FRAGILE X SYNDROME

A 3-in-1 Medical Reference

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

TO INTERNET REFERENCES

ICON Group International, Inc.

Fragile X Syndrome

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-

Fragile X Syndrome: 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: 0-497-11214-0
1. Fragile X Syndrome-Popular works.I. Title.

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Acknowledgements

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

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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with fragile X syndrome is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about fragile X syndrome, using the most advanced research tools available and spending the least amount of time doing so.

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

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

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

The Editors

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

CHAPTER 1. STUDIES ON FRAGILE X SYNDROME

Overview

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

Genetics Home Reference

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

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

What Is Fragile X Syndrome?[3]

Fragile X syndrome is a genetic condition that causes a range of developmental problems including learning disabilities and mental retardation. Usually males are more severely affected by this disorder than females. In addition to learning difficulties, affected males tend to be restless, fidgety, and inattentive. About one-third of males with fragile X also have autism, a developmental disorder that affects communication and social interaction.

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

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

Most males with fragile X have characteristic physical features that become more apparent with age. These features include a long and narrow face, large ears, prominent jaw and forehead, unusually flexible fingers, and enlarged testicles (macroorchidism) after puberty.

How Common Is Fragile X Syndrome?

Fragile X syndrome occurs in approximately 1 in 4,000 males and 1 in 8,000 females.

What Genes Are Related to Fragile X Syndrome?

Mutations in the **FMR1** (**http://ghr.nlm.nih.gov/gene=fmr1**) gene cause fragile X syndrome.

Nearly all cases of fragile X syndrome are caused by a mutation in which a DNA segment, known as the CGG triplet repeat, is expanded within the FMR1 gene. Normally, this DNA segment is repeated from 5 to about 40 times. In people with fragile X syndrome, however, the CGG segment is repeated more than 200 times. The abnormally expanded CGG segment inactivates (silences) the FMR1 gene, which prevents the gene from producing a protein called fragile X mental retardation protein. Loss or a shortage (deficiency) of this protein leads to the signs and symptoms of fragile X syndrome.

Men and women with 55 to 200 repeats of the CGG segment are said to have an FMR1 premutation. Most people with a premutation are intellectually normal. In some cases, however, individuals with a premutation have lower than normal amounts of the fragile X mental retardation protein and features of fragile X syndrome.

In women, the premutation can expand to more than 200 repeats in cells that develop into eggs. This means that women with the FMR1 premutation have an increased risk of having a child with fragile X syndrome. By contrast, the premutation CGG repeat in men remains a premutation as it is passed to the next generation.

In a small percentage of cases, other types of mutations cause fragile X syndrome. These mutations delete part or all of the FMR1 gene or change one of the building blocks (amino acids) used to make the fragile X mental retardation protein. As a result, no protein is produced, or the protein is disabled because its size or shape is altered.

How Do People Inherit Fragile X Syndrome?

This condition is inherited in an X-linked dominant pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes. The inheritance is dominant if one copy of the altered gene in each cell is sufficient to cause the condition. In most cases, males experience more severe symptoms of the disorder than females. A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Where Can I Find Additional Information about Fragile X Syndrome?

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

NIH Publications - National Institutes of Health

- National Center for Biotechnology Information: Genes and Disease:
  http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View.ShowSection&rid=gnd.section.172
- National Institute of Child Health and Human Development:
  http://www.nichd.nih.gov/health/topics/fragile_x_syndrome.cfm

MedlinePlus - Health Information

- Encyclopedia: Fragile X syndrome:
  http://www.nlm.nih.gov/medlineplus/ency/article/001668.htm
- Health Topic: Fragile X Syndrome:
  http://www.nlm.nih.gov/medlineplus/fragilexsyndrome.html

Educational Resources - Information Pages

- American College of Medical Genetics Practice Guideline:
  http://www.acmg.net/resources/policies/FragileX_GIM_2005.pdf
- California Department of Developmental Services: fragile X syndrome:
  http://www.ddhealthinfo.org/ggrc/doc2.asp?ParentID=3169
- CDC fact sheet: FMR1 Gene and Fragile X Syndrome:
  http://www.cdc.gov/genomics/hugenet/factsheets/FS_FragileX.htm
- CDC HuGE Review: FMR1 and Fragile X Syndrome:
  http://www.cdc.gov/genomics/hugenet/reviews/FragileX.htm
- Centre for Genetics Education (Australia):
  http://www.genetics.com.au/factsheet/32.htm
- Emory University School of Medicine:
  http://www.genetics.emory.edu/docs/Fragile+X.pdf
- Fragile X Information Center, University of North Carolina at Chapel Hill:
  http://www.fpg.unc.edu/~fxic/
- Kennedy Krieger Institute:
  http://www.kennedykrieger.org/kki_diag.jsp?pid=1086
- Madisons Foundation:
  http://www.madisonsfoundation.org/content/3/1/display.asp?did=77
- NOAH: New York Online Access to Health:
  http://www.noah-health.org/en/genetic/conditions/fragilex/index.html
- Orphanet:
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=908

- Public Health Genetics Unit (UK):
  http://www.phgu.org.uk/pages/info/diseases/fragilex.htm
- Stanford University:
  http://spnl.stanford.edu/disorders/fragilex.htm
- The Wellcome Trust:
  http://genome.wellcome.ac.uk/doc_WTD022302.html
- University of Michigan Health System:
  http://www.med.umich.edu/1libr/yourchild/fragilex.htm

Patient Support - for Patients and Families

- Carolina Fragile X Project:
  http://www.fpg.unc.edu/~fx/
- Conquer Fragile X Foundation:
  http://www.conquerfragilex.org/about.php
- FRAXA Research Foundation:
  http://www.fraxa.org
- March of Dimes:
  http://www.marchofdimes.com/pnhec/4439_9266.asp
- National Fragile X Foundation:
  http://www.fragilex.org/html/home.shtml
- National Organization for Rare Disorders (NORD):
  http://www.rarediseases.org/search/rdbdetail_abstract.html?disname=Fragile+X+Syndrome

Professional Resources

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

- Gene Reviews - Clinical summary:
  http://www.genetests.org/query?dz=fragilex
- Gene Tests - DNA tests ordered by healthcare professionals:
  http://ghr.nlm.nih.gov/condition=fragilexsyndrome/show/Gene+Tests;jsessionid=252503BA524741F34F577D9D0C09B8EF
- Genetic Tools - Teaching cases:
  http://www.genetests.org/servlet/access?fcn=y&filename=/tools/cases/fragilex-16/
- ClinicalTrials.gov - Linking patients to medical research:
  http://clinicaltrials.gov/search/condition=%22fragile+x+syndrome%22?recruiting=fals
- **PubMed - Recent literature:**
  http://ghr.nlm.nih.gov/condition=fragilexsyndrome/show/PubMed;jsessionid=252503BA524741F34F577D9D0C09B8EFe
- OMIM - Genetic disorder catalog:
  http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=309550

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

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- Van Esch H. The Fragile X premutation: new insights and clinical consequences. Eur J Med Genet. 2006 Jan-Feb;49(1):1-8. Epub 2005 Dec 5. PubMed citation
- Willemsen R, Oostra BA, Bassell GJ, Dictenberg J. The fragile X syndrome: from molecular genetics to neurobiology. Ment Retard Dev Disabil Res Rev. 2004;10(1):60-7. Review. PubMed citation

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

What Is the Official Name of the FMR1 Gene?[4]

The official name of this gene is "fragile X mental retardation 1."

FMR1 is the gene's official symbol. The FMR1 gene is also known by other names, listed below.

[4] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/gene=fmr1;jsessionid=252503BA524741F34F577D9D0C09B8EF**.

What Is the Normal Function of the FMR1 Gene?

The FMR1 gene provides instructions for making a protein called fragile X mental retardation 1, or FMRP. This protein is present in many tissues, especially in the brain and testes. In the brain, it may play a role in the development of connections (synapses) between nerve cells, where cell-to-cell communication occurs. The connections between nerve cells can change and adapt over time in response to experience (a characteristic called synaptic plasticity). FMRP may help regulate synaptic plasticity, which is important for learning and memory.

Researchers believe that FMRP acts as a shuttle within cells by transporting molecules called messenger RNA (mRNA), which contain information for making proteins. FMRP likely carries mRNA molecules from the nucleus to areas of the cell where proteins are assembled. Some of these mRNA molecules may be important for the function of nerve cells.

One region of the FMR1 gene contains a particular DNA segment known as a CGG trinucleotide repeat, so called because this segment of three DNA building blocks (bases) is repeated multiple times within the gene. In most people, the number of CGG repeats ranges from fewer than 10 to about 40.

What Conditions Are Related to the FMR1 Gene?

Fragile X Syndrome - Caused by Mutations in the FMR1 Gene

Almost all cases of fragile X syndrome are caused by an expansion of the CGG trinucleotide repeat in the FMR1 gene. In these cases, CGG is abnormally repeated from 200 to more than 1,000 times, which makes this region of the gene unstable. As a result, the FMR1 gene is turned off (silenced) and does not make any protein. Without adequate FMRP, severe learning problems, mental retardation, and the other features of fragile X syndrome can develop.

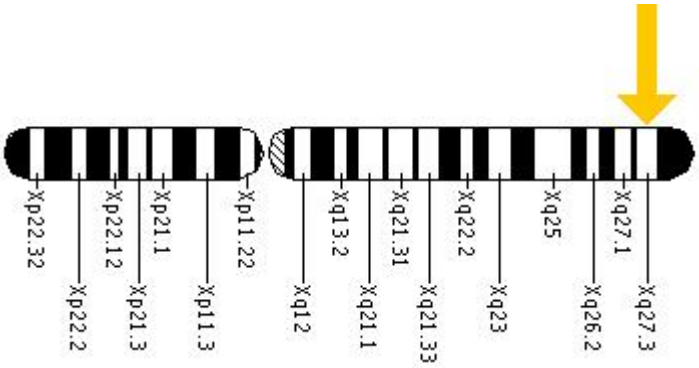
Other Disorders - Increased Risk from Variations of the FMR1 Gene

Almost all cases of fragile X syndrome are caused by an expansion of the CGG trinucleotide repeat in the FMR1 gene. In these cases, CGG is abnormally repeated from 200 to more than 1,000 times, which makes this region of the gene unstable. As a result, the FMR1 gene is turned off (silenced) and does not make any protein. Without adequate FMRP, severe learning problems, mental retardation, and the other features of fragile X syndrome can develop.

Where Is the FMR1 Gene Located?

Cytogenetic Location: Xq27.3

Molecular Location on the X chromosome: base pairs 146,801,200 to 146,840,302



The FMR1 gene is located on the long (q) arm of the X chromosome at position 27.3.

More precisely, the FMR1 gene is located from base pair 146,801,200 to base pair 146,840,302 on the X chromosome.

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These sources were used to develop the Genetics Home Reference gene summary on the FMR1 gene.

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- Oostra BA, Chiurazzi P. The fragile X gene and its function. Clin Genet. 2001 Dec;60(6):399-408. Review. PubMed citation
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- Willemsen R, Mientjes E, Oostra BA. FXTAS: a progressive neurologic syndrome associated with Fragile X premutation. Curr Neurol Neurosci Rep. 2005 Sep;5(5):405-10. Review. PubMed citation

Federally Funded Research on Fragile X Syndrome

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

CRISP (Computerized Retrieval of Information on Scientific Projects)

CRISP is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions. Search the CRISP Web site at **http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen**. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to fragile X syndrome.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore fragile X syndrome. The following is typical of the type of information found when searching the CRISP database for fragile X syndrome:

- **Project Title: 10TH INTERNATIONAL FRAGILE X CONFERENCE**

  Principal Investigator & Institution: Miller, Robert Michael.; National Fragile X Foundation 1615 Bonanza St., Ste 320 Walnut Creek, Ca 94596

  Timing: Fiscal Year 2006; Project Start 14-JUN-2006; Project End 13-DEC-2006

  Summary: (Provided by the Applicant): 10th International Fragile X Conference: The National Fragile X Foundation's 10th International Fragile X Conference in Atlanta, Georgia, at the OMNI Hotel - CNN Center, July 19-23, 2006, will bring together the world's leading researchers in molecular biology and genetics as well as leading clinicians and treatment specialists, selected by its Scientific and Clinical Advisory Committee, with hundreds of parents, extended family members and students engaged in research training. Both scientific and family-friendly sessions covering the three

[5] Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

conditions resulting from the fragile X gene mutation will be addressed: **fragile X syndrome;** fragile X associated tremor ataxia syndrome; fragile X related premature ovarian failure. Keynote presentations, breakout session lectures, research abstract sessions, panels and posters will present the latest knowledge regarding the underlying mechanisms for the fragile X related conditions, plus evidence-based medical, therapeutic and educational interventions. The conference will benefit multiple disciplines including those engaged in clinical practice, epidemiology and delivery system organization. The National Fragile X Foundation will publish and disseminate the results in conference proceedings as well as other formats and utilize the recommendations as the basis for advancing the research and treatment fields.

- **Project Title: 16TH BIENNIAL MEETING OF THE INTERNATIONAL SOCIETY FOR DEVELOPMENTAL NEUROBIOLOGY**

  Principal Investigator & Institution: Levitt, Pat R.; Director; Pharmacology; Vanderbilt University Medical Center Nashville, Tn 372036869

  Timing: Fiscal Year 2006; Project Start 01-JUL-2006; Project End 30-JUN-2007

  Summary: (provided by applicant): The 2006 International Society for Developmental Neuroscience (ISDN) meeting will take place in Banff, Canada in August, 2006, and represents the biannual meeting of the ISDN, an international organization based in the United States. This meeting is a premier developmental neuroscience meeting open to all, which usually attracts 400-500 international participants. The meeting itself has three primary goals. First, to disseminate information and unpublished data in both the development and neurological/psychiatric disease fields, and to promote enhanced links between these different communities. Second, to foster interactions and collaborations amongst scientists worldwide. Third, to provide a forum for interactions between students and postdoctoral fellows and more established senior scientists. In this regard, the meeting is very cost-attractive for trainees, and as a consequence, this group usually comprises approximately half of the attendees. The program for ISDN 2006 has been established, and is comprised of 55 scientists who are both well known and at more junior stages of their careers (see attached program; all of the speakers are confirmed). Five of six plenary speakers (including Nobel prize winner Linda Buck) and 30 of the symposium chairs/speakers are based in the USA, and 10 of the speakers are women. The program spans many areas of developmental neuroscience, as well as psychiatric and nervous system conditions and diseases that include autism, **Fragile X Syndrome,** perinatal stroke, and brain tumors. The meeting runs from the evening of Aug. 24th to the afternoon of Aug. 28th, and is comprised of (a) two hour-long plenary lectures per day, (b) two sets of two concurrent symposia, which include both invited speakers and short oral presentations chosen from the abstracts, and (c) poster sessions. Project Narrative (Relevance): Mental health and neurological disabilities currently represent major unmet medical needs in our society. Many mental health disorders, including autism and schizophrenia, and many neurological disorders, such as mental retardation and cerebral palsy, arise developmentally. In this meeting, we hope to make a major contribution to resolving these medical problems by bringing together scientists interested in development of the nervous system with those interested in these major public health problems. Such interactions are essential if we are to attack these problems in a cohesive, rational fashion.

- **Project Title: A LINK BETWEEN RNAI AND FRAGILE X MENTAL RETARDATION**

  Principal Investigator & Institution: Hammond, Scott M.; Assistant Professor; Cell and Developmental Biology; University of North Carolina Chapel Hill Office of Sponsored Research Chapel Hill, Nc 27599

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

  Summary: (provided by applicant): Fragile X is the most common form of inherited mental retardation in males. It currently has no treatment. The pathology results from loss of expression of the Fmr1 gene. The protein product of Fmr1, FMRP, is an RNA binding protein that has been shown to interact with a limited subset of neuronal mRNAs. It is believed that translational regulation of these genes is the primary function of FMRP. We recently reported the presence of the Drosophila Fragile X homolog, dFxr, as a component of the RNA interference (RNAi) machinery. Based on this finding we developed the following hypothesis: FMRP functions as part of the RNAi machinery, and dysfunction of this shared biological machinery is responsible for Fragile X mental retardation. This hypothesis will be tested in this proposal. In the first Aim we will define the composition of this shared FMRP/RNAi machinery in mammalian cells. This will be done using fractionation methods and assays we have developed. In the second Aim we will identify mRNA targets that are regulated by this activity. In the third Aim we investigate the mechanism of gene regulation by the FMRP/RNAi machinery. This pathway is known to regulate mRNA translation. We have developed the hypothesis that translation is interrupted during the elongation step. We will employ polyribosome analysis of cell extracts and in vitro extracts to test the hypothesis. This work will have several important benefits. Functional validation of Fragile X targets will improve our understanding of Fragile X mental retardation, as well as providing new drug targets for the therapy of the human disease. This work will also define a role for RNAi in the regulation of mammalian genes, a biological pathway that is presently totally unknown. While this project focuses on FMRP regulation of neuronal genes, it will provide a general framework for studies on all aspects of RNAi regulation of mammalian cellular pathways.

- **Project Title: A PROGRAM OF INVESTIGATION INTO FRAGILE X SYNDROME**

  Principal Investigator & Institution: Warren, Stephen T.; William Patterson Timmie Professor and c; Human Genetics; Emory University 1784 North Decatur Road, Suite 510 Atlanta, Ga 30322

  Timing: Fiscal Year 2005; Project Start 10-SEP-1997; Project End 30-JUN-2006

  Summary: (provided by applicant): **Fragile X syndrome** is a leading cause of mental retardation. The molecular basis of **fragile X syndrome** is the expansion of a trinucleotide repeat within the FMR1 gene, resulting in the absence of the encoded protein, FMRP. Although there has been a spectacular increase in the understanding of this disorder in recent years, much remains to be learned. To capitalize upon this trajectory of understanding, a well focused, multidisciplinary group effort to further elucidate the molecular basis of **fragile X syndrome** was initiated in September of 1997 with the funding of this program project composed of seven projects and one core. This revised proposal, in response to the formal review following three years of funded research, reflects a tighter, more thematic program of five interrelated and collaborative projects and one core at Emory University School of Medicine. These projects dramatically expand the scope of contemporary **fragile X syndrome** research and specifically address issues crucial for future investigation and intervention. A central program theme of FMRP expression and function cover the five broad, multidisciplinary projects. Project II will seek to understand the mechanistic details of chromatin changes

leading to the transcriptional suppression of FMR1, the disease-causing consequence of full repeat expansion. Project I aims determine the biochemical and clinical consequences of smaller intermediate and premutation alleles that are found in 5% of the population. Projects V seeks to understand the biochemistry of FMRP with structure/function studies that are key in our continued understanding of the consequences of the absence of FMRP or a more subtle reduction of FMRP levels, studied in the prior two projects. Project III develops model systems where genetically modified mice and cell lines are produced where FMRP expression can be temporally and quantitatively controlled, both pre- and postnatally as well as in vitro. Along with the other projects, these novel biological resources will be used to explore new aspects of the pathophysiology of **fragile X syndrome.** This program of investigation into **fragile X syndrome,** by a highly interactive and multidisciplinary team with proven collaborative abilities, represents one of the largest research centers on this disorder in the world and aims to further our continued understanding of this important and common form of mental retardation.

- **Project Title: ACTION TREMOR & DEMENTIA IN MALE CARRIERS OF FRAGILE X**

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

  Timing: Fiscal Year 2005; Project Start 15-SEP-2003; Project End 30-JUN-2008

  Summary: (provided by applicant): The purpose of this application is to define the clinical features of a newly identified, progressive neurologic disorder consisting of intention tremor, ataxia, and dementia, with generalized brain atrophy and inclusion bodies, among older men with the fragile X premutation. **Fragile X syndrome** (FXS) is a developmental disorder involving a trinucleotide repeat expansion (CGG) in the fragile X mental retardation 1 gene (FMR1). The full mutation is associated with mental retardation among males and milder impairment of cognition among females. Carriers of the FXS gene are said to possess the premutation, a smaller trinucleotide expansion (55 to 200 CGG repeats). The premutation generally has been associated with a normal or nearly normal cognitive and anatomic phenotype, but recent data suggest the premutation phenotype may include subtle developmental anomalies. Our research over the past two years suggests that a subgroup of adult males with the premutation develop a neurologic disorder resembling some of the spinocerebellar ataxias. It is first clinically apparent when the men are in their fifties or sixties, and is characterized by action tremor and other motor findings, dementia, and generalized brain atrophy. The prevalence of this disorder has not been definitively established, but our data suggest it may be between 20 and 78 per I00,000 males, which is common enough that it would represent an important public health problem. Since our previous submission of this application, we have obtained neurologic, radiologic, neuropsychological, and neuropathologic data on a number of additional patients, and the condition has become the focus of study for other investigators in the United States. and abroad. The proposed study will compare a sample of FXS carrier males with this tremor-ataxia disorder to an age- and education-matched sample of carrier males without tremor or other signs of neurologic disorder, and a matched group of healthy men without FXS involvement. The measures used include a comprehensive standardized neurological evaluation, neuropsychological examination, functional assessment, MRI of the brain, and basic molecular studies. Data will be collected at baseline, and at 18-month and 36-month follow-up points. Data analysis will include between-groups and repeated measures methods. The results of this study will provide important information on the clinical features of this previously unidentified disorder, including its rate of progression and its

relationship to the FXS premutation. Further knowledge of the nature of this phenotype, and of its association with the FMR1 gene, is of substantial clinical importance for the differential diagnosis, management, and appropriate treatment of movement disorders among older males.

- **Project Title: ATTENTION, MEMORY, AND EXECUTIVE FUNCTION IN FRAGILE X**

  Principal Investigator & Institution: Bailey, Donald B.; Director of Early Childhood Research; Pediatrics; University of North Carolina Chapel Hill Office of Sponsored Research Chapel Hill, Nc 27599

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

  Summary: Although considerable research has examined general intellectual functioning and adaptive behavior in **fragile X syndrome** (FXS), only a few studies have examined specific domains of neurocognitive functioning, especially in males. Existing research has been limited by cross-sectional designs, lack of comparison groups, a wide age range in the samples, and inconsistencies in assessment methodologies. The proposed project would add substantially to our knowledge about neurocognitive function in FXS by conducting more detailed, systematic, and expansive assessments of attention, memory, and executive function. The project builds on an existing sample of children with FXS participating in a prospective, longitudinal study who are about to enter puberty. We will describe in detail the nature of cognitive function and development over time during early adolescence, and relate function and development to other clinical, genetic, neuropsychological, biological, and sociodemographic variables in order to describe more precisely the FXS phenotype and understand the variability within this population. The study will incorporate a sample of 68 children with FXS between the ages of 8 and 13 years. A comparison group of 68 mental-age-matched typically developing children will provide insights into relative cognitive strengths and weaknesses in FXS in relation to their own mental age. Each child will be assessed annually using a comprehensive battery of attention, memory, and executive function measures. Additional measures will be collected of FMRP, pubertal status, socioeconomics status, temperament, autistic behavior, language development, visual processing skills, and behavior problems. These additional assessments will test the relationship between protein expression and neurocognitive function, identify changes in patterns of development as a function of puberty, provide some insights into the role of environment in affecting outcomes, and increase the specificity of the FXS phenotype by providing a comprehensive description of a range of features likely to be associated with FXS. A range of analytic procedures, including hierarchical linear modeling, will be used to answer four specific aims related to determining neurocognitive profiles, comparing profiles with the comparison group, examining change over time, and testing the relationship between neurocognitive function and other variables of interest.

- **Project Title: ATTENTIONAL DYSFUNCTION IN FRAGILE X SYNDROME**

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

  Timing: Fiscal Year 2005; Project Start 11-AUG-2003; Project End 31-JUL-2008

  Summary: This abstract is not available.

- **Project Title: BAYLOR FRAGILE X RESEARCH CENTER - SUPPLEMENT**

  Principal Investigator & Institution: Zoghbi, Huda Y.; Professor and Investigator; Pediatrics; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 770303498

  Timing: Fiscal Year 2006; Project Start 01-AUG-1997; Project End 30-JUN-2009

  Summary: (provided by applicant): The **fragile X syndrome** (FXS), a type of inherited mental retardation, is due to the silencing of the FMR1 X-linked gene. In over 98% of cases, the mutation is due to the expansion of an unstable CGG repeat sequence located in the 5' untranslated region (UTR) of the gene. Once expanded to over 200 repeats, the FMR1 gene is hypermethylated and consequently no message is transcribed and no protein (FMRP) produced. Until recently, the unmethylated long CGG repeat track found in premutation carriers (60-200 repeats) was thought to have little phenotype consequence. The original goal of this study was to substantiate reports of an association between premutation male carriers and a late-onset neurodegenerative disorder resulting in action tremors - this has been accomplished through this project and others. This syndrome, now referred to as fragile X-associated tremor/ataxia syndrome (FXTAS), has a variable age at onset and progression. The principal investigator's focus now is to characterize the natural history of the syndrome and to identify risk factors associated with expression and severity. She will delineate the FMR1-related molecular correlates that best predict the risk for FXTAS among premutation males and females. Identification of such risk factors will provide clues for the underlying molecular etiology. In the last two years of the study, the investigator has gained significant experience with this syndrome and the issues related to recruiting participants. The investigator has an established infrastructure and study protocol to identify families with FXS, and to systematically ascertain all individuals in a sibship with a premutation carrier. The investigator's test battery to assess an individual's tremor/ataxia phenotype is unique, as she has instrumentation that objectively quantifies outcome measures. However, she has come upon several roadblocks that she did not anticipate with this study, and has requested a supplement to enhance the value of this study. First, the investigator requests funds to cover travel costs to expand her study population. She finds it necessary to travel to a participant's home to conduct the phenotype assessments due to their limitations. Second, imaging studies are essential to better characterize FXTAS and provide diagnostic criteria to the neurology community. Thirdly, the investigator is in great need of a genetic counselor to provide results and discuss FXTAS with family members. The older men in the families with FXS typically have not come to clinics with their grandsons who have FXS - they do not understand inheritance of this disorder and certainly had no idea that they may be at risk for a neurodegenerative disorder. Thus it is essential to have a genetic counselor associated with the study and one who will identify counseling issues specific to FXTAS and establish guidelines for others in this situation. With these additional funds, the results of this project will be immediately translatable to the medical community.

- **Project Title: BLOOD-BRAIN BARRIER GENE DELIVERY IN KNOCK-OUT MICE.**

  Principal Investigator & Institution: Cornford, Eain M.; Professor; Brentwood Biomedical Research Institute 11301 Wilshire Blvd, Bldg. 114, Room 218 Los Angeles, Ca 90073

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

  Summary: (provided by applicant): In addition to Lafora's Progressive Myoclonic Epilepsy, there are numerous single-gene defect diseases that have devastating effects on the children of adult carriers (e.g. Rett's syndrome, **fragile X syndrome,** Canavan's disease, and Tay-Sachs disease). For all of these diseases, there are support groups

formed by parents and friends of afflicted children. In all cases, the mutated gene is known and cloned. But copies of the potentially life-saving genes sit dormant in research laboratories because of problems in expressing an exogenous gene throughout the brain. Due to the difficulties in delivering large molecule therapeutics across the brain capillaries, there is a perception that the blood-brain barrier (BBB) may be an insoluble problem. Heroic measures, such the transient disruption of the BBB with osmotic shock, have yet to be evaluated for delivery of gene therapeutics in clinical trials. Alternative methods are also not without problems; within the current year the NIH placed a halt on all trials where viral vectors were being used to deliver gene therapies. This action suggests a need to develop and test non-viral alternatives for the delivery of (large-molecule) genes across the BBB. We will test the hypothesis that recently developed immunoliposome BBB delivery systems can be used to successfully promote a gene therapeutic through the BBB of knock-out mice with Lafora's Progressive Myoclonic Epilepsy (PME), after intravenous administration. We propose that if this non-viral delivery system can treat the disease in animal models, an immunoliposome-based cure for this fatal epilepsy can be developed for clinical use. The aims are: (1) To prepare pegylated immunoliposomes (PIL) for delivery of the normal EPM2a/laforin gene; (2) to administer PILs in a knockout mouse model of Lafora's Disease; (3) to confirm uniform delivery of the gene to the brain after intravenous injection, with amelioration of the progressive disease; and (4) to develop an optimal therapeutic regimen which arrests the fatal onset of Lafora's disease in the knock-out mice.

- **Project Title: CHARACTERIZATION OF A NOVEL FRAGILE X INTERACTING GENE**

  Principal Investigator & Institution: Zarnescu, Daniela C.; Cell Biology; Emory University 1784 North Decatur Road, Suite 510 Atlanta, Ga 30322

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

  Summary: (provided by applicant): **Fragile X syndrome** is the most frequent form of inherited mental retardation, affects about 1 in 3,500 males and to date has no cure. Patients have a pleiotropic phenotype that includes mental retardation, facial dismorphia as well as attention deficit and hyperactivity disorder. The disease is caused by mutations in the Fmr1 gene which has a single homolog in Drosophila: dFmr1. To unravel novel players with key roles in the disease mechanism of **fragile X syndrome,** we recently developed and conducted a genetic screen for dominate modifiers of dFmr1 over-expression in Drosophila. We identified a single major autosomal modifier which we mapped to the lethal (2)giant larvae (I(2)gl)locus). I(2)gl is a component of the cytoskeleton and loss of function mutations lead to neoplastic tumors. On one hand, Lgl bindsmyosin II and interacts genetically with both myosin II and V and on the other hand, FMR protein is involved in transport and translational regulation of target mRNAs. In addition, the latter associates with myosin V to form a common Ribo-Nuclear Particle (RNP). Taken together this data suggest that Lgl and FMR associate physically in a protein complex, perhaps an RNP equiped with molecular motors which enable its travels on the major cellular highways comprised of microtubule and microfilament networks. Specific predictions of this model will be tested in the proposed project: i) I(2)gl phenotypes should overlap with those of dFmrl mutants; ii) 1(2)gl interacts genetically with dFmr1; iii) Lgl and Fmr1 associate in a common protein complex, be it directly, or through an intermediate partner.

- **Project Title: CK2 REGULATION OF FRAGILE X IN CIRCADIAN CLOCKS**

  Principal Investigator & Institution: Merrill, Catherine E.; Neurobiology and Physiology; Northwestern University Evanston, Il 602081110

  Timing: Fiscal Year 2006; Project Start 01-SEP-2006; Project End 31-AUG-2007

  Summary: (provided by applicant): Fragile X mental retardation is the most common form of inherited mental disorders, and occurs due to the loss of a single gene, FMR. In Drosophila, it was revealed that dFMR plays a role in modulating circadian locomotor behavior. dFMR is phosphorylated by CK2, and loss of this kinase also impairs function of the clock. While aspects of the core transcriptional feedback loop that drives the clock have been well defined, little is known about the way in which the clock communicates timing information. We hypothesize that dfmr and CK2 interact in vivo and that dfmr function in Drosophila pacemaker neurons influences output of the circadian clock. To test these ideas in vivo behavioral, genetic, and molecular investigations of the interaction between dFMR and CK2 will be employed. Results of this study may uncover an example of dfmr regulation in the circadian rhythm pathway and provide novel means of adjusting circadian outputs to modulate sleep and other daily rhythms. Moreover, analysis of dfmr will bring about increased understanding of the function, and consequence of loss, of this disease gene, potentially leading to unique interventions in Fragile X mental retardation.

- **Project Title: COGNITIVE AND GENETIC CORRELATES OF EARLY MATH SKILLS**

  Principal Investigator & Institution: Mazzocco, Michele M.; Associate Professor; Kennedy Krieger Research Institute, Inc. 707 North Broadway, Rm 614 Baltimore, Md 21205

  Timing: Fiscal Year 2005; Project Start 01-AUG-1997; Project End 31-MAR-2007

  Summary: (provided by applicant): The proposed research is an extension and expansion of our prospective, longitudinal study of math skills -development in primary school age children. The broad, long-term objectives of this project are to contribute toward understanding math ability, math disability (MD), and MD subtypes. Towards these objectives, the following specific aims are proposed: (1) To examine the stability of math skills in children with or without MD, from grades K to 5. Of interest is whether distinct profiles corresponding to Visuospatial, Semantic Memory, and Procedural MD subtypes proposed by Geary (1993) persist over time; (2) To address whether MD emerges in some students beyond grade 2, and if so, if it persists over time and is linked to a specific MD subtype; (3) To evaluate cognitive and behavioral correlates, including attentional components, of concurrent and later math performance; (4) To examine how children with fragile X or Turner syndrome serve as potential models of MD subtypes, in view of their risk for poor math achievement; and (5) to identify molecular-clinical correlates in children with fragile X or Turner syndrome. The health-relatedness of the project is its contribution to defining and identifying MD, and to finding correlates and possible core cognitive deficits of MD. Enhanced awareness of core deficits and MD subtypes will guide identification and intervention of MD. The research design involves the study of various groups at risk for MD, and of normally achieving children. The methods include: 1) continued testing of a school-based sample of 220 children (110 boys, 110 girls) through grade 5, to examine stability of math achievement and early predictors of MD in elementary school; 2) recruitment of 44 additional children with MD, to increase sample size for MD versus Non-MD group comparisons; and 3) testing a sample of children with fragile X or Turner syndrome, two groups at risk for poor math achievement, inclusion of normative and genetic models of

MD will provide a unique perspective from which to examine the trajectory and normal variation in the development of MD and MD subtypes.

- **Project Title: COGNITIVE-BRAIN PHENOTYPING OF ATYPICAL CHINESE CHILDREN**

  Principal Investigator & Institution: Karmiloff-Smith, Annette; U of L University College London London, Wc1e 6Bt

  Timing: Fiscal Year 2005; Project Start 28-SEP-2003; Project End 28-FEB-2006

  Summary: (provided by applicant): The present proposal describes a series of planning activities to develop an international collaborative program of research on cognitive and brain phenotypes of mentally retarded Chinese children with genetic disorders. Specifically, an international team of medical, psychological, genetic, and computational researchers from P.R. China, the United Kingdom, the United States, and Canada will collaborate to study Chinese children with Fragile-X syndrome (FXS), Williams syndrome (WS), and Down syndrome (DS). The specific aims of the present research planning proposal are:(1) To assess the existing research infrastructure at the Chinese institution (Zhejiang University) for conducting the proposed research activities, (2) To enhance the research capacities of our Chinese research team through workshops and short-term training; (3) To conduct pilot studies that (a) test the feasibility of a computer-assisted 3D photography-based system for identifying a large population of mentally retarded children whose facial dysmorphology may suggest FXS, WS or DS and verify such identifications by genetic tests, (b) translate, adapt, and pilot-test procedures developed by the researchers in UK, US, and Canada to assess children with genetic disorders in terms of their abilities in the areas of language, executive function, and faces and visual-spatial information processing, and compare the Chinese children's cognitive profiles with the existing profiles of affected Western children; (c) use event-related potential techniques to examine the neuro-physiological correlates of a small group of the Chinese children with WS, FXS, and DS when they process language and face-spatial information, and compare the results with those obtained with the existing samples of affected Western children. Based on the outcome of 1,2, and 3, the international interdisciplinary team will develop a R01 research proposal that will systematically examine cognitive and brain functions or dysfunctions of Chinese children with Williams, Fragile-X, and Down syndromes from infancy to middle childhood. Our long-term goal is to chart the developmental trajectories of cognitive and brain development in children with genetic disorders, to understand the interaction between genetic abnormality and neuro-cognitive development in different socio-cultural contexts, and to provide information for the creation of syndrome-specific and, if necessary, culture-specific intervention programs.

- **Project Title: CONTROL OF DENDRITIC DEVELOPMENT BY FMR1**

  Principal Investigator & Institution: Gao, Fen-Biao; Assistant Professor; J. David Gladstone Institutes 1650 Owens St San Francisco, Ca 94158

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

  Summary: (provided by applicant): The nervous system is composed of a vast number of neurons that vary dramatically in size and shape. Neurons are highly polarized cells with distinct subcellular compartments, including one or more dendritic processes arising from the cell body and a single, extended axon. Elucidating the mechanisms that control neuronal polarity and dendritic development is of critical importance for understanding the development and plasticity of a functional nervous system. In addition, alternations in the number of dendritic branches and dendritic spines are often

found in patients with neurological disorders, such as **fragile X syndrome. Fragile X syndrome** is the most common form of inherited mental retardation in humans, with an estimated incidence of 1 in 4000 males and 1 in 8000 females. The disorder is caused by the loss of the fragile X mental retardation 1 (fmr1) gene activity. FMR1 is an RNA-binding protein that contains two ribonucleoprotein K homology domains (KH domains) and an arginine- and glycine-rich domain (RGG box). The physiological function of FMR1 in neural development remains largely unknown. The long-term goal of this laboratory is to understand the molecular mechanisms underlying dendritic outgrowth, branching, and remodeling during development. The peripheral nervous system (PNS) of the fruitfly Drosophila is an ideal model system for these studies. PNS neurons can be individually identified, and their dendritic morphology can be studied in real time in living animals. A large number of genes identified in PNS also affect dendritic development of central nervous system (CNS) neurons. In addition, the Drosophila model allows powerful genetic and molecular manipulations. Recently, we have generated specific mutations in the Drosophila fmr1 (dfmr1) gene. Our preliminary studies indicate that dfmr1 mutations primarily affect the formation of higher-order dendritic branches. In this proposal, we will carry out a series of experiments to further understand how FMR1 controls dendritic development. Specially, (1) we will further characterize the dendritic overextension phenotype caused by dfmr1 mutations, (2) we will investigate how dFMR1 functions at the mechanistic level, and (3) we will use genetic approaches to identify other proteins that also control dendritic development and may interact with dFMR1. Molecular mechanisms underlying many biological processes are highly conserved throughout evolution. Studies of the mechanisms that control dendritic development in Drosophila may help us understand similar processes in human brains. The insights gained from these studies may also contribute to our understanding of **fragile X syndrome.**

- **Project Title: DEFINITION AND DEVELOPMENT OF THE PHENOTYPE OF AUTISM**

  Principal Investigator & Institution: Rogers, Sally J.; Professor of Psychiatry; Psychiatry & Behavioral Sciences; University of California Davis Office of Research - Sponsored Programs Davis, Ca 95618

  Timing: Fiscal Year 2005; Project Start 01-JUN-1997; Project End 31-MAY-2007

  Summary: (provided by applicant): This program of research will continue its dual foci: 1) defining the phenotype of autism at multiple levels of analysis: behavior, neuropsychology, brain function, brain structure, and familial aspects; and 2) defining the continuities and discontinuities in the developmental course of autism using comparative longitudinal studies. In the first five years of funding, the investigators were able to eliminate or refine four of the competing neuropsychological explanations of autism: a basic sensory deficit, a praxis deficit, a cognitive intersubjectivity deficit, and an executive deficit. The investigators' past work has narrowed and deepened their focus to four key areas: 1) imitation, 2) core affective processes, 3) spatial working memory, and 4) relationships of brain structure and language functioning. In the proposed studies, they will examine these areas in autism again at multiple levels of analysis: behavior, neuropsychology, brain function and structure, and familial aspects. The investigators will conduct longitudinal studies comparing autism, **fragile X syndrome,** Down syndrome, other developmental delays, and typical development across ages spanning from early infancy (through the use of home videos) to middle childhood, and will also include familial data from parents. Research methods including behavioral and neuropsychological measures, brain imaging techniques including magnetoencephalography and magnetic resonance imaging, psychophysiological

paradigms involving eye movements, electrodermal responses, electromyography, and comparison of data from children and their parents. The main aims of this program are: 1) to refine and delineate autism-specific impairments, spared abilities, and familial aspects of imitation, emotional processes, spatial working memory, and a relationship between language and brain structure; 2) to examine whether skills in these areas are independent or whether relationships among them exist concurrently and longitudinally; 3) to determine whether the patterns of deficits are more suggestive of homogeneity or heterogeneity (suggesting potential subtypes); and 4) to participate in cross-network projects that examine the biological, neuropsychological, and behavioral aspects of autism.

- **Project Title: DEVELOPMENT OF MALADAPTIVE BEHAVIOR**

  Principal Investigator & Institution: Reite, Martin L.; Professor; Psychiatry; University of Colorado Denver/Hsc Aurora P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2005; Project Start 01-JUL-1978; Project End 30-JUN-2006

  Summary: (provided by applicant): This training grant has been in progress for the past 22 years in the Department of Psychiatry at the University of Colorado School of Medicine. We are requesting 5 years of support for a total of eight postdoctoral trainees, including one position per year identified specifically for research training for a child psychiatrist. During the past 22 years, we have graduated 73 young scientists from this research training program, 23 of whom are M.D.'s, and 54 (74 percent} of whom are still actively involved in research and/or academic careers. Trainee candidates are M.D.'s or Ph.D.'s, including physicians trained in psychiatry, child psychiatry or pediatrics, and Ph.D.'s trained in psychology, anthropology, molecular biology, neurobiology, or genetics. Special efforts to recruit under-represented minorities have been successful, with six minority trainees recruited during the past five years. Our faculty consists of 22 scientists, and the program has been characterized since its inception by multidisciplinary research with a focus on translation of basic science to clinical care. A core curriculum includes bi-weekly Developmental Psychobiology Research Group (DPRG) seminars, an ethics seminar series, biennial DPRG retreats, a career development retreat, a grant-writing seminar, and, for physician trainees, statistics. An elective curriculum is also available. Research training opportunities include training in cognitive, emotional, and perceptual development in normal and high-risk infants and children, biochemical and pharmacological studies of brain maturation, neuropsychological and genetic studies of dyslexia, studies of developmental disability in autism, Down's Syndrome and **Fragile X syndrome,** early affective regulation of chronically ill pediatric patients, molecular biology of schizophrenia, behavioral immunology in humans and animal models, animal models of mental illness, and magnetoencephalographic (MEG) and electroencephalographic (EEG) correlates of psychoses. Faculty provide access to under-represented minority subjects and special clinical populations, including developmentally disabled, autistic and psychotic children, infant and adolescent populations, children with other psychiatric disorders, research diagnosed psychotic patients, children and family members of schizophrenic subjects, and learning disordered populations. The training program is normally 2 years in duration. Trainees completing this program will be able to assume the role of an independent investigator in one of the multiple areas encompassed by the training program.

- **Project Title: DISSECTING THE MOLECULAR BASIS OF FRAGILE X SYNDROME IN DROSOPHILA**

  Principal Investigator & Institution: Jin, Peng; Assistant Professor; Human Genetics; Emory University 1784 North Decatur Road, Suite 510 Atlanta, Ga 30322

  Timing: Fiscal Year 2006; Project Start 01-FEB-2006; Project End 31-JAN-2011

  Summary: (provided by applicant): **Fragile X syndrome,** a common form of inherited mental retardation, is caused by the loss of the fragile X mental retardation protein (FMRP). FMRP is a selective RNA-binding protein that forms a messenger ribonucleoprotein (mRNP) complex associating with polyribosomes. Evidence suggests that FMRP is involved in local regulation of protein synthesis at synapses. The loss of FMRP leads to abnormal translation of selective mRNAs, delayed maturation of dendritic spines, and abnormal behavioral phenotypes. However, mechanism by which FMRP regulates the translation of its mRNA ligands remains unclear. Since Drosophila model allows powerful genetic and molecular manipulations, in the last several years, fruit fly has been increasingly used to study **fragile X syndrome.** Phenotypic analyses have demonstrated an array of neuronal and behavioral defects similar to the phenotypes reported in mouse models as well as in human patients. The long-term goal of this proposal is to delineate the molecular pathogenesis of **fragile X syndrome** using Drosophila as a model system. MicroRNAs (miRNAs) are a new class of noncoding RNAs that are believed to control translation of specific target mRNAs by pairing with the mRNA in an antisense manner. Members of the PIWI/PAZ-domain protein (Argonaute) family facilitate processing and downstream functions of miRNAs. The recent studies from our group and other laboratories have demonstrated biochemical and genetic interaction between FMRP and the components of the miRNA pathway, including Dicer and Argonaute proteins, suggesting that FMRP could potentially utilize the miRNA pathway to regulate the translation of its mRNA ligands, and modulate cellular and behavioral phenotypes. Here we propose to further decipher the functional importance of the interaction between FMRP and the miRNA pathway using the available Drosophila Argonaute mutants (dAGO1 and dAGO2) along with fragile X models. Three specific aims are proposed: 1) To test the hypothesis that dFmr1 protein interacts with specific miRNAs and determine the role of dFmr1 protein (dFmrp) in miRNA-mediated translational regulation. 2) To determine the domains required for the interaction between dFmrp and Argonaute proteins, and to test the hypothesis that the level of Argonaute proteins modulates c/Fmrp-mediated neuronal plasticity and behavioral activities in vivo. 3) To identify and characterize the genetic modifiers of dAGO1.

- **Project Title: EXPERIENCE-DEPENDENT REGULATION OF THE FRAGILE X GENE**

  Principal Investigator & Institution: Fallon, Justin R.; Professor; Neuroscience; Brown University 164 Angell Street Providence, Ri 02912

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

  Summary: (provided by applicant): A fundamental problem in neuroscience is understanding how ephemeral episodes of experience are transformed into stable changes in synaptic architecture and efficacy. The creation of such long-lasting synaptic modifications requires new protein synthesis, which in turn is regulated at both transcriptional and translational levels. Moreover, the transcriptional profile of the neuron is a function of its developmental stage - e.g. critical period - and its history of activation. A major challenge in unraveling the mechanisms of long term plasticity then is to relate both developmental timing and experience-induced neural activity to the

regulation of identified molecules that play key roles in synaptic plasticity. **Fragile X Syndrome** (FXS) offers a portal to the heart of this problem. FXS affects about 1:4000 boys and is caused by a triplet repeat expansion and hypermethylation of the Fmr1 promoter, leading to gene silencing. The protein product of the Fmr1 gene, FMRP, plays a central role in regulating protein synthesis-dependent synaptic plasticity. Our laboratory has established in vivo and cell culture systems for the study of Fmr1 transcription and expression. We find that Fmr1 transcripts are highly abundant in the developing and adult olfactory bulb and are bi-directionally regulated by olfactory experience. Preliminary in vivo and ce|l culture studies have provided evidence for two molecular mechanisms that regulate Fmr1 transcription: the transcription factor AP-2a and the selective, developmentally-regulated epigenetic modification of the Fmr1 gene regulatory regions. In the proposed studies we will use the olfactory system together with genetic and cell culture models to elucidate the molecular logic of Fmr1 gene regulation in the intact CNS.

- **Project Title: EXPLORING ENDOPHENOTYPES OF MOUSE SOCIAL BEHAVIOR**

  Principal Investigator & Institution: Lahvis, Garet P.; Surgery; University of Wisconsin Madison Suite 6401 Madison, Wi 537151218

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

  Summary: (provided by applicant): Many neurodevelopmental disorders, including autism, **fragile X syndrome,** and schizophrenia, feature aberrant social behavior as a core characteristic. These disorders include a broad array of social impairments, ranging from deficits in shared attention, to communication delays, to social withdrawal. The underlying genetic causes of these social impairments remain largely unknown. Mouse models have tremendous value for elucidating the roles of genes in development. To more fully understand the genetics of social behavior, the investigators propose an expanded panel of mouse behavioral tests that allow them to explore small functional units of social behavior, or social endophenotypes. Specifically, three features of social functioning will be evaluated: the extent to which a social stimulus affects a trained goal-directed behavior, the extent to which social interaction can serve as reward or reinforcement, and the degree that a social stimulus can serve as a spatial cue for learning and memory. We propose to determine if these endophenotypes can be distinguished in five common inbred mouse strains. We then propose to determine if these endophenotypes are anomalous in knockout mice with known deficits in social behavior, including oxytocin and fosB knockout mice, and the N-methyl-D-aspartate receptor 1 hypomorphic mouse. It is expected that some of the knockout mice will exhibit more profound deficits in these measures than both wild-type littermates and the five inbred strains. By developing new measures of mouse social endophenotypes, the investigators can more precisely delineate the roles of particular genes in social functionality. In future projects, this work is likely to provide greater understanding of the neurobiological mechanisms underlying the social impairments that are associated with developmental disorders, such as autism.

- **Project Title: FRAGILE X RELATED GENES MENTAL RETARDATION/DEVELOPMENT**

  Principal Investigator & Institution: Nelson, David Loren.; Cullen Professor of Molecular and Human; Molecular and Human Genetics; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 770303498

  Timing: Fiscal Year 2005; Project Start 10-AUG-1999; Project End 31-MAY-2010

Summary: (provided by applicant): This application seeks renewed funding for a joint project between the Nelson, Oostra and Paylor groups to create and study mouse models for human **Fragile X syndrome.** Prior aims of the project sought to develop and perform initial characterization of mice carrying conditional (Cre-lox) alleles at each of the 3 FMR1-like genes present in the mouse genome. Progress has been excellent; Fxr2 knockouts have been characterized, and models carrying conditional alleles have been created for Fmr1 and Fxr1. Double knockouts of Fmr1 and Fxr2 have been created; these show enhanced phenotypes beyond those found in the single mutants. Moreover, a unique circadian rhythm defect has been observed in double knockouts-these animals are hyperactive and show no rhythm in light/dark or dark/dark cycles. Fxr1 loss of function results in neonatal lethality, while animals with reduced levels of Fxr1 are affected, but viable. Mouse models for the human Fragile X premutation-associated tremor ataxia syndrome (termed FXTAS) have also been developed and are being characterized. These models recapitulate several aspects of this late onset neurodegenerative disorder. These studies offer the opportunity to create and characterize mouse models for genetic disorders (Fragile X syndrome and FXTAS) that result from a common human mutation. Such models will allow the determination of a number of the functions of the FMR1 class of proteins, and provide a resource for other groups interested in utilizing such models to test hypotheses regarding Fmr1 function and the consequences of its absence, as well as the newly described FXTAS disorder. This renewal request seeks to continue these studies through the pursuit of the following specific aims: 1) Development of models and assays for testing FMR1 and paralog functions in mice. 2) Development and use of mouse models to determine the mechanistic basis of Fragile X-premutation-associated tremor ataxia syndrome. Successful completion of these aims will allow the definition of function and dysfunction in **Fragile X syndrome** and FXTAS.

- **Project Title: FRAGILE X REPRESSION OF LOCALIZED MRNA TRANSLATION**

  Principal Investigator & Institution: Pepper, Anita S.; Neurology; University of Pennsylvania Office of Research Services Philadelphia, Pa 19104

  Timing: Fiscal Year 2005; Project Start 30-APR-2005; Project End 29-APR-2007

  Summary: (provided by applicant): Loss of Fragile X Mental Retardation protein (FMRP) causes Fragile X mental retardation syndrome. The molecular role of FMRP is not known. We established a model to study Fragile X using the Drosophila Fragile X protein homologue, dFMRl. We have shown that dFMR1 associates in a ribonucleoprotein complex and colocalizes with oo18 RNA binding (Orb) protein. dFMRl represses translation of Orb and Orb regulated mRNAs required for oogenesis. Orb is a Cytoplasmic Poly-adenylation Element Binding (CPEB) homologue. CPEBs are ribonucleoprotein complex components that regulate mRNA translation. Both CPEB and FMRP localize in vertebrate neurons. We hypothesize that dFMRl masks Orb's function as a regulator of cytoplasmic poly-adenylation induced translation of specific mRNAs during oogenesis. A CPEB/FMRP complex may act similarly in neurons. Loss of FMRP repression of CPEB may underlie **Fragile X syndrome.** I will investigate our hypothesis as follows: Specific Aim I: To determine how dFMRl represses Orb regulated translation of target mRNAs. Specific Aim II: To determine if the dFMR1/ORB interaction is direct and specific. Specific Aim III: To identify and functionally analyze other members of the Orb/dFMR1 complex.

- **Project Title: FRAGILE X SYNDROME: BANBURY CONFERENCES**

  Principal Investigator & Institution: Greenough, William T.; Swanlund Professor of Psychology,; Psychology; University of Illinois Urbana-Champaign Office of Sponsored Programs & Research Admin Champaign, Il 61820

  Timing: Fiscal Year 2006; Project Start 01-MAR-2001; Project End 28-FEB-2011

  Summary: (provided by applicant): This proposal requests support for a 5 year continuation of the Banbury Conferences on **Fragile X syndrome** (FXS). Including an initial conference, six such meetings have been held at Banbury Conference Center at Cold Spring Harbor Laboratory on Long Island NY. We propose a series of five annual interdisciplinary conferences on basic and clinical research relevant to **fragile X syndrome** (FXS). The conferences are intended to bring together a broad range of scientists, both those working on FXS and others in allied, relevant fields. Another goal is to introduce young scientists, including females and minorities, to the area. **Fragile X syndrome** is the most common inherited cause of mental retardation. It arises due to expansion of an unstable region of trinucleotide repeats in the 5' untranslated promoter region of the FMR-1 gene, causing hypermethylation of cytosine residues and, generally, silencing of the gene. A number of mouse FMR-1 knockout models for the syndrome have or are about to become available. The function of the fragile X mental retardation protein (FMRP) is believed to be the transport and translational regulation of a subset of mRNAs with a diverse set of cellular functions. FMRP appears to be translated at synapses in response to activation of metabotropic glutamate receptors. Relatively subtle phenotypic effects of the disorder are seen in the gross size of several brain regions and in the fine structure of synapses in humans and in the knockout mouse model. As the Banbury Conferences have made clear (summarized in Sec. C), advances in our knowledge of this disorder are occurring very rapidly. There is no other meeting devoted exclusively to basic and clinical research on FXS, and the participants consistently report the Banbury Conference to be extremely valuable.

- **Project Title: FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME**

  Principal Investigator & Institution: Hagerman, Paul J.; Professor; Biological Chemistry; University of California Davis Office of Research - Sponsored Programs Davis, Ca 95618

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

  Summary: (provided by applicant): The principal objective of the proposed research is the identification of the mechanistic basis for a progressive neurological disorder, fragile X-associated tremor/ataxia syndrome (FXTAS), which involves intention tremor, gait ataxia, and dementia, and affects at least 1/3 of males over 50 years of age who carry small (premutation, CGGrepeat) expansions of the fragile X mental retardation 1 (FMR1) gene. The neuropathological hallmark of FXTAS is the presence of intranuclear neuronal and astrocytic inclusions, found in the brains of all individuals examined to date who had suffered from the neurodegenerative disorder. The inclusions are ubiquitin-positive, and possess the shape and range of sizes found with the polyglutamine (GAG repeat) disorders. However, there is no known protein abnormality associated with carriers of premutation alleles. The apparent absence of this disorder among males with full mutation alleles (> 200 repeats), whose FMR1 gene is generally silenced, coupled with substantially elevated levels of FMR1 mRNA among the premutation carriers, has led to the central hypothesis of this proposal, namely, that the neurological disorder is the consequence of a "toxic" gain-of-function of the FMR1 mRNA. The first 2 aims of this project are to identify the proteins and RNA species that are contained within purified populations of inclusions. These aims will be met through a combination of state-of-the-art mass spectroscopic analysis of protein/peptide identities, and detailed probing of

RNA species now known to exist within the inclusions. The third aim of this project will be to determine the potential functional significance of the proteins/RNA species identified under the first 2 aims. Aim 4, a major component of the proposed research, will be to further define the nature of the molecular dysregulation that leads to both inclusion formation and FXTAS, using primary, cultured astrocytes (already established in the laboratory) from both normal individuals and premutation carriers. This neural cell system will be used to define the factors and temporal sequence of events leading to inclusion formation. Several features of the intranuclear inclusions associated with FXTAS are shared with the cytoplasmic inclusions found in Parkinson's disease and the Lewy body dementias, and the glial cytoplasmic inclusions found in multiple system atrophy. Thus, knowledge of the mechanisms leading to the inclusions in FXTAS, as a single-gene disorder, should lead to a broader understanding of the events leading to inclusion formation in other neurodegenerative disorders.

- **Project Title: FUNCTION OF FMRP IN THE MOUSE OLFACTORY SYSTEM**

  Principal Investigator & Institution: Larson, John R.; Associate Professor; Psychiatry; University of Illinois at Chicago 310 Aob, M/C 672 Chicago, Il 60612

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

  Summary: (provided by applicant): **Fragile X syndrome** is the most common inherited cause of mental retardation. The disorder is caused by mutation in a gene, FMR1, that encodes the fragile X mental retardation protein (FMRP). How loss of FMRP produces mental retardation is not known. FMR1 knockout mice have been produced, providing a mouse model for **fragile X syndrome.** The experiments proposed in this application will use the mouse olfactory system to investigate the normal function of FMRP and the consequences of the protein's absence in knockout mice. FMRP is normally expressed in olfactory brain structures. The project has three specific aims. First, behavioral analyses will be conducted to determine how lack of FMRP results in impairment of memory formation for olfactory information. Second, electrophysiological methods will be used to determine how absence of FMRP alters synaptic function and synaptic plasticity in the primary olfactory cortex. Third, olfactory stimulation and learning paradigms will be used to determine how expression of FMRP is regulated by neuronal activity in the olfactory system. The results of these studies should provide new information regarding the function of FMRP in the normal brain and may identify behavioral or physiological functions that are reliably disrupted in mice lacking this important protein. Such new information would be vital for evaluating novel treatment strategies for a class of developmental disabilities.

- **Project Title: G QUARTET RNA-FMRP INTERACTIONS IN FRAGILE X SYNDROME**

  Principal Investigator & Institution: Mihailescu, Mihaela R.; Chemistry and Biochemistry; Duquesne University 600 Forbes Avenue Pittsburgh, Pa 15282

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

  Summary: (provided by applicant): This grant focuses on the investigation of the fragile X mental retardation protein (FMRP) interactions with G quartet forming RNA target(s). **Fragile X syndrome** is the most common form of inherited mental retardation, affecting ~ 1 in 4000 males and ~ 1 in 8000 females. The syndrome is caused by the loss of a normal cellular protein (FMRP), which is thought to act as a translational repressor of specific messenger RNA (mRNA). Although the in vivo RNA targets of the protein remain elusive, it has been reported that FMRP binds with high affinity to RNA sequences rich in guanine content, which fold into G quartet structures. Given the

importance of the FMRP RNA binding activity for its function, one of the specific aims of this grant is to investigate the molecular basis of RNA recognition by FMRP. Is the G-quartet containing RNA recognized via a sequence specific, via a structure specific mechanism, or both? Is FMRP stabilizing or destabilizing these structures? FMRP binds the G quartet forming RNA using its arginine-glycine rich domain (RGG box), a domain found in many other RNA binding proteins. Another aim of the proposal is to determine the level of specificity with which the G quartet structures are recognized by this domain, by analyzing the interactions of 2 different RGG boxes derived from other RNA binding proteins with these RNA sequences. The third aim of the proposal is to determine if protein arginine methylation, a common posttranslational modification involving the methylation of arginine residues within the RGG box, plays a role in modulating the FMRP-RNA interactions. Answers to such questions will contribute to our ability to identify the in vivo targets of FMRP, in an effort to understand the link between the absence of the protein and the phenotype of the **fragile X syndrome.** To accomplish these goals, molecular biology and biochemistry methods will be used to produce the RNA and protein and biophysical techniques such as NMR spectroscopy, fluorescence spectroscopy, UV-Vis spectroscopy will be employed to study these biomolecules and their interactions.

- **Project Title: GENE REPRESSION IN FRAGILE X SYNDROME**

  Principal Investigator & Institution: Cedar, Howard; Hebrew University of Jerusalem Authority for Research & Development Jerusalem, 91904

  Timing: Fiscal Year 2005; Project Start 21-MAY-2001; Project End 30-APR-2007

  Summary: (Adapted from the applicant?s description) **Fragile X syndrome** is caused by molecular defects in the structure and expression pattern of the FMR1 gene on the X chromosome. It is fairly well accepted that CGG repeat expansion leads to DNA methylation which then inhibits FMR1 activity, but very little is known about how this occurs. In order to decipher this mechanism, the investigators will use transgenic mice and embryonic cell culture systems. Studies on the cis acting elements and trans acting factors which regulate normal DNA methylation in the early embryo will form the basis for investigating the aberrant factors which bring about faulty methylation at the FMR1 locus. Studies on chromatin structure will be aimed at explaining how DNA methylation actually causes transcriptional inhibition. Another structural parameter which is affected in **fragile X syndrome** is DNA replication timing. Using FISH technology, the investigators plan to elucidate the mechanism which causes the FMR1 region to replicate so late in the cell cycle, and thus understand how this brings about regional repression. Unlike other genetic diseases, the molecular changes in **fragile X syndrome** are epigenetic in nature, so that once these mechanisms have been better defined, it should be possible to design new strategies for reactivating FMR1, thereby reversing the molecular defect.

- **Project Title: GENETIC CHARACTERIZATION OF PATIENTS WITH AUTISM**

  Principal Investigator & Institution: Gambello, Michael J.; Pediatrics; University of Texas Hlth Sci Ctr Houston Box 20036 Houston, Tx 77225

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

  Summary: (provided by applicant): The goal of this application is to initiate genetic studies of a cohort of well characterized autistic patients already enrolled in a program project, titled "Orbitofrontal-limbic dysfunction in autism". Autism is a neurodevelopmental disorder with considerable heterogeneity among affected children. This heterogeneity is due, to a large extent, to many known and unknown genetic

factors. Therefore the neurobehavioral development and dysfunction in autism must be understood within a genetic context. Consequently this application will focus on recalling autistic patients and their families so a thorough medical genetics evaluation can be performed. Medical histories and physical examinations will enable the diagnosis of known and novel genetic syndromes. Specifically the frequency of macrocephaly, a physical finding associated with autism, will be assessed and correlated with cognitive functioning and genetic testing. Routine genetic studies will be performed, including G-banded karyotypes at the 550-600 band resolution, **fragile X syndrome** molecular testing, and plasma amino and urine organic acid analyses. Array Comparative Genomic Hybridization (CGH) will be performed on all mentally retarded and/or dysmorphic patients to screen for subtle, unrecognized genomic deletions or duplications. Metabolic studies will include the novel assessment of creatine metabolism. To further genetic studies, lymphoblastoid cell lines from patients and DNA from patients and parents will be banked. Patient DNA will be used to screen for novel mutations in the tuberous sclerosis complex genes TSC1 and TSC2. The specific role of these genes in autism is still unclear. Results from these studies will further delineate autistic phenotypes, allow the correlation of specific genetic lesions with data from other aspects of the program project, and provide a foundation for larger genetic studies of autism.

- **Project Title: GENETICS AND PHYSIOLOGY OF SOCIAL ANXIETY IN FRAGILE X**

  Principal Investigator & Institution: Hessl, David R.; Psychiatry & Behavioral Sciences; University of California Davis Office of Research - Sponsored Programs Davis, Ca 95618

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

  Summary: (provided by applicant): The aim of this application is to develop the candidate's knowledge and skills in patient-oriented clinical research in the domain of neurodevelopmental disorders. Toward this aim, he will complete a program including formal coursework, mentored training, and a research project on the molecular genetics and psychophysiology of social anxiety in children with **fragile X syndrome** and the fragile X premutation. The research project includes measurement of biobehavioral markers of autonomic and amygdala function, fragile X mental retardation 1 (FMR1) mRNA and gene expression, and behavioral measures in children with fragile X and matched comparison samples of children with idiopathic developmental disability and typical development. The primary underlying hypothesis of the project is that the FMR1 mutation causes over-responsiveness of the amygdala to social stimuli, leading to symptoms of social anxiety and avoidance that are hallmark behavioral features of the fragile X behavioral phenotype. The study will also investigate whether this mechanism of increased anxiety contributes to autistic behaviors, particularly deficits in reciprocal social behavior, in children with fragile X. The candidate's ultimate goals are to become a clinical researcher able to compete for independent grant support, and to conduct high quality studies that will directly lead to improvement in the lives of individuals with fragile X, as well as to contribute to a better understanding of the genetic and physiological mechanisms underlying emotional and behavioral disturbance in children with neurodevelopmental disorders. By the end of the award period, the candidate will become a recognized clinical researcher in the area of neurodevelopmental disorders, and will receive funding to conduct research as an independent investigator.

- **Project Title: GENETICS EPIDEMIOLOGY OF THE FMR1 GENE**

  Principal Investigator & Institution: Sherman, Stephanie L.; Professor of Human Genetics; Human Genetics; Emory University 1784 North Decatur Road, Suite 510 Atlanta, Ga 30322

  Timing: Fiscal Year 2005; Project Start 05-MAY-1994; Project End 30-MAY-2010

  Summary: (provided by applicant): Until recently, the Unmethlyated, long CGG repeat track in the FMR1 5' UTR was thought to have little or no phenotype consequence. Now, it is well established that this expanded repeat track leads to an increased risk for premature ovarian failure (POP) among women who carry the premutation (55-199 repeats) and an increased risk for a late-onset tremor/ataxia syndrome (FXTAS), primarily among men with the premutation. We hypothesize that the high repeat tract in the FMR1 gene increases the risk for these age-related disorders through a dominant negative toxic effect of the FMR1 transcript. The goal of this study is to identify the full phenotypic spectrum of the high repeat track alleles of the FMR1 gene among adult carriers and to elucidate the risk factors associated with phenotype expression. In previous grant period, we established an infrastructure to identify individuals from the general population and from families with **fragile X syndrome** (FXS) who carry high repeat alleles. Our results suggest that the increased risk is primarily associated with premutation allele carriers. Thus, in this re-submission, we will focus on ascertaining all first-degree relatives of premutation carriers-all subjects will be ascertained in a systematic manner to reduce the bias in estimates of relative risk and penetrance among repeat size groups. We will test the hypothesis that the FMR1 repeat length is a QTL that influences an individual's pattern of relative strengths and weaknesses within their neuropsychological functioning, but is generally not associated with clinical problems. We will also test the hypothesis that there are age-dependent, presymptomatic signs related to FXTAS that can be identified among premutation carriers. We will establish quantitative parameters that can be tracked over time to examine the natural history of FXTAS and determine if other health factors are associated with onset, progression and severity of symptoms. These studies will begin to unravel one aspect of the complex pathways related to neuropsychological function and age-associated neurological and cognitive decline.

- **Project Title: GENOTYPE-PHENOTYPE RELATIONSHIPS IN FRAGILE X FAMILIES**

  Principal Investigator & Institution: Hagerman, Randi J.; Professor & Chair; Pediatrics; University of California Davis Office of Research - Sponsored Programs Davis, Ca 95618

  Timing: Fiscal Year 2005; Project Start 15-JUN-1998; Project End 31-MAY-2006

  Summary: (provided by applicant): Our studies over the last 2 and a half years have lead to significant breakthroughs in. our understanding of genotype-phenotype relationships in **fragile X syndrome.** We have discovered a significant translation problem in the conversion of mRNA into FMR1 protein (FMRP), which begins in the premutation range. Significant elevation in. mRNA levels abo"e controls are seen in males and females with the premutation. For premutation carriers who are significantly affected, mRNA levels may be up to 10 times normal and associated with a mild FMRP deficit. Executive function deficits are usually present in males with the premutation and a subgroup of these males who are older than 50 years demonstrate a cerebellar tremor associated with brain atrophy and a slowly progressive neurocognitive decline. These problems may be related to additive genetic effects and/or elevated mRNA levels. We do not yet know the prevalence of these neurological problems in older males with the premutation, or whether these problems may also occur in older females with

the premutation. We also have preliminary evidence that autism in association with **fragile X syndrome** may be related to background gene effects. Our competitive renewal will focus on both of these problems: the association of autism and **fragile X syndrome,** and the emerging neurological phenotype in. older carriers with the premutation. We will study these problems within the format of our family study design (40 families per year) which provides controls within the family and allows an analysis of background gene effects with the pedigree analysis statistical approach from our collaborators Drs. Danuta Loesch and Richard Huggins at La Trobe University in Melbourne, Australia. We will utilize state of the art autism diagnostic tools including the Autism Diagnostic Interview (ADI-R) and the Autism Diagnostic Observation scale (ADOS-G) in addition to a family questionnaire to assess the extended autism phenotype. We will expand the family studies to consistently include grandparents and their siblings to better understand the aging process in carriers with neurological and neuropsychological assessments. Volumetric MRI studies will be done on older carriers with and without tremors and controls and all phenotypic findings will be correlated with FMR1 gene studies including mRNA, FMR1 protein, COG repeat number, methylation status, and activation ratio. In addition to the FMR1 gene studies, we will assess additional alleles, in collaboration with Gerard Schellenberg, Ph.D., including the serotonin receptor (5-HTT), and the GABA receptor (GABRB3) which are associated with autism, and ApoE and tau haplotypes associated with neurodegeneration.

- **Project Title: HYPOTHALAMIC-PITUITARY-ADRENAL FUNCTION FRAGILE X MOUSE**

  Principal Investigator & Institution: Lauterborn, Julie C.; Anatomy and Neurobiology; University of California Irvine Irvine, Ca 926977600

  Timing: Fiscal Year 2006; Project Start 10-MAR-2006; Project End 28-FEB-2008

  Summary: (provided by applicant): **Fragile X syndrome** (fraX), resulting from the loss of fragile X mental retardation protein (FMRP), is the most common cause of inheritable mental retardation. In addition to cognitive impairment, fraX is characterized by abnormal "stress-related" behaviors, and children with fraX have greater basal and stress-induced salivary levels of the adrenal hormone cortisol, as compared to unaffected siblings. These data suggest that hypothalamic-pituitary-adrenal (HPA) axis function is altered in fraX. A murine model of fraX has been developed that exhibits several features of this syndrome and holds promise for identifying the cellular and behavioral consequences of Fmr1 deletion. Work by the investigator has demonstrated that fragile X mental retardation 1 gene knockout (Fmr1-K0) mice also have greater responses to stress including elevated gene expression and glucocorticoid levels than do wild-type mice. These data indicate that Fmr1-KOs are exhibiting a hyper-stress response, similar to the phenotype in human fraX, yet more information is needed as to the extent the HPA axis is altered, the cellular basis of this dysfunction, and potential therapeutic targets. The goal of the proposed research is to obtain such information and lay the groundwork for understanding the contribution of an exaggerated stress response to cognitive impairment in fraX. Three aims are proposed. Specific Aim 1 will test the hypothesis that there is a generalized increase in HPA tone in fragile X mutants (Aims 1A & 1B), and that the disparity among genotypes is enhanced by chronic stress (Aim 1A). In Aim 1A, adrenocorticotropic hormone (ACTH) release and corticotropin-releasing factor receptor 1 (CRH-R1) mRNA levels will be analyzed at three ages (3 mo, 12 mo, 24 mo) in handled (unstressed) and stressed Fmr1-KO and WT mice. Aim 1B will examine basal, diurnal corticosterone fluctuations in Fmr1-KOs and WTs to determine if levels are altered as in fraX humans. Specific Aim 2 will test the hypothesis that immobilization stress will alter the subcellular compartmentalization of the

glucocorticoid receptor in fraX mutants as compared to WT mice (Aim 2A) at the light microscopic level and, in particular, that there are greater levels of glucocorticoid receptor in nuclear fractions of cortical cells from Fmr1-KOs as compared to WTs under basal conditions and following stress (2B) using Western blot analysis. Specific Aim 3 will test the hypothesis that fraX mutant mice have an exaggerated stress-induced hyperthermic response, and that this is attenuated by antagonism of group I metabotropic glutamate receptor type 5 (mGluR5) function. The proposed research will build upon initial findings in the adult male Fmr1-KO to test the general hypothesis that in fraX there is a dysregulated HPA axis that leads to a heightened stress response, and that antagonism of the group I mGluR5 will reduce stress-related anxiety seen in this syndrome. Given that stress results in cognitive impairment and has been reported by some to increase dendritic spine densities, two attributes of fraX, studies on stress and the HPA axis in fraX may give valuable insight into the cause of mental retardation in this syndrome.

- **Project Title: ID OF GENES RESPONSIBLE FOR X-LINKED MENTAL RETARDATION**

  Principal Investigator & Institution: Wang, Tao; Institute of Genetic Medicine; Johns Hopkins University W400 Wyman Park Building Baltimore, Md 212182680

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

  Summary: (provided by applicant): Mental retardation is the most common cause of handicap in children and young adults and accounts for 2-3% in the general population. X-linked mental retardation (XLMR) occurs in 1 in 600 males and is genetically heterogeneous. Among the estimated more than 150-200 responsible loci on the X chromosome, less than 40 genes have been cloned. Delineation of the molecular basis of XLMR will contribute to our understanding of human cognitive development, and will lead to development of strategies for clinical management of XLMR patients. The candidate is interested in the study of the molecular mechanism of XLMR, with a long-term career goal to become a successful clinician scientist. To accomplish this goal, he developed a comprehensive career development plan to be carried at the Johns Hopkins University. There are three key components to the research plan: (1) training in bioinformatics and genomic research; (2) training in the clinical evaluation and care for patients with mental retardation; and (3) training in the patient-oriented clinical investigation. The candidate will attend graduate courses and seminars on genome research and on principles of clinical investigation. He will receive mentored training in clinical evaluation and care for patients with mental retardation. He will be responsible for the development of a clinical research protocol for this project. In addition, the candidate will participate in the weekly Genetic Clinic at the Johns Hopkins Hospital and the Mental Retardation Clinic at the Kennedy Krieger Institute. He has developed a strategy of using human X chromosome-specific cDNA microarray to identify responsible genes. This approach is designed to detect mutations that result in a change in the abundance of mRNA due to mechanism such as promoter mutations, gene deletions, and nonsense or frameshift mutations associated with nonsense-mediated mRNA decay. Once a candidate gene is identified, Northern blot and real-time PCR will be used to verify mRNA reduction followed by mutation analysis in the proband. Additional in vitro and in vivo studies will then be carried out to delineate the molecular mechanism of XLMR for each identified gene. Through the combined laboratory research and clinical training, the candidate wishes to develop a solid knowledge base and gain precious experiences in research and clinical care for patients with mental retardation. This will be invaluable to the advancement of the candidate's career to become an independent physician scientist.

- **Project Title: IDENTIFICATION AND VALIDATION OF FMRP TARGET RNAS**

  Principal Investigator & Institution: Darnell, Jennifer C.; Research Assistant Professor; Lab/Molecular Neurooncology; Rockefeller University 1230 York Avenue New York, Ny 100216399

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

  Summary: (provided by applicant): This is a proposal to test the hypothesis that Fragile-X mental retardation results from a failure of FMRP to bind specific RNAs, and to identify those RNAs. The foundation of this proposal is our finding of sequence and structure-specific targets for the FMRP RGG box and KH2 domain, the latter of which is associated with severe disease in a patient with a missense mutation (I304N) in this RNA-binding domain. We have related the KH2 RNA target, termed a kissing complex RNA, to disease by demonstrating that it competes FMRP off of brain polyribosomes, suggesting that this RNA motif is used by FMRP to effect translational regulation of specific mRNAs. Three aspects of FMRP sequence-specific RNA binding will be definitively addressed here. First, FMRP RNA targets will be identified using several methods: bioinformatic screens complemented by structural studies, microarray analysis of coimmunoprecipitating RNAs, microarray analysis of RNAs whose distribution on polyribosomes is shifted in the absence of FMRP, and cross-linking IP (CLIP) studies. Second, to help validate these new RNA targets in vivo, we will generate three new mouse models of Fragile-X mental retardation. Third, these new model systems will be used in conjunction with the existing FMR1-null mouse to validate identified RNA targets of FMRP in mouse brain. Taken together, these studies will address the hypothesis that mental retardation associated with the I304N mutation, and likely the Fragile-X syndrome more generally, may relate to a crucial role for RNAs harboring the kissing complex motif as targets for FMRP translational regulation.

- **Project Title: IDENTIFICATION OF MICRORNA TARGETS AND MACHINERY**

  Principal Investigator & Institution: Pei, Yi; Lab/Rna Molecular Biology; Rockefeller University 1230 York Avenue New York, Ny 100216399

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

  Summary: (provided by applicant): MicroRNAs (miRNAs) represent a class of endogenous small RNAs that sequence-specifically regulate target gene expression at the post-transcriptional level. In animals, miRNAs predominantly specify translational repression via binding to sites of imperfect complementarity in the 3' untranslated region of the target mRNAs. miRNA regulation has been linked to several human diseases including cancer and **fragile X syndrome.** In aim 1, I propose a biochemical strategy for systematic identification of the bona fide mRNA target segments recognized by miRNAs. The protein components of the miRNA effector complexes can be identified concurrently. The strategy is applicable to various human cells and tissues. In aim 2, I propose to develop cell-based assay systems recapitulating miRNA-mediated translational control in order to validate the targets and protein factors identified biochemically. I anticipate that comprehensive identification of miRNA targets will expand our knowledge of miRNA function and unravel more linkages between miRNA regulation and human diseases. In addition, identification of the components of the miRNA effector complexes will facilitate our efforts to elucidate the mechanism underlying miRNA regulation.

- **Project Title: IDENTIFYING AUTISM SUSCEPTIBILITY GENES BY HIGH-THROUGHPUT CHIP RESEQUENCING**

  Principal Investigator & Institution: Zwick, Michael E.; Human Genetics; Emory University 1784 North Decatur Road, Suite 510 Atlanta, Ga 30322

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

  Summary: (provided by applicant): A major goal of human genetics is to identify and discern how genetic variation contributes to variation in human disease risk. Human geneticists have made remarkable progress identifying disease gene variants with large phenotypic effects, but finding the genetic causes of common, complex disorders like autism, has proven more difficult. While family-based linkage studies have identified regions of the genome harboring putative autism susceptibility alleles, the apparent great genetic heterogeneity of the disorder has prevented the identification of disease causing variants. We aim to reduce this heterogeneity by performing high-throughput, highly accurate microarray-based resequencing of 2 270kb X chromosomes regions among 314 male affected sibpairs from the Autism Genetic Resource Exchange (ACRE) sample collection. The first region contains the FMR1 gene. **Fragile X syndrome** is caused by a trinucleotide repeat sequence at FMR1 and approximately 20% of patients with this disorder exhibit symptoms consistent with the DSM IV diagnosis of autism. Our goal is to identify others mutations leading to a diagnosis of autism. The second region contains candidate genes in the vicinity of marker DXS1047 that shows suggestive linkage in the AGRE sample. Rare alleles will be confirmed within pedigrees while common alleles will be genotyped across the entire AGRE sample collection. Rapid resequencing can identify disease gene variants, reduce heterogeneity in mapping studies, and provide insight into autism enabling a greater concordance between the patient genotype and autism phenotype. We believe that the approach we propose will eventually be required to dissect human genomic regions harboring susceptibility alleles to common complex diseases like autism, whether these regions are discovered through family-based linkage studies or whole genome association studies in a case-control design. The genetic causes of autism, a common pervasive developmental disorder (FDD), remain largely undiscovered. We propose using DMA chips to resequence genes that may harbor mutations that cause autism. Identifying the genetic basis of autism could enable more rapid diagnostic testing and provide insight into the root causes and eventually pave the way for better treatments of this increasingly common disorder.

- **Project Title: IMAGING FMRP REGULATION AND FUNCTION**

  Principal Investigator & Institution: Bassell, Gary J.; Associate Professor; Neuroscience; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2005; Project Start 15-DEC-2004; Project End 30-NOV-2005

  Summary: (provided by applicant): Elucidating the mechanistic function of Fragile X Mental Retardation Protein (FMRP) in neurons is a critical goal in understanding the basis of **Fragile X Syndrome.** This proposal will test the hypothesis that FMRP is required for the glutamatergic regulation of mRNA transport in dendrites and its subsynaptic translation. Recent identification of mRNAs that are bound by FMRP now makes it possible to investigate whether these RNA-protein interactions occur in dendrites and at synapses. An inherent difficulty in studying RNA-protein interactions in dendrites has been the lack of suitable high resolution microscopic technology to visualize mRNA transport and identify sites of local translation. A new view of FMRP function is made possible by utilizing novel microscopic and imaging technology to visualize mRNP complexes in live neurons. We have recently shown that FMRP is localized in the form of RNA granules that exhibit dynamic and activity-dependent

movements in dendrites and spines. Experiments in Specific Aim 1 will apply high resolution fluorescence in situ hybridization methods and quantitative digital imaging analysis to determine whether specific mRNAs have altered localization and regulation in hippocampal cultures from Fmr1 knockout mice. We will determine whether FMRP binding elements function as zipcodes to localize FMRP target mRNAs using transfection of reporter constructs. Experiments in Specific Aim 2 will use live cell imaging technology to determine whether glutamatergic signaling and synaptic activity regulates the dynamic trafficking of FMRP and bound mRNAs in dendrites and spines. Experiments in Specific Aim 3 will use combined imaging and biochemical methods to elucidate a role for FMRP in the glutamatergic regulation of dendritic and synaptic protein synthesis. These studies will provide new insight into the molecular and cellular basis for altered synaptic plasticity in **Fragile X Syndrome.**

- **Project Title: IMPROVED METHODS FOR SINGLE SUBJECT FMRI ANALYSIS**

  Principal Investigator & Institution: Mazaika, Paul K.; Psychiatry and Behavioral Sci; Stanford University 1215 Welch Road, Mod B Stanford, Ca 943055402

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

  Summary: (provided by applicant): Mental illness is a great burden for the affected individual and economically costly for society. The annual cost of mental disorders has been estimated to be $150 billion, increasing every year, and this total does not include more than three million people receiving disability benefits due to mental disorders. It is imperative that we prioritize research efforts focused on understanding brain function in order to improve diagnostic strategies and discover more effective therapies. Functional Magnetic Resonance Imaging (fMRI) is a powerful tool to visualize and measure typical and atypical cognitive processing. However, many important cognitive processing systems, such as those associated with memory, language, emotion and executive control, only produce small BOLD signals and thus measurements are noisy and have low statistical confidence. Hence, fMRI has not been readily adopted for clinical diagnosis of individual patients. I propose to develop greatly improved methods to suppress the noise sources in fMRI data in order to transform fMRI from a research tool about populations to a consistent and accurate diagnostic tool to study individual cognitive functions. Using the strategy that every noise suppression algorithm must perform well to reliably detect single trial fMRI BOLD signals, I developed visualization methods to "see" deeply into fMRI data to evaluate the quality of the data at every step of fMRI data processing. The preliminary studies indicate that there are clear opportunities to improve fMRI image analysis techniques. The proposed research will first develop and test methods to improve suppression of errors from motion and physiological fluctuations. Then it will translate this research by combining these techniques with pattern recognition to characterize individual cognitive activation patterns in typical and atypical populations. My quantitative science expertise is in image processing, algorithm design, and pattern recognition. The research directly supports my interdisciplinary career development with hands-on experience in experiment planning, fMRI scanner operation, neuroscience coursework, and new software methods for application to severely brain disordered populations. In particular, the subjects for this research will include important clinical psychiatric populations with disorders such as **fragile X syndrome,** Turner syndrome, autism, Williams syndrome, depression, and bipolar disorder, so that all newly developed methods can be immediately put into practice.

- **Project Title: IN VIVO FUNCTIONS OF THE DROSOPHILA FRAGILE X ORTHOLOGUE**

  Principal Investigator & Institution: Dockendorff, Thomas C.; Zoology; Miami University Oxford 500 E High St Oxford, Oh 45056

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 30-JUN-2007

  Summary: (provided by applicant): Fragile X mental retardation is caused by loss-of-function of the FMR1 gene and is the most prevalent inherited form of mental retardation resulting from a single gene defect. The frequency with which this disorder appears (about every 5000 births) and its global distribution make fragile X mental retardation one of the most prominent human genetic disorders. Although it is known that the FMR1 protein is an RNA-binding protein that interacts with a small subset of messages, the identity of these messages and the effect FMR1 protein binding has on such messages is poorly understood. The long-term objective of this proposal is to gain insight into specific biochemical functions of the FMR1 protein through a molecular genetics approach that utilizes the fruit fly Drosophila melanogaster as a model system. The fruit fly has a single orthologue to the human FMR1 gene referred to as dfmrl. The amenability of Drosophila to transgenic studies allows for in vitro engineered mutant alleles of dfmrl to be introduced into flies lacking an endogenous wild-type allele. This experimental approach will allow studies of these mutant alleles for defects in RNA processing, behavior, and neuroanatomy to be performed in a physiologically and developmentally relevant context. These studies will allow an assessment of biochemical processes and modes of regulation associated with dfmrl that will likely be applicable to understanding the in vivo function and regulation of all members of the FMR1 gene family.

- **Project Title: INFANT SCREENING AND DIAGNOSIS OF DUCHENNE MUSCULAR DYS***

  Principal Investigator & Institution: Fernhoff, Paul M.; Associate Professor; Human Genetics; Emory University 1784 North Decatur Road, Suite 510 Atlanta, Ga 30322

  Timing: Fiscal Year 2005; Project Start 30-SEP-2004; Project End 29-SEP-2007

  Summary: OF PROPOSED PROJECT: The applicant proposes to establish a screening program for male infants by utilizing the first well-baby visit at six months of age to recruit the parents into the screening program. The reasoning behind this delayed newborn screening is that screening at the time of birth does not provide the optimum timing for discussion of all the parameters around Duchenne Muscular Dystrophy (DMD) testing, nor does it provide the best opportunity for obtaining informed consent. The applicant argues that presenting the screening at the first visit, but collecting the specimen at the second visit (9-12 months), allows time for the mother to investigate the decision fully and make a reasoned choice. Furthermore, the applicant notes that at the second planned visit a finger stick is performed to determine hematocrit, thus allowing an easy opportunity to collect another drop of blood for the DMD screening. Focus groups and surveys are planned among parents and healthcare providers to develop an informed consent instrument and educational materials to use in recruiting and screening infants. Participants will be recruited through the use of various methods (television, newspaper, magazines, Internet) and targeted education of managed care and private providers. A bioluminescence assay will be used to measure creatine kinase (CK) levels and multiplex ligation-dependent probe amplification (MLPA) techniques to detect deletions and duplications in all 79 exons of the dystrophin gene. Participants choosing to undergo screening and the participating healthcare providers will be asked to complete a "screening experience" survey to assess their attitudes towards DMD

screening and to evaluate the effectiveness of the program. While making a sound argument of the merits of newborn screening for DMD (including: 1) avoidance of the "diagnostic odyssey" of prolonged and multiple medical evaluations; 2) allowing families earlier access to physical therapy and other supportive services, and; 3) providing an opportunity for choice of reproductive options in subsequent pregnancies) the applicant argues that the immediate post-natal period is not the best time for this decision to be made. Citing the DMD screening program in Wales as a model program, the authors point out that neonatal DMD screening may not give parents sufficient time for informed consent or education about DMD and may interfere with normal parental bonding to the new baby. A better option, they argue, would be to delay the testing, as was done in one study in which males were screened at 18 months of age; however, this timing allowed birth of subsequent affected males. Therefore, the applicant settles on the 6-12 month interval as the optimum, feeling that no new pregnancies would evolve before detection of an affected male, while allowing for true informed consent and parental bonding. It is noted that this timing affords another benefit unrelated to DMD screening in that it provides the opportunity for other screening programs under development, notably **Fragile X syndrome.** To oversee the project, an advisory board is planned consisting of representatives from the Muscular Dystrophy Association (MDA), the MDA clinics (six in Georgia), parents of sons with DMD, pediatric neurologists, and primary care providers. This board will meet twice yearly. The authors propose to use focus groups to assist in development of the informed consent instrument. With membership from parents of normal male infants as well as parents of children previously diagnosed with DMD, these groups will help determine the type and format of information that create the best opportunity for optimal informed consent. A clinical psychologist will provide guidance on establishing the focus groups, the development of surveys, and analyzing the results. The applicant proposes to use a marketing research company to recruit individuals for the parent focus groups. Consent forms are planned in English and Spanish. Educational materials for DMD will be developed from existing materials used by DMD screening programs. These culturally-sensitive materials will be distributed to parents in the primary care physician's (PCPs) office and maintained on a web-based DMD screening site. The educational materials are planned so as to present a balanced case for and against DMD screening and contain the consent form. Working with the Georgia Academy of Pediatricians and the Georgia Academy of Family Practitioners, the applicant proposes to develop information for PCPs that explains the rationale and operations of the DMD infant screening program. The applicant proposes to recruit participants for the DMD screening study in three ways: 1) An educational campaign using newspapers, parent magazines, parent websites, Georgia American Academy of Pediatrics (AAP) Blast fax, professional organization newsletters, prenatal classes, and development of parent-targeted posters and information brochures. An 800 line and a DMD screening website will provide parents other opportunities to acquire information; 2) Involvement of large managed care providers of pediatric primary care services; 3) Large multi-provider private primary care practices in rural and urban settings. An innovative "lunch and learn" program is proposed for these groups in which the genetic counselor will provide seminars to these groups throughout the state. Additionally, the authors propose to conduct surveys of PCPs (medical doctors, office nurses, and office personnel) from various practice settings (urban and rural managed care and traditional point of service practices) to determine how best to incorporate screening of target male infants into their practice setting and to evaluate the acceptability of screening among health care professionals. The applicant proposes to use a standard bioluminescence screening test to measure CK levels in dried blood spots. It plans to recruit 500 samples from unaffected, healthy males, six weeks to 12 months of age, including normal males from the major

ethnic/racial groups for assay development and validation prior to initiation of the screening program. CK values from affected males, age 0-6 months, will be used to determine positive cutoff values. A newborn male population of 66,500 is potentially available annually, allowing, it suggests, the detection of 18 affected males. The actual screening will consist of an initial CK determination. Those specimens testing positive with the CK assay will be submitted for isoenzyme determination. Those with CK-BB isoenzyme will be considered negative for DMD. Those with CK-MM isozyme will be considered screen positive and will be tested by the Molecular Genetics Laboratory within the screening laboratory for gene deletion or duplication. Parents of screen positive males will be contacted and offered a serum CK test with a 24-hour turnaround, in order minimize the waiting period before a diagnosis is made. For the molecular testing the authors propose to use a new technique, MLPA that will identify all 79 exons in the dystrophin gene following a DNA extraction using the Quiagen protocol. Families of all confirmed males will be referred to an MDA clinic. The applicant intends to obtain information on the screening program from four sources: 1) the focus groups and surveys of parents and primary care providers with data analysis by the clinical psychologist; 2) the CK pilot screening data set with data analysis and interpretation of this and the molecular testing provided by the director of the biochemical laboratory and director of the deoxyribonucleic acid (DNA) laboratory; 3) the molecular diagnostic testing; and 4) the post-screening surveys with data analysis by the clinical psychologist. Several groups will be queried in the post-screening surveys: 1) parents who received information and declined testing for their infant son; 2) parents who had their son screened, and he was found to be normal; 3) parents who had their son screened and had to be retested and found on a second screen to be normal (false positives); 4) parents whose son was screened positive and diagnosed with DMD, and; 5) primary care providers of parents who chose to have their son screened. In these surveys, data will be sought toward these points: 1) factors that influence access to and uptake of infant screening; 2) parental understanding of informed consent; 3) factors that influence loss to follow-up; 4) acceptability of screening; 5) impact of transient positive screening results on families; 6) attitudes of diagnosed families toward the screening and diagnostic process; 7) attitudes of false positive and true negative families toward the screening process, and; 8) assessments of other potential risks and benefits of infant screening for DMD. Healthcare providers of screened families will be surveyed to evaluate: 1) their perception of the parents understanding of informed consent; 2) acceptability of screening in their primary care practice setting; 3) impact of transient positive screening results on families, and; 4) other potential risks and benefits of infant screening for DMD. Outcome measures for the project include: 1) number of males diagnosed; 2) percentage of parents who complete screening who would choose to have another son tested; 3) ratings for the screening experience as positive or negative on a scale of 1-5; 4) ratings for the program's level of support on a scale of 1-5; 5) age at diagnosis of DMD in the screened population versus the historical age of diagnosis of DMD patients in the Georgia population; 6) the sensitivity, specificity, and PPV of the CK screening and molecular diagnostic tests; 7) cost of infant CK screening compared to costs of newborn screening for metabolic disorders; 8) time from screening to diagnosis compared to existing metabolic screening programs; 9) the informed consent process to determine how well it informed; 10) ratings of risk and benefits associated with the screen; 11) provider attitudes toward screening of patients in a PCP practice setting; 12) amount of time and cost added to the provider visit to discuss and collect the test; 13) level of inconvenience experienced by the parents or providers, and; 14) provider and parent opinions and suggestions about program improvements. These data points will be tracked throughout the project.

- **Project Title: INSTABILITY OF TRIPLET REPEATS IN MAMMALIAN CELLS**

  Principal Investigator & Institution: Wilson, John H.; Assistant Professor; Biochem and Molecular Biology; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 770303498

  Timing: Fiscal Year 2005; Project Start 01-APR-1987; Project End 30-JUN-2006

  Summary: Expansions of trinucleotide (triplet) repeats at specific sites in the human genome cause a number of neurological diseases, including myotonic dystrophy, Huntington disease, **fragile X syndrome,** and several others. At the myotonic dystrophy locus, normal individuals have up to 30-40 CTG/CAG repeats, whereas affected individuals may have up to several thousand repeats. CTG/CAG repeats have a propensity to form a variety of stable secondary structures in vitro, and it is thought that these unusual structures interfere with aspects of DNA metabolism in cells, leading to repeat expansion and disease. Studies in E. coli and S. cerevisiae have shown that triplet repeat stability is sensitive to processes that expose single strands of DNA, including transcription, replication, repair, and recombination. This application seeks to develop novel selective systems for investigation CTG/CAG triplet repeat stability in vertebrate cells. Instability during recombination and the effects of triplet repeats on the recombination processes, which have already been demonstrated at the APRT locus in CHO cells, will be defined using a variety of tandem duplication substrates, I-SceI-mediated double-strand breaks, and ERCC1-deficient cells. Instability of repeats due to all causes will be investigated using a novel, direct-selection assay based on the length-dependent effects on gene expression by intronic CAG repeats, which have already been demonstrated. Long repeats placed in the intron of the HPRT minigene, which render it HPRT , can be used to select for repeat contractions (HPRT- to HPRT+). Similarly, short CAG repeats that are compatible with gene expression can be used to select for repeat contractions (HPRT- to HPRT+). Similarly, show CAG repeats that are compatible with gene expression can be used to select for expansions (HPRT- to HPRT+). The boundaries for these length- dependent effects will be defined, the mechanism of interference will be determined, and appropriate CAG-containing, HPRT-minigene substrates will be deposited in the chromosomes of vertebrate cells. These substrates will allow testing of the effects of genes involved in replication, repair, and in recombination and cell treatments that stress these processes. In summary, we propose and integrated and comprehensive set of experiments to define the molecular basis of the CTG/CAG repeat instability that underlies myotonic dystrophy and other neurological diseases. These studies will also provide a set of experimental reagents that will e useful in the design and evaluation of potential therapeutic strategies directed at preventing expansion or promoting contraction of CTG/CAG repeats.

- **Project Title: LANGUAGE DEVELOPMENT IN FRAGILE X SYNDROME**

  Principal Investigator & Institution: Abbeduto, Leonard J.; Professor; Waisman Ctr/Mr & Human Devlmt; University of Wisconsin Madison Suite 6401 Madison, Wi 537151218

  Timing: Fiscal Year 2005; Project Start 01-SEP-1987; Project End 31-MAR-2009

  Summary: (provided by applicant): We propose to conduct a five-year prospective longitudinal study of language development in adolescents with **fragile X syndrome** (FXS). The data collected will address three specific aims. (1) We will describe the developmental trajectory of important, theoretically motivated domains of language and the ways in which those trajectories differ for males and females with FXS. In doing so, we will use nonverbal cognitive development as a benchmark and thereby determine whether language poses a challenge beyond that created by general cognitive limitations. (2) We will identify the determinants of within-syndrome variation in language development and differences in those determinants across males and females

with FXS. In doing so, we will focus on the adolescent's psychological and behavioral characteristics (e.g., memory, autism status), his or her biological characteristics (e.g, FMRP levels), and the supportiveness of the environment, particularly the mother. Moderating and mediating relationships involving selected predictors will also be tested. (3) We will begin the process of distinguishing between those properties of the language development profile of FXS that are specific to it rather than shared with other forms of mental retardation. In doing so, we will compare the developmental trajectories of language in FXS and Down syndrome (DS). DS is a useful comparison because it overlaps substantially with FXS in terms of overall severity of impairment and because its phenotype contrasts with that of FXS in ways that can illuminate the factors affecting language development. Data will be collected at yearly intervals from adolescent boys and girls with FXS and from younger typically developing (TD) children and adolescents with DS. The TD children and adolescents with DS will be selected so that over the course of the project they traverse the same period of nonverbal cognitive development as do the adolescents with FXS. In addition, the comparison between FXS and DS will involve groups matched on age and nonverbal IQ. Measures will include standardized tests, experimental tasks, and informant reports. Dependent variables will be composites of variables reflecting important conceptual distinctions in understanding language development (e.g., mastery of forms vs. mastery of the social uses of language, expression vs. reception). Hierarchical Linear Modeling (HLM) will be used to analyze the data.

- **Project Title: LONGITUDINAL FMRI STUDY OF COGNITIVE DEVELOPMENT**

  Principal Investigator & Institution: Menon, Vinod; Associate Professor; Psychiatry and Behavioral Sci; Stanford University 1215 Welch Road, Mod B Stanford, Ca 943055402

  Timing: Fiscal Year 2005; Project Start 16-APR-2001; Project End 31-MAR-2006

  Summary: (provided by applicant): The candidate for the proposed quantitative career development award has multidisciplinary training and research experience in physics and the computer sciences as well as in neurophysiology and functional brain imaging. The overarching goal of the current proposal is to enhance the candidate's expertise in developmental cognitive neuroscience. Through a multidisciplinary program combining education, mentoring, and the completion of an innovative research study, the candidate seeks to investigate brain function in both typically developing children and children with specific neurodevelopmental disorders. As a result, the proposed program will not only improve the candidate's research skills and expertise, but will also contribute to the discovery of essential knowledge about the normal cognitive development and its disruption. The institutional resources, environment, and opportunities for research and collaboration in functional neuroimaging of children and adults at Stanford University are exemplary. At the end of the award, the candidate expects to: (1) possess the skills needed to be an independent investigator in developmental cognitive neuroscience; (2) to have received funding as an independent investigator; and (3) to become a leader in the scientific study of basic and clinical developmental cognitive and systems neuroscience. As part of this award the candidate will complete a mentored research project titled "Longitudinal fMRI study of cognition in children" under the mentorship of Dr. Allan Reiss at Stanford University. In this proposal, the candidate plans to use fMRI to investigate the typical and atypical patterns of development of cognitive functions in children during a critical stage in the development of higher cognitive function. Twentyfive typically developing children and twentyfive children with Fragile X, a neurodevelopmental disorder, who are 68 yrs old (mean age 7 yrs) at the start of the study will be imaged twice, two years apart. Brain images will be acquired while children perform working memory and arithmetic

reasoning tasks. Behavioral performance measures will be acquired simultaneously to determine how well and how efficiently individual children perform these tasks. Standardized neuropsychological. assessment will be performed on each individual to determine the overall level of cognitive ability in each child. The relation between changes in the level and extent of brain activation, task performance and overall IQ will be analyzed to determine domain specific and domain nonspecific features underlying the neurobiology of cognitive development. The proposed fMRI research project will yield important new and more precise information about the neural bases of the development of higher cognitive processes in children as well as its disruption in atypical development.

- **Project Title: LONGITUDINAL MRI STUDY OF BRAIN DEVELOPMENT IN FRAGILE X**

  Principal Investigator & Institution: Piven, Joseph; Professor; Psychiatry; University of North Carolina Chapel Hill Office of Sponsored Research Chapel Hill, Nc 27599

  Timing: Fiscal Year 2005; Project Start 26-SEP-2002; Project End 30-JUN-2007

  Summary: (provided by applicant): Fragile X (FRAX) is the most common known inherited cause of neurodevelopmental disability, resulting from a disruption in expression of the fragile X mental retardation 1 gene (FMRI). Associated with increased risk for a particular profile of cognitive deficits (including mental retardation) and a number of aberrant behaviors (including attentional dysfunction, hyperactivity, perseveration, stereotypies, hyperarousal and social deficits), this life long condition results in considerable impairment to individuals and confers a substantial burden on families and society. A series of cross-sectional neuroimaging studies of older children and adults, from our collaborative group of investigators, demonstrate an association between reduced FMR1 function and a pattern of brain abnormalities in the frontal, striatal, parietal, cerebellar and temporal lobe (hippocampus and superior temporal gyrus) regions. Further, these brain abnormalities are associated with selected cognitive and behavioral abnormalities that are characteristic of FRAX (e.g., enlarged caudate and stereotyped behavior and hyperactivity). In this Collaborative R01, between Stanford (PI: Allan Reiss) and UNC-Duke (PI: Joe Piven), we propose to conduct a longitudinal MM study of 60 FRAX, 60 developmentally-delayed (DD) and 30 typically-developing (TYP) males at age 18-42 months and again 24 months later at age 42-66 months. The overarching aim of this application is to examine the trajectory of gene, brain and behavior relationships, from a developmental perspective, beginning at the earliest ages that it is feasible to undertake such a study (in the three proposed study groups). We believe that this study requires a collaborative effort to: (1) insure a sufficient sample size for study and, (2) to combine a wide range of necessary and complementary expertise and experience. We have assembled a unique team of investigators, experienced in longitudinal behavioral studies of very young children with FRAX, neuroimaging of FRAX and autism, multi-site neuroimaging studies and advanced methods of image processing, that we believe is ideally suited to conduct this study. FRAX offers an important model for understanding the developmental relationships between a complex pattern of cognitive and behavioral abnormalities, brain structure and function, and gene function. Further study of this model system is likely to provide important insights into the pathogenesis and treatment of FRAX and other developmental disorders and abnormalities of behavior and cognition.

- **Project Title: LONGITUDINAL OUTCOMES AND NEUROIMAGING OF FRAGILE X SYND**

  Principal Investigator & Institution: Reiss, Allan L.; Professor; Psychiatry and Behavioral Sci; Stanford University 1215 Welch Road, Mod B Stanford, Ca 943055402

  Timing: Fiscal Year 2005; Project Start 01-MAY-1993; Project End 30-JUN-2007

  Summary: (provided by applicant): **Fragile X syndrome** (fraX) is the most common known cause of inherited mental impairment with well over 100,000 individuals affected in the U.S. Mutations in the FMR1 gene give rise to a clinical phenotype that includes increased risk for aberrant cognitive, behavioral and emotional function. The major emphasis of the 5-year study proposed in this application is a prospective, longitudinal extension o the work completed during the current grant period, during which key cognitive, behavioral, neuroendocrinological, genetic and environmental data were collected from 120 families across the U.S. and Canada, each having a child proband affected with fraX and a typically developing sibling. To the best of our knowledge, this study would be the first longitudinal investigation of a large, school-age fraX cohort in which both biological and environmental factors contributing to clinical outcome were assessed on a prospective basis. We also propose to extend our investigation into the neurobiology of this disorder using advanced brain imaging techniques. Specifically, longitudinal imaging studies will be used to explicate the developmental trajectory of brain structure and function in children with fraX as compared to key control groups. Specific Aims: 1) 10 use a longitudinal, prospective experimental design (with "Time 1" and "Time 2? assessments) to elucidate the developmental trajectory of cognitive, behavioral and emotional development in probands with fraX compared to their like-gender siblings; 2) to specify the longitudinal trajectory of hypothalamic-pituitary-adrenal (HPA) function and measures of FMR1 gene expression in probands with fraX; and 3) to utilize neuromaging techniques to specify the trajectory of brain structure and function in children with fraX compared to specific age-, gender-, handedness-, SES- and lQ-matched control groups. Although knowledge of cognition, behavior and the brain in children and adults with fraX has grown considerably over the past 20 years, longitudinal data from school-age children with this condition are limited. Cross-sectional findings and limited longitudinal data to date support the hypothesis that an age-related decline in standardized cognitive and adaptive behavioral scores occurs among school-age children with fraX. However, many questions remain unanswered regarding this phenomenon, in particular as related to extent, timing and neural basis. These unanswered questions offer a compelling rationale for conducting a longitudinal study of a large group of school-age boys and girls with fraX as proposed in this application.

- **Project Title: MECHANISMS OF GENETIC INSTABILITES OF TRIPLET REPEATS**

  Principal Investigator & Institution: Wells, Robert D.; Director; Center for Genome Research; Texas A&M University Health Science Ctr Research Foundation College Station, Tx 778433578

  Timing: Fiscal Year 2005; Project Start 01-JUN-2001; Project End 31-MAY-2007

  Summary: (Applicant's abstract): Genetic instabilities (expansion and deletions of simple repeating sequences) are important in the life cycles of both prokaryotic and eukaryotic cells. This fundamental mechanism of mutagenesis has been found in mycoplasma, bacteria, yeast, mammalian cells, and in humans. In lower organisms, these genetic polymorphisms are the basis for phase variations which control the expression of genes. In humans, the expansions and deletions of simple repeating sequences are closely tied to the etiologies of cancers as well as hereditary neurological diseases. Prior work has

revealed that expansions are mediated by DNA replication and repair by the slippage of the complementary strands of the repeats to form hairpin loop structures with differing relative stabilities. The principal investigator has recently demonstrated that recombination is a powerful mechanism for generating large expansions. To the extent that this work can be extrapolated to human diseases, recombination may be an important mechanism for the large expansions found in **fragile X syndrome,** myotonic dystrophy, and SCA8. The first Specific Aim is to elucidate the mechanisms of genetic recombination which mediate the triplet repeat sequence (TRS) expansions. Specific Aim 2 will evaluate the role of recombinational repair of double strand breaks in genetic instabilities. The third Specific Aim is to establish a genetic assay for determining the recombination frequency. Specific Aim 4 will investigate tandem duplication-based instabilities in vivo in recA- cells. In summary, the principal investigator will investigate the molecular mechanisms (replication, recombination, repair) that cause genetic instabilities in simple repeat sequences.

- **Project Title: MODELING FRAGILE X SYNDROME IN DROSOPHILA**

  Principal Investigator & Institution: Jongens, Thomas A.; Associate Professor; Genetics; University of Pennsylvania Office of Research Services Philadelphia, Pa 19104

  Timing: Fiscal Year 2005; Project Start 15-SEP-2004; Project End 30-APR-2008

  Summary: (provided by applicant): **Fragile X syndrome** is one of the most commonly inherited forms of human mental retardation with an incidence rate of 1 in 4000 males and 1 in 6000 females. It is caused by the loss of FMR1 gene function. Patients with **Fragile X syndrome** suffer from a variety of symptoms including; mental retardation, attention deficit, hyperactivity, sleep disorders, anxiety, unstable mood and autistic-like behaviors. Physical defects include macroorchidism and irregular dendritic spine morphology. In previous studies, our lab developed a Fragile X model in Drosophila. This model is based on the dfmr1 (also called dfxr) gene, which has a high degree of sequence identity/similarity to the FMR1 gene. The dFMR1 protein has similar RNA binding properties, developmental expression pattern and subcellular distribution to the FMR1 protein (FMRP). In recent studies, we have shown that dfmr1 null mutants display several behavioral defects that bear similarity to symptoms of Fragile X patients. The relevant phenotypes in Drosophila include arrhythmic circadian behavior, attention deficit during courtship, memory defects and subtle defects of neuronal morphology. The similarities in the biochemical properties of dFMR1 and FMRP and their loss of function phenotypes suggest that these two proteins have conserved function in similar behavioral and developmental processes. Thus the Drosophila dfmr1 mutants are a relevant model to study aspects of **Fragile X syndrome.** To ameliorate **Fragile X syndrome** it is imperative that we understand when and how FMR1 activity functions to prevent cognitive and behavioral defects. The temporal requirements and molecular role of FMR1 are currently not known. We propose to use the Drosophila model of Fragile X to determine when dfmr1 activity is required to determine if the behavioral defects are due to developmental or physiological defects. We are also investigating possible physiological pathways affected by loss of dfmr1 function. Through these studies we have identified a pharmacological treatment that rescues the courtship and memory defects displayed in our dfmr1 mutants. In this proposal we will determine and verify a route of action of this drug to identify potential targets for the treatment of **Fragile X syndrome.**

- **Project Title: MOLECULAR MECHANISMS OF NUCLEIC ACID DAMAGE BY ENEDIYNES**

  Principal Investigator & Institution: Goldberg, Irving H.; Professor and Chairman; Biological Chemistry and Molecular Pharmacology; Harvard University (Medical School) Medical School Campus Boston, Ma 02115

  Timing: Fiscal Year 2005; Project Start 15-DEC-1995; Project End 30-NOV-2007

  Summary: (provided by applicant): Nucleic acid bulges have been implicated in a number of biological processes, including TAR (transactivation response element) RNA function in HIV AIDS and as intermediates in the unstable expansion of nucleotide repeats due to DNA strand slippage in at least 12 human neurodegenerative genetic diseases, including Huntington's disease and **fragile X syndrome,** and certain cancers, especially colon. The goal is to design and synthesize spirocyclic bulge-specific, wedge-shaped molecules, based on earlier work with the enediyne antitumor antibiotic neocarzinostatin that modulate these processes. These agents have been found to promote DNA strand slippage synthesis in simple model systems; their structures will be modified to optimize this process and then derivatized to generate alkylating and cleaving species that interfere with the expansion. Mechanistic studies will be undertaken to determine the molecular and structural basis for this action, and the model systems will be modified to more closely resemble the disease situation. Mammalian cell culture systems, developed as Huntington's disease models, will be used to test the effect of these agents. The use of small synthetic molecules to modify gene replication and expression represents a novel way of treating "gain-of-function" genetic diseases. Solution structures of relevant drug/nucleic acid complexes will be elucidated by high resolution NMR spectroscopy. Selection from RNA diversity libraries (SELEX) will be used to identify the structural parameters for optimal RNA bulge binding. Enediyne antibiotics have been used recently in the treatment of relapsed acute myelogenous leukemia. One of the most potent members of this family of agents, C-1027, forms interstrand crosslinks involving the deoxyribose moieties of opposite DNA strands, especially under anaerobic conditions. This lesion, postulated to account for cell killing in oxygen-poor centers of solid cancers, will be isolated and its unique chemical structure determined. The conformational changes induced by this lesion in duplex DNA will be analyzed by NMR. These studies will provide insight into its action and offer a basis for the design of more effective drugs.

- **Project Title: MRDD RESEARCH CENTER**

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

  Timing: Fiscal Year 2005; Project Start 01-AUG-1988; Project End 30-JUN-2008

  Summary: [provided by applicant]: The University of Colorado Mental Retardation and Developmental Disabilities Research Center requests support for nine cores (eight previously funded and one proposed) for a comprehensive research program on MRDD. The research strengths of the Center encompass several themes. The first is studies in inborn errors of metabolism, including glutaric acidemic types I and II that were discovered at this Center, propronic academia, and homocystinuria. The second area of strength is in exploring the genes responsible for single and multigene disorders: autism, Down syndrome, **fragile X syndrome,** dyslexia, attention deficit hyperactivity disorder, and schizophrenia. A third group seeks to understand the phenotype and core deficits in very young children with autism and the inter-relationship between autism and **fragile X syndrome.** Determination of the neuropsychology of a variety of these

disorders is a fourth strength of the proposed Center. The investigators will utilize a wide range of investigative techniques to approach these important problems, from studies of emotional development in humans, through the use of anatomic and behavioral studies of animal models, to very basic molecular understanding of gene regulation, to solving of the crystal structure of enzymes. The cores that support this research include Tissue Culture, Molecular Biology, Mass Spectrometry, Proteomics, and Analytical Chemistry, Developmental Neuropsychology, Animal Housing and Assessment, and Research Support Services. With the last funding cycle, the investigators initiated an Enzyme and Molecular Diagnosis Core that has been extremely successful in supporting the research of Center investigators. In addition, the investigators have started a new facility, the Human Subjects Recruitment and Evaluation Core. The Colorado Center has received substantial support from all levels of the University of Colorado and looks forward to a new era on a new campus, in which basic scientists, clinical investigators, and all clinical facilities will be united for the first time. An adjacent biotechnology park will facilitate the translation of Center findings into treatments. The investigators have been chosen to be in the first group of researchers to move to the new campus, and their space has been carefully designed to meet the needs as a center, and to put the Center investigator into proximity to other groups, such as Human Molecular Genetics, that can enhance Center scientific interactions. Strategic planning has led the investigators to initiate a series of hires, principally in basic neurosciences, and has led to considerable enhancement of cores.

- **Project Title: MUTIDISCIPLINARY TRAINING; BRAIN DISORDERS & DEVELOPMENT**

  Principal Investigator & Institution: Swann, John W.; Professor; Pediatrics; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 770303498

  Timing: Fiscal Year 2005; Project Start 01-JUL-2002; Project End 30-JUN-2007

  Summary: (provided by applicant) The goal of this new postdoctoral program is to train young scientists, particularly physician scientists, and promote careers focused on understanding the basic mechanisms underlying disorders of the developing nervous system. Multidisciplinary training is planned in scientific disciplines relevant to the study of neurodevelopmental disorders. Thus, 19 training faculty were selected from 5 departments. The faculty includes 4 MDs, 2 MD/Ph.Ds and 13 Ph.Ds. Their ranks are: 11 Professors, 3 Associate Professors and 5 Assistant Professors. Dr. Swann will serve as Program Director and be responsible for the day-to-day operation of the program. Dr. Zoghbi and Dr. Noebels will serve as Co-Directors. Major training areas include the genetic and molecular basis of inherited neurodevelopmental disorders including: Rett Syndrome, Angelman's Syndrome, **Fragile X Syndrome,** Downs Syndrome, Miller-Dicker Lissencephaly and Generalized Spike-Wave Epilepsy. Another, shared focus of study will be epilepsy where neuroscience laboratories use advanced imaging and electrophysiological techniques to study the cellular and molecular abnormalities relevant to chronic models of both inherited and acquired seizure disorders. All the laboratories of the faculty provide expertise in cutting-edge biotechnology for the creation and study of animal models. Three separate training tracks are planned. One is for MD/PhDs and MDs with substantial basic science research experience. Another is for less experienced MDs and the third for PhDs. These latter MD students will be advised by individualized research advisory committees on their choice of laboratory rotations and graduate level courses. PhDs will receive substantial training in the clinical aspects of neurodevelopmental disorders through clinical conferences, subspeciality clinics and hospital rounds. Baylor College of Medicine has committed substantial resources to the study of the basic mechanisms of diseases including those of

the developing brain. Laboratory space and core laboratories are outstanding. Pediatric Neurology clinics, laboratories and centers, including a NIH funded Mental Retardation Research Center, will be important resources for postdoctoral trainees. There are currently 84 postdoctoral students in the laboratories of the training faculty, including 14 MD/PhDs, 8 MDs and 62 PhDs. By training a new generation of outstanding research scientists, we hope new approaches for the treatment and cure of devastating developmental disorders in infants and young children will emerge.

- **Project Title: NEUROLOGICAL FUNCTION OF FRAGILE X GENE IN DROSOPHILA**

  Principal Investigator & Institution: Broadie, Kendal; Professor of Biological Sciences; Biological Sciences; Vanderbilt University Medical Center Nashville, Tn 372036869

  Timing: Fiscal Year 2005; Project Start 20-APR-2001; Project End 31-MAR-2007

  Summary: (Adapted from the applicant's Description) **Fragile X syndrome** is caused by a triplet nucleotide CGG expansion within the 5' untranslated region in the gene FMR1, resulting in the absence of the gene product, FMRP, a selective RNA-binding protein associated with ribosomes and enriched in nervous system. The compelling challenge in fragile X research is to understand the cellular pathogenesis by which the lack of FMRP gives rise to mental retardation and associated behavioral abnormalities. One potential approach is to assay the FMR1 within a simpler, well-characterized model organism. The investigators propose to uncover the synaptic defects of **fragile X syndrome,** and identify and characterize novel FMR1 interacting genes in Drosophila. They have identified a FMR1 gene homologue in Drosophila, dFXR, and hypothesized that the function of FMR1 is conserved between Drosophila and human. Taking advantage of powerful Drosophila genetics, they propose to systemically investigate the neurological functions of FMRP by a three-step approach. Specific Aim 1 will generate a series of dFXR mutants, including "loss of function" mutants by targeted knockout and "gain of function" mutants by manipulating the expression of transgenes. Specific Aim 2 will characterize the neurological functions of dFXR, focusing on synaptic development, function, and plasticity. Specific Aim 3 will search for novel dFXR interacting genes with a genetic enhancer / suppressor screening and microarray technology. This application therefore complements and extends the parallel studies on mammalian systems.

- **Project Title: NEUROLOGY AND THE MOLECULAR ROLE OF N-RBPS IN THE BRAIN**

  Principal Investigator & Institution: Darnell, Robert B.; Professor; Lab/Molecular Neurooncology; Rockefeller University 1230 York Avenue New York, Ny 100216399

  Timing: Fiscal Year 2005; Project Start 01-SEP-1995; Project End 31-JUL-2007

  Summary: (provided by applicant): The goal of this proposal is to examine the functions of the Nova family of paraneoplastic neurologic disease antigens in neurons, and to compare them with those of the closely related fragile X mental retardation protein FMRP. We have developed new methodology to identify neuronal RNAs bound by these proteins. Specific hypotheses regarding these interactions will be examined in vitro, and extended in vivo, using genetically modified mice, to provide direct evidence for the function of these RNA binding proteins in the brain. We will identify new RNA targets using RNA selection from a transcribed sequence library, by biochemical purification, and by using array analysis. We will explore two hypotheses regarding how Nova functions on these RNAs. First, we will examine the role of Nova in binding nuclear RNA sequences for the regulation of alternative splicing. Second, we will explore the function of cytoplasmic Nova, following up preliminary data suggesting

that it is involved in translational control. We will compare our findings with actions of FMRP on target RNAs we have identified. To validate these studies, we will move from in vitro and cell based biochemistry to in vivo biochemistry by repeating our analyses of Nova and FMRP function in genetically defined mice. One set of mice will include Nova and FMRP KO mice. A second set will consist of BAC transgenic mice modified to test the function of specific protein-RNA actions we have identified. These studies will allow us to formulate a model comparing and contrasting the role that the Nova and FMRP RNA binding proteins in neurons and in neurologic disease.

- **Project Title: NEUROPHYSIOLOGICAL-MOLECULAR ASSOCIATION IN FXS INFANTS**

  Principal Investigator & Institution: Hill Karrer, Jennifer; Associate Professor; University of Victoria 3800 Finnerty Road Victoria, Bc V8p 5C2

  Timing: Fiscal Year 2005; Project Start 01-JUL-2000; Project End 31-AUG-2006

  Summary: Fragile X syndrome (FXS) is an inherited abnormality responsible for mild to moderate mental retardation among individuals with expanded DNA material (greater than 230 CGG repeats) on the FMR-1 gene. Prevalence in the general population is problematic since one in 250 females are carriers of FXS. The purpose of this research project is to investigate the impact of FXS on early neurocognitive development among infants, toddlers and preschoolers. Neurophysiological, molecular and behavioral measures will be integrated in this study to explain, in part, biobehavioral dysfunction responsible for the decline in cognitive functioning during the first five years of life. For the first time, event-related brain potentials (ERPs) will be recorded from infants and children with FXS. Unaffected and premutation siblings of subjects with FXS and (unrelated) subjects without known risk of developmental delay will serve as comparison groups. Subjects with Down syndrome (DS) will likewise serve as a contrast study group. Studies within this project will investigate syndrome-specific strengths and weaknesses related to attention, expectancy, stimulus encoding, sequential information processing, visual recognition memory and social gaze. Results will therefore provide new knowledge concerning genotypic-specific neural organization of early cognitive development among subjects with FXS (as compared to subjects with DS). Specific ERP components will thereafter be correlated to CGG repeat region size, FMRP (FMR-1 gene protein), percent methylation, mRNA and, among females, the X activation ratio. The integration of neurophysiological, molecular and behavioral measures through Hierarchical Linear Modeling will assess the impact of FXS upon human neurocognitive development. At the conclusion of our projects, measures developed within our studies will provide new methodologies in the assessment of the effectiveness of early intervention. Outcome measures will likewise provide the means to critique subsequent pharmacotherapy and gene therapy specific to FXS. Results of this study will provide a time course of onset of neuropathology due to deficiencies of FMRP during early development and, accordingly, provide a more precise target of the ideal age at which FMRP protein replacement should be applied among children with FXS.

- **Project Title: NUMERICAL DEFICITS ACROSS MULTIPLE GENETIC DISORDERS**

  Principal Investigator & Institution: Simon, Tony J.; Research Assistant; Psychiatry & Behavioral Sciences; University of California Davis Office of Research - Sponsored Programs Davis, Ca 95618

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

Summary: (provided by applicant): The central aim of the proposed research is to investigate whether there is a common basis for the numerical cognition deficits associated with three neurogenetic disorders: Turner, Williams, and full mutation fragile X syndromes. Despite many differences, numerical deficits have been consistently reported in individuals with Turner, Williams, full mutation fragile X, and 22q11.2 deletion (velocardiofacial/DiGeorge) syndromes, among others. The investigators hypothesize that some key aspects of visuospatial function are disturbed in each of these syndromes, and characterization of these basic processes will generate explanations of, and possibly indicate treatments for, these numerical deficits. On the other hand, the differences among these genetic syndromes will allow the investigators to control for a range of critical factors such as intelligence level, brain volume, cardiac status, and other cognitive performance domains. This project aims to study seven to fourteen year old children with Williams, Turner, and full mutation fragile X syndromes in parallel with a study of 22q11.2 deletion syndrome children already being carried out by the principal investigator. This will constitute the first parallel study of children with all of these disorders using the same methodology. Thus it has the potential to reveal critical information about a putative "common pathway" for foundational numerical cognitive competence. Little is known about why a set of neurogenetic disorders that produce such different physical and intellectual outcomes should share what appears to be a common deficit in the numerical cognition domain. The investigators' hypothesis is that the disorders all create some form of anomalous in brain development that affects the parietal lobes, as well as other brain areas, in such a way as to disturb the normal development of visual/spatial cognition. Therefore, the investigators propose a program of research in three genetic disorders: Turner, Williams, full mutation fragile X syndromes with the following aims: (1) Characterize the cognitive deficit with performance tests; (2) Specify the volumetric changes in brains of children with these disorders; (3) Determine, via diffusion tensor imaging, white matter anomalies that might contribute to cognitive dysfunction; and (4) Directly measure, via functional magnetic resonance imaging (fMRI), cortical activity as children attempt visuospatial and numerical cognition tasks. The investigators expect that the results of these studies will provide the first extensive explanation of the similarities and/or differences in foundational numerical cognitive processes that exist among these different disorders. Findings are likely to indicate critical neurocognitive factors in the development of normal and disturbed early numerical ability. It should be possible to use these results to develop interventions for children with numerical disabilities and improved teaching methods in the numerical domain for typically developing children.

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

  Principal Investigator & Institution: Klein, Hannah W.; Neurology; University of Iowa Iowa City, Ia 52242

  Timing: Fiscal Year 2005; Project Start 18-SEP-2004; Project End 17-SEP-2009

  Summary: (provided by applicant): The areas of neuroscience that interest me most are the genetic and molecular aspects of development. I would like to focus my PhD work on either the factors involved in normal brain development, or on how abnormal signaling or gene mutations can lead to abnormal development. I am interested in these areas because of their application to learning disabilities, mental retardation, and to other developmental syndromes.

- **Project Title: PROTEIN-RNA RECOGNITION IN NEURODEGENERATIVE SYNDROMES**

  Principal Investigator & Institution: Patel, Dinshaw J.; Professor; Sloan-Kettering Institute for Cancer Res 1275 York Ave New York, Ny 100216007

  Timing: Fiscal Year 2005; Project Start 05-DEC-1989; Project End 30-JUN-2009

  Summary: (provided by applicant): A number of cancer-related autoimmune and neurologic diseases are associated with RNA-binding proteins. This revised application focuses on a structural (x-ray and NMR) and functional (impact of mutations) investigation of protein-RNA recognition in Fragile X mental retardation (FXMR) and paraneoplastic opsoclonus-myoclonus ataxia (POMA) syndromes. This project represents a collaborative effort with the Robert Darnell laboratory, which has biochemically identified the relevant protein-RNA complexes, and is currently addressing biological and clinical issues associated with these syndromes. Project 1: Our structural efforts on the FXMR syndrome have focused on the complex between an RGG peptide and a quadruplex-duplex neuronal RNA scaffold for which we have obtained exceptional NMR spectra, including spectra of samples uniformly 13C,15N-labeled in the peptide and RNA components. These structural efforts will be followed up by mutational experiments coupled with affinity measurements using surface plasmon resonance to identify energetic contributions involving key residues associated with molecular recognition. A new project involves the structure determination of a complex between one of the two FXMR KH domains and its in vitro-selected RNA target identified in the Darnell laboratory. We also propose to solve structures of three distinct sets of crystals of FXMR syndrome r(CGG)n repeats, n = 3, which have been grown in various space groups, one of which diffracts to 1.0 A resolution. Project 2: Our proposed structural studies of the POMA syndrome are directed towards our long-term goal of providing a structural understanding of how full length Nova (KH1-KH2-KH3) proteins target and regulate alternative splicing events within the alpha-2 glycine receptor subunit pre-mRNA, where the RNA target contains the UCAU-Y-UCAU-Y-UCAU sequence. We have already determined a crystal structure ol a Nova KH1/KH2 construct bound to its UCAN-UCAN-containing RNA hairpin, where KH1 targets one of the two UCAN RNA segments, while KH2 is involved in protein dimerization. We are currently mutating residues at the unanticipated KH dimeric interface to evaluate its functional role, as well as attempting to provide a molecular explanation for protein engineering efforts aimed at extending the KH-RNA interface.

- **Project Title: PSYCHOPATHOLOGY IN YOUNG PEOPLE WITH MENTAL RETARDATION**

  Principal Investigator & Institution: Hofer, Scott M.; Professor; Gerontology Center; Pennsylvania State University-Univ Park 110 Technology Center University Park, Pa 16802

  Timing: Fiscal Year 2005; Project Start 01-APR-2000; Project End 31-JAN-2008

  Summary: (provided by applicant): The purpose of this application is to support an ongoing program of research aimed at determining risk and resilience factors in the evolution of psychopathology in an internationally unique cohort of young people with mental retardation that forms the Australian Child to Adult Development (ACAD) Study. The broad aims of this application are to 1) study the course and pattern of psychopathology in children with mental retardation; 2) examine potential biopsychosocial risk and protective factors which may be associated with psychopathology; and 3) evaluate and refine the measurement properties of the DEC, the principal instrument used to assess psychopathology in this study and in broad use

internationally. The fourth wave of the ACAD study (14 years of follow-up) has now been completed and permits analysis of the development of psychopathology from childhood through adolescence to young adulthood. Advanced statistical methods, including growth mixture models, will be used to identify developmental trajectories of emotional and behavioral disturbance in these groups, to investigate risk, mediating and moderating factors, and to empirically delineate subpopulations showing distinct patterns of change over time. A separate aim is to evaluate and refine the psychometric properties of the Developmental Behavioral Checklist (DEC) in the longitudinal ACAD study and in several international cross-sectional datasets. The analysis of psychometric properties of the DEC will use new developments for multiple-group factor analysis of categorical data and item-response models to construct and evaluate a short-form measure of psychopathology. This application provides an extraordinary opportunity to evaluate the mental health pathway of this vulnerable population through the transition into adulthood. The unifying purpose of this project is to apply advanced statistical modeling techniques to the existing ACAD data and to strengthen the findings by incorporating comparable data collected in a number of other countries.

- **Project Title: REGULATING TRANSLATION DURING NEURAL DEVELOPMENT BY FMRP**

  Principal Investigator & Institution: Lau, Anthony G.; Pharmacology; Emory University 1784 North Decatur Road, Suite 510 Atlanta, Ga 30322

  Timing: Fiscal Year 2006; Project Start 01-JUL-2006; Project End 30-JUN-2009

  Summary: (provided by applicant): **Fragile X syndrome,** the most common form of inheritable mental retardation, results from the loss of function of the fragile X mental retardation protein (FMRP). FMRP is a selective RNA-binding protein shown to effect the translation and translocation of mRNA in the brain. Recently, FMRP has been shown to associate with the microRNA pathway. However, the molecular mechanisms controlling the activity of FMRP to effect translation remain elusive. The aims of this proposal are: 1) to determine the effects of FMRP on the expression levels of microRNA, and in particular let-7b, during brain development and 2) to determine the existence of a coordinated role of microRNA and FMRP to suppress translation. To examine these aims, MAPI B will be used as the experimental model due to preliminary data showing that both FMRP and microRNA can regulate the protein levels of MAP1B in the brain. By determining these mechanisms, a clearer understanding and potential, novel therapeutic targets of **fragile X syndrome** will be obtained, along with an improved understanding of FMRP's role in normal brain development.

- **Project Title: REGULATION OF MRNA SPLICING BY MER1P**

  Principal Investigator & Institution: Spingola, Marc; Biology; University of Missouri-St. Louis One University Boulevard Saint Louis, Mo 631214400

  Timing: Fiscal Year 2007; Project Start 01-JAN-2007; Project End 31-DEC-2008

  Summary: (provided by applicant): Mer1p is produced during meiosis in the yeast Saccharomyces cerevisiae and activates the splicing of at least three introns in genes whose products are required for completion of meiosis. The mRNAs of these genes contain a positive regulatory element, or splicing enhancer, in their introns that binds to Mer1p in vitro. A hypothesis for how Mer1p regulates the splicing of these genes is that Mer1p stabilizes early splicing complexes that form on these introns allowing them to continue assembling into an active spliceosome. Without Mer1p these early splicing complexes lack sufficient stability to continue assembling into an active enzyme. The specific aims of this project include measuring the stability and rates of formation of

these complexes with and without Mer1p, and with and without other splicing factors that are critical for Mer1p- activated splicing. This will be achieved with kinetic studies and competition stability studies using splicing extracts and RNAs containing the Mer1p enhancer element. The long-term goals of the PI's research are to understand the mechanisms that govern differential splicing and how aberrant splicing leads to disease in humans. Mer1p contains an evolutionarily conserved KH domain RNA binding motif, and several putative Mer1p homologues can be identified in the human genome. KH domain proteins have been implicated in several diseases in humans including **Fragile X Syndrome** and Paraneoplastic Disease. Unfortunately there is little understanding of how KH domain proteins regulate splicing. A pursuit of the function of KH domain proteins in a tractable model organism like yeast will facilitate the understanding of the mechanisms of this family of proteins in humans and provide opportunities for the PI to transition into animal model systems. Many diseases and cancers result from the improper metabolism of RNA, which are molecules made from DNA and are used in the production of proteins in cells. Unfortunately there is little understanding of how RNA metabolism is regulated by molecules like the Mer1p protein. This project will elucidate how Mer1p and similar proteins function and will offer important insights towards the basis of diseases like **Fragile X Syndrome** in humans.

- **Project Title: REGULATION OF RAS-SIGNALING PATHWAYS BY SYNGAP**

  Principal Investigator & Institution: Carlisle, Holly; None; California Institute of Technology Office of Sponsored Research, Mail Code 201-15 Pasadena, Ca 91125

  Timing: Fiscal Year 2005; Project Start 01-MAR-2004; Project End 28-FEB-2007

  Summary: (provided by applicant): The overall objective of this project is to further elucidate the role of SynGAP, a synapse specific Ras GTPase activating protein, in the regulation of activity-dependent Ras activation and downstream Ras effectors. The specific aims are to (1) determine if homeostasis of active Ras is perturbed in the absence of SynGAP in mature synapses, (2) examine whether regulation of actin remodeling through a Ras/PI3K/Rac pathway is influenced by SynGAP activity, and (3) test whether phosphorylation of KV4.2 channels via the Ras/MAPK pathway is altered by disruption of SynGAP activity. The research methods will include techniques routinely performed in the Kennedy lab (Ras activation assays, western immunoblotting, immunocytochemistry, and confocal microscopy) combined with techniques that I learned during my graduate work (hippocampal slice preparation and electrophysiology). Abnormal regulation of Ras and its downstream effectors has been implicated in several human cognitive disorders including Neurefibromatosis, Coffin-Lowry Syndrome, Rubinstein-Taybi Syndrome, and **Fragile X Syndrome.** Understanding how Ras signaling pathways are regulated in adult neurons may further our understanding of the molecular underpinnings of these disorders.

- **Project Title: RESEARCH IN MENTAL RETARDATION AND CHILD DEVELOPMENT**

  Principal Investigator & Institution: Guralnick, M J.; Professor; None; University of Washington Office of Sponsored Programs Seattle, Wa 98105

  Timing: Fiscal Year 2005; Project Start 01-AUG-1989; Project End 30-JUN-2009

  Summary: (provided by applicant): The University of Washington's Mental Retardation and Developmental Disabilities Research Center (MRDDRC), based at the Center on Human Development and Disability (CHDD), provides a comprehensive interdisciplinary research program in the field of mental retardation/developmental

disabilities and related aspects of human development. Research is carried out in three major domains: (1) Developmental and Molecular Genetics, (2) Developmental Neuroscience, and (3) Developmental Processes and Behavioral Science. Interdisciplinary collaborations are emphasized in research carried out in 12 Research Emphasis Areas: Autism, Craniofacial Malformations, Developmental Toxicology, Ecological Factors, Epilepsy, Fetal Alcohol Syndrome, **Fragile X Syndrome,** Infectious Disease and Immunology, Joubert Syndrome, Learning Disabilities, Neural Plasticity, and Neurodegenerative Disorders. Through this grant application, support is requested for five scientific core facilities and one administrative core to enhance the effectiveness of scientists carrying out their research as part of our MRDDRC. The scientific core support facilities are as follows: (1) Genetics, (2) Neuroscience, (3) Behavioral Science, (4) Infant Primate Research Laboratory, and (5) Instrument Development Laboratory. Other MRDDRC objectives include training researchers in various disciplines, disseminating research findings, and maintaining linkages to clinical training activities and exemplary service programs.

- **Project Title: ROLE OF FMRP IN SYNAPTIC FUNCTION AND PLASTICITY**

  Principal Investigator & Institution: Pfeiffer, Brad E.; Physiology; University of Texas Sw Med Ctr/Dallas Dallas, Tx 753909105

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

  Summary: (provided by applicant): **Fragile X Syndrome** (FXS), the most common form of inherited mental retardation, is caused by the loss of function of the Fragile X Mental Retardation Protein (FMRP). Studies of FXS patients and mouse models of FXS suggest that FMRP is critical for proper synaptic function and plasticity. I propose to investigate the role of FMRP in synaptic function through three major aims: 1) Electrophysiological measurements of synaptic function following transient alteration of FMRP expression levels in organotypic hippocampal slice cultures (OHSCs) and through the use of FMRP mutants; 2) Electrophysiological analysis of synaptic plasticity in FMRP-overexpressing mice and in OHSCs following transient overexpression of FMRP and FMRP mutants; and 3) Biochemical analysis of glutamate receptor expression and trafficking in FMRP-overexpressing and FMRP-knockout mice and in OHSCs following transient alterations in FMRP expression. This research should give substantial insight into the role of FMRP at the synapse and may provide impetus for the generation of a treatment for FXS.

- **Project Title: SPEECH OF YOUNG MALES WITH FRAGILE X SYNDROME**

  Principal Investigator & Institution: Roberts, Joanne E.; Senior Scientist and Research Professor; Pediatrics; University of North Carolina Chapel Hill Office of Sponsored Research Chapel Hill, Nc 27599

  Timing: Fiscal Year 2005; Project Start 07-JUL-2003; Project End 30-APR-2008

  Summary: (provided by applicant): **Fragile X syndrome** is the most common inherited cause of mental retardation, and unintelligible speech is a very common characteristics of young males with **fragile X syndrome** (FXS). It is unclear what aspects of speech (e.g., rate, prosody, oral structure/function, articulation, phonological processes) cause poor intelligibility. Furthermore, it has not been determined what is the role of motor speech/FMR1 protein (FMRP) levels, cognitive/linguistic factors, and the communicative context in affecting intelligibility of conversational speech of males with FXS. Identifying these factors is important because the ability to be understood is critical for effective communication, and poor speech intelligibility compromises all aspects of daily verbal interactions. The proposed study builds on a currently funded R0-3 pilot study Hearing and Speech of Young with Males with **Fragile X Syndrome,** funded by

the RFA "Neurobiology and Genetics of Fragile X Syndrome" in April of 2001, which examined at one point in time the speech and hearing skills of young males with **fragile X syndrome.** The proposed research will expand this research by examining longitudinally over a five year period the factors that affect changes in the speech intelligibility of 8 to 12 year old males with FXS in comparison to developmental age matched males with Down syndrome (DS) and males who are typically developing (TD). It will identify if motor speech/FMRP levels, cognitive/linguistic factors, and the social demands of the communicative context affect speech intelligibility. The specific objectives of this study are to: a) compare the development of phonological, prosodic, and segmental factors in the speech of males with FXS, males with DS, and TD males; b) identify the phonological, prosodic, and segmental factors affecting the speech intelligibility in conversational speech of males with FXS and determine if similar patterns of association are observed among males with DS and TD males; and c) to identify the motor speech/FMRP, cognitive/linguistic, and communicative contextual factors associated with speech intelligibility in conversational speech among males with FXS, and determine if similar patterns of association are observed among males with DS and TD males. Sixty males with FXS between 8 and 12 years of age, 40 males with Down syndrome between 8 and 12 years of age and 40 typically developing males matched for nonverbal intelligence age will be followed for five years. Speech production in isolated words, imitated sentences, spontaneous conversational speech, and narratives will be examined for prosodic and segmental features, phonological processes, and speech intelligibility for the three groups. In addition, children's oral motor skills, phonological processing, and selective listening will be examined. Fragile X DNA testing and FMRP analysis from blood samples will be done only on males with FXS. Growth curve methods will be used to quantify patterns of change over time in the overall level and rate of speech development including speech intelligibility. Of particular interest will be longitudinal analyses of speech intelligibility designed to determine the degree to which motor speech/FMRP, cognitive/linguistic, and contextual factors predict speech intelligibility among males with FXS. Subsequent analyses will ask whether factors associated with intelligibility among males with FXS are also associated among males with DS and TD males. Findings will contribute to a better understanding of the factors that affect speech intelligibility in young males with FXS and provide an essential knowledge base for speech intervention.

- **Project Title: STABILITY & FRAGILITY OF TRINUCLEOTIDE REPEATS IN YEAST**

  Principal Investigator & Institution: Freudenreich, Catherine H.; Assistant Professor; Biology; Tufts University Medford 20 Professors Row Medford, Ma 02155

  Timing: Fiscal Year 2005; Project Start 01-MAY-2001; Project End 30-APR-2007

  Summary: (Verbatim from the applicant's abstract): Expansion of trinucleotide repeat (TNR) sequences is the causative mutation for a number of hereditary diseases, including myotonic dystrophy, the most common dystrophy in adults, **Fragile X syndrome,** the most common form of inherited mental retardation, and neurodegenerative diseases such as Huntington's and the spinocerebellar ataxias. The mechanism of TNR instability is interesting both for understanding the etiology and inheritance of the triplet repeat diseases, and for a basic understanding of genome stability in humans. In addition, expanded CGG/CCG and CTGICAG sequences are sites of chromosome fragility, areas prone to breakage in vivo. Chromosome breakage is implicated in the generation of translocations and deletions found in many types of cancer. The aim of this proposal is to elucidate the mechanisms involved in TNR instability and fragility, and determine how these two unusual characteristics are interrelated using Saccharomyces cerevisiae. A novel genetic assay has been developed

that produces a selectable phenotype when a TNR tract expands or breaks. This assay will be used to screen for proteins whose over-expression influences TNR expansion or fragility. The proteins found to influence TNRs will be characterized to determine both their normal cellular functions and their influence on repeat maintenance. In addition, the hypothesis that TNR expansions occur by aberrant lagging strand replication will be tested by analyzing tract stability (by PCR) and fragility (by genetic and physical analysis) in specific yeast replication mutants. The role of the G2IM checkpoint in detecting TNR tract damage and preventing chromosome breakage will be investigated by comparing rates of TNR tract breakage in wild-type and cheokpoint-defective cells. Lastly, these analyses will be extended to other types of minisatellite sequences that act as fragile sites in human cells. The proposed experiments are designed to elucidate not only how simple repeats expand to cause human disease, but also the consequences of and cellular response to expanded tracts, with the goal of understanding how genomic instability can affect human health.

- **Project Title: STABILITY OF EPIGENETIC STRUCTURES IN ART CHILDREN**

  Principal Investigator & Institution: Sapienza, Carmen; Professor; Fels Institute for Cancer Rearch & Molecular Biology; Temple University 1601 N. Broad Street Philadelphia, Pa 19122

  Timing: Fiscal Year 2006; Project Start 15-APR-2006; Project End 31-MAR-2011

  Summary: (provided by applicant): Involuntary infertility affects approximately one in ten couples, worldwide. This fraction of the population translates to a large number of individuals who are potential candidates for assisted reproductive technology (ART). In fact, more than a million children have been born as the result of in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) and children conceived by these procedures account for more than 1% of all births in several western countries. Despite the many reassuring reports on the safety of ART, there have been a small number of recent reports suggesting that ART children may be at increased risk for rare congenital malformation syndromes that are related to defects in genome imprinting. At least three children conceived by ICSI have been diagnosed with Angelman syndrome and at least 28 ART children (both IVF and ICSI cases) have been diagnosed with Beckwith-Wiedemann syndrome. The suggestion that ART children may be at modestly increased risk for rare, congenital disorders associated with defects in imprinting is troubling on two counts. The first is the obvious and direct impact of these particular syndromes on affected children and their families. The second, and more troubling, consideration is that these data may portend more widespread effects of ART on the establishment or maintenance of genome imprints, or other epigenetic marks, than can be assessed by screening for rare congenital abnormalities. For example, a strong association between sporadic colon cancer and constitutional loss of imprinting at the insulin-like growth factor 2 gene has been reported independently by two laboratories. The purpose of the proposed study is to determine whether ART increases the possibility of deregulated expression of imprinted genes and/or destabilizes epigenetic chromosomal marking. Seven measures of epigenetic chromosomal marking (DNA methylation at three differentially methylated regions, transcription of alleles at three imprinted genes, and X-chromosome inactivation ratios in females) will be analyzed on a population of 500 newborns conceived through ART and a control population of 500 newborns conceived in the traditional fashion. The incidence of abnormal epigenetic marks will be compared between the two populations to determine whether any aspect of the ART procedure results in destabilization of epigenetic structures in the genomes of early human embryos.

- **Project Title: THE ETIOLOGY OF FRAGILE X MENTAL RETARDATION SYNDROME**

  Principal Investigator & Institution: Dolen, Gul; Neuroscience; Brown University 164 Angell Street Providence, Ri 02912

  Timing: Fiscal Year 2005; Project Start 20-MAR-2003; Project End 31-AUG-2007

  Summary: (provided by applicant): Fragile X mental retardation syndrome is one of the most common heritable forms of mental retardation in humans. The molecular genetic basis of **fragile X syndrome** has been identified; mutation of the fragile X mental retardation-1 gene(FMR1) leads to a loss of the protein product, the fragile X mental retardation protein (FMRP). Despite our genetic understanding of **fragile X syndrome,** the biological function of FMRP remains unknown. The role of FMRP can now be studied using the Fmrl-KO mouse, a transgenic model of **fragile X syndrome** in which FMRP has been genetically knocked out. Recent work in our lab has used these mice to identify a functional role for FMRP in regulating activity-dependent synaptic plasticity in the brain; FMR1-KO mice exhibit increased long-term depression (LTD) of synaptic strength induced by metabotropic glutamate receptor (mGluR) activation. We hypothesize that a lack of FMRP increases mGluR-dependent protein synthesis and/or long-term depression (LTD) in the brain and might be an underlying cause of fragile X mental retardation. Specifically, we aim to test the possibility that the abnormal dendritic spine formation and increased susceptibility to epileptiform activity associated with **fragile X syndrome** is a direct consequence of inappropriate mGluR regulation. Through this mechanistic link, we hope to account for the morphological, physiological, and behavioral characteristics of **fragile X syndrome** and to devise strategies for therapeutic treatments.

- **Project Title: TRANSLATION REGULATION IN HIPPOCAMPAL LTP AND LTD**

  Principal Investigator & Institution: Klann, Eric; Professor; Molecular Physiology & Biophysics; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 770303498

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

  Summary: (provided by applicant): This proposal is designed to investigate the biochemical signaling mechanisms underlying metabotropic glutamate receptor-dependent (mGluR) long-term depression (LTD) and late-phase long-term potentiation (L-LTP) in area CA1 of the mouse hippocampus. These forms of synaptic plasticity previously have been shown to be dependent on new protein synthesis. However, virtually nothing is known about the signaling cascades that couple either mGluRs or N-methyl-D-aspartate (NMDA) receptors to the protein translation machinery during these forms of plasticity. If both mGluR-LTD and L-LTP are both dependent on protein synthesis, then several critical questions arise. Are the same signaling pathways required to couple mGluRs and NMDA receptors to the translation machinery during mGluR-LTD and L-LTP, respectively? Are there mRNAs that are preferentially translated during mGluR-LTD versus L-LTP? Using a combination of biochemical, immunocytochemical, pharmacological, and electrophysiological techniques, as well as genetically-modified mice, we propose to 1) test the hypothesis that cap-dependent translation signaling pathways are involved in mGluR-dependent LTD and late-phase LTP, 2) test the hypothesis that S6-directed translation signaling pathways are involved in mGluR-dependent LTD and late-phase LTP, and 3) test the hypothesis that fragile X mental retardation protein is involved in the regulation of mGluR-dependent LTD but not late-phase LTP, and that translation is regulated improperly during mGluR-dependent LTD in mouse models of fragile X mental retardation. These studies should provide insights into the signaling cascades that couple mGluRs and NMDA receptors

to protein translation forms of synaptic plasticity that may be important for learning and memory. These studies may also elucidate unique signaling cascades in the hippocampus that will be critical for understanding the behavioral abnormalities and memory impairments associated with fragile X mental retardation.

- **Project Title: TRANSLATIONAL REGULATION OF FRAGILE X SYNDROME GENE**

  Principal Investigator & Institution: Lim, Jae H.; Neuroscience; Brown University 164 Angell Street Providence, Ri 02912

  Timing: Fiscal Year 2005; Project Start 01-JUL-2002; Project End 31-AUG-2007

  Summary: (provided by applicant): Fragile X mental retardation syndrome is the most common form of inherited mental retardation. It is transmitted as a X-linked dominant trait with reduced penetrance and is associated with a fragile site known as FRAXA (Fragile site, X chromosome, A site) at Xq27.3. The pathogenesis of **fragile X syndrome** is thought to be due to a massive trinucleotide repeat expansion in the 5'UTR of the fragile X mental retardation-i gene (FMR1), which results in the loss of its protein product, FMRP. Although the precise function of FMRP has not yet been elucidated, it is believed to be a RNA-binding protein that associates with polyribosomes and the rough endoplasmic reticulum. And because FMRP is translated in the synapse in response to synaptic activation, it has been suggested to play important roles in protein translation and in synaptic plasticity. Interestingly, a growing body of evidence indicates a defect in translational processing of FMR1 as a potential mechanism leading to **fragile X syndrome.** Presently, however, the mechanism behind the regulation of FMR1 translation is poorly understood. Such understanding is necessary for elucidating the pathogenesis of **fragile X syndrome** and for identifying potential molecular targets for therapy. Therefore, I will examine the molecular basis behind the regulation and activation of FMR1 translation.

- **Project Title: TYROSINE KINASE PATHWAYS THAT CONTROL AXON GUIDANCE**

  Principal Investigator & Institution: Van Vactor, David L.; Associate Professor; Beth Israel Deaconess Medical Center 330 Brookline Avenue, Br 264 Boston, Ma 02215

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

  Summary: The synapse is the fundamental unit of the nervous system. Failure in synaptic development and/or function appears to underlie a wide variety of human neurological disorders from epilepsy and schizophrenia to congenital mental retardation. **Fragile X Syndrome** is the most common cause of hereditary mental retardation, and has been linked to defects in synapse morphogenesis through the FMR locus which encodes an RNA-binding protein that controls protein synthesis, likely via a microRNA-dependent mechanism. However, the neuronal targets that FMR controls, and the pathways that regulate FMR activity in space and time are poorly understood. Drosophila has recently emerged as an exciting model system to study the role of FMR (dfmr1) in synaptogenesis. Work from the initial funding period of this grant suggests that dfmrl acts in collaboration with the Abelson (Abl) tyrosine kinase to restrict synapse size. Additional work from our lab suggests that the LAR receptor tyrosine phosphatase acts upstream to antagonize Abl and dfmrl to promote synapse growth, implicating the coordination of cytoskeletal remodeling and translational control, and a link between dfmr1 and extracellular signals. Our identification of two low-nanomolar LAR ligands that have opposite effects on synapse growth extends this hypothesis, raising the possibility that competing signals fine-tune synapse morphogenesis or stabilization

upstream of the Abl kinase. During the next funding period, we will determine the order of gene activities in this pathway, define the link between Abl and dfmr1 activity, and determine whether dfmr1 acts via miroRNAs to regulate key synaptic targets.

- **Project Title: WHAT ABOUT ADOLESCENCE? LIVING WITH GENETIC RISK**

  Principal Investigator & Institution: Mcconkie-Rosell, Allyn; Pediatrics; Duke University 2424 Erwin Rd. Durham, Nc 27705

  Timing: Fiscal Year 2005; Project Start 05-AUG-2004; Project End 31-JUL-2007

  Summary: (provided by applicant): Understanding of the consequences to children of learning genetic risk information is based primarily on data extrapolated from adults. No studies have been done that assess the relationship between knowledge of genetic risk and a child's self-concept. We also have yet to learn how children cope with genetic information and how their coping strategies are affected by their parents' approach to coping. The purpose of this study is to describe the relationship among adolescent girl's self-concept, coping, and adjustment associated with knowledge of genetic risk of an X-linked disorder, fragile X. We will also describe strategies mothers use to help their daughters cope with this information. Using a multigroup cohort design, we will study 60 girls (15- 18 yrs) and their mothers from families with fragile X. We will enroll mother/daughter dyads with 3 categories of knowledge about the girl's genetic risk: 1) carrier, 2) noncarrier, and 3) at-risk to be a carrier. Each mother/daughter dyed will complete a number of quantitative and qualitative measures. Our specific aims are to: 1) Describe self-concept, coping, and adjustment in adolescent girls with knowledge of their genetic risk (carrier, noncarrier, and at-risk) for an X-linked disorder. 2) To describe a) how mothers have chosen to discuss genetic risk information with their daughters, b) parental "coaching" of coping behaviors, and c) their perceptions of how their daughters are managing this information. 3) Describe adolescent girls' knowledge of fragile X and how it is inherited; how they learned their carrier, noncarrier, or at-risk status; their own definitions of the words carrier, noncarrier, and at-risk; and how they think knowledge of genetic risk influences family and peer relationships. 4) To establish baseline measurements on a cohort of adolescent girls with these 3 categories of knowledge of genetic risk so that we can follow the developing self-concept in future longitudinal studies considering developmental tasks, coping behaviors, adjustment, and parental role experimentation. We hypothesize that: a. Carrier and at-risk adolescent girls will be more similar than noncarriers in self-concept, coping, and adjustment, b. Carrier and at-risk adolescent girls who place a high value on a future parental role will have a lower self-concept than those that do not.

- **Project Title: X-LINKED MENTAL RETARDATION-LINKAGE**

  Principal Investigator & Institution: Schwartz, Charles E.; Director, Jc Self Research Institute; Greenwood Genetic Center 113 Gregor Mendel Circle Greenwood, Sc 296462316

  Timing: Fiscal Year 2005; Project Start 01-JUL-1990; Project End 31-MAR-2007

  Summary: (provided by applicant): A 20 to 30 percent excess of males among the mentally retarded population is well documented. At least half of the excess is likely due to mutations of X-linked genes. An estimated 30-40 loci are associated with nonsyndromic X-linked mental retardation (XLMR) and one hundred thirty are associated with specific XLMR syndromes. The best known of these is the **Fragile X syndrome** but it accounts for only a third of XLMR families. Because of the X-linked mode of inheritance and current molecular methodologies, these disorders are especially amenable to study. The hypothesis to be tested is that a full understanding of

the genetics and pathogenesis of these disorders will lead to improved diagnosis and (ultimately) therapy. The immediate goal of the study is to identify the causative genes and the genetic pathways leading to XLMR. In addition, we will better define the clinical and neurobehavioral phenotypes of these disorders, each of which presents unique aspects about brain development and function. Over the last ten years, 55 large XLMR families and 68 smaller families have been admitted to the study for gene localization, gene testing and neurobehavioral studies. Thirty-two of the families have been localized to a discrete region of the X chromosome. In addition to these families, 2 males with inversions of the X chromosome associated with mental retardation and 3 males with small deletions are available for molecular studies. We have deposited brains from three XLMR study families are in the Miami Brain Bank and will utilize them for both molecular studies and comprehensive histological analysis. Three new investigators, (Srivastava, Inana, and Warren) have joined the study. A variety of appropriate microarray systems, subtractive cDNA and other appropriate methods (including maximal utilization of the new human genorne data) will be used to identify and characterize ten to fifteen XLMR genes over the next five years. We will continue to admit five new families and a number of smaller families each year. Neurobehavioral studies will be closely integrated into the clinical evaluation of each of the new large families. More extensive neurobehavioral studies along with MRI morphometric analysis will be conducted in three XLMR entities: Coffin-Lowry, ATRX and Allan-Herndon Syndrome. In summary, this represents a unique study that combines a variety of methodologies and disciplines in order to better understand the role of genes on the X chromosome in brain development and function.

NTIS (National Technical Information Service)

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

- **"Mapping and ordered cloning of the human X chromosome. Progress report, September 1991--November 1992,"** published in December 1992.

  Sponsored by: Baylor Univ., Houston, TX. Inst. of Molecular Genetics.; Department of Energy, Washington, DC.

  Written by: C. T. Caskey and D. L. Nelson.

  Abstract: Progress is reported on gathering X chromosome specific libraries and integrating those with the library produced in this project. Further studies on understanding **Fragile X syndrome** and other hereditary diseases related to the X chromosome are described.

The National Library of Medicine: PubMed

One of the quickest and most comprehensive ways to find academic studies in both English and other languages is to use PubMed, maintained by the National Library of Medicine.[6]

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

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

- **A comparison of phonological skills of boys with fragile X syndrome and Down syndrome.**
  Author(s): Roberts J, Long SH, Malkin C, Barnes E, Skinner M, Hennon EA, Anderson K.
  Source: Journal of Speech, Language, and Hearing Research : Jslhr.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16411789&query_hl=51&itool=pubmed_docsum

- **A controlled study of folic acid treatment in three fragile X syndrome males.**
  Author(s): Madison LS, Wells TE, Fristo TE, Benesch CG.
  Source: Journal of Developmental and Behavioral Pediatrics : Jdbp.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=3528223&query_hl=51&itool=pubmed_docsum

- **A neuropsychological investigation of male premutation carriers of fragile X syndrome.**
  Author(s): Moore CJ, Daly EM, Schmitz N, Tassone F, Tysoe C, Hagerman RJ, Hagerman PJ, Morris RG, Murphy KC, Murphy DG.
  Source: Neuropsychologia.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15381024&query_hl=51&itool=pubmed_docsum

- **A new genetic model for the fragile X syndrome involving an autosomal suppressor gene--comments on the paper by M.H. Israel.**
  Author(s): Sherman SL.
  Source: American Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=3812575&query_hl=51&itool=pubmed_docsum

- **A new insight into fragile X syndrome among Basque population.**
  Author(s): Penagarikano O, Gil A, Telez M, Ortega B, Flores P, Veiga I, Peixoto A, Criado B, Arrieta I.
  Source: Am J Med Genet A.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15216545&query_hl=51&itool=pubmed_docsum

- **A step-wise diagnosis of fragile X syndrome in Taiwan.**
  Author(s): Huang YT, Chiang SC, Tzeng CC, Liu CH, Chien YH, Hwu WL.
  Source: Acta Paediatr Taiwan.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15335113&query_hl=51&itool=pubmed_docsum

- **A woman with spontaneous premature ovarian failure gives birth to a child with fragile X syndrome.**
  Author(s): Corrigan EC, Raygada MJ, Vanderhoof VH, Nelson LM.
  Source: Fertility and Sterility.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16275254&query_hl=51&itool=pubmed_docsum

- **Academic skills of boys with fragile X syndrome: profiles and predictors.**
  Author(s): Roberts JE, Schaaf JM, Skinner M, Wheeler A, Hooper S, Hatton DD, Bailey DB Jr.
  Source: Am J Ment Retard.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15762821&query_hl=51&itool=pubmed_docsum

- **ACOG committee opinion. No. 338: Screening for fragile X syndrome.**
  Author(s): American College of Obstetricians and Gynecologists Committee on Genetics.
  Source: Obstetrics and Gynecology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16738187&query_hl=51&itool=pubmed_docsum

- **Adaptive behavior in children with fragile X syndrome.**
  Author(s): Hatton DD, Wheeler AC, Skinner ML, Bailey DB, Sullivan KM, Roberts JE, Mirrett P, Clark RD.
  Source: Am J Ment Retard.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14561110&query_hl=51&itool=pubmed_docsum

- **Alternative splicing modulates protein arginine methyltransferase-dependent methylation of fragile X syndrome mental retardation protein.**
  Author(s): Dolzhanskaya N, Merz G, Denman RB.
  Source: Biochemistry.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16922515&query_hl=51&itool=pubmed_docsum

- **An analysis of autism in fifty males with the fragile X syndrome.**
  Author(s): Hagerman RJ, Jackson AW 3rd, Levitas A, Rimland B, Braden M.
  Source: American Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=3953654&query_hl=51&itool=pubmed_docsum

- **Annotation: Deconstructing the attention deficit in fragile X syndrome: a developmental neuropsychological approach.**
  Author(s): Cornish KM, Turk J, Wilding J, Sudhalter V, Munir F, Kooy F, Hagerman R.
  Source: Journal of Child Psychology and Psychiatry, and Allied Disciplines.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15257661&query_hl=51&itool=pubmed_docsum

- **Aortic root dilatation and mitral valve prolapse in the fragile X syndrome.**
  Author(s): Loehr JP, Synhorst DP, Wolfe RR, Hagerman RJ.
  Source: American Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=3953647&query_hl=51&itool=pubmed_docsum

- **Auditory brainstem responses in young males with Fragile X syndrome.**
  Author(s): Roberts J, Hennon EA, Anderson K, Roush J, Gravel J, Skinner M, Misenheimer J, Reitz P.
  Source: Journal of Speech, Language, and Hearing Research : Jslhr.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15989407&query_hl=51&itool=pubmed_docsum

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  Author(s): Fisch GS, Cohen IL, Wolf EG, Brown WT, Jenkins EC, Gross A.
  Source: The American Journal of Psychiatry.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=3455802&query_hl=51&itool=pubmed_docsum

- **Autism spectrum disorder in fragile X syndrome: communication, social interaction, and specific behaviors.**
  Author(s): Kaufmann WE, Cortell R, Kau AS, Bukelis I, Tierney E, Gray RM, Cox C, Capone GT, Stanard P.
  Source: Am J Med Genet A.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15326621&query_hl=51&itool=pubmed_docsum

- **Autism spectrum disorder in Fragile X syndrome: differential contribution of adaptive socialization and social withdrawal.**
  Author(s): Budimirovic DB, Bukelis I, Cox C, Gray RM, Tierney E, Kaufmann WE.
  Source: Am J Med Genet A.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16906564&query_hl=51&itool=pubmed_docsum

- **Autistic behavior in children with fragile X syndrome: prevalence, stability, and the impact of FMRP.**
  Author(s): Hatton DD, Sideris J, Skinner M, Mankowski J, Bailey DB Jr, Roberts J, Mirrett P.
  Source: Am J Med Genet A.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16700053&query_hl=51&itool=pubmed_docsum

- **Autistic-like behaviour profile and psychiatric morbidity in Fragile X Syndrome: a prospective ten-year follow-up study.**
  Author(s): Sabaratnam M, Murthy NV, Wijeratne A, Buckingham A, Payne S.
  Source: European Child & Adolescent Psychiatry.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14505067&query_hl=51&itool=pubmed_docsum

- **Behavior and autonomic nervous system function assessed via heart period measures: the case of hyperarousal in boys with fragile X syndrome.**
  Author(s): Boccia ML, Roberts JE.
  Source: Behavior Research Methods, Instruments, & Computers : a Journal of the Psychonomic Society, Inc.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10758659&query_hl=51&itool=pubmed_docsum

- **Behavior phenotype of the fragile X syndrome.**
  Author(s): Einfeld S, Hall W.
  Source: American Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1605235&query_hl=51&itool=pubmed_docsum

- **Behavior problems of young girls with fragile X syndrome: factor scores on the Conners' Parent's Questionnaire.**
  Author(s): Lachiewicz AM, Dawson DV.
  Source: American Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7943000&query_hl=51&itool=pubmed_docsum

- **Behavioral assessment of social anxiety in females with Turner or fragile X syndrome.**
  Author(s): Lesniak-Karpiak K, Mazzocco MM, Ross JL.
  Source: Journal of Autism and Developmental Disorders.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12708580&query_hl=51&itool=pubmed_docsum

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  Author(s): Reiss AL, Freund L.
  Source: American Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1605210&query_hl=51&itool=pubmed_docsum

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  Author(s): Steinhausen HC, Von Gontard A, Spohr HL, Hauffa BP, Eiholzer U, Backes M, Willms J, Malin Z.
  Source: American Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12210296&query_hl=51&itool=pubmed_docsum

- **Behavioral relationship between autism and fragile X syndrome.**
  Author(s): Demark JL, Feldman MA, Holden JJ.
  Source: Am J Ment Retard.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12901707&query_hl=51&itool=pubmed_docsum

- **Behavioral style of young boys with fragile X syndrome.**
  Author(s): Hatton DD, Bailey DB Jr, Hargett-Beck MQ, Skinner M, Clark RD.
  Source: Developmental Medicine and Child Neurology.
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  Author(s): Einfeld SL, Tonge BJ, Florio T.
  Source: American Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7943004&query_hl=51&itool=pubmed_docsum

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  Author(s): Weiskop S, Richdale A, Matthews J.
  Source: Developmental Medicine and Child Neurology.
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  Author(s): Kranjc BS, Brezigar A, Peterlin B.
  Source: Optometry and Vision Science : Official Publication of the American Academy of Optometry.
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  Author(s): Glaser B, Hessl D, Dyer-Friedman J, Johnston C, Wisbeck J, Taylor A, Reiss A.
  Source: Am J Med Genet A.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12548736&query_hl=51&itool=pubmed_docsum

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  Author(s): Miller G.
  Source: Science.
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  Author(s): Jeffries FM, Reiss AL, Brown WT, Meyers DA, Glicksman AC, Bandyopadhyay S.
  Source: Biological Psychiatry.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8448271&query_hl=51&itool=pubmed_docsum

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  Author(s): Ferri R, Musumeci SA, Elia M, Del Gracco S, Scuderi C, Bergonzi P.
  Source: Neurophysiologie Clinique = Clinical Neurophysiology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7723725&query_hl=51&itool=pubmed_docsum

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  Author(s): Roberts JE, Symons FJ, Johnson AM, Hatton DD, Boccia ML.
  Source: Journal of Intellectual Disability Research : Jidr.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16108982&query_hl=51&itool=pubmed_docsum

- **Brain anatomy, gender and IQ in children and adolescents with fragile X syndrome.**
  Author(s): Eliez S, Blasey CM, Freund LS, Hastie T, Reiss AL.
  Source: Brain; a Journal of Neurology.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11459752&query_hl=51&itool=pubmed_docsum

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  Author(s): Hashimoto O, Shimizu Y, Kawasaki Y.
  Source: Journal of Autism and Developmental Disorders.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8463200&query_hl=51&itool=pubmed_docsum

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  Source: Human Molecular Genetics.
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  Source: American Journal of Medical Genetics.
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CHAPTER 2. ALTERNATIVE MEDICINE AND FRAGILE X SYNDROME

Overview

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

National Center for Complementary and Alternative Medicine

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

- **A population-based twin study of parentally reported tactile and auditory defensiveness in young children.**
  Author(s): Goldsmith HH, Van Hulle CA, Arneson CL, Schreiber JE, Gernsbacher MA.
  Source: Journal of Abnormal Child Psychology.
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  Author(s): Hall BD.
  Source: American Journal of Medical Genetics.
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  Author(s): Castren M, Paakkonen A, Tarkka IM, Ryynanen M, Partanen J.
  Source: Brain Topography.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12705812&query_hl=1&itool=pubmed_docsum

- **Autism: a medical primer.**
  Author(s): Prater CD, Zylstra RG.
  Source: American Family Physician.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12449265&query_hl=1&itool=pubmed_docsum

- **DNA damage and repair in lymphoblastoid cell lines from normal donors and fragile X syndrome patients.**
  Author(s): Wang TS, Hsieh LJ, Hsu TY, Chung CH, Li SY.
  Source: Archives of Medical Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11886710&query_hl=1&itool=pubmed_docsum

- **Exaggerated behavioral phenotypes in Fmr1/Fxr2 double knockout mice reveal a functional genetic interaction between Fragile X-related proteins.**
  Author(s): Spencer CM, Serysheva E, Yuva-Paylor LA, Oostra BA, Nelson DL, Paylor R.
  Source: Human Molecular Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16675531&query_hl=1&itool=pubmed_docsum

- **Fmrp is required for the establishment of the startle response during the critical period of auditory development.**
  Author(s): Yun SW, Platholi J, Flaherty MS, Fu W, Kottmann AH, Toth M.
  Source: Brain Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16887106&query_hl=1&itool=pubmed_docsum

- **Fragile X mice develop sensory hyperreactivity to auditory stimuli.**
  Author(s): Chen L, Toth M.
  Source: Neuroscience.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11301211&query_hl=1&itool=pubmed_docsum

- **Fragile X syndrome.**
  Author(s): Gelbart M.
  Source: Nurs Times.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9934149&query_hl=1&itool=pubmed_docsum

- **Fragile X syndrome: an update and review for the primary pediatrician.**
  Author(s): Visootsak J, Warren ST, Anido A, Graham JM Jr.
  Source: Clinical Pediatrics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15965543&query_hl=1&itool=pubmed_docsum

- **High dose folic acid treatment of fragile (X) males.**
  Author(s): Brown WT, Cohen IL, Fisch GS, Wolf-Schein EG, Jenkins VA, Malik MN, Jenkins EC.
  Source: American Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=3513568&query_hl=1&itool=pubmed_docsum

- **Language use in females with fragile X or Turner syndrome during brief initial social interactions.**
  Author(s): Mazzocco MM, Thompson L, Sudhalter V, Belser RC, Lesniak-Karpiak K, Ross JL.
  Source: Journal of Developmental and Behavioral Pediatrics : Jdbp.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16906008&query_hl=1&itool=pubmed_docsum

- **Oligomerization properties of fragile-X mental-retardation protein (FMRP) and the fragile-X-related proteins FXR1P and FXR2P.**
  Author(s): Tamanini F, Van Unen L, Bakker C, Sacchi N, Galjaard H, Oostra BA, Hoogeveen AT.
  Source: The Biochemical Journal.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10527928&query_hl=1&itool=pubmed_docsum

- **Sensorimotor gating abnormalities in young males with fragile X syndrome and Fmr1-knockout mice.**
  Author(s): Frankland PW, Wang Y, Rosner B, Shimizu T, Balleine BW, Dykens EM, Ornitz EM, Silva AJ.
  Source: Molecular Psychiatry.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14981523&query_hl=1&itool=pubmed_docsum

- **Spatial learning, contextual fear conditioning and conditioned emotional response in Fmr1 knockout mice.**
  Author(s): Van Dam D, D'Hooge R, Hauben E, Reyniers E, Gantois I, Bakker CE, Oostra BA, Kooy RF, De Deyn PP.
  Source: Behavioural Brain Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11099766&query_hl=1&itool=pubmed_docsum

- **Spontaneous chromosome loss and colcemid resistance in lymphocytes from patients with myotonic dystrophy type 1.**
  Author(s): Casella M, Lucarelli M, Simili M, Beffy P, Del Carratore R, Minichilli F, Chisari C, Simi S.
  Source: Cytogenetic and Genome Research.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14526184&query_hl=1&itool=pubmed_docsum

- **The fragile X mental retardation protein is a ribonucleoprotein containing both nuclear localization and nuclear export signals.**
  Author(s): Eberhart DE, Malter HE, Feng Y, Warren ST.
  Source: Human Molecular Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8842725&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/**
- 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/**
- Open Directory Project: **http://dmoz.org/Health/Alternative/**
- Yahoo.com: **http://dir.yahoo.com/Health/Alternative_Medicine/**

General References

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

CHAPTER 3. PATENTS ON FRAGILE X SYNDROME

Overview

Patents can be physical innovations (e.g. chemicals, pharmaceuticals, medical equipment) or processes (e.g. treatments or diagnostic procedures). The United States Patent and Trademark Office defines a patent as a grant of a property right to the inventor, issued by the Patent and Trademark Office.[7] Patents, therefore, are intellectual property. For the United States, the term of a new patent is 20 years from the date when the patent application was filed. If the inventor wishes to receive economic benefits, it is likely that the invention will become commercially available within 20 years of the initial filing. It is important to understand, therefore, that an inventor's patent does not indicate that a product or service is or will be commercially available. The patent implies only that the inventor has "the right to exclude others from making, using, offering for sale, or selling" the invention in the United States. While this relates to U.S. patents, similar rules govern foreign patents.

In this chapter, we show you how to locate information on patents and their inventors. If you find a patent that is particularly interesting to you, contact the inventor or the assignee for further information. **IMPORTANT NOTE:** When following the search strategy described below, you may discover non-medical patents that use the generic term "fragile X syndrome" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on fragile X syndrome, we have not necessarily excluded non-medical patents in this bibliography.

Patent Applications on Fragile X Syndrome

As of December 2000, U.S. patent applications are open to public viewing.[8] Applications are patent requests which have yet to be granted. (The process to achieve a patent can take several years.) The following patent applications have been filed since December 2000 relating to fragile X syndrome:

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

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

- **Method and identification of downstream mrna ligands to fmrp and their role in fragile X syndrome and associated disorders**

  Inventor(s): Brown-Kennerly, Victoria; (Decatur, GA), Ceman, Stephanie; (Atlanta, GA), Darnell, Jennifer C.; (Pelham, NY), Darnell, Robert B.; (Pelham, NY), Jin, Peng; (Marietta, GA), Keene, Jack D.; (Durham, NC), Tenenbaum, Scott A.; (Albany, NY), Warren, Stephen T; (Atlanta, GA)

  Correspondence: Alston & Bird Llp; Bank OF America Plaza; 101 South Tryon Street, Suite 4000; Charlotte; NC; 28280-4000; US

  Patent Application Number: 20050130151

  Date filed: February 16, 2005

  Abstract: Compositions and methods for identifying and/or modulating RNA transcripts and/or genes involved in **fragile X syndrome** and other associated disorders are provided. In particular, RNA targets for fragile X mental retardation protein (FMRP) have been identified by a novel monoclonal antibody to FMRP and a consensus sequence for the RNA binding region has been identified. Arrays for identifying compounds, proteins, nucleotides, and the like that modulate the RNA targets or associated genes are provided. Additionally, methods for modulating RNA targets are provided.

  Excerpt(s): The invention relates to methods for the identification of downstream mRNA targets of the FMRP protein and the role of these mRNAs in **fragile X syndrome** and associated disorders. The **fragile X syndrome** is the most common form of inherited mental retardation in humans and is estimated to afflict roughly 1 in 2500 males and 1 in 5000 females. Conditions associated with the syndrome include mild to moderate cognitive abnormalities, as well as behavioral disorders similar to autism, attention deficit disorder, obsessive-compulsive tendencies, hyperactivity, slow development of motor skills, and anxiety fear disorder. The syndrome is also frequently accompanied by seizures, by macroorchidism, and by subtle craniofacial dysmorphia. Studies have shown that **fragile X syndrome** results from a deficiency of the fragile X mental retardation protein, FMRP, which is encoded by the X-linked FMR1 gene. **Fragile X syndrome** usually results from the transcriptional silencing of this gene brought about by the expansion and hypermethylation of a (CGG).sub.n trinucleotide repeat in the gene's 5' untranslated region (UTR), indicating that the presence of FMRP is essential for higher cognitive function.

Keeping Current

In order to stay informed about patents and patent applications dealing with fragile X syndrome, you can access the U.S. Patent Office archive via the Internet at the following Web address: **http://www.uspto.gov/patft/index.html**. You will see two broad options: (1) Issued Patent, and (2) Published Applications. To see a list of issued patents, perform the following steps: Under **Issued Patents**, click **Quick Search**. Then, type **fragile X syndrome** (or a synonym) into the **Term 1** box. After clicking on the search button, scroll down to see the various patents which have been granted to date on fragile X syndrome.

You can also use this procedure to view pending patent applications concerning fragile X syndrome. Simply go back to **http://www.uspto.gov/patft/index.html**. Select **Quick Search** under **Published Applications**. Then proceed with the steps listed above.

CHAPTER 4. BOOKS ON FRAGILE X SYNDROME

Overview

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

Book Summaries: Online Booksellers

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

- **A critical review of the literature of the relationship between fragile X syndrome and autism in males** Michelle M Roberts (2002); ISBN: B0006RZ4QM; http://www.amazon.com/exec/obidos/ASIN/B0006RZ4QM/icongroupinterna
- **Behavior and Development in Fragile X Syndrome (Developmental Clinical Psychology and Psychiatry)** Elisabeth Dykens, Robert M. Hodapp, and James F. Leckman (1993); ISBN: 0803948883; http://www.amazon.com/exec/obidos/ASIN/0803948883/icongroupinterna
- **Boys with fragile X syndrome (Fragile X awareness series for children)** Rebecca O'Connor (1995); ISBN: 0964735504; http://www.amazon.com/exec/obidos/ASIN/0964735504/icongroupinterna
- **Do women with fragile X syndrome have problems in switching attention: Preliminary findings from ERP and fMRI** K. Cornish, R. Swainson, R. Cunnington, and

J. Wilding (2004); ISBN: B000M5M65K;
http://www.amazon.com/exec/obidos/ASIN/B000M5M65K/icongroupinterna

- **Facts about fragile X syndrome (SuDoc HE 20.3352:F 84)** U.S. Dept of Health and Human Services (1996); ISBN: B00010R692;
http://www.amazon.com/exec/obidos/ASIN/B00010R692/icongroupinterna
- **Supporting Children with Fragile X Syndrome (Supporting Children)** Learning Servic (2004); ISBN: 184312226X;
http://www.amazon.com/exec/obidos/ASIN/184312226X/icongroupinterna
- **The Fragile X Syndrome (Molecular Medicine)** Kay E. Davies (1989); ISBN: 0192618369;
http://www.amazon.com/exec/obidos/ASIN/0192618369/icongroupinterna

APPENDICES

APPENDIX A. HELP ME UNDERSTAND GENETICS

Overview

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

The Basics: Genes and How They Work

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

What Is a Cell?

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

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

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

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

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

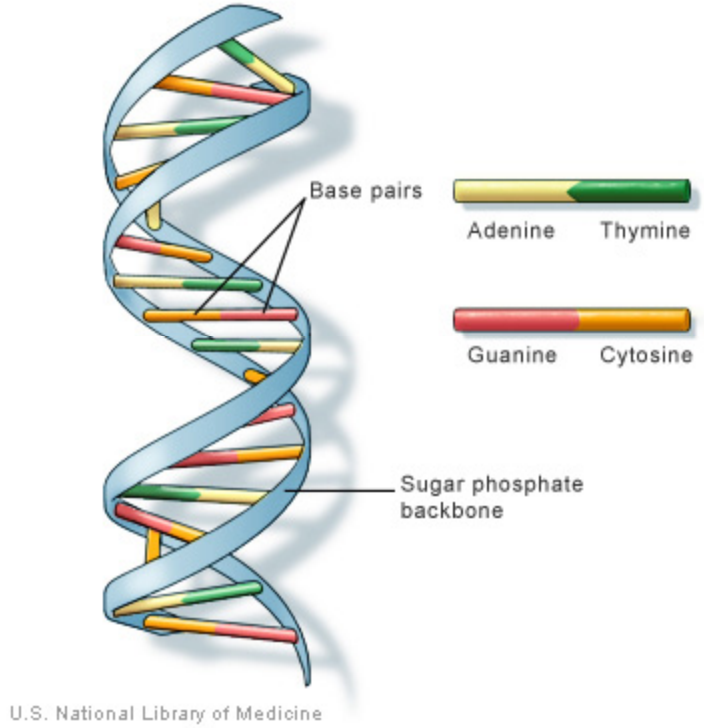
What Is DNA?

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

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

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

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



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

What Is Mitochondrial DNA?

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

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

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

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

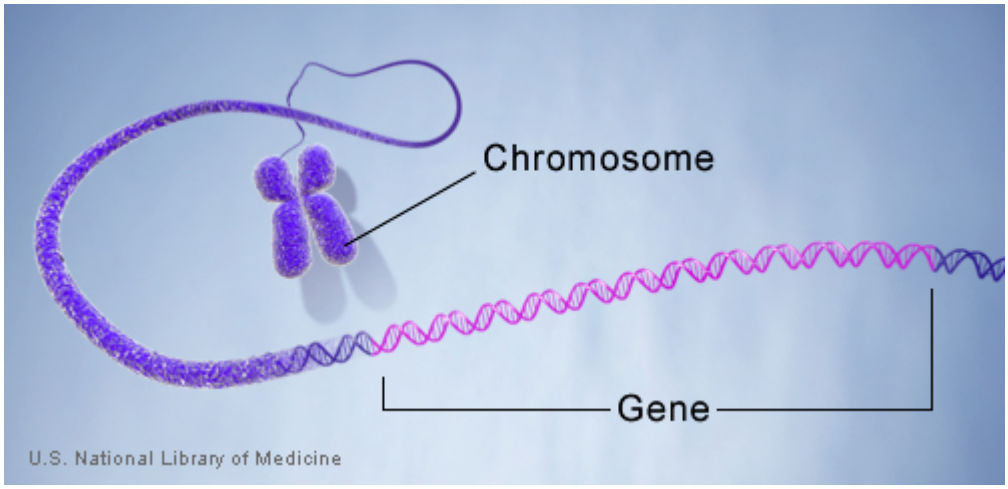
Mitochondrial DNA contains 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation. The remaining genes provide instructions for making molecules called transfer RNAs (tRNAs) and ribosomal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

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

What Is a Gene?

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

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



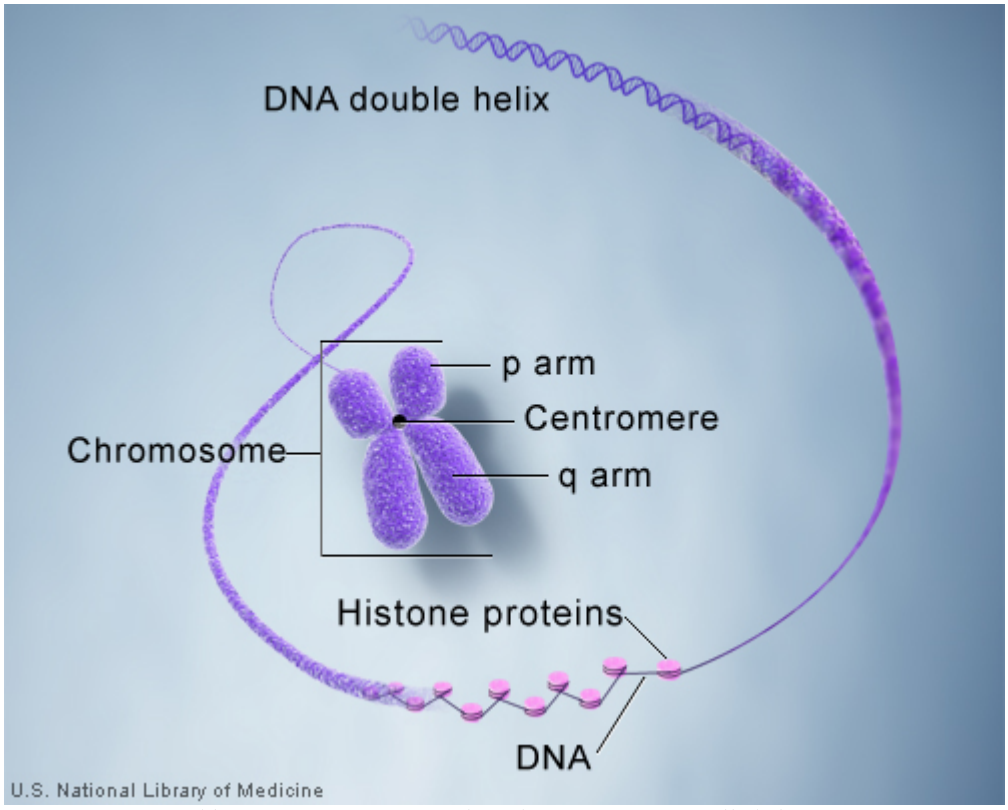
Genes are made up of DNA. Each chromosome contains many genes.

What Is a Chromosome?

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

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

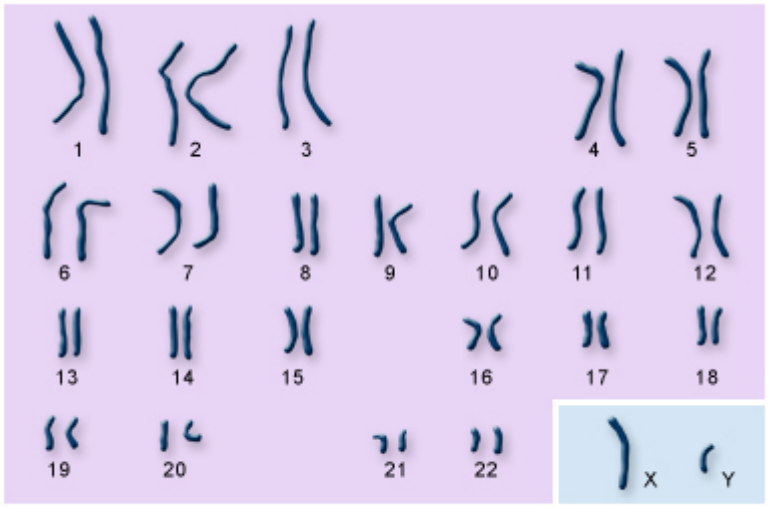
Each chromosome has a constriction point called the centromere, which divides the chromosome into two sections, or "arms." The short arm of the chromosome is labeled the "p arm." The long arm of the chromosome is labeled the "q arm." The location of the centromere on each chromosome gives the chromosome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



DNA and histone proteins are packaged into structures called chromosomes.

How Many Chromosomes Do People Have?

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



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

How Do Geneticists Indicate the Location of a Gene?

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

Cytogenetic Location

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

17q12

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

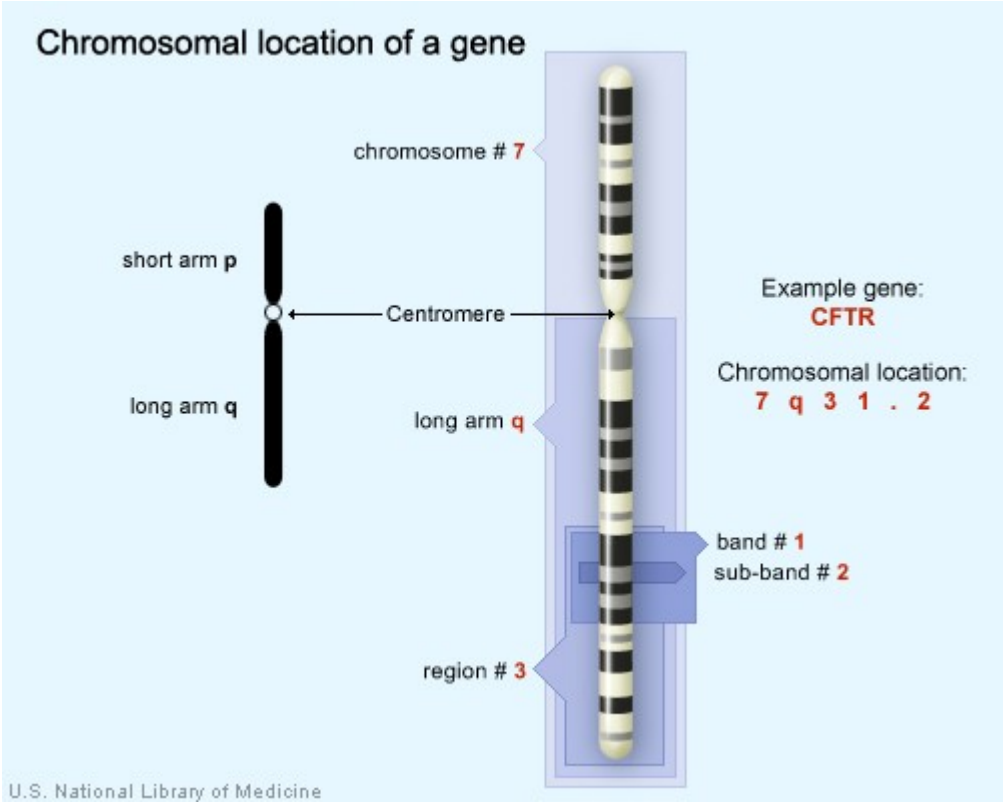
17q12-q21

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

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

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

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



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

Molecular Location

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

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

What Are Proteins and What Do They Do?

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

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

Examples of Protein Functions

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

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

How Does a Gene Make a Protein?

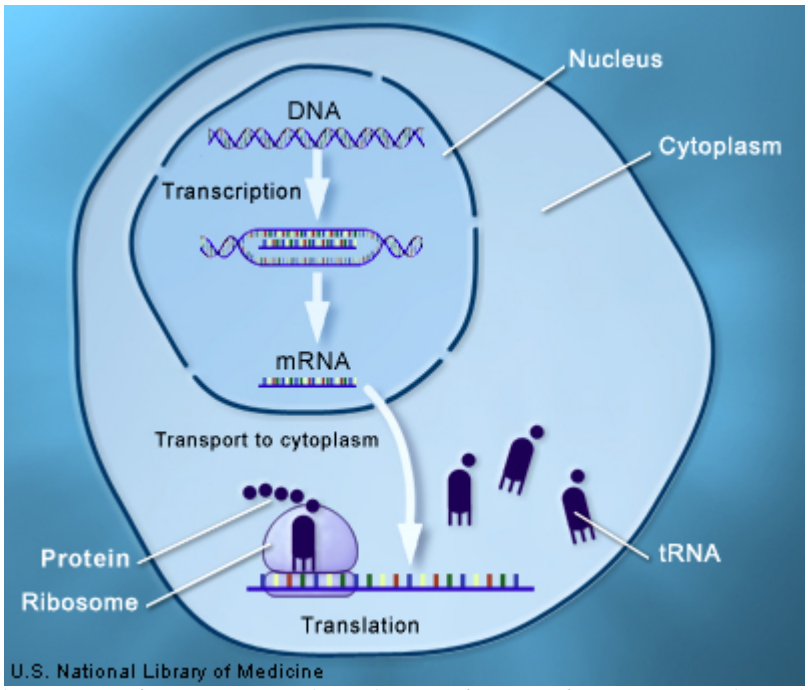
Most genes contain the information needed to make functional molecules called proteins. (A few genes produce other molecules that help the cell assemble proteins.) The journey from gene to protein is complex and tightly controlled within each cell. It consists of two major steps: transcription and translation.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

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

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

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

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



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

Can Genes Be Turned On and Off in Cells?

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

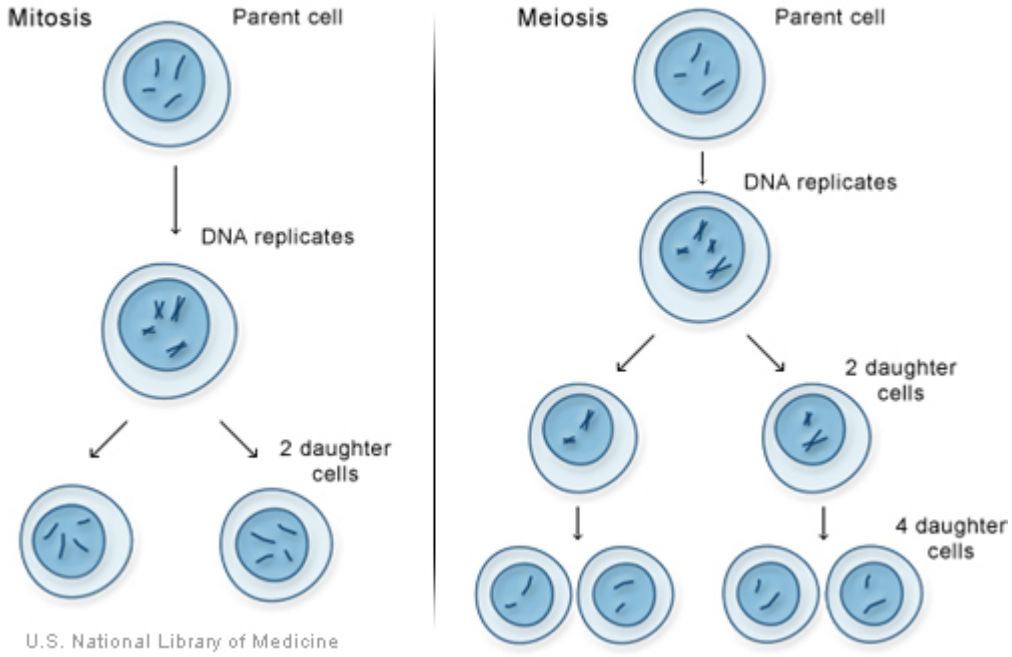
Gene regulation can occur at any point during gene expression, but most commonly occurs at the level of transcription (when the information in a gene's DNA is transferred to mRNA). Signals from the environment or from other cells activate proteins called transcription factors. These proteins bind to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

How Do Cells Divide?

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

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

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



Mitosis and meiosis, the two types of cell division.

How Do Genes Control the Growth and Division of Cells?

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

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

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

Genetic Mutations and Health

This section presents basic information about gene mutations, chromosomal changes, and conditions that run in families.[10]

What Is a Gene Mutation and How Do Mutations Occur?

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

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

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

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

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

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

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

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

How Can Gene Mutations Affect Health and Development?

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

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

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

Do All Gene Mutations Affect Health and Development?

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

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

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

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

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

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

What Kinds of Gene Mutations Are Possible?

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

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

Can Changes in Chromosomes Affect Health and Development?

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

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

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

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

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

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

Can Changes in Mitochondrial DNA Affect Health and Development?

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

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

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

What Are Complex or Multifactorial Disorders?

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

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

What Information about a Genetic Condition Can Statistics Provide?

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

Common Statistical Terms

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

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

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

Naming Genetic Conditions

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

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

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

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

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

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

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

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

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

Inheriting Genetic Conditions

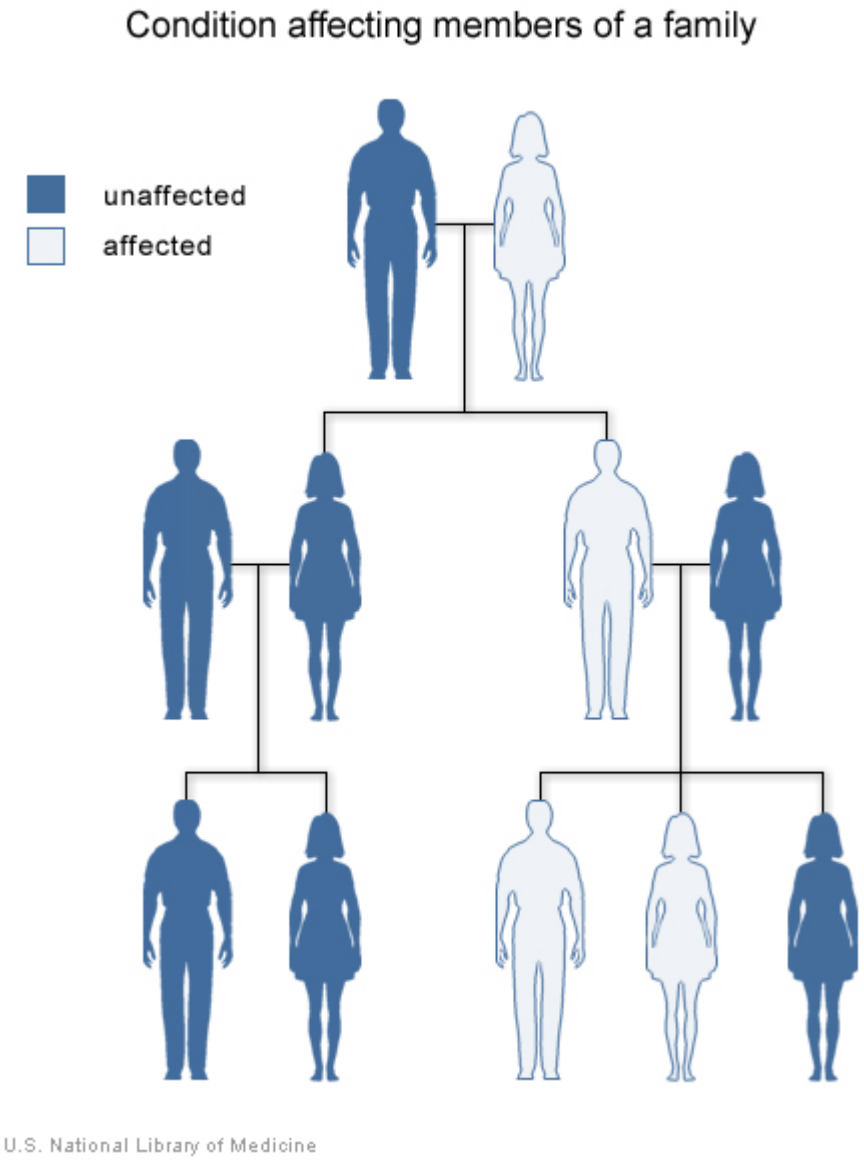
This section gives you information on inheritance patterns and understanding risk.

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

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

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

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



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

Why Is It Important to Know My Family Medical History?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Factors that Influence the Effects of Particular Genetic Changes

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

Reduced Penetrance

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

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

Variable Expressivity

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

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

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

What Do Geneticists Mean by Anticipation?

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

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

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

What Is Genomic Imprinting?

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

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

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

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

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

What Is Uniparental Disomy?

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

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

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

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

Are Chromosomal Disorders Inherited?

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

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

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

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

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

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

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

Genetic Consultation

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

What Is a Genetic Consultation?

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

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

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

Why Might Someone Have a Genetic Consultation?

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

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

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

What Happens during a Genetic Consultation?

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

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

During a consultation, a genetics professional will:

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

A genetics professional will NOT:

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

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

How Can I Find a Genetics Professional in My Area?

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

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

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

Genetic Testing

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

What Is Genetic Testing?

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

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

What Are the Types of Genetic Tests?

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

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

How Is Genetic Testing Done?

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

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

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

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

What Is Direct-to-Consumer Genetic Testing?

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

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

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

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

What Do the Results of Genetic Tests Mean?

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

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

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

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

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

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

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

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

Will Health Insurance Cover the Costs of Genetic Testing?

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

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

What Are the Benefits of Genetic Testing?

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

What Are the Risks and Limitations of Genetic Testing?

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

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

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

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

What Is Genetic Discrimination?

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

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

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

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

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

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

Gene Therapy

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

What Is Gene Therapy?

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

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

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

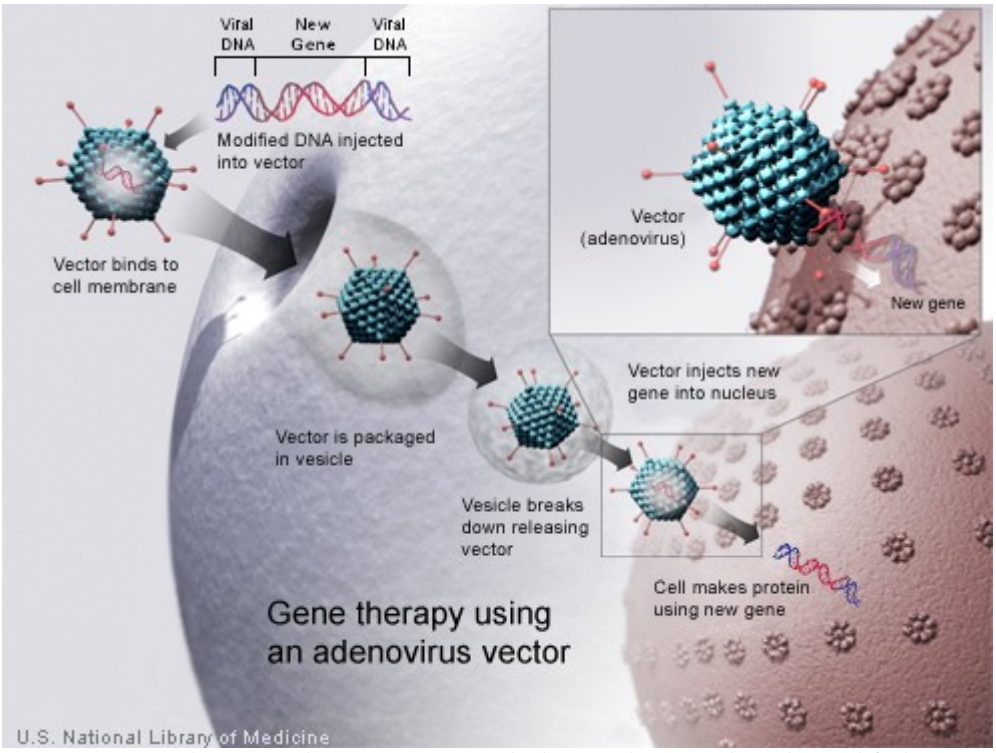
How Does Gene Therapy Work?

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

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

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

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



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

Is Gene Therapy Safe?

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

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

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

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

What Are the Ethical Issues surrounding Gene Therapy?

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

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

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

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

Is Gene Therapy Available to Treat My Disorder?

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

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

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

The Human Genome Project and Genomic Research

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

What Is a Genome?

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

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

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

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

What Were the Goals of the Human Genome Project?

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

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

What Did the Human Genome Project Accomplish?

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

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

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

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

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

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

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

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

What Are the Next Steps in Genomic Research?

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

The objectives of continued genomic research include the following:

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

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

What Is Pharmacogenomics?

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

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

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

APPENDIX B. PHYSICIAN RESOURCES

Overview

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

NIH Guidelines

Commonly referred to as "clinical" or "professional" guidelines, the National Institutes of Health publish physician guidelines for the most common diseases. Publications are available at the following by relevant Institute[11]:

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

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

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

NIH Databases

In addition to the various Institutes of Health that publish professional guidelines, the NIH has designed a number of databases for professionals.[12] Physician-oriented resources provide a wide variety of information related to the biomedical and health sciences, both past and present. The format of these resources varies. Searchable databases, bibliographic

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

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

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

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

The NLM Gateway[14]

The NLM (National Library of Medicine) Gateway is a Web-based system that lets users search simultaneously in multiple retrieval systems at the U.S. National Library of Medicine (NLM). It allows users of NLM services to initiate searches from one Web interface, providing one-stop searching for many of NLM's information resources or databases.[15] To use the NLM Gateway, simply go to the search site at **http://gateway.nlm.nih.gov/gw/Cmd**. Type **fragile X syndrome** (or synonyms) into the search box and click **Search**. The results will be presented in a tabular form, indicating the number of references in each database category.

Results Summary

Category	Items Found
Journal Articles	3145
Books / Periodicals / Audio Visual	38
Consumer Health	71
Meeting Abstracts	5
Other Collections	3
Total	3262

HSTAT[16]

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

Coffee Break: Tutorials for Biologists[19]

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

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

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

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

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

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

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

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

Other Commercial Databases

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

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

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

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

APPENDIX C. PATIENT RESOURCES

Overview

Official agencies, as well as federally funded institutions supported by national grants, frequently publish a variety of guidelines written with the patient in mind. These are typically called **Fact Sheets** or **Guidelines**. They can take the form of a brochure, information kit, pamphlet, or flyer. Often they are only a few pages in length. Since new guidelines on fragile X syndrome can appear at any moment and be published by a number of sources, the best approach to finding guidelines is to systematically scan the Internet-based services that post them.

Patient Guideline Sources

This section directs you to sources which either publish fact sheets or can help you find additional guidelines on topics related to fragile X syndrome. Due to space limitations, these sources are listed in a concise manner. Do not hesitate to consult the following sources by either using the Internet hyperlink provided, or, in cases where the contact information is provided, contacting the publisher or author directly.

The National Institutes of Health

The NIH gateway to patients is located at **http://health.nih.gov/**. From this site, you can search across various sources and institutes, a number of which are summarized below.

Topic Pages: MEDLINEplus

The National Library of Medicine has created a vast and patient-oriented healthcare information portal called MEDLINEplus. Within this Internet-based system are **health topic pages** which list links to available materials relevant to fragile X syndrome. To access this system, log on to **http://www.nlm.nih.gov/medlineplus/healthtopics.html**. From there you can either search using the alphabetical index or browse by broad topic areas. Recently, MEDLINEplus listed the following when searched for **fragile X syndrome**:

Birth Defects
http://www.nlm.nih.gov/medlineplus/birthdefects.html

Developmental Disabilities
http://www.nlm.nih.gov/medlineplus/developmentaldisabilities.html

Fragile X Syndrome
http://www.nlm.nih.gov/medlineplus/fragilexsyndrome.html

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

Movement Disorders
http://www.nlm.nih.gov/medlineplus/movementdisorders.html

Turner's Syndrome
http://www.nlm.nih.gov/medlineplus/turnerssyndrome.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:

- **MedlinePlus: Fragile X Syndrome**

  Source: www.nlm.nih.gov

  http://www.nlm.nih.gov/medlineplus/fragilexsyndrome.html

The NIH Search Utility

The NIH search utility allows you to search for documents on over 100 selected Web sites that comprise the NIH-WEB-SPACE. Each of these servers is "crawled" and indexed on an ongoing basis. Your search will produce a list of various documents, all of which will relate in some way to fragile X syndrome. The drawbacks of this approach are that the information is not organized by theme and that the references are often a mix of information for professionals and patients. Nevertheless, a large number of the listed Web sites provide useful background information. We can only recommend this route, therefore, for relatively rare or specific disorders, or when using highly targeted searches. To use the NIH search utility, visit the following Web page: **http://health.nih.gov/index.asp**. Under **Search Health Topics**, type **fragile X syndrome** (or synonyms) into the search box, and click **Search**.

Additional Web Sources

A number of Web sites are available to the public that often link to government sites. These can also point you in the direction of essential information. The following is a representative sample:

- Family Village: **http://www.familyvillage.wisc.edu/specific.htm**
- Google: **http://directory.google.com/Top/Health/Conditions_and_Diseases/**
- Med Help International: **http://www.medhelp.org/HealthTopics/A.html**
- Open Directory Project: **http://dmoz.org/Health/Conditions_and_Diseases/**
- Yahoo.com: **http://dir.yahoo.com/Health/Diseases_and_Conditions/**
- WebMD®Health: **http://www.webmd.com/diseases_and_conditions/default.htm**

Finding Associations

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

The National Health Information Center (NHIC)

The National Health Information Center (NHIC) offers a free referral service to help people find organizations that provide information about fragile X syndrome. For more information, see the NHIC's Web site at **http://www.health.gov/NHIC/** or contact an information specialist by calling 1-800-336-4797.

Directory of Health Organizations

The Directory of Health Organizations, provided by the National Library of Medicine Specialized Information Services, is a comprehensive source of information on associations. The Directory of Health Organizations database can be accessed via the Internet at **http://sis.nlm.nih.gov/dirline.html**. It is composed of two parts: DIRLINE and Health Hotlines.

The DIRLINE database comprises some 10,000 records of organizations, research centers, and government institutes and associations that primarily focus on health and biomedicine. Simply type in **fragile X syndrome** (or a synonym), and you will receive information on all relevant organizations listed in the database.

Health Hotlines directs you to toll-free numbers to over 300 organizations. You can access this database directly at **http://healthhotlines.nlm.nih.gov/**. On this page, you are given the option to search by keyword or by browsing the subject list. When you have received your search results, click on the name of the organization for its description and contact information.

The National Organization for Rare Disorders, Inc.

The National Organization for Rare Disorders, Inc. has prepared a Web site that provides, at no charge, lists of associations organized by health topic. You can access this database at the following Web site: **http://www.rarediseases.org/search/orgsearch.html**. Type **fragile X syndrome** (or a synonym) into the search box, and click **Submit Query**.

Resources for Patients and Families

The following are organizations that provide support and advocacy for patient with genetic conditions and their families[22]:

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

For More Information on Genetics

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

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

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

ONLINE GLOSSARIES

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

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

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

- **Basic Guidelines for Fragile X Syndrome**

  ADHD
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/001551.htm

  Fragile X syndrome
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/001668.htm

  Fragile X syndrome chromosome analysis
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003413.htm

- **Signs & Symptoms for Fragile X Syndrome**

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

- **Diagnostics and Tests for Fragile X Syndrome**

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

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

  Chromosome analysis
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003935.htm

  Venipuncture
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003423.htm

- **Background Topics for Fragile X Syndrome**

  Adolescent test or procedure preparation
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002054.htm

  Bleeding
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000045.htm

  Chromosome
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002327.htm

  Genetic counseling
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002053.htm

  Genetics
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002048.htm

  Infant test or procedure preparation
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002055.htm

  Prenatal diagnosis
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002053.htm

  Preschooler test or procedure preparation
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002057.htm

  Schoolage test or procedure preparation
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002058.htm

  Testes
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002334.htm

  Toddler test or procedure preparation
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002056.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

FRAGILE X SYNDROME DICTIONARY

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

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

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

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

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

Actinin: A protein factor that regulates the length of R-actin. It is chemically similar, but immunochemically distinguishable from actin. [NIH]

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

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

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

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

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

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

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

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

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

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

Adolescence: The period of life beginning with the appearance of secondary sex characteristics and terminating with the cessation of somatic growth. The years usually referred to as adolescence lie between 13 and 18 years of age. [NIH]

Adrenal Cortex: The outer layer of the adrenal gland. It secretes mineralocorticoids, androgens, and glucocorticoids. [NIH]

Adrenergic: Activated by, characteristic of, or secreting epinephrine or substances with similar activity; the term is applied to those nerve fibres that liberate norepinephrine at a synapse when a nerve impulse passes, i.e., the sympathetic fibres. [EU]

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]

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]

Alexia: The inability to recognize or comprehend written or printed words. [NIH]

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

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

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]

Alternative Splicing: A process whereby multiple protein isoforms are generated from a single gene. Alternative splicing involves the splicing together of nonconsecutive exons during the processing of some, but not all, transcripts of the gene. Thus a particular exon may be connected to any one of several alternative exons to form messenger RNA. The alternative forms produce proteins in which one part is common while the other part is different. [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]

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

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

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

Amygdala: Almond-shaped group of basal nuclei anterior to the inferior horn of the lateral ventricle of the brain, within the temporal lobe. The amygdala is part of the limbic system. [NIH]

Anaerobic: 1. Lacking molecular oxygen. 2. Growing, living, or occurring in the absence of molecular oxygen; pertaining to an anaerobe. [EU]

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

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

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

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

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

Anesthesia: A state characterized by loss of feeling or sensation. This depression of nerve function is usually the result of pharmacologic action and is induced to allow performance of surgery or other painful procedures. [NIH]

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

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]

Anomalies: Birth defects; abnormalities. [NIH]

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

Anthropology: The science devoted to the comparative study of man. [NIH]

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

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

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

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

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

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

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

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

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

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

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

Aqueous: Having to do with water. [NIH]

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

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

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

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

Articulation: The relationship of two bodies by means of a moveable joint. [NIH]

Aspartate: A synthetic amino acid. [NIH]

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

Astrocytes: The largest and most numerous neuroglial cells in the brain and spinal cord. Astrocytes (from "star" cells) are irregularly shaped with many long processes, including those with "end feet" which form the glial (limiting) membrane and directly and indirectly

contribute to the blood brain barrier. They regulate the extracellular ionic and chemical environment, and "reactive astrocytes" (along with microglia) respond to injury. Astrocytes have high- affinity transmitter uptake systems, voltage-dependent and transmitter-gated ion channels, and can release transmitter, but their role in signaling (as in many other functions) is not well understood. [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]

Atrial: Pertaining to an atrium. [EU]

Atrioventricular: Pertaining to an atrium of the heart and to a ventricle. [EU]

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

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

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

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

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

Autonomic Nervous System: The enteric, parasympathetic, and sympathetic nervous systems taken together. Generally speaking, the autonomic nervous system regulates the internal environment during both peaceful activity and physical or emotional stress. Autonomic activity is controlled and integrated by the central nervous system, especially the hypothalamus and the solitary nucleus, which receive information relayed from visceral afferents; these and related central and sensory structures are sometimes (but not here) considered to be part of the autonomic nervous system itself. [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]

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]

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

Bifida: A defect in development of the vertebral column in which there is a central deficiency of the vertebral lamina. [NIH]

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

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

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

Bioluminescence: The emission of light by living organisms such as the firefly, certain mollusks, beetles, fish, bacteria, fungi and protozoa. [NIH]

Biomolecular: A scientific field at the interface between advanced computing and biotechnology. [NIH]

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]

Bipolar Disorder: A major affective disorder marked by severe mood swings (manic or major depressive episodes) and a tendency to remission and recurrence. [NIH]

Bladder: The organ that stores urine. [NIH]

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

Blood Cell Count: A count of the number of leukocytes and erythrocytes per unit volume in a sample of venous blood. A complete blood count (CBC) also includes measurement of the hemoglobin, hematocrit, and erythrocyte indices. [NIH]

Blood Glucose: Glucose in blood. [NIH]

Blood Platelets: Non-nucleated disk-shaped cells formed in the megakaryocyte and found in the blood of all mammals. They are mainly involved in blood coagulation. [NIH]

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

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

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

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

Blotting, Western: Identification of proteins or peptides that have been electrophoretically separated by blotting and transferred to strips of nitrocellulose paper. The blots are then detected by radiolabeled antibody probes. [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]

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

Brain Diseases: Pathologic conditions affecting the brain, which is composed of the intracranial components of the central nervous system. This includes (but is not limited to) the cerebral cortex; intracranial white matter; basal ganglia; thalamus; hypothalamus; brain stem; and cerebellum. [NIH]

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

Carcinogenic: Producing carcinoma. [EU]

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]

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

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

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

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

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

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

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

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

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

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

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

Cell Extracts: Preparations of cell constituents or subcellular materials, isolates, or substances. [NIH]

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

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

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

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

Cerebellar: Pertaining to the cerebellum. [EU]

Cerebellar Diseases: Diseases that affect the structure or function of the cerebellum. Cardinal manifestations of cerebellar dysfunction include dysmetria, gait ataxia, and muscle hypotonia. [NIH]

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

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

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

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

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]

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

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 Breakage: A type of chromosomal aberration which may result from spontaneous or induced breakage. Alkylating agents, various types of irradiation, and chemical mutagens have been found to cause induced chromosomal breakage. Breakage can induce base pair translocations, deletions, or chromatid breakage. [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]

Circadian: Repeated more or less daily, i. e. on a 23- to 25-hour cycle. [NIH]

Circadian Rhythm: The regular recurrence, in cycles of about 24 hours, of biological processes or activities, such as sensitivity to drugs and stimuli, hormone secretion, sleeping, feeding, etc. This rhythm seems to be set by a 'biological clock' which seems to be set by recurring daylight and darkness. [NIH]

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

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

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

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

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

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

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

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

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

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

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

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

C1s. The proteins of the alternative pathway (collectively referred to as the properdin system) and complement regulatory proteins are known by semisystematic or trivial names. Fragments resulting from proteolytic cleavage of complement proteins are designated with lower-case letter suffixes, e.g., C3a. Inactivated fragments may be designated with the suffix 'i', e.g. C3bi. Activated components or complexes with biological activity are designated by a bar over the symbol e.g. C1 or C4b,2a. The classic pathway is activated by the binding of C1 to classic pathway activators, primarily antigen-antibody complexes containing IgM, IgG1, IgG3; C1q binds to a single IgM molecule or two adjacent IgG molecules. The alternative pathway can be activated by IgA immune complexes and also by nonimmunologic materials including bacterial endotoxins, microbial polysaccharides, and cell walls. Activation of the classic pathway triggers an enzymatic cascade involving C1, C4, C2 and C3; activation of the alternative pathway triggers a cascade involving C3 and factors B, D and P. Both result in the cleavage of C5 and the formation of the membrane attack complex. Complement activation also results in the formation of many biologically active complement fragments that act as anaphylatoxins, opsonins, or chemotactic factors. [EU]

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

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

Computational Biology: A field of biology concerned with the development of techniques for the collection and manipulation of biological data, and the use of such data to make biological discoveries or predictions. This field encompasses all computational methods and theories applicable to molecular biology and areas of computer-based techniques for solving biological problems including manipulation of models and datasets. [NIH]

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

Conception: The onset of pregnancy, marked by implantation of the blastocyst; the formation of a viable zygote. [EU]

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

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

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

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

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

Conserved Sequence: A sequence of amino acids in a polypeptide or of nucleotides in DNA or RNA that is similar across multiple species. A known set of conserved sequences is

represented by a consensus sequence. Amino acid motifs are often composed of conserved sequences. [NIH]

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

Constriction: The act of constricting. [NIH]

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

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

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]

Controlled study: An experiment or clinical trial that includes a comparison (control) group. [NIH]

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

Cor: The muscular organ that maintains the circulation of the blood. c. adiposum a heart that has undergone fatty degeneration or that has an accumulation of fat around it; called also fat or fatty, heart. c. arteriosum the left side of the heart, so called because it contains oxygenated (arterial) blood. c. biloculare a congenital anomaly characterized by failure of formation of the atrial and ventricular septums, the heart having only two chambers, a single atrium and a single ventricle, and a common atrioventricular valve. c. bovinum (L. 'ox heart') a greatly enlarged heart due to a hypertrophied left ventricle; called also c. taurinum and bucardia. c. dextrum (L. 'right heart') the right atrium and ventricle. c. hirsutum, c. villosum. c. mobile (obs.) an abnormally movable heart. c. pendulum a heart so movable that it seems to be hanging by the great blood vessels. c. pseudotriloculare biatriatum a congenital cardiac anomaly in which the heart functions as a three-chambered heart because of tricuspid atresia, the right ventricle being extremely small or rudimentary and the right atrium greatly dilated. Blood passes from the right to the left atrium and thence disease due to pulmonary hypertension secondary to disease of the lung, or its blood vessels, with hypertrophy of the right ventricle. [EU]

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

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

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

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

Corticosteroids: Hormones that have antitumor activity in lymphomas and lymphoid leukemias; in addition, corticosteroids (steroids) may be used for hormone replacement and for the management of some of the complications of cancer and its treatment. [NIH]

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

Courtship: The mutual attraction between individuals of the opposite sex. [NIH]

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

Creatine: An amino acid that occurs in vertebrate tissues and in urine. In muscle tissue, creatine generally occurs as phosphocreatine. Creatine is excreted as creatinine in the urine. [NIH]

Creatine Kinase: A transferase that catalyzes formation of phosphocreatine from ATP + creatine. The reaction stores ATP energy as phosphocreatine. Three cytoplasmic isoenzymes have been identified in human tissues: MM from skeletal muscle, MB from myocardial tissue, and BB from nervous tissue as well as a mitochondrial isoenzyme. Macro-creatine kinase refers to creatine kinase complexed with other serum proteins. EC 2.7.3.2. [NIH]

Creatinine: A compound that is excreted from the body in urine. Creatinine levels are measured to monitor kidney function. [NIH]

Cribriform: Pierced with small holes as in a sieve. Refers to the appearance of a tumor when viewed under a microscope. The tumor appears to have open spaces or small holes inside. [NIH]

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

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

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

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

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]

Data Collection: Systematic gathering of data for a particular purpose from various sources, including questionnaires, interviews, observation, existing records, and electronic devices. The process is usually preliminary to statistical analysis of the data. [NIH]

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

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

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

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

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

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

Dendritic: 1. Branched like a tree. 2. Pertaining to or possessing dendrites. [EU]

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

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]

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

Diagnostic procedure: A method used to identify a disease. [NIH]

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

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

Dimerization: The process by which two molecules of the same chemical composition form a condensation product or polymer. [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]

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

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

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]

Diurnal: Occurring during the day. [EU]

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

Down syndrome: A disorder caused by the presence of an extra chromosome 21 and characterized by mental retardation and distinguishing physical features. [NIH]

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

Dynein: A transport protein that normally binds proteins to the microtubule. [NIH]

Dyskinesias: Abnormal involuntary movements which primarily affect the extremities, trunk, or jaw that occur as a manifestation of an underlying disease process. Conditions which feature recurrent or persistent episodes of dyskinesia as a primary manifestation of disease may be referred to as dyskinesia syndromes (movement disorders). Dyskinesias are also a relatively common manifestation of basal ganglia diseases. [NIH]

Dyslexia: Partial alexia in which letters but not words may be read, or in which words may be read but not understood. [NIH]

Dysostosis: Defective bone formation. [NIH]

Dysplasia: Cells that look abnormal under a microscope but are not cancer. [NIH]

Dystrophin: A muscle protein localized in surface membranes which is the product of the Duchenne/Becker muscular dystrophy gene. Individuals with Duchenne muscular dystrophy usually lack dystrophin completely while those with Becker muscular dystrophy have dystrophin of an altered size. It shares features with other cytoskeletal proteins such as spectrin and alpha-actinin but the precise function of dystrophin is not clear. One possible role might be to preserve the integrity and alignment of the plasma membrane to the myofibrils during muscle contraction and relaxation. MW 400 kDa. [NIH]

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

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

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]

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]

Electroencephalography: Recording of electric currents developed in the brain by means of electrodes applied to the scalp, to the surface of the brain, or placed within the substance of the brain. [NIH]

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

Electromyography: Recording of the changes in electric potential of muscle by means of surface or needle electrodes. [NIH]

Electrons: Stable elementary particles having the smallest known negative charge, present in all elements; also called negatrons. Positively charged electrons are called positrons. The numbers, energies and arrangement of electrons around atomic nuclei determine the chemical identities of elements. Beams of electrons are called cathode rays or beta rays, the latter being a high-energy biproduct of nuclear decay. [NIH]

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

Embryology: The study of the development of an organism during the embryonic and fetal stages of life. [NIH]

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

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

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

Energetic: Exhibiting energy : strenuous; operating with force, vigour, or effect. [EU]

Enhancer: Transcriptional element in the virus genome. [NIH]

Entorhinal Cortex: Cortex where the signals are combined with those from other sensory systems. [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]

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]

Epilepticus: Repeated and prolonged epileptic seizures without recovery of consciousness between attacks. [NIH]

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

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

Ethmoid: An unpaired cranial bone which helps form the medial walls of the orbits and contains the themoidal air cells which drain into the nose. [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]

Exhaustion: The feeling of weariness of mind and body. [NIH]

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

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

Extracellular: Outside a cell or cells. [EU]

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

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

Extrapyramidal: Outside of the pyramidal tracts. [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]

Eye Movements: Voluntary or reflex-controlled movements of the eye. [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]

Fetal Alcohol Syndrome: A disorder occurring in children born to alcoholic women who continue to drink heavily during pregnancy. Common abnormalities are growth deficiency (prenatal and postnatal), altered morphogenesis, mental deficiency, and characteristic facies - small eyes and flattened nasal bridge. Fine motor dysfunction and tremulousness are observed in the newborn. [NIH]

Fetal Blood: Blood of the fetus. Exchange of nutrients and waste between the fetal and maternal blood occurs via the placenta. The cord blood is blood contained in the umbilical vessels at the time of delivery. [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]

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

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

Focus Groups: A method of data collection and a qualitative research tool in which a small group of individuals are brought together and allowed to interact in a discussion of their opinions about topics, issues, or questions. [NIH]

Folate: A B-complex vitamin that is being studied as a cancer prevention agent. Also called folic acid. [NIH]

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

Folic Acid: N-(4-(((2-Amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl)amino)benzoyl)-L-glutamic acid. A member of the vitamin B family that stimulates the hematopoietic system. It is present in the liver and kidney and is found in mushrooms, spinach, yeast, green leaves, and grasses. Folic acid is used in the treatment and prevention of folate deficiencies and megaloblastic anemia. [NIH]

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

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

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

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

Functional magnetic resonance imaging: A noninvasive tool used to observe functioning in the brain or other organs by detecting changes in chemical composition, blood flow, or both. [NIH]

Gait: Manner or style of walking. [NIH]

Gait Ataxia: Impairment of the ability to coordinate the movements required for normal ambulation which may result from impairments of motor function or sensory feedback. This condition may be associated with brain diseases (including cerebellar diseases and basal ganglia diseases); spinal cord diseases; or peripheral nervous system diseases. [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]

Gastrin: A hormone released after eating. Gastrin causes the stomach to produce more acid. [NIH]

Gastrointestinal: Refers to the stomach and intestines. [NIH]

Gastrointestinal tract: The stomach and intestines. [NIH]

Gene: The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein. [NIH]

Gene Deletion: A genetic rearrangement through loss of segments of DNA or RNA, bringing sequences which are normally separated into close proximity. This deletion may be

detected using cytogenetic techniques and can also be inferred from the phenotype, indicating a deletion at one specific locus. [NIH]

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

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

Gene Silencing: Interruption or suppression of the expression of a gene at transcriptional or translational levels. [NIH]

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

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

Genetic Code: The specifications for how information, stored in nucleic acid sequence (base sequence), is translated into protein sequence (amino acid sequence). The start, stop, and order of amino acids of a protein is specified by consecutive triplets of nucleotides called codons (codon). [NIH]

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

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

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

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

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

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

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

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]

Glomeruli: Plural of glomerulus. [NIH]

Glucocorticoid: A compound that belongs to the family of compounds called corticosteroids (steroids). Glucocorticoids affect metabolism and have anti-inflammatory and immunosuppressive effects. They may be naturally produced (hormones) or synthetic (drugs). [NIH]

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

Glutamate: Excitatory neurotransmitter of the brain. [NIH]

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

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

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

Grade: The grade of a tumor depends on how abnormal the cancer cells look under a microscope and how quickly the tumor is likely to grow and spread. Grading systems are different for each type of cancer. [NIH]

Gram-negative: Losing the stain or decolorized by alcohol in Gram's method of staining, a primary characteristic of bacteria having a cell wall composed of a thin layer of peptidoglycan covered by an outer membrane of lipoprotein and lipopolysaccharide. [EU]

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

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

Grasses: A large family, Gramineae, of narrow-leaved herbaceous monocots. Many grasses produce highly allergenic pollens and are hosts to cattle parasites and toxic fungi. [NIH]

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

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

Handedness: Preference for using right or left hand. [NIH]

Handicap: A handicap occurs as a result of disability, but disability does not always constitute a handicap. A handicap may be said to exist when a disability causes a substantial and continuing reduction in a person's capacity to function socially and vocationally. [NIH]

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

Haptens: Small antigenic determinants capable of eliciting an immune response only when coupled to a carrier. Haptens bind to antibodies but by themselves cannot elicit an antibody response. [NIH]

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

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

Hemochromatosis: A disease that occurs when the body absorbs too much iron. The body

stores the excess iron in the liver, pancreas, and other organs. May cause cirrhosis of the liver. Also called iron overload disease. [NIH]

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

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

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

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

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

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

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]

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]

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

Histones: Small chromosomal proteins (approx 12-20 kD) possessing an open, unfolded structure and attached to the DNA in cell nuclei by ionic linkages. Classification into the various types (designated histone I, histone II, etc.) is based on the relative amounts of arginine and lysine in each. [NIH]

Homeostasis: The processes whereby the internal environment of an organism tends to remain balanced and stable. [NIH]

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 Development: Continuous sequential changes which occur in the physiological and psychological functions during the individual's life. [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]

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]

Hypothalamic: Of or involving the hypothalamus. [EU]

Hypothalamus: Ventral part of the diencephalon extending from the region of the optic chiasm to the caudal border of the mammillary bodies and forming the inferior and lateral walls of the third ventricle. [NIH]

Idiopathic: Describes a disease of unknown cause. [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]

Immunoblotting: Immunologic methods for isolating and quantitatively measuring immunoreactive substances. When used with immune reagents such as monoclonal antibodies, the process is known generically as western blot analysis (blotting, western). [NIH]

Immunology: The study of the body's immune system. [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 Situ Hybridization: A technique that localizes specific nucleic acid sequences within intact chromosomes, eukaryotic cells, or bacterial cells through the use of specific nucleic acid-labeled probes. [NIH]

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

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

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

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

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]

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]

Inositol: An isomer of glucose that has traditionally been considered to be a B vitamin although it has an uncertain status as a vitamin and a deficiency syndrome has not been identified in man. (From Martindale, The Extra Pharmacopoeia, 30th ed, p1379) Inositol phospholipids are important in signal transduction. [NIH]

Inotropic: Affecting the force or energy of muscular contractions. [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]

Insulin-like: Muscular growth factor. [NIH]

Intermittent: Occurring at separated intervals; having periods of cessation of activity. [EU]

Intoxication: Poisoning, the state of being poisoned. [EU]

Intracellular: Inside a cell. [NIH]

Intravenous: IV. Into a vein. [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]

Investigative Techniques: Investigative techniques used in pre-clinical and clinical research,

epidemiology, chemistry, immunology, genetics, etc. They do not include techniques specifically applied to diagnosis; therapeutics; anesthesia and analgesia, surgery, operative, and dentistry. [NIH]

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]

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]

Irradiation: The use of high-energy radiation from x-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 from materials called radioisotopes. Radioisotopes produce radiation and can be placed in or near the tumor or in the area near cancer cells. This type of radiation treatment is called internal radiation therapy, implant radiation, interstitial radiation, or brachytherapy. Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. Irradiation is also called radiation therapy, radiotherapy, and x-ray therapy. [NIH]

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

Isoenzyme: Different forms of an enzyme, usually occurring in different tissues. The isoenzymes of a particular enzyme catalyze the same reaction but they differ in some of their properties. [NIH]

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

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

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

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

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]

Lactation: The period of the secretion of milk. [EU]

Language Development: The gradual expansion in complexity and meaning of symbols and sounds as perceived and interpreted by the individual through a maturational and learning process. Stages in development include babbling, cooing, word imitation with cognition, and use of short sentences. [NIH]

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

Lethal: Deadly, fatal. [EU]

Leucocyte: All the white cells of the blood and their precursors (myeloid cell series, lymphoid cell series) but commonly used to indicate granulocytes exclusive of lymphocytes. [NIH]

Leukemia: Cancer of blood-forming tissue. [NIH]

Life cycle: The successive stages through which an organism passes from fertilized ovum or spore to the fertilized ovum or spore of the next generation. [NIH]

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

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

Limbic: Pertaining to a limbus, or margin; forming a border around. [EU]

Limbic System: A set of forebrain structures common to all mammals that is defined functionally and anatomically. It is implicated in the higher integration of visceral, olfactory, and somatic information as well as homeostatic responses including fundamental survival behaviors (feeding, mating, emotion). For most authors, it includes the amygdala, epithalamus, gyrus cinguli, hippocampal formation (see hippocampus), hypothalamus, parahippocampal gyrus, septal nuclei, anterior nuclear group of thalamus, and portions of the basal ganglia. (Parent, Carpenter's Human Neuroanatomy, 9th ed, p744; NeuroNames, http://rprcsgi.rprc.washington.edu/neuronames/index.html (September 2, 1998)). [NIH]

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

Lipid: Fat. [NIH]

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

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]

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

Longitudinal Studies: Studies in which variables relating to an individual or group of individuals are assessed over a period of time. [NIH]

Longitudinal study: Also referred to as a "cohort study" or "prospective study"; the analytic method of epidemiologic study in which subsets of a defined population can be identified

who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of this type of study is to observe large numbers of subjects over an extended time, with comparisons of incidence rates in groups that differ in exposure levels. [NIH]

Long-Term Care: Care over an extended period, usually for a chronic condition or disability, requiring periodic, intermittent, or continuous care. [NIH]

Long-Term Potentiation: A persistent increase in synaptic efficacy, usually induced by appropriate activation of the same synapses. The phenomenological properties of long-term potentiation suggest that it may be a cellular mechanism of learning and memory. [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]

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

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

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

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

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

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]

Magnetoencephalography: The measurement of magnetic fields over the head generated by electric currents in the brain. As in any electrical conductor, electric fields in the brain are accompanied by orthogonal magnetic fields. The measurement of these fields provides information about the localization of brain activity which is complementary to that provided by electroencephalography. Magnetoencephalography may be used alone or together with electroencephalography, for measurement of spontaneous or evoked activity, and for research or clinical purposes. [NIH]

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

Malformation: A morphologic defect resulting from an intrinsically abnormal developmental process. [EU]

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

Mammography: Radiographic examination of the breast. [NIH]

Manic: Affected with mania. [EU]

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]

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

Megaloblastic: A large abnormal red blood cell appearing in the blood in pernicious anaemia. [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]

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

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

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

Menarche: The establishment or beginning of the menstrual function. [EU]

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

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

Mental deficiency: A condition of arrested or incomplete development of mind from inherent causes or induced by disease or injury. [NIH]

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

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

Mental Processes: Conceptual functions or thinking in all its forms. [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]

Metabolic disorder: A condition in which normal metabolic processes are disrupted, usually because of a missing enzyme. [NIH]

Metabotropic: A glutamate receptor which triggers an increase in production of 2 intracellular messengers: diacylglycerol and inositol 1, 4, 5-triphosphate. [NIH]

Methyltransferase: A drug-metabolizing enzyme. [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]

Microglia: The third type of glial cell, along with astrocytes and oligodendrocytes (which together form the macroglia). Microglia vary in appearance depending on developmental stage, functional state, and anatomical location; subtype terms include ramified, perivascular, ameboid, resting, and activated. Microglia clearly are capable of phagocytosis and play an important role in a wide spectrum of neuropathologies. They have also been suggested to act in several other roles including in secretion (e.g., of cytokines and neural growth factors), in immunological processing (e.g., antigen presentation), and in central nervous system development and remodeling. [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]

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

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

Mitosis: A method of indirect cell division by means of which the two daughter nuclei normally receive identical complements of the number of chromosomes of the somatic cells of the species. [NIH]

Mitral Valve: The valve between the left atrium and left ventricle of the heart. [NIH]

Mitral Valve Prolapse: Abnormal protrusion of one or both of the leaflets of the mitral valve into the left atrium during systole. This may be accompanied by mitral regurgitation, systolic murmur, nonejection click, or cardiac arrhythmia. [NIH]

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

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

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

Molecular Motors: Protein based machines that are involved in or cause movement such as the rotary devices (flagellar motor and the F1 ATPase) or the devices whose movement is directed along cytoskeletal filaments (myosin, kinesin and dynein motor families). [NIH]

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

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

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

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

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

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]

Motion Perception: The real or apparent movement of objects through the visual field. [NIH]

Motor Skills: Performance of complex motor acts. [NIH]

Movement Disorders: Syndromes which feature dyskinesias as a cardinal manifestation of the disease process. Included in this category are degenerative, hereditary, post-infectious, medication-induced, post-inflammatory, and post-traumatic conditions. [NIH]

MRNA: The RNA molecule that conveys from the DNA the information that is to be translated into the structure of a particular polypeptide molecule. [NIH]

Muscle Contraction: A process leading to shortening and/or development of tension in muscle tissue. Muscle contraction occurs by a sliding filament mechanism whereby actin filaments slide inward among the myosin filaments. [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]

Mycoplasma: A genus of gram-negative, facultatively anaerobic bacteria bounded by a plasma membrane only. Its organisms are parasites and pathogens, found on the mucous membranes of humans, animals, and birds. [NIH]

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

Myoclonus: Involuntary shock-like contractions, irregular in rhythm and amplitude, followed by relaxation, of a muscle or a group of muscles. This condition may be a feature of some central nervous systems diseases (e.g., epilepsy, myoclonic). Nocturnal myoclonus may represent a normal physiologic event or occur as the principal feature of the nocturnal myoclonus syndrome. (From Adams et al., Principles of Neurology, 6th ed, pp102-3). [NIH]

Myofibrils: Highly organized bundles of actin, myosin, and other proteins in the cytoplasm of skeletal and cardiac muscle cells that contract by a sliding filament mechanism. [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]

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]

Neonatal: Pertaining to the first four weeks after birth. [EU]

Neonatal Screening: The identification of selected parameters in newborn infants by various tests, examinations, or other procedures. Screening may be performed by clinical or laboratory measures. A screening test is designed to sort out healthy neonates from those not well, but the screening test is not intended as a diagnostic device, rather instead as epidemiologic. [NIH]

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

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

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

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]

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

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

Neuronal Plasticity: The capacity of the nervous system to change its reactivity as the result of successive activations. [NIH]

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

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

Neurophysiology: The scientific discipline concerned with the physiology of the nervous system. [NIH]

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

Neurosciences: The scientific disciplines concerned with the embryology, anatomy, physiology, biochemistry, pharmacology, etc., of the nervous sytem. [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]

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

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

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

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

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

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

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

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

Nystagmus: An involuntary, rapid, rhythmic movement of the eyeball, which may be horizontal, vertical, rotatory, or mixed, i.e., of two varieties. [EU]

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

Olfactory Bulb: Ovoid body resting on the cribriform plate of the ethmoid bone where the olfactory nerve terminates. The olfactory bulb contains several types of nerve cells including the mitral cells, on whose dendrites the olfactory nerve synapses, forming the olfactory glomeruli. The accessory olfactory bulb, which receives the projection from the vomeronasal organ via the vomeronasal nerve, is also included here. [NIH]

Olfactory Nerve: The 1st cranial nerve. The olfactory nerve conveys the sense of smell. It is formed by the axons of olfactory receptor neurons which project from the olfactory epithelium (in the nasal epithelium) to the olfactory bulb. [NIH]

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

Oogenesis: The formation, development, and maturation of the female germ cell. [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]

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]

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]

Otitis: Inflammation of the ear, which may be marked by pain, fever, abnormalities of hearing, hearing loss, tinnitus, and vertigo. [EU]

Otitis Media: Inflammation of the middle ear. [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]

Ovum: A female germ cell extruded from the ovary at ovulation. [NIH]

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

Oxytocin: A nonapeptide posterior pituitary hormone that causes uterine contractions and stimulates lactation. [NIH]

Pacemaker: An object or substance that influences the rate at which a certain phenomenon occurs; often used alone to indicate the natural cardiac pacemaker or an artificial cardiac pacemaker. In biochemistry, a substance whose rate of reaction sets the pace for a series of interrelated reactions. [EU]

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

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

Parietal: 1. Of or pertaining to the walls of a cavity. 2. Pertaining to or located near the parietal bone, as the parietal lobe. [EU]

Parietal Lobe: Upper central part of the cerebral hemisphere. [NIH]

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

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

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

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

PDQ: Physician Data Query. PDQ is an online database developed and maintained by the National Cancer Institute. Designed to make the most current, credible, and accurate cancer

information available to health professionals and the public, PDQ contains peer-reviewed summaries on cancer treatment, screening, prevention, genetics, and supportive care; a registry of cancer clinical trials from around the world; and directories of physicians, professionals who provide genetics services, and organizations that provide cancer care. Most of this information is available on the CancerNet Web site, and more specific information about PDQ can be found at http://cancernet.nci.nih.gov/pdq.html. [NIH]

Pediatrics: A medical specialty concerned with maintaining health and providing medical care to children from birth to adolescence. [NIH]

Pedigree: A record of one's ancestors, offspring, siblings, and their offspring that may be used to determine the pattern of certain genes or disease inheritance within a family. [NIH]

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

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

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

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

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

Pericardium: The fibroserous sac surrounding the heart and the roots of the great vessels. [NIH]

Perinatal: Pertaining to or occurring in the period shortly before and after birth; variously defined as beginning with completion of the twentieth to twenty-eighth week of gestation and ending 7 to 28 days after birth. [EU]

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

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

Pharmacologic: Pertaining to pharmacology or to the properties and reactions of drugs. [EU]

Pharmacotherapy: A regimen of using appetite suppressant medications to manage obesity by decreasing appetite or increasing the feeling of satiety. These medications decrease appetite by increasing serotonin or catecholamine—two brain chemicals that affect mood and appetite. [NIH]

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]

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]

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]

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

Physical Therapy: The restoration of function and the prevention of disability following disease or injury with the use of light, heat, cold, water, electricity, ultrasound, and exercise. [NIH]

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

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

Pilot study: The initial study examining a new method or treatment. [NIH]

Placenta: A highly vascular fetal organ through which the fetus absorbs oxygen and other nutrients and excretes carbon dioxide and other wastes. It begins to form about the eighth day of gestation when the blastocyst adheres to the decidua. [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]

Plasticity: In an individual or a population, the capacity for adaptation: a) through gene changes (genetic plasticity) or b) through internal physiological modifications in response to changes of environment (physiological plasticity). [NIH]

Plastids: Self-replicating cytoplasmic organelles of plant and algal cells that contain pigments and may synthesize and accumulate various substances. Plastids are used in phylogenetic studies. [NIH]

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]

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

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

Polymorphism: The occurrence together of two or more distinct forms in the same population. [NIH]

Polypeptide: A peptide which on hydrolysis yields more than two amino acids; called tripeptides, tetrapeptides, etc. according to the number of amino acids contained. [EU]

Polysaccharide: A type of carbohydrate. It contains sugar molecules that are linked together chemically. [NIH]

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

Postnatal: Occurring after birth, with reference to the newborn. [EU]

Post-traumatic: Occurring as a result of or after injury. [EU]

Postural: Pertaining to posture or position. [EU]

Practice Guidelines: Directions or principles presenting current or future rules of policy for the health care practitioner to assist him in patient care decisions regarding diagnosis, therapy, or related clinical circumstances. The guidelines may be developed by government agencies at any level, institutions, professional societies, governing boards, or by the convening of expert panels. The guidelines form a basis for the evaluation of all aspects of health care and delivery. [NIH]

Precursor: Something that precedes. In biological processes, a substance from which another, usually more active or mature substance is formed. In clinical medicine, a sign or symptom that heralds another. [EU]

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

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

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]

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

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

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

Prophase: The first phase of cell division, in which the chromosomes become visible, the nucleus starts to lose its identity, the spindle appears, and the centrioles migrate toward opposite poles. [NIH]

Prospective study: An epidemiologic study in which a group of individuals (a cohort), all free of a particular disease and varying in their exposure to a possible risk factor, is followed over a specific amount of time to determine the incidence rates of the disease in the exposed and unexposed groups. [NIH]

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 Isoforms: Different forms of a protein that may be produced from different genes, or from the same gene by alternative splicing. [NIH]

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

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

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

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

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]

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

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

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

Psychoactive: Those drugs which alter sensation, mood, consciousness or other psychological or behavioral functions. [NIH]

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

Psychopathology: The study of significant causes and processes in the development of mental illness. [NIH]

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

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

Pulmonary hypertension: Abnormally high blood pressure in the arteries of the lungs. [NIH]

Purines: A series of heterocyclic compounds that are variously substituted in nature and are known also as purine bases. They include adenine and guanine, constituents of nucleic

acids, as well as many alkaloids such as caffeine and theophylline. Uric acid is the metabolic end product of purine metabolism. [NIH]

Pyrimidines: A family of 6-membered heterocyclic compounds occurring in nature in a wide variety of forms. They include several nucleic acid constituents (cytosine, thymine, and uracil) and form the basic structure of the barbiturates. [NIH]

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

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

Radiation therapy: The use of high-energy radiation from x-rays, gamma rays, neutrons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body in the area near cancer cells (internal radiation therapy, implant radiation, or brachytherapy). Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. Also called radiotherapy. [NIH]

Radioactive: Giving off radiation. [NIH]

Randomized: Describes an experiment or clinical trial in which animal or human subjects are assigned by chance to separate groups that compare different treatments. [NIH]

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

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

Receptors, Serotonin: Cell-surface proteins that bind serotonin and trigger intracellular changes which influence the behavior of cells. Several types of serotonin receptors have been recognized which differ in their pharmacology, molecular biology, and mode of action. [NIH]

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

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

Rectum: The last 8 to 10 inches of the large intestine. [NIH]

Recurrence: The return of a sign, symptom, or disease after a remission. [NIH]

Red Nucleus: A pinkish-yellow portion of the midbrain situated in the rostral mesencephalic tegmentum. It receives a large projection from the contralateral half of the cerebellum via the superior cerebellar peduncle and a projection from the ipsilateral motor cortex. [NIH]

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

Reflex: An involuntary movement or exercise of function in a part, excited in response to a stimulus applied to the periphery and transmitted to the brain or spinal cord. [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]

Regurgitation: A backward flowing, as the casting up of undigested food, or the backward

flowing of blood into the heart, or between the chambers of the heart when a valve is incompetent. [EU]

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

Remission: A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although there still may be cancer in the body. [NIH]

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]

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

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]

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

Retroviral vector: RNA from a virus that is used to insert genetic material into cells. [NIH]

Ribonucleic acid: RNA. One of the two nucleic acids found in all cells. The other is deoxyribonucleic acid (DNA). Ribonucleic acid transfers genetic information from DNA to proteins produced by the cell. [NIH]

Ribose: A pentose active in biological systems usually in its D-form. [NIH]

Ribosome: A granule of protein and RNA, synthesized in the nucleolus and found in the cytoplasm of cells. Ribosomes are the main sites of protein synthesis. Messenger RNA attaches to them and there receives molecules of transfer RNA bearing amino acids. [NIH]

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

Saliva: The clear, viscous fluid secreted by the salivary glands and mucous glands of the mouth. It contains mucins, water, organic salts, and ptylin. [NIH]

Salivary: The duct that convey saliva to the mouth. [NIH]

Scatter: The extent to which relative success and failure are divergently manifested in qualitatively different tests. [NIH]

Schizoid: Having qualities resembling those found in greater degree in schizophrenics; a

person of schizoid personality. [NIH]

Schizophrenia: A mental disorder characterized by a special type of disintegration of the personality. [NIH]

Schizotypal Personality Disorder: A personality disorder in which there are oddities of thought (magical thinking, paranoid ideation, suspiciousness), perception (illusions, depersonalization), speech (digressive, vague, overelaborate), and behavior (inappropriate affect in social interactions, frequently social isolation) that are not severe enough to characterize schizophrenia. [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]

Scrotum: In males, the external sac that contains the testicles. [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]

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]

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

Serotonin: A biochemical messenger and regulator, synthesized from the essential amino acid L-tryptophan. In humans it is found primarily in the central nervous system, gastrointestinal tract, and blood platelets. Serotonin mediates several important physiological functions including neurotransmission, gastrointestinal motility, hemostasis, and cardiovascular integrity. Multiple receptor families (receptors, serotonin) explain the broad physiological actions and distribution of this biochemical mediator. [NIH]

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

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

Shock: The general bodily disturbance following a severe injury; an emotional or moral upset occasioned by some disturbing or unexpected experience; disruption of the circulation, which can upset all body functions: sometimes referred to as circulatory shock. [NIH]

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

Signs and Symptoms: Clinical manifestations that can be either objective when observed by

a physician, or subjective when perceived by the patient. [NIH]

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]

Social Behavior: Any behavior caused by or affecting another individual, usually of the same species. [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]

Socialization: The training or molding of an individual through various relationships, educational agencies, and social controls, which enables him to become a member of a particular society. [NIH]

Soft tissue: Refers to muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body. [NIH]

Solitary Nucleus: Gray matter located in the dorsomedial part of the medulla oblongata associated with the solitary tract. The solitary nucleus receives inputs from most organ systems including the terminations of the facial, glossopharyngeal, and vagus nerves. It is a major coordinator of autonomic nervous system regulation of cardiovascular, respiratory, gustatory, gastrointestinal, and chemoreceptive aspects of homeostasis. The solitary nucleus is also notable for the large number of neurotransmitters which are found therein. [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]

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]

Spectrin: A high molecular weight (220-250 kDa) water-soluble protein which can be

extracted from erythrocyte ghosts in low ionic strength buffers. The protein contains no lipids or carbohydrates, is the predominant species of peripheral erythrocyte membrane proteins, and exists as a fibrous coating on the inner, cytoplasmic surface of the membrane. [NIH]

Spectroscopic: The recognition of elements through their emission spectra. [NIH]

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

Speech Intelligibility: Ability to make speech sounds that are recognizable. [NIH]

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

Spina bifida: A defect in development of the vertebral column in which there is a central deficiency of the vertebral lamina. [NIH]

Spinal cord: The main trunk or bundle of nerves running down the spine through holes in the spinal bone (the vertebrae) from the brain to the level of the lower back. [NIH]

Spinal Cord Diseases: Pathologic conditions which feature spinal cord damage or dysfunction, including disorders involving the meninges and perimeningeal spaces surrounding the spinal cord. Traumatic injuries, vascular diseases, infections, and inflammatory/autoimmune processes may affect the spinal cord. [NIH]

Spinal Nerves: The 31 paired peripheral nerves formed by the union of the dorsal and ventral spinal roots from each spinal cord segment. The spinal nerve plexuses and the spinal roots are also included. [NIH]

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

Stabilization: The creation of a stable state. [EU]

Stereotyped Behavior: Relatively invariant mode of behavior elicited or determined by a particular situation; may be verbal, postural, or expressive. [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]

Stimulants: Any drug or agent which causes stimulation. [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]

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]

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]

Subiculum: A region of the hippocampus that projects to other areas of the brain. [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]

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]

Surface Plasmon Resonance: A biosensing technique in which biomolecules capable of binding to specific analytes or ligands are first immobilized on one side of a metallic film. Light is then focused on the opposite side of the film to excite the surface plasmons, that is, the oscillations of free electrons propagating along the film's surface. The refractive index of light reflecting off this surface is measured. When the immobilized biomolecules are bound by their ligands, an alteration in surface plasmons on the opposite side of the film is created which is directly proportional to the change in bound, or adsorbed, mass. Binding is measured by changes in the refractive index. The technique is used to study biomolecular interactions, such as antigen-antibody binding. [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]

Sympathomimetic: 1. Mimicking the effects of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. 2. An agent that produces effects similar to those of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. Called also adrenergic. [EU]

Synapse: The region where the processes of two neurons come into close contiguity, and the nervous impulse passes from one to the other; the fibers of the two are intermeshed, but, according to the general view, there is no direct contiguity. [NIH]

Synapsis: The pairing between homologous chromosomes of maternal and paternal origin during the prophase of meiosis, leading to the formation of gametes. [NIH]

Synaptic: Pertaining to or affecting a synapse (= site of functional apposition between neurons, at which an impulse is transmitted from one neuron to another by electrical or chemical means); pertaining to synapsis (= pairing off in point-for-point association of homologous chromosomes from the male and female pronuclei during the early prophase of meiosis). [EU]

Systemic: Affecting the entire body. [NIH]

Systemic lupus erythematosus: SLE. A chronic inflammatory connective tissue disease

marked by skin rashes, joint pain and swelling, inflammation of the kidneys, inflammation of the fibrous tissue surrounding the heart (i.e., the pericardium), as well as other problems. Not all affected individuals display all of these problems. May be referred to as lupus. [NIH]

Systole: Period of contraction of the heart, especially of the ventricles. [NIH]

Systolic: Indicating the maximum arterial pressure during contraction of the left ventricle of the heart. [EU]

Temperament: Predisposition to react to one's environment in a certain way; usually refers to mood changes. [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]

Temporal Lobe: Lower lateral part of the cerebral hemisphere. [NIH]

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

Testicles: The two egg-shaped glands found inside the scrotum. They produce sperm and male hormones. Also called testes. [NIH]

Testicular: Pertaining to a testis. [EU]

Testis: Either of the paired male reproductive glands that produce the male germ cells and the male hormones. [NIH]

Thalamic: Cell that reaches the lateral nucleus of amygdala. [NIH]

Thalamic Diseases: Disorders of the centrally located thalamus, which integrates a wide range of cortical and subcortical information. Manifestations include sensory loss, movement disorders; ataxia, pain syndromes, visual disorders, a variety of neuropsychological conditions, and coma. Relatively common etiologies include cerebrovascular disorders; craniocerebral trauma; brain neoplasms; brain hypoxia; intracranial hemorrhages; and infectious processes. [NIH]

Therapeutics: The branch of medicine which is concerned with the treatment of diseases, palliative or curative. [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]

Tinnitus: Sounds that are perceived in the absence of any external noise source which may take the form of buzzing, ringing, clicking, pulsations, and other noises. Objective tinnitus refers to noises generated from within the ear or adjacent structures that can be heard by other individuals. The term subjective tinnitus is used when the sound is audible only to the affected individual. Tinnitus may occur as a manifestation of cochlear diseases; vestibulocochlear nerve diseases; intracranial hypertension; craniocerebral trauma; and other conditions. [NIH]

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

Tonus: A state of slight tension usually present in muscles even when they are not undergoing active contraction. [NIH]

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

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

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

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

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

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

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

Transgenes: Genes that are introduced into an organism using gene transfer techniques. [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]

Tremor: Cyclical movement of a body part that can represent either a physiologic process or a manifestation of disease. Intention or action tremor, a common manifestation of cerebellar diseases, is aggravated by movement. In contrast, resting tremor is maximal when there is no attempt at voluntary movement, and occurs as a relatively frequent manifestation of Parkinson disease. [NIH]

Tricuspid Atresia: Absence of the orifice between the right atrium and ventricle, with the presence of an atrial defect through which all the systemic venous return reaches the left heart. As a result, there is left ventricular hypertrophy because the right ventricle is absent or not functional. [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]

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

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

Ultraviolet radiation: Invisible rays that are part of the energy that comes from the sun. UV radiation can damage the skin and cause melanoma and other types of skin cancer. UV radiation that reaches the earth's surface is made up of two types of rays, called UVA and UVB rays. UVB rays are more likely than UVA rays to cause sunburn, but UVA rays pass deeper into the skin. Scientists have long thought that UVB radiation can cause melanoma and other types of skin cancer. They now think that UVA radiation also may add to skin damage that can lead to skin cancer and cause premature aging. For this reason, skin specialists recommend that people use sunscreens that reflect, absorb, or scatter both kinds of UV radiation. [NIH]

Uremia: The illness associated with the buildup of urea in the blood because the kidneys are not working effectively. Symptoms include nausea, vomiting, loss of appetite, weakness, and mental confusion. [NIH]

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

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]

Uterine Contraction: Contraction of the uterine muscle. [NIH]

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

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

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

Vagal: Pertaining to the vagus nerve. [EU]

Vagus Nerve: The 10th cranial nerve. The vagus is a mixed nerve which contains somatic afferents (from skin in back of the ear and the external auditory meatus), visceral afferents (from the pharynx, larynx, thorax, and abdomen), parasympathetic efferents (to the thorax and abdomen), and efferents to striated muscle (of the larynx and pharynx). [NIH]

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

Vasodilator: An agent that widens blood vessels. [NIH]

Vector: Plasmid or other self-replicating DNA molecule that transfers DNA between cells in nature or in recombinant DNA technology. [NIH]

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

Venous: Of or pertaining to the veins. [EU]

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]

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

Vertebral: Of or pertaining to a vertebra. [EU]

Vertigo: An illusion of movement; a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo). The term is sometimes erroneously used to mean any form of dizziness. [EU]

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

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

Viral vector: A type of virus used in cancer therapy. The virus is changed in the laboratory and cannot cause disease. Viral vectors produce tumor antigens (proteins found on a tumor cell) and can stimulate an antitumor immune response in the body. Viral vectors may also be used to carry genes that can change cancer cells back to normal cells. [NIH]

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

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

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

Visceral: , from viscus a viscus) pertaining to a viscus. [EU]

Visceral Afferents: The sensory fibers innervating the viscera. [NIH]

Visual field: The entire area that can be seen when the eye is forward, including peripheral vision. [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]

Vomeronasal Organ: A specialized part of the olfactory system located anteriorly in the nasal cavity within the nasal septum. Chemosensitive cells of the vomeronasal organ project via the vomeronasal nerve to the accessory olfactory bulb. The primary function of this organ appears to be in sensing pheromones which regulate reproductive and other social behaviors. While the structure has been thought absent in higher primate adults, data now suggests it may be present in adult humans. [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]

Withdrawal: 1. A pathological retreat from interpersonal contact and social involvement, as may occur in schizophrenia, depression, or schizoid avoidant and schizotypal personality disorders. 2. (DSM III-R) A substance-specific organic brain syndrome that follows the cessation of use or reduction in intake of a psychoactive substance that had been regularly used to induce a state of intoxication. [EU]

Womb: A hollow, thick-walled, muscular organ in which the impregnated ovum is developed into a child. [NIH]

Xenograft: The cells of one species transplanted to another species. [NIH]

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

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

Zygote: The fertilized ovum. [NIH]

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

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