. [NIH]

Thalamic Diseases: Disorders of the centrally located thalamus, which integrates a wide range of cortical and subcortical information. Manifestations include sensory loss, movement disorders; ataxia, pain syndromes, visual disorders, a variety of neuropsychological conditions, and coma. Relatively common etiologies include cerebrovascular disorders; craniocerebral trauma; brain neoplasms; brain hypoxia; intracranial hemorrhages; and infectious processes. [NIH]

Therapeutics: The branch of medicine which is concerned with the treatment of diseases,

palliative or curative. [NIH]

Thermal: Pertaining to or characterized by heat. [EU]

Thoracic: Having to do with the chest. [NIH]

Threonine: An essential amino acid occurring naturally in the L-form, which is the active form. It is found in eggs, milk, gelatin, and other proteins. [NIH]

Threshold: For a specified sensory modality (e. g. light, sound, vibration), the lowest level (absolute threshold) or smallest difference (difference threshold, difference limen) or intensity of the stimulus discernible in prescribed conditions of stimulation. [NIH]

Thrombin: An enzyme formed from prothrombin that converts fibrinogen to fibrin. (Dorland, 27th ed) EC 3.4.21.5. [NIH]

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]

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

Tissue Distribution: Accumulation of a drug or chemical substance in various organs (including those not relevant to its pharmacologic or therapeutic action). This distribution depends on the blood flow or perfusion rate of the organ, the ability of the drug to penetrate organ membranes, tissue specificity, protein binding. The distribution is usually expressed as tissue to plasma ratios. [NIH]

Tomography: Imaging methods that result in sharp images of objects located on a chosen plane and blurred images located above or below the plane. [NIH]

Tone: 1. The normal degree of vigour and tension; in muscle, the resistance to passive elongation or stretch; tonus. 2. A particular quality of sound or of voice. 3. To make permanent, or to change, the colour of silver stain by chemical treatment, usually with a heavy metal. [EU]

Tonometry: The standard to determine the fluid pressure inside the eye (intraocular pressure). [NIH]

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

Toxaemia: 1. The condition resulting from the spread of bacterial products (toxins) by the bloodstream. 2. A condition resulting from metabolic disturbances, e.g. toxaemia of pregnancy. [EU]

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]

Tracer: A substance (such as a radioisotope) used in imaging procedures. [NIH]

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

Traction: The act of pulling. [NIH]

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

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

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

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

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

Translocation: The movement of material in solution inside the body of the plant. [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]

Transport Vesicles: Vesicles that are involved in shuttling cargo from the interior of the cell to the cell surface, from the cell surface to the interior, across the cell or around the cell to various locations. [NIH]

Trauma: Any injury, wound, or shock, must frequently physical or structural shock, producing a disturbance. [NIH]

Triad: Trivalent. [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]

Tuberous Sclerosis: A rare congenital disease in which the essential pathology is the appearance of multiple tumors in the cerebrum and in other organs, such as the heart or kidneys. [NIH]

Tubulin: A microtubule subunit protein found in large quantities in mammalian brain. It

has also been isolated from sperm flagella, cilia, and other sources. Structurally, the protein is a dimer with a molecular weight of approximately 120,000 and a sedimentation coefficient of 5.8S. It binds to colchicine, vincristine, and vinblastine. [NIH]

Tumor marker: A substance sometimes found in an increased amount in the blood, other body fluids, or tissues and which may mean that a certain type of cancer is in the body. Examples of tumor markers include CA 125 (ovarian cancer), CA 15-3 (breast cancer), CEA (ovarian, lung, breast, pancreas, and gastrointestinal tract cancers), and PSA (prostate cancer). Also called biomarker. [NIH]

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

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

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

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

Ultraviolet radiation: Invisible rays that are part of the energy that comes from the sun. UV radiation can damage the skin and cause melanoma and other types of skin cancer. UV radiation that reaches the earth's surface is made up of two types of rays, called UVA and UVB rays. UVB rays are more likely than UVA rays to cause sunburn, but UVA rays pass deeper into the skin. Scientists have long thought that UVB radiation can cause melanoma and other types of skin cancer. They now think that UVA radiation also may add to skin damage that can lead to skin cancer and cause premature aging. For this reason, skin specialists recommend that people use sunscreens that reflect, absorb, or scatter both kinds of UV radiation. [NIH]

Uraemia: 1. An excess in the blood of urea, creatinine, and other nitrogenous end products of protein and amino acids metabolism; more correctly referred to as azotemia. 2. In current usage the entire constellation of signs and symptoms of chronic renal failure, including nausea, vomiting anorexia, a metallic taste in the mouth, a uraemic odour of the breath, pruritus, uraemic frost on the skin, neuromuscular disorders, pain and twitching in the muscles, hypertension, edema, mental confusion, and acid-base and electrolyte imbalances. [EU]

Urea: A compound (CO(NH2)2), formed in the liver from ammonia produced by the deamination of amino acids. It is the principal end product of protein catabolism and constitutes about one half of the total urinary solids. [NIH]

Uremia: The illness associated with the buildup of urea in the blood because the kidneys are not working effectively. Symptoms include nausea, vomiting, loss of appetite, weakness, and mental confusion. [NIH]

Ureters: Tubes that carry urine from the kidneys to the bladder. [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]

Urinary tract: The organs of the body that produce and discharge urine. These include the kidneys, ureters, bladder, and urethra. [NIH]

Urinary tract infection: An illness caused by harmful bacteria growing in the urinary tract. [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]

Urogenital: Pertaining to the urinary and genital apparatus; genitourinary. [EU]

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]

Vagina: The muscular canal extending from the uterus to the exterior of the body. Also called the birth canal. [NIH]

Vaginal: Of or having to do with the vagina, the birth canal. [NIH]

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

Vasculitis: Inflammation of a blood vessel. [NIH]

Vasodilation: Physiological dilation of the blood vessels without anatomic change. For dilation with anatomic change, dilatation, pathologic or aneurysm (or specific aneurysm) is used. [NIH]

Vasodilators: Any nerve or agent which induces dilatation of the blood vessels. [NIH]

Vasopressins: Octapeptide antidiuretic hormones released by the neurohypophysis of all vertebrates (chemical composition varies with species). They control water metabolism and balance by regulating lung, gill, kidney, etc., and water loss, and also contract smooth muscle. They may also be neurotransmitters. Also included are synthetic vasopressin derivatives. Vasopressins are used pharmacologically as renal agents, vasoconstrictor agents, and hemostatics. [NIH]

Vector: Plasmid or other self-replicating DNA molecule that transfers DNA between cells in nature or in recombinant DNA technology. [NIH]

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

Vena: A vessel conducting blood from the capillary bed to the heart. [NIH]

Venous: Of or pertaining to the veins. [EU]

Venter: Belly. [NIH]

Ventilation: 1. In respiratory physiology, the process of exchange of air between the lungs and the ambient air. Pulmonary ventilation (usually measured in litres per minute) refers to the total exchange, whereas alveolar ventilation refers to the effective ventilation of the alveoli, in which gas exchange with the blood takes place. 2. In psychiatry, verbalization of one's emotional problems. [EU]

Ventral: 1. Pertaining to the belly or to any venter. 2. Denoting a position more toward the belly surface than some other object of reference; same as anterior in human anatomy. [EU]

Ventricle: One of the two pumping chambers of the heart. The right ventricle receives oxygen-poor blood from the right atrium and pumps it to the lungs through the pulmonary artery. The left ventricle receives oxygen-rich blood from the left atrium and pumps it to the body through the aorta. [NIH]

Ventricular: Pertaining to a ventricle. [EU]

Ventricular Function: The hemodynamic and electrophysiological action of the ventricles. [NIH]

Venules: The minute vessels that collect blood from the capillary plexuses and join together

to form veins. [NIH]

Vertebrae: A bony unit of the segmented spinal column. [NIH]

Vesicular: 1. Composed of or relating to small, saclike bodies. 2. Pertaining to or made up of vesicles on the skin. [EU]

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

Villi: The tiny, fingerlike projections on the surface of the small intestine. Villi help absorb nutrients. [NIH]

Vinblastine: An anticancer drug that belongs to the family of plant drugs called vinca alkaloids. It is a mitotic inhibitor. [NIH]

Vincristine: An anticancer drug that belongs to the family of plant drugs called vinca alkaloids. [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]

Visual field: The entire area that can be seen when the eye is forward, including peripheral vision. [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]

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]

Vulva: The external female genital organs, including the clitoris, vaginal lips, and the opening to the vagina. [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]

Zebrafish: A species of North American fishes of the family Cyprinidae. They are used in embryological studies and to study the effects of certain chemicals on development. [NIH]

Zygote: The fertilized ovum. [NIH]

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

INDEX

S