DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

www.nih.gov

MAY 20 2004

The Honorable Judd Gregg
Chairman, Committee on Health,
Education, Labor and Pensions
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

I am pleased to submit to you the National Institutes of Health (NIH) Annual Report on Rare Diseases Research Activities: FY 2003. Section 404F of the Public Health Service Act, as amended by Public Law 107-280, the Rare Diseases Act of 2002, requires an annual report to Congress on the activities that NIH conducted and supported through our Institutes and Centers with respect to rare diseases research.

This report presents the contributions and research advances of the NIH research programs and the Office of Rare Diseases (ORD). These basic, clinical, and research training programs contribute to the development and dissemination of information on the prevention, etiology, diagnosis, and treatment of rare diseases. Many advances presented in the report are the results of years of basic research sponsored by the NIH. Patients with rare diseases and their families continue to benefit from the treatment applications realized from the diverse nature of and emphasis placed on both basic and translational research by NIH.

Should you or your staff have any questions regarding the report, please feel free to contact Dr. Stephen Groft, Director of ORD, at 301-402-4336.

Sincerely,

Elias A. Zerhouni, M.D.
Director

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

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MAY 20 2004

The Honorable Joe Barton
Chairman, Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

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Director

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MAY 20 2004

The Honorable Edward M. Kennedy
Committee on Health, Education,
Labor and Pensions
United States Senate
Washington, D.C. 20510

Dear Senator Kennedy:

I am pleased to submit to you the National Institutes of Health (NIH) Annual Report on Rare Diseases Research Activities: FY 2003. Section 404F of the Public Health Service Act, as amended by Public Law 107-280, the Rare Diseases Act of 2002, requires an annual report to Congress on the activities that NIH conducted and supported through our Institutes and Centers with respect to rare diseases research.

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Bethesda, Maryland 20892

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MAY 20 2004

The Honorable John D. Dingell
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Dingell:

I am pleased to submit to you the National Institutes of Health (NIH) Annual Report on Rare Diseases Research Activities: FY 2003. Section 404F of the Public Health Service Act, as amended by Public Law 107-280, the Rare Diseases Act of 2002, requires an annual report to Congress on the activities that NIH conducted and supported through our Institutes and Centers with respect to rare diseases research.

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Sincerely,

Elias A. Zerhouni, M.D.
Director

Enclosure

Report on the Rare Diseases Research Activities at the National Institutes of Health

FY 2003

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National Institutes of Health
Department of Health and Human Services

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Executive Summary

Research Activities on Rare Diseases Supported by NIH: FY 2003

The Rare Diseases Act of 2002, P.L. 107-280, instructs the Director of the Office of Rare Diseases, National Institutes of Health (NIH), to prepare the NIH Director's annual report to Congress on rare disease research activities. The annual report presents the contributions and research advances of the fiscal year (FY) 2003 NIH extramural and intramural research programs and of the Office of Rare Diseases (ORD) and other research offices.

Responses from the individual Institutes and Centers (ICs), ORD, and other offices highlight four major rare diseases areas: An overview of ongoing rare diseases research activities, recent scientific advances in rare diseases research, new or planned rare diseases research initiatives, and rare disease-related activities such as scientific workshops and symposia, information dissemination, and other rare diseases related activities. Many advances presented are the direct result of years of basic rare diseases research sponsored by NIH. Patients with rare diseases continue to benefit from the treatment applications realized by the emphasis NIH places on both basic and clinical intramural and extramural research.

This report uses the definition of rare diseases as set forth in the Orphan Drug Act: A disease or condition with a prevalence of fewer than 200,000 people in the United States. *Prevalence* refers to the number of individuals alive with the disease within a geographic parameter, i.e., the United States. There are more than 6,000 rare diseases in the United States (for a listing of rare diseases terms see http://rarediseasesinfo.aspensys.com/asp/diseases/diseases.asp). Rare diseases are thought to affect approximately 25 million people (Rare Diseases Act of 2002, Section 2, Findings).

Activities undertaken in FY 2003 by ORD included:

- Initiating the ORD Rare Diseases Extramural Research Program by cosponsoring with NIH ICs seven rare diseases clinical research center consortia and a data coordination center all of which comprise the Rare Diseases Clinical Research Network. The Network is described in detail later in this report. The Network is co-sponsored by NCRR, NIAMS, NICHD, NIDDK, and NINDS.
- Initiating the ORD rare diseases intramural research program that promotes fellowship training in the areas of clinical and basic research into rare diseases, fosters protocol-based initiatives into rare diseases not currently investigated in the intramural program, assists in the investigation of select, unique disorders of unknown etiology, and provides overall research support for diagnostics and therapeutics of rare diseases.
- Cosponsoring 57 scientific conferences in FY 2003 and, in to date in FY 2004, 39 scientific conferences, the titles of which are listed in this report. The scientific conferences continue to establish research priorities, develop program announcements, establish diagnostic and monitoring criteria, develop animal models, support development of patient and tissue registries, development of research protocols and collaborative research arrangements, and disseminate workshop results.

- Expanding together with the NHGRI the reach of the Genetic and Rare Diseases Information Center by providing information services in Spanish as well as English to bring information about rare diseases research to patients and their families, healthcare providers, researchers, and the public.
- Providing support for Bench-to-Bedside Grants in the NIH Clinical Center. With support from the ICs, ORD plans to increase the number to 20 active grants each year.
- Soliciting applications for Rare Diseases Demonstration Projects (R-21) or proof-of-concept studies with National Heart, Lung, and Blood Institute. Awards are expected to be made in FY 2004.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

Overview of Rare Diseases Research Activities

The National Institute on Alcohol Abuse and Alcoholism conducts and supports research on the causes, consequences, and treatment of alcoholism and alcohol abuse. In addition to various liver diseases, alcoholism can cause disease in the brain, pancreas, heart, and other organs. Because of the widespread consequences of alcoholism, knowledge gained in related research programs has wide application to other areas of human health and disease.

Recent Scientific Advances in Rare Diseases Research

Alcoholic Pancreatitis

Long-term heavy alcohol consumption is associated with both acute and chronic pancreatitis. Progression of pancreatitis may lead to multiple co-morbidities, including maldigestion, diabetes, and pancreatic cancer. NIAAA-funded researchers have made significant progress in understanding the underlying mechanisms by which alcohol intake leads to the development of pancreatitis.

Role of Hypoxia and Oxidative Stress

The effect of chronic intestinal ethanol on pancreatic hypoxia and oxidative stress was investigated in male Wistar rats. Ethanol feeding for three weeks resulted in pancreatic damage. This was associated with increased hypoxia as well as oxidative stress, suggesting that these factors may be involved in the mechanisms of chronic alcoholic pancreatitis.

Role of Viral Infection

The coxsackievirus B (CVB) group is commonly associated with pancreatitis, especially the CVB3 viruses. A study was undertaken to determine whether alcohol consumption by experimental animals would result in a more severe pancreatitis induced by infection with CVB3. These results suggest that alcohol consumption makes the pancreas more susceptible to CVB-3-induced pancreatitis.

Gene Expression and Pancreatic Injury

Studies were undertaken to investigate an association between chronic alcohol consumption and gene expression of various factors that may be linked to pancreatitis. Male Wistar rats administered with alcohol for four weeks showed increased gene expressions of pancreatic fatty acid ethyl ester synthases. This research also revealed how other aspects of gene expression may contribute to pancreatic tissue injury.

Ethanol and NF-KappaB (pro-inflammatory transcription factor) Activation

Ethanol was shown to differentially affect the Ca (2+)/calcineurin- and PKC-mediated pathways of NF-kappaB activation in pancreatic acinar cells. These effects may play a role in the ability of ethanol to sensitize pancreas to the inflammatory response and pancreatitis.

Curcumin Ameliorates Ethanol and Non-ethanol Experimental Pancreatitis

Curcumin, a natural phytochemical, was shown to ameliorate pancreatitis in two rat models of pancreatitis induced by cerulein, and by a combination of ethanol diet and low-dose cholecystokinin. Other findings indicate that blocking key signals of the inflammatory response ameliorates pancreatitis in both ethanol and non-ethanol models.

Fetal Alcohol Syndrome

Prenatal exposure to alcohol can produce a spectrum of problems, including postnatal growth retardation, neurological abnormalities, developmental delays, behavioral dysfunction, intellectual impairment, and skull or brain malformations. Collectively, these abnormalities are referred to as fetal alcohol syndrome (FAS). Research continues on characterizing the neurodevelopmental dysfunction of FAS-affected children.

New Animal Models

An NIAAA researcher has established that teratogenic effects of ethanol can be detected in Zebrafish embryos at physiologically relevant doses. Craniofacial defects include loss of neural crest cells (also seen in rodent and chick models), a correlated reduction in intraocular distance, and abnormal development of the craniofacial skeleton. These findings suggest that Zebrafish can be used as a model system for aspects of fetal alcohol syndrome, and subsequently as a viable model for other teratogenic compounds. Other investigators have demonstrated that exposing ferrets to ethanol during the early postnatal period (third trimester equivalent) results in impaired cortical plasticity of the visual system which was manipulated at a later age. Exposure to alcohol at a later postnatal age had no effect on plasticity. Because the mechanism of visual plasticity involves the NMDA receptor system, which is important in many models of learning and long-term memory, and because the ferret visual system is very similar to the human system, the findings from mechanistic studies may be translated more readily to human fetal alcohol spectrum disorders than findings from other models.

Validation of a New Biomarker of Fetal Exposure to Alcohol

Fatty acid ethyl esters (FAEE), a product of non-oxidative alcohol metabolism, have been identified in meconium and may be a potential biological marker for exposure of neonates to alcohol during prenatal development. With previous methods of measuring FAEE, sensitivity and specificity for detecting any reported maternal drinking was low. In this study ethyl oleate indicated maternal alcohol use with sensitivity and specificity >80 percent. A clinically useful biomarker for risk levels of drinking during pregnancy would permit earlier identification and

intervention for affected infants and would facilitate recognition of women who are likely to drink during their next pregnancy.

New/Planned Extramural or Intramural Research Initiatives

Rare Disease-Specific RFPs or RFAs

In a program announcement titled "Mechanisms of Alcoholic Pancreatitis," NIAAA, in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Institute on Drug Abuse (NIDA), is seeking research grant applications that will investigate the underlying molecular, biochemical, and cellular mechanisms by which long-term alcohol ingestion leads to the development of pancreatitis. Research is also encouraged to understand the role of various predisposing factors, including substance abuse, that make the pancreas susceptible to alcoholic injury. Understanding the mechanisms as well as the role of predisposing factors may help in developing strategies for the prevention or treatment of the alcohol pancreatitis.

Significant Ongoing Rare Diseases Research Initiatives

Fetal Alcohol Syndrome: Craniofacial Defects Associated with Embryonic Ethanol Exposure

The goal of this study is to establish a zebrafish model to study the craniofacial defects associated with embryonic ethanol exposure, as well as to establish that craniofacial abnormalities and developmental deficits occur through defects in the hedgehog (hh) signaling pathway. In the first year of this study, the investigator showed that ethanol reduces intra-ocular distance (resulting from loss of tissue between the eyes) without causing abnormal facial development. He also found that these effects are dose-dependent. In future work, the effects of ethanol will be compared to the general hedgehog inhibitor, forskolin, which also decreased the intraocular distance in a dose-dependent manner. The development of head cartilage and neural crest markers are currently being examined.

Rare Disease-Specific Conferences, Symposia, and Meetings

Alcohol and Upper Alimentary Tract Cancer (squamous cell carcinoma)

Alcohol consumption is a major risk factor for upper alimentary tract cancer, including cancer of the oropharynx, larynx, and the esophagus. About 75 percent of esophageal cancers and 50 percent of cancers of mouth, pharynx, and larynx are associated with chronic heavy drinking. Results of many studies support the concept that alcohol is a co-carcinogen or a tumor promoter but not a carcinogen. Various mechanisms have been proposed for these effects of alcohol. In a nitrosamine-induced esophageal tumor animal model, addition of ethanol to the drinking water promoted esophageal cell proliferation. Chronic ethanol consumption induces mucosal hyper-regeneration in the throat and esophagus and this increased cell proliferation renders the mucosa susceptible to transformations that cause tumors. Oxidant stress could be a factor that may mediate the tumor-promoting effect of alcohol in upper alimentary tract. With support from the Office of Rare Diseases, in the fall of 2004, NIAAA will convene a symposium to: 1) stimulate

research and build an alcohol research portfolio that focuses on the mechanistic role alcohol plays in promotion of upper alimentary tract cancers; 2) attract basic and clinical researchers working in cancer biology to alcohol research; and 3) formulate recommendations for enhancing research in this area.

Basic and clinical researchers working in the area of cancer biology, alcohol researchers interested in cancer and immunology, epidemiologists, and clinicians will participate in the symposium. A range of topics will be presented on the role of alcohol as a co-carcinogen in the occurrence of upper alimentary tract cancers. Issues that will be addressed include: molecular mechanisms of alcohol-induced cell proliferation in upper alimentary tract mucosa; types, sources, and mechanisms of reactive oxygen species formation in response to alcohol; effects of alcohol on mucosal lining integrity and the lesion repair process; interaction between alcohol use and smoking in the promotion of upper alimentary tract cancers; the role of alcohol-induced impaired immune function and associated increased susceptibility to tumor promotion; the impact of alcohol-induced dietary deficiencies on cancer; and the role of alcohol metabolism on the development of alimentary tract tumors. Research gaps and opportunities will also be discussed.

Fetal Alcohol Syndrome and Other Alcohol-Related Birth Defects

Fetal alcohol spectrum disorders (FASD) describes a spectrum of prenatal alcohol effects resulting from drinking by the mother during pregnancy. The most serious disorder arising from prenatal alcohol exposure is fetal alcohol syndrome (FAS), a cluster of defects that includes mild craniofacial abnormalities, growth retardation, and central nervous system impairments manifested by deficits in executive function, memory and learning, and motor activity. Alcohol-related neurodevelopmental disorder (ARND) is more variable in phenotype but can be equally debilitating. A variety of alcohol-related organ system birth defects have also been reported among children diagnosed with FAS or ARND, including congenital heart defects, ocular abnormalities, and increased susceptibility to certain infections.

The effects of prenatal alcohol exposure on the developing brain have been well-characterized, and significant progress has been made in elucidating the underlying mechanisms of brain injury. Much less attention has been given to the deleterious effects of fetal exposure to alcohol on growth and the development of other body systems. This research is important because these effects can cause significant morbidity as well as increase health care costs associated with treating FASD.

In the summer of 2004, the NIAAA will collaborate with the Teratology and the Fetal Alcohol Syndrome Study Group, an affiliate of the Research Society on Alcoholism, on a meeting to: 1) stimulate research and build a portfolio of basic research grants that focus on co-morbid alcohol-related birth defects; 2) attract teratologists, developmental biologists and toxicologists with expertise in organ system development into fetal alcohol research; and 3) discuss research gaps and opportunities.

Clinical evidence of morbidity and the state of knowledge in basic laboratory research on prenatal alcohol effects will be presented. Discussion topics will include: 1) tissue specific

expression of alcohol-metabolizing enzymes and the implications for impaired organ development, 2) immune system dysfunction, 3) endocrine dysfunction, 4) cardiovascular defects, 5) ocular system defects, and 6) growth retardation.

Duchenne's Muscular Dystrophy and Other Myo- and Leukodystrophies

Duchenne's muscular dystrophy is an X-linked recessive disease affecting 1/3,600 male births. It results from failure to express the protein dystrophin resulting in loss of skeletal muscle mass and strength and cardiac malfunction. Patients are wheel chair bound by 10 to 12 years with death occurring generally in the mid-twenties. Attempts to treat the disease have not been successful.

The NIAAA intramural program sponsored a workshop in September 2003 on ketosis as a therapy for Duchenne's muscular dystrophy and other Myo- and Leukodystrophies. Participants presented observations that support the hypothesis that induction of mild ketosis appears, on the basis of animal studies, to be a practical therapy for the treatment of this presently untreatable and fatal disease. A recent clinical demonstration of the effectiveness of mild ketosis in the treatment of cardiomyopathy and leukodystrophy was also discussed. Attendees opined that a thorough understanding of the disease phenotype exhibited in rare genetic diseases has the potential for treating more prevalent diseases and disorders.

NATIONAL INSTITUTE ON AGING (NIA)

Overview of Rare Diseases Research Activities

The National Institute on Aging conducts and supports biomedical, social and behavioral research, training, health information dissemination, and other programs with respect to the aging process. The Institute does not focus on rare diseases per se; however, certain rare conditions/diseases are studied as they relate to the process of aging or the diseases of aging. Of particular interest are progeroid syndromes such as Werner syndrome, Bloom's syndrome, and Cockayne syndrome that have implications for age-related diseases.

Recent Scientific Advances in Rare Disease Research

Werner Syndrome (WS)

WS is a rare autosomal recessive disorder characterized by genome instability and premature onset of several age-related diseases. The gene defective in WS encodes a DNA helicase (WRN) that belongs to the RecQ helicase family. Researchers have purified a multisubunit complex from human cells that contains WRN and several associated polypeptides and have found that this complex has multiple enzymatic activities. Recently, investigators have discovered a number of new functional and physical protein interactions with Werner protein, suggesting that the WRN protein in involved in DNA repair processes, in particular the pathways of base excision repair and recombination. Ongoing and future studies are being directed towards elucidation of the causes of the accelerated aging phenotype in WS that may have implications to both the aging of cells and organisms in general.

Bloom Syndrome (BS)

BS is a rare autosomal recessive disorder characterized by short stature, sensitivity to sunlight, reduced fertility, and higher incidence of cancer. The human BS gene has been identified and encodes a member of RecQ family of DNA helicases. Researchers have purified three multiprotein complexes containing the BS gene product and identified most of their components. Recent studies suggest that these complexes could function as DNA-unwinding machines to repair aberrant DNA structures formed during metabolism.

Cockayne Syndrome (CS)

CS is an autosomal recessive disorder with diverse clinical symptoms that include severe mental and growth retardation, microcephaly, progressive neurological and retinal degeneration, skeletal abnormalities, and a hypersensitivity to sunlight. Two genetic complementation groups, CSA and CSB, have been identified. At the cellular level, CS is characterized by a defect in transcription-coupled repair (TCR) of DNA damage induced by UV light and certain forms of oxidative stress. Intramural investigators have studied the functional significance of conserved motifs in the CSB protein in an effort to determine the biological role of CSB in DNA repair and

transcription. These studies will increase understanding of the underlying cellular defects of CS-B cells responsible for the clinical symptoms of the syndrome. CSB mutant alleles with site-directed mutations were tested for genetic complementation of various phenotypes in both human and hamster CS-B null cell lines. Findings indicate that the integrity of the ATPase domain in the CSB protein is critical for cellular resistance to DNA damaging agents, RNA synthesis, and a normal apoptotic response after treatment of cells with UV light. In contrast, a highly acidic region of the CSB protein is dispensable for DNA repair. Present studies address the characterization of other regions of the CSB protein using genetic and biochemical assays to assess function. The roles of CSB in repair of specific oxidative lesions and transcriptional regulation after oxidative stress using cDNA arrays is also being investigated. The CSB protein appears to be directly involved in the repair process of oxidative DNA damage removal, and a primary question is to ascertain the underlying defects of CS (repair, transcription, or both) using a structure-function approach.

Ruthmund-Thompson Syndrome (RTS)

RTS represents a human genome instability disorder caused by mutation in a particular RecQ helicase. RTS is characterized by skin and skeletal abnormalities and some features of premature aging, including a predisposition to cancer. Researchers have recently purified the endogenous RTS gene product and are investigating its biological function.

Stickler Syndrome

This disorder of connective tissue causes premature osteoarthritis, retinal detachments, and premature hearing loss. It is known to be caused by mutations in the genes encoding collagen types II and XI, but in some families with Stickler syndrome the phenotype is not linked to any of these loci. The relationship between phenotype and genetic locus in those families for which the locus is known is currently being studied. Linkage studies are being used to search for the locus or loci causing the disorder in those families for which the locus is still unknown. Researchers have recently documented an increased risk of femoral head failure in children with Stickler syndrome. Investigators are developing proposed diagnostic criteria for Stickler syndrome based on clinical and molecular studies of this population.

Corticobasal Degeneration

Corticobasal degeneration is a rare parkinsonian disorder characterized by dementia and focal signs in addition to the parkinsonian trait. Alien limb syndrome is a frequent part of the phenotype. Pathologically it is characterized by neurofibrillary tangles made up of the tau protein. Recent research has shown that the tau gene is a risk factor locus for this disease which afflicts about 1/500,000 in the Caucasian population.

Severe Achondroplasia with Acanthosis Nigricans and Developmental Delay (SADDAN)

This rare skeletal dysplasia causes severe short-limbed dwarfism with serious respiratory and neurologic sequelae in infancy and young childhood. The disorder is caused by a specific missense mutation in the tyrosine kinase domain of the gene encoding Fibroblast Growth Factor

Receptor 3. A mouse model for this mutation, K650M, has been developed and genomic and proteomic strategies are being used to understand the signaling consequences of the mutation in affected organ systems.

Hypochondroplasia

Hypochondroplasia is among the more common, and least severe, of the human skeletal dysplasias. Affected persons have short-limbed dwarfism. Learning disabilities are a common feature of this disorder, which is caused by two different specific mutations in the gene encoding Fibroblast Growth Factor Receptor 3 (FGFR3). A mouse model for one of these mutations, K650N, is under development. Genomic and proteomic strategies will be used to understand the signaling consequences of the mutation in cartilage and in the central nervous system.

Ehlers-Danlos Syndrome (EDS)

This disorder of connective tissue has multiple different varieties, most common of which are the classical and hypermobile types. Both of these forms of EDS are associated with chronic musculoskeletal pain, which may be severe and disabling. The mechanism of chronic pain in this condition and potential modes of intervention are under investigation.

Marfan Syndrome

The Marfan syndrome is caused by mutations in the gene encoding fibrillin 1 (FBN1). The phenotype includes tall stature with long, thin limbs and digits, dislocated ocular lenses, and dilatation and dissection of the ascending aorta. Recently developed animal models for Marfan syndrome have demonstrated several complications previously unrecognized in the human disorder. A detailed clinical study of persons with Marfan syndrome is looking for the frequency of these complications in humans.

Simpson-Golabi-Behmel Syndrome (SGBS)

SGBS is an overgrowth syndrome, with very tall stature associated with enlarged internal organs. The gene mutated in patients, GPC3, produces a matrix protein around cells. Scientists have now shown that disruption of the gene in mice produces comparable overgrowth by a mechanism that is unknown, but is independent of the well-studied growth-promoting effects of insulin-like growth factors (IGFs).

Fanconi Anemia (FA)

FA is an autosomal recessive disorder characterized by diverse congenital abnormalities and a predisposition to bone marrow failure and cancer, particularly acute myelogenous leukemia. FA is comprised of eight distinct complementation groups. Researchers have purified a complex containing gene products of 5 FA genes and identified many components of this complex. Researchers also discovered a novel biochemical activity of this complex that linked this disease to DNA repair. Recent evidence suggests that FA proteins function in a DNA damage response

pathway involving the proteins produced by the breast cancer susceptibility genes BRCA1 and BRCA2.

ATRX Syndrome

ATRX syndrome represents a combination of α-thalassemia, mental retardation and multiple associated developmental abnormalities. The gene defective in ATRX encodes a gene product containing a SWI2/SNF2-type DNA-dependent ATPase domain. Many proteins with such a domain are present in multi-protein complexes, which often have ATP-dependent chromatin-remodeling activities. Researchers have purified an ATRX-containing multi-protein complex and identified most components of this complex. Recent studies show that this complex has multiple chromatin-modifying activities that are an entry point to studying its function.

Rett Syndrome

With the demonstration that up to 80 percent of Rett syndrome cases are caused by mutation in a methyl DNA-binding protein, MeCP2, the analysis of neurological effects and mental retardation in this disease must focus on associated changes in chromatin. Current research is trying to understand the function of MeCP2 in vivo and whether phosphorylation of MeCP2 plays a role in the etiology of Rett syndrome.

Amyotrophic Lateral Sclerosis (ALS)

ALS is a severe progressive condition affecting 0.5 - 3 persons per 100,000 individuals. This degenerative disease is characterized by motor neuron death in the cortex, brainstem, and spinal cord. Clinically the disorder presents as a disease of progressive muscle weakness and atrophy. Scientists have recently undertaken a project to analyze the genetic contribution of neurofilament to ALS. Investigators have sequenced the coding region of all three neurofilament genes in a series of 100 familial ALS cases, 100 sporadic ALS cases, and 100 age-matched neurologically normal controls. They have identified 16 novel coding mutations.

Rare Disease Research Initiatives

Ongoing rare disease research projects include studies of premature aging disorders, including studies of DNA repair and transcription in Bloom syndrome, Cockayne syndrome, and Werner syndrome. Other studies are investigating the genetics of connective tissue disorders such as Ehlers-Danlos syndrome, Sticklers syndrome, and Rett syndrome. All of these studies of relatively rare diseases could hold important clues not only to the specific etiology of these diseases, but to other diseases and conditions prominent in the older population, including cancer, cardiovascular disease, arthritis, and musculoskeletal pain.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

Overview of Rare Diseases Research Activities

The National Institute of Allergy and Infectious Diseases supports research activities on rare diseases that are classified into four areas: infectious diseases, primary immunodeficiency diseases, autoimmune diseases, and other immune system-mediated conditions. Infectious diseases can be caused by viruses, bacteria, fungi, and other parasites. Primary immunodeficiency diseases are hereditary disorders caused by intrinsic defects in the cells of the immune system and are characterized by unusual susceptibility to infection. Autoimmune diseases result from a dysfunction of the immune system in which the body attacks its own organs, tissues and cells. NIAID research on rare diseases is aimed at delineating the mechanisms of disease pathogenesis and developing new and more effective strategies for the diagnosis, treatment, and prevention of these diseases.

Recent Scientific Advances in Rare Diseases Research

Rare Infectious Diseases

African Trypanosomiasis

African trypanosomiasis, also known as sleeping sickness, is caused by the protozoan parasite *Trypanosoma brucei*, which is spread to humans through the bite of a tsetse fly and is almost always fatal if not treated. Only one new drug has been developed in the past 40 years, but it is toxic and has limited effectiveness. Thus, there is a critical need for new drugs. NIAID-supported scientists identified a trypanosome enzyme critical for DNA replication, which may provide a new target for the development of less toxic and more effective anti-trypanosomal drugs.

Anthrax

NIAID-supported scientists analyzed the full genome sequence of *Bacillus anthracis*, the bacteria that causes anthrax. Their analysis indicates that the regulation of gene activity, rather than the presence or absence of specific genes, plays an important role in the bacterium's ability to cause severe disease and death. In addition, the researchers identified a number of genes encoding proteins that *B. anthracis* may use to enter host cells, which may be important targets for the development of vaccines and drugs.

The results of an NIAID intramural study of anthrax lethal toxin in mice suggested that anthrax lethal toxin induces circulatory shock and lethality differently from other bacterial toxins. Anthrax lethal toxin does not appear to act via excess release of inflammatory cytokines and nitric oxide, which are the targets for treatment of shock caused by other bacterial toxins. Therefore, anthrax induced shock may require alternate therapeutic strategies.

Blastomycosis

Blastomycosis is an infectious disease caused by inhaling spores of a fungus found in soil called *Blastomyces dermatitidis*. Serious fungal infections of immunocompromised people, including those with AIDS, are often due in part to low numbers of a type of immune cells called CD4+ T. Researchers studying mice with low CD4+ T-cell counts have discovered that vaccination against *B. dermatitidis* can increase survival from infection with this fungi. This finding demonstrates that fungal vaccines might help people with weakened immune systems fight disease-causing fungi by compensating for their low CD4+ T cell counts until those counts can return to normal.

Cholera

NIAID-supported researchers used a genetic system to force the cholera bacterium *Vibrio cholerae* to express proteins in the laboratory that are only expressed within humans during disease. They found that several proteins involved in attaching cholera to the intestine surface were recognized by antibodies obtained from the blood of patients who were recovering from cholera. These results may inform the development of improved cholera vaccines and therapeutics. In addition, another group of NIAID-supported researchers determined the atomic structure of the *V. cholerae* pilus, which attaches the bacteria to the human gut. By studying the fine structure of the cholera pilus, the scientists gained insights in to the mechanism through which the pilus maintains its strength, flexibility, and multi-functionality.

Cryptococcosis

Cryptococcosis, which is caused by the fungus *Cryptococcus neoformans*, is a life-threatening infection of the central nervous system that commonly affects immunocompromised individuals. Current antifungal drug treatments used to treat cryptococcus are toxic and frequently ineffective in eradicating central nervous system infection. Utilizing an animal model of *C. neoformans* infection, NIAID-supported scientists determined that the combination of antimicrobial drugs amphotericin B and fluconazole was more effective than currently used antifungal drug therapies. NIAID-supported scientists also discovered that when certain radioactive compounds were attached to monoclonal antibodies (mAB) which bind to the *C. neoformans* fungus, the radiation emitting mABs inhibited fungal growth in mice to a greater extent than unmodified mABs and did so without apparent toxicity. These results suggest radioimmunotherapy as a potential new treatment for fungal infections.

Cryptosporidiosis

Cryptosporidiosis is an important cause of waterborne outbreaks of acute diarrhea, childhood diarrhea in developing countries, and AIDS-related diarrhea. In AIDS patients, the disease may cause a life-threatening chronic diarrheal illness that leads to wasting and death. NIAID-supported scientists have found that there is a positive correlation between the expression of a molecule called substance P and the severity of diarrhea in patients with cryptosporidiosis.

Cytomegalovirus(CMV) Disease

CMV is the virus most frequently transmitted to newborns during pregnancy. More than 90 percent of infants infected at birth who survive develop severe brain damage and/or profound hearing or visual problems. NIAID-supported scientists recently developed a guinea pig model that more closely mimics CMV infection in human newborns than the previously developed mice and rat models. This model system will be a valuable tool for gaining a better understanding of CMV infection in newborn human babies as well as evaluating potential new drugs or vaccines.

Two teams of NIAID-supported scientists have identified several host cell receptors that recognize CMV. The first team of NIAID-supported scientists demonstrated that the host cell receptors Toll-like receptor 2 and CD14 recognize CMV. The binding of CMV to these receptors triggers the production of inflammatory cytokines, which are immune system signaling proteins. Since many of the pathological processes associated with CMV disease are facilitated or directly mediated by inflammatory cytokines, identification of these cell receptors may ultimately lead to improved therapeutics. A second team of NIAID-supported scientists has identified another CMV cell surface receptor called epidermal growth factor receptor that is necessary for CMV entry into a host cell.

Dengue

NIAID researchers have developed a live, weakened candidate vaccine against dengue virus, which is carried by mosquitoes and causes millions of cases of dengue fever each year. The virus also causes dengue hemorrhagic fever, which is lethal approximately 5 percent of the time. The experimental vaccine is chimeric, meaning that the structural genes from one type of dengue virus have been replaced with those of another type. NIAID is also supporting human clinical trials of a candidate Yellow Fever/dengue chimeric vaccine.

Escherichia coli (diarrheagenic)

Harmless strains of *E. coli* can be found widely in nature, including the intestinal tracts of humans and warm-blooded animals. Disease-causing strains, however, are a frequent cause of both intestinal and urinary-genital tract infections. *E. coli* and other bacteria communicate with one another using a system called quorum sensing, which is mediated by bacterial compounds called autoinducers. NIAID-supported scientists have identified a new autoinducer, AI-3, which is similar to the human hormones epinephrine and norephinephrine. The researchers speculate that the bacteria recognize AI-3 and epinephrine via the same bacterial receptor and that pathogenic *E. coli* use this receptor to "listen" to the hormonal communication of the host.

E. coli infections, as well as other microbial infections, are increasingly difficult to treat because of the emergence of drug-resistance strains. Multidrug efflux pumps, which are bacterial cell membrane structures, render antimicrobial drugs ineffective by pumping specific drugs out of the cell. The *E. coli* multidrug efflux pump AcrB pumps out the widest range of drugs, including penicillin, tetracycline, chloramphenicol, and streptomycin. NIAID-supported researchers used a

novel technology to show that drugs are taken up from the thin space between the two outer membrane layers by a certain region of the AcrB efflux pump, and that this region seems to determine which drugs will be removed by the pump. Their analysis of clinical strains of drug-resistant bacteria showed that overproduction of these pumps is partially responsible for currently prevalent resistant bacteria.

Ebola

Ebola virus is a rare and deadly microbe that causes hemorrhagic fever, characterized by high fever and massive internal bleeding. NIAID researchers have developed a fast-acting candidate Ebola vaccine that protects monkeys from the virus within one month following immunization. If this vaccine proves similarly effective in humans, it could one day be used to quickly contain Ebola outbreaks with ring vaccination—the same strategy used in the past against smallpox. Additionally, NIAID scientists have developed a human monoclonal antibody that neutralizes Ebola and protects guinea pigs from a lethal challenge with Ebola. These research results indicate it is possible to generate antibodies in cell culture that may be useful for passive immunization against Ebola virus infection.

NIAID researchers have also discovered that only three viral proteins are required for capsid assembly, a key life-cycle stage that renders Ebola infectious. In addition, they found that the sugar molecules that coat one of the capsid proteins are essential for virus formation. These findings could lead to the development of antiviral drugs for Ebola hemorrhagic fever.

Histoplasmosis

Histoplasmosis is an infectious disease caused by inhaling spores of a fungus called *Histoplasma capsulatum*. Severe fungal infections in immunocompromised people, such as those with AIDS, are due in part to the low number of a type of immune cell called CD4+ T, which are needed to fight invading microbes. Researchers studying mice with low CD4+ T-cell counts have discovered that vaccines can increase survival from infection with *H. capsulatum*. When the researchers vaccinated mice against this fungus, another kind of T cell, called CD8+, helped overcome the lack of CD4+ T cells and enabled the mice to rid themselves of fungal infections.

Hepatitis E (HEV)

HEV is one of the most important causes of acute clinical hepatitis among adults in southeast and central Asia, the Middle East and North Africa. HEV also poses a risk to those who travel to areas where HEV is endemic, including military personnel. NIAID scientists have developed a HEV vaccine that is highly effective in preventing HEV in a nonhuman primate model of the disease. In addition, they found that the vaccine protected against several different strains of HEV, thus suggesting that a single vaccine may protect against HEV strains found worldwide.

Leishmaniasis

Leishmaniasis is caused by infection with the *Leishmania protozoa*, which is transmitted by sand flies. In mammalian hosts, the parasites invade host macrophages, the cells responsible for destroying invading pathogens, and are able to persist even after patients recover from the active disease. NIAID investigators, studying mice resistant to Leishmania reinfection, discovered that the persistence of Leishmania in the skin following healing is controlled by a type of immune cell called CD4+CD25+ regulatory T cells. During the course of the infection, CD4+CD25+T cells were shown to accumulate at the site of infection and to inhibit the elimination of the parasite by the immune system. Paradoxically, when the activity of the CD4+CD25+ cells was inhibited, the parasite was eliminated, but the mice lost their immunity to re-infection.

Using a mouse model, NIAID-supported investigators sought to determine which parasite components are responsible for the parasite's persistence after active disease is under control. They injected the mice with parasites that lack a particular *Leishmania* surface factor called lpg2. Parasites lacking this factor do not cause illness in the animals, but they do persist in the macrophages. *Leishmania* deficient in lpg2 may prove to be useful as vaccine candidates, since they have been shown to induce and maintain host immunity. In another study, NIAID researchers and their colleagues have developed a method to improve the safety of a Leishmania vaccine. Working with mice and monkey models, they found that injecting short pieces of DNA called CpG oligodeoxynucleotides at the time and site of vaccination with the live Leishmania vaccine improved the safety of the currently used vaccine while maintaining its effectiveness.

Lyme Disease

NIAID scientists detected *Borrelia burgdorferi*, the causative agent of Lyme disease, in mice nine months after treatment with therapeutic doses of antibiotics, though the remaining *B. burgdorferi* bacteria could not be transmitted to healthy mice. These results show that noninfectious *B. burgdorferi* can persist in mice for an extended period of time after antibiotic treatment, but the lingering bacteria are not associated with disease.

NIAID-supported scientists conducted a clinical trial to examine the effectiveness of antimicrobial therapy in reducing symptoms of patients with Lyme disease who have persistent severe fatigue at least six or more months after initial antibiotic therapy. The results indicated that additional antibiotic therapy in patients with post Lyme disease syndrome with severe fatigue resulted in an improvement in fatigue, but not an improvement in cognitive function or an experimental laboratory measure of infection.

All current blood tests using cultured *Borrelia burgdorferi* as their antigen source have been rendered obsolete by the widespread use of the recombinant OspA (rOspA) Lyme disease vaccine, LYMErix®. To address this problem, NIAID-supported scientists have developed a new assay to detect the Lyme disease pathogen, which can differentiate between naturally infected individuals and individuals vaccinated with the OspA LYMErix® vaccine.
The genome of the *B. burgdorferi* has been sequenced and thousands of potential genes identified. During its life cycle, *B. burgdorferi* exists in distinctly different host environments, cycling between a tick vector and a mammalian host and therefore must regulate the activity of

different genes depending on its current environmental conditions. Temperature is one environmental factor known to affect which genes are switched on and off. NIAID scientists have identified 215 genes that are differently expressed between 23ºC and 35º. Interestingly, 63 percent of the differently expressed genes lie outside the chromosome on a form of DNA called plasmids, which can be exchanged between individual bacteria.

Lymphatic Filariasis

Lymphatic filariasis, also known as elephantiasis, is best known from dramatic photos of people with grossly enlarged or swollen arms and legs. The disease is caused by parasitic worms, including *Wuchereria bancrofti, Brugia malayi,* and *Brugia timori,* and is transmitted by mosquitoes. NIAID-supported scientists at Case Western Reserve University, in collaboration with scientists in Papua New Guinea (PNG), studied the transmission rates of lymphatic filariasis before and after administration of the drug diethylcarbamazine. The scientists found that mass treatment of the population reduced the reservoir of the parasite to such a degree that transmission to humans by mosquitoes was dramatically reduced. Overall, the incidence of infection dropped by 86 percent. In addition, the treatments reduced clinical symptoms. The results of this study suggest that mass treatment with diethylcarbamazine can virtually eliminate the parasite reservoir and greatly reduce infection and clinical symptoms of lymphatic filariasis.

Microsporidiosis

Microsporidiosis is caused by parasitic organisms of the phylum *Microspora.* The majority of cases of microsporidiosis involve diarrhea, but these parasites also cause respiratory, renal, and eye disease in immunocompromised people, such as those with AIDS. Microsporidia have a polar tube, which is a unique component of the organism used for invasion of the host. NIAID-supported scientists have identified modifications of polar tube proteins that may help explain how the organism interacts with the host cell. Interference with this mechanism may be a useful strategy to prevent infection.

Mycobacterium Avium Complex

Mycobacterium Avium complex disease is caused by a common bacterium found in water, soil, dust, and food. Prior to the introduction of highly active antiretroviral therapy (HAART) for the treatment of HIV/AIDS, disseminated infection with *Mycobacterium avium* complex (DMAC) was a common life threatening infection in HIV-infected patients. The standard of care for HIV-infected patients with DMAC was lifelong treatment with antibiotics because relapses of DMAC were common. In a recent study, NIAID-supported scientists showed that the withdrawal of preventative therapy could be safely accomplished in HIV-infected patients receiving HAART who been previously diagnosed with DMAC. This study demonstrated that the immune system of patients on HAART had been restored to a level sufficient for protection from a recurrence of DMAC.

Pertussis

Pertussis (whooping cough) is a preventable cause of cough illness in all age groups, but is rarely considered or diagnosed in older children or adults. NIAID scientists recently completed an adult efficacy trial of an acellular pertussis vaccine (a vaccine composed of bacterial fragments rather than whole bacteria). The results indicate that the vaccination of adults with the acellular pertussis vaccine provides protection for a finite period of time and boosters should be considered every 5 to 10 years.

Plague

Plague is caused by the bacterium *Yersinia pestis*, which is transmitted to people mainly through the bite of a flea. People with pneumonic lung plague can spread the bacterium directly to others. NIAID-supported researchers have identified a membrane protein that contributes to the ability of *Y. pestis* to evade the immune system. Identification of the role of this molecule may advance the development of novel therapeutic approaches for the treatment of plague.

Pneumocystis Pneumonia

Although the frequency of *Pneumocystis carinii* pneumonia (PCP) has decreased in the past decade, it continues to be one of the most common AIDS-defining illnesses. PCP is usually diagnosed by histological identification of the organism or by clinical assessment. NIAID-supported scientists have developed a new method for rapid diagnosis of PCP by measuring concentrations of the metabolite S-adenosylmethionine (S-AdoMet) in blood. This metabolite is essential for the pathogen's survival, but during infection it is depleted. The detection method developed reveals that individuals with confirmed PCP have undetectable plasma concentration of S-AdoMet; those with no PCP have adequate plasma concentrations of S-AdoMet.

Q-fever

NIAID-funded scientists have sequenced the complete genome of the bacterium that causes Q-fever, *Coxiella brunetti*, which can cause a debilitating, though rarely fatal, flu-like illness in humans. The researchers have identified genes involved in cell entry, growth, and replication of the bacterium, and the mechanisms it uses to evade host defenses. This information may lead to new targets for vaccines, therapies, and diagnostics against Q-fever and other intracellular bacterial infections.

Severe Acute Respiratory Syndrome (SARS)

NIAID-supported investigators were the first to report to the World Health Organization the isolation of a virus that was conclusively linked to SARS patients. In addition, NIAID-supported scientists also discovered that the live animal markets in China may have been the origin of SARS transmission to humans. The researchers collected specimens from more than 25 animals in a live animal retail market in Shenzhen. Genetic tests on the samples confirmed that two animal species, the Himalayan palm civet and the raccoon-dog, were positive for a virus nearly identical to the virus that causes SARS.

NIAID scientists have discovered that the SARS virus replicates in the respiratory tract of mice and African Green monkeys to levels that will permit an evaluation of the efficacy of vaccines, immunotherapeutic, and antiviral drug treatment strategies. The researchers, using the mouse model, observed that primary infection with the SARS virus provides protection from re-infection and that antibody alone can protect against viral replication. These results suggest that vaccines which induce neutralizing antibodies, strategies for immunoprophylaxis, and immunotherapy may be effective in SARS.

Schistosomiasis

Schistosomiasis is caused by parasitic worms. NIAID investigators have demonstrated that IL-13, the immune system regulatory molecule that is the primary stimulus for liver fibrosis in schistosomiasis-infected individuals, induces expression of a similar decoy molecule that acts as a potent inhibitor of tissue scarring. When mice are deficient in the decoy receptor, liver disease caused by schistosome infection is exacerbated significantly. Nevertheless, when the receptor deficient animals are treated with a soluble form of the receptor, disease is ameliorated.

Smallpox

NIAID researchers have developed a rapid and sensitive test for measuring antibodies to vaccinia virus, a virus similar to the smallpox virus, which can neutralize the smallpox virus. In addition, NIAID-supported investigators have identified molecular regions (peptides) of two different proteins that are common to the smallpox virus and the related vaccinia virus, and have shown how the human immune system recognizes these peptides. These findings indicate how vaccination with vaccinia may provide immunity to smallpox and also could pave the way to the development of safer smallpox vaccines.

Streptococcal Group A Invasive Disease

The vast majority of infections caused by the common bacterium Group A *Streptococcus* (GAS) are noninvasive and milder than the more severe invasive form of the disease, which is relatively rare in the United States. It is difficult to treat invasive GAS disease, which is associated with high morbidity and mortality. By examining the interaction between disease-fighting cells called white blood cells and a strain of GAS that causes abundant disease in North America and Western Europe, NIAID scientists have discovered how this bacteria elicits its protective response to evade destruction by the human immune system. The scientists found that GAS becomes more resilient to attack by the host immune system over time, and that this resiliency is demonstrated by the increased expression of various GAS genes associated with the bacteria's virulence and cell wall repair as well as genes that encode proteins likely to promote immune evasion.

Streptoccus Group B

Group B *streptococcus* (GBS) is a type of bacteria that causes illness in newborn babies, pregnant women, the elderly, and adults with other illnesses. GBS remains a leading cause of serious neonatal infection, despite the reduction in early-onset GBS disease in infants by the administration of antibiotics at the time of delivery. Immunization offers advantages over the use of antibiotics since it is less invasive, does not need to be administered during each pregnancy, is cost effective, and has the potential to prevent early- and late-onset GBS disease. NIAID scientists conducted a phase 1 clinical trial in pregnant women to determine the safety and immunogenicity of a GBS vaccine. They found that the vaccine was well tolerated and that there was excellent transfer of GBS-specific antibodies across the placenta to infants. Maternal immunization with this GBS vaccine may prevent GBS disease in pregnant women, neonates, and young infants.

Streptococcus Pnemoniae, Drug Resistant Invasive Disease

Streptococcus pneumoniae causes thousands of cases of meningitis and pneumonia in the United States each year. Currently, about 30 percent of *S. pneumoniae* isolates are resistant to penicillin, the primary drug used to treat this infection. Many penicillin-resistant strains are also resistant to other antimicrobial drugs. NIAID scientists had previously identified a set of genes that play a critical role in the expression of penicillin resistance in pneumococci. They have recently discovered three important functions of these genes: (i) they are essential for the biosynthesis of components of the bacterial cell wall; (ii) they are essential for the expression of penicillin resistance; (iii) and, when inactivated, they make the bacteria hypersensitive to the action of several antibiotics.

Toxoplasmosis

Infection with the common protozoan parasite *Toxoplasma gondii* causes a range of symptoms from asymptomatic chronic illness to mental retardation, retinal disease, and fatal brain infection. It is particularly threatening to developing fetuses and to immunocompromised individuals. To aid in the diagnosis and treatment of toxoplasmosis, NIAID researchers have developed an assay that distinguishes between virulent and non-virulent strains of *T. gondii* parasites. In addition, NIAID researchers have discovered that today's predominant strains of *Toxoplasma gondii* gained the ability to infect nearly all warm-blooded vertebrates about 10,000 years ago through a genetic cross. This study established that parasites like *T. gondii* can sometimes rapidly adapt to new hosts and present potential new public health threats.

NIAID-supported scientists characterized the primary structure of a gene for an enzyme essential for *T. gondii* replication and virulence. Understanding the structural and functional differences between the human and parasite enzymes may lead to the discovery of a drug that inhibits the parasite enzyme but not the human one.

Transmissible Spongiform Encephalopathies

Transmissible spongiform encephalopathies (TSEs) are fatal neurodegenerative diseases such as scrapie of sheep, Creutzfeldt-Jakob disease (CJD) of humans, bovine spongiform encephalopathy ("mad cow" disease), and chronic wasting disease (CWD) of deer and elk. TSEs are caused by accumulation of prion protein, an abnormal form of a protein found in humans and animals. Recently, NIAID scientists established that the TSE disease hamster scrapie can cause subclinical disease and jump species, adapting to and causing disease in mice. NIAID scientists have also demonstrated that cells used in some vaccine applications can be easily infected with TSE agents.

To expedite the identification of more effective TSE drugs, NIAID investigators have developed a high throughput screen for inhibitors of TSE prion protein accumulation. Using this assay, the investigators screened over 2000 FDA-approved drugs and natural products, 310 of which inhibited the accumulation of the abnormal prion form associated with scrapie in cells grown in culture.

Tularemia

Tularemia (also known as deerfly fever or rabbit fever) is an infectious disease caused by the bacterium *Francisella tularensis.* It is naturally found in small mammals such as rabbits, rodents, and hares, as well as the insects that feed on these animals. NIAID-supported scientists studying mice infected with *F. tularensis* have discovered that the immune cells and signaling molecules necessary to combat the early stages of systemic tularemia do not appear to combat early pulmonary tularemia. This finding suggests that the effectiveness of particular antibacterial host defenses varies depending on the invasion site.

West Nile Virus (WNV)

NIAID-supported scientists have developed a novel immunoassay that can differentiate WNV infection from other similar flavivirus infection. The newly-developed assay, which targets a WNV protein not found in other flaviviruses substantially improves the specificity of the assay and decreases the frequency of false positive results.

NIAID scientists have created a promising vaccine against WNV by replacing parts of a distantly related virus known as dengue type 4 with the corresponding proteins from the WNV. The researchers found that the resultant hybrid virus vaccine protected monkeys from West Nile infection. To ensure the safety of this vaccine in humans, the scientists further weakened the West Nile/dengue 4 virus by deleting some of the genetic material from the dengue virus.

Rare Primary Immunodeficiency Diseases

Chronic Granulomatous Disease (CGD)

CGD is an inherited genetic disorder characterized by failure of white blood cells (neutrophils, which are a type of immune cell) to produce the hydrogen peroxide needed to kill microorganisms, thus resulting in an increased susceptibility to bacterial and fungal infections. The results from a ten-year clinical trial of patients with CGD conducted by NIAID scientists indicate that the addition of the anti-fungal agent itraconazole to the routine medicines used in the management of CGD can significantly reduce the occurrence of fungal infections in these patients. In addition, NIAID scientists developed an animal model to study gene therapy or blood cell transplantation therapy in patients with CGD and other inherited diseases of the immune system. They transferred human blood stem cells from patients with CGD into a mouse strain that accepts human cell transplants to generate mice with the CGD phenotype (failure to produce hydrogen peroxide). When a functional copy of the CGD gene was inserted into CGD patient blood stem cells before they were transferred into mice, the resultant mice did not have the CGD phenotype.

DiGeorge Syndrome

DiGeorge syndrome is a congenital primary immunodeficiency disorder in which the thymus gland, heart, and parathyroid glands fail to develop normally. People with complete DiGeorge syndrome have no thymus, the organ located in the upper chest cavity. The thymus is required for the normal development of T lymphocytes, which are a type of immune cell crucial for protection against certain bacterial and viral infections. Complete DiGeorge syndrome is 100 percent fatal by three years of age. NIAID-supported researchers found that the transplantation of thymus tissue into patients with complete DiGeorge resulted in substantially enhanced survival and in partial restoration of immune function.

Wiskott-Aldrich Syndrome (WAS)

Wiskott-Aldrich syndrome (WAS) is an X-linked primary immunodeficiency caused by mutations in the gene encoding the WAS protein (WASP). WASP plays an important role in signaling by T lymphocytes, a key component of immune system. WAS is characterized by a decreased ability to destroy infectious pathogens, which results in severe, recurrent, and/or life-threatening infections in affected individuals. Working with mice lacking a functional WASP gene, NIAID-supported scientists found that the WAS-associated immune cell signaling defects in these mice could be improved through the transplantation of blood stem cells containing the normal WASP gene.

Other Rare Immune-Mediated Conditions

Autoimmune Lymphoproliferative Syndrome (ALPS) and Related Disorders

ALPS is a disease affecting children which leads to the production of an abnormal number of specialized immune cells called lymphocytes, thus resulting in swollen lymph glands and organs and an autoimmune attack on the patient's own tissues. Through the study of an ALPS-like genetic condition known to exist in only two individuals, NIAID scientists discovered that an enzyme called caspase-8, which is known to help trigger apoptosis (programmed death of cells) is also involved in activating many immune system cells needed to fight infections. This information may provide important insights into the pathogenesis and treatment of ALPS and related disorders, as well as more common autoimmune diseases such as diabetes, rheumatoid arthritis, and multiple sclerosis.

Systemic Lupus Erythematosus (SLE)

SLE is a serious, relapsing, systemic autoimmune disease, which is much more prevalent in women than in men. The disease is multisystemic, affecting a number of organs and tissues, including the joints, skin, kidneys, lungs, heart, and brain. NIAID scientists have developed an animal model for SLE using mice that do not make a protein that inhibits antibody production and inflammatory responses. These mice develop a spontaneous disease that resembles lupus in humans. Studies using this SLE animal model may provide insights that lead to the identification of therapeutic targets.

A NIAID-supported research team has shown that the female hormone prolactin can influence the development of cells that produce the type of antibodies responsible for symptoms of SLE. The treatment of mice susceptible to SLE with prolactin allowed the survival of antibody-producing cells that are normally eliminated by the immune system and led to the development of symptoms of SLE in the treated mice. The results may help explain why SLE is much more common in women than men.

In another study, NIAID-supported investigators measured the proteins encoded by over 12,000 genes and discovered that only 33 are elevated during periods of active lupus. These same genes are stimulated by interferon, an immune system signaling molecule, suggesting that the interferon pathway has a key role in SLE activity. These findings suggest that lupus has a relatively simple "signature" of gene activity, which may provide much-needed objective measures of disease activity (biomarkers), suggest approaches to treatment, and help to identify the causes of the disease.

New Activities

Rare Infectious Diseases

- In FY 2003, NIAID issued a series of new RFAs and PAs that invited investigator-initiated research grant applications focusing on the development of new diagnostics, preventions, and treatments for toxins and pathogens listed in the NIAID categories A, B,

and C list of priority pathogens, as well as the newly recognized SARS coronavirus. The newly issued initiatives included: Cooperative Research for the Development of Vaccines, Adjuvants, Therapeutics, Immunotherapeutics, and Diagnostics for Biodefense; Biodefense Partnerships: Vaccines, Adjuvants, Therapeutics, Diagnostics, and Resources; NIAID Investigator-initiated Small Research Grants; and Small Business Biodefense Program.

- In FY 2003, NIAID announced two new programs, the Food and Waterborne Diseases Integrated Research Network and the Respiratory Pathogens Research Network. These programs expand NIAID's capacity to conduct clinical research studies of food and waterborne pathogens, including those that could be potential agents of bioterrorism.

- In FY 2003, NIAID issued the RFP *In Vitro* and Animal Models for Emerging Infections and Biodefense. This initiative aims to provide NIAID with a ready capability to test the efficacy of new vaccines and therapeutics for biodefense and emerging diseases. Tasks awarded in FY 2003 will use anthrax models to ultimately support FDA licensure applications for currently approved antibiotics determined to be efficacious for the treatment of inhalational anthrax.

- In FY 2003, NIAID announced funding for the construction of two National Biocontainment Laboratories (NBLs) and nine Regional Biocontainment Laboratories (RBLs). The NBLs and RBLs will include state-of-the-art Biosafety level (BSL)-3 and BSL-4 laboratory facilities in which researchers can study potential agents of bioterrorism as well as naturally occurring infectious diseases in a safe, secure environment.

- In FY 2003 NIAID funded eight Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCE) located throughout the country that will provide the scientific information and translational research capacity to make the next generation of therapeutics, vaccines, and diagnostics against the NIAID Category A-C Agents and emerging infectious diseases.

- In FY 2003, NIAID issued the Small Research Grants for International Research in Infectious Diseases at NIAID International Sites. The aim of this initiative is to advance the development of local scientific expertise and to increase collaborative research partnerships at NIAID international sites.

<u>Rare Immune-System Mediated Diseases</u>

- NIAID, along with NICHD, established the Primary Immunodeficiency Diseases Consortium. The Consortium will: (l) provide leadership and mentoring; facilitate collaborations; enhance coordination of research efforts; and solicit, review, recommend, and make awards for pilot or small research projects; (2) maintain and expand a primary immunodeficiency diseases registry, which will provide data to the research community about the clinical characteristics and prevalence of these diseases; and (3) develop a repository of specimens from subjects with primary immunodeficiency diseases.

Ongoing Activities

Rare Infectious Diseases

- In FY 2003, NIAID announced the expansion of the Vaccine Treatment and Evaluation Units (VTEUs) by approximately 60 percent. In the past year, eight clinical trials of various smallpox vaccines have been completed or are underway at VTEU sites. In addition, clinical trials for new anthrax and West Nile vaccines are being planned.

- In FY 2003, NIAID expanded its support of a contract with Utah State University to conduct the evaluation of potential therapeutics for viral hemorrhagic fevers and encephalitides in animal models. In addition, NIAID scientists continue their work to develop a vaccine that would protect against multiple hemorrhagic fever viruses, including Ebola, Marburg, and possibly Lassa virus.

- NIAID continues to collaborate with the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) under an Inter-Agency Agreement to develop vaccine strategies for Ebola and other viral hemorrhagic fevers.

- In FY 2003, NIAID and FDA, through an inter-agency agreement, supported the screening of compounds that may be effective against biodefense-related and emerging viruses (vaccinia, cowpox, West Nile, yellow fever, SARS, etc.).

- In FY 2003, in response to the rapid need for expanded research activities on the basic biology and immunology of the SARS coronavirus, NIAID awarded supplements to grantees to: produce SARS virus proteins, generate diagnostic/therapeutic monoclonal antibodies, analyze mechanisms for SARS specific antibody neutralization, and animal model development; evaluate selected compounds that stimulate the innate immune system to treat SARS; initiate studies at the China CDC on the interactions between SARS, HIV, and TB; develop viral replication-based therapies to the SARS coronavirus, including protease inhibitors; and identify antibody inducing epitopes of SARS proteins that can be used for vaccine development.

- NIAID is supporting the development of SARS coronavirus vaccines through a variety of grants and contracts. In FY 2003, NIAID awarded separate contracts to Aventis Pasteur and Baxter for the development of inactivated SARS coronavirus vaccines. NIAID also awarded a contract to Protein Sciences for the development of a recombinant SARS vaccine. In addition, NIAID initiated the development of three different SARS vaccine projects through a grant supplement to the China CDC and their collaborators. NIAID scientists are also developing a DNA-based SARS vaccine and a strategy to combine these various vaccine approaches with inactivated SARS coronavirus proteins to see if a combination vaccine is more immunogenic.

- NIAID, in collaboration with USAMRIID and the CDC, is supporting the *in vitro* screening of candidate drugs against the SARS coronavirus. In addition, NIAID awarded

two contracts for screening for antiviral drugs that can be used to treat SARS. One contract was awarded to Utah State University and the other was awarded to the Southern Research Institute at the University of Alabama at Birmingham. NIAID intramural scientists also began developing antiviral peptides that will block the SARS coronavirus from entering cells and might be useful as a therapeutic drug to treat or prevent SARS.

- In FY 2003, NIAID provided funding through a contract to the Massachusetts Biologic Laboratories for the development of a type of antibody that can be used to treat people infected with SARS.

- In FY 2003, NIAID has expanded its Pandemic Preparedness contract at St. Jude Children's Hospital to: expand efforts to identify the animal reservoirs for coronaviruses in Asia; establish cell-based laboratory assays to assess the immune response in infected patients; and conduct studies of family members and other close contacts of SARS patients to assess the rates of asymptomatic infections.

- In FY 2003, NIAID awarded two contracts to support pre-clinical and clinical studies to control selected human respiratory pathogens. The contract awarded to the University of Iowa will support research focused on bacterial respiratory pathogens. The second contract, awarded to the Baylor College of Medicine, will focus on viral pathogenesis and evaluation of new viral vaccines and therapeutics.

- In FY 2003, NIAID provided initial support via a fast-track grant to Acambis, Inc. to develop a live, attenuated vaccine for WNV. Thus far, this vaccine has demonstrated good safety, efficacy, and protection against disease in animal models. NIAID intramural researchers are also working to develop another live, attenuated WNV vaccine.

- In FY 2003, a phase I/II randomized, placebo-controlled clinical trial was initiated at 35 sites in the United States to assess the safety and tolerability and efficacy of intravenous immunoglobulin G (Omr-IgG-am^{TM}) containing high anti-West Nile virus antibody titers in patients with or at risk for progression to WNV encephalitis and/or myelitis.

- In FY 2003, NIAID converted a grant awarded to the University of Texas Medical Branch supporting the World Reference Center for Arboviruses into a contract titled World Reference Center for Emerging Viruses and Arboviruses. The center provides scientists with basic and applied research resources on arboviruses (including WNV) and other emerging viruses and provides a forum to train investigators in virus identification and characterization techniques.

- In FY 2003, NIAID issued the RFP, *In Vitro* Antiviral Screening Program. The goal of this initiative is to provide drug screening resources for researchers engaged in antiviral research and to promote the discovery and development of new therapeutics for medically important, emerging, and rare viral diseases.

- In FY 2003, NIAID continued its support for the Collaborative Antiviral Study Group (CASG), which is a collaborative network, composed of 63 institutions, that conducts

clinical studies of therapies for viral infections. Through the CASG, NIAID supports four pediatric clinical trials aimed at treating neonatal herpes simplex virus infections, sepsis caused by a group of viruses called enteroviruses, and CMV infections involving the central nervous system.

- NIAID awarded a contract to the University of Alabama for a Respiratory Pathogens Reference Laboratory. This contract will provide a resource facility with a major effort on reagent and assay development for measurement of the human immune response to targeted bacterial respiratory pathogens.

- NIAID continues to support Phase I/II trials for two different candidate vaccines for human cytomegalovirus. In one of the studies for which enrollment is ongoing, a vaccine against CMV is being evaluated in post-partum CMV-seronegative women for its ability to prevent infection in these women. In another study, four live recombinant viruses are being evaluated for safety in seropositive individuals. This vaccine was well-tolerated with no significant side effects in this population.

- In FY 2003, NIAID continued its support of an ongoing phase III clinical trial conducted by the Adult AIDS Clinical Trials Group to determine whether the antiviral drug valganciclovir is safe and effective in preventing CMV organ damage in HIV-infected subjects.

- NIAID has continued its support of the Bacteriology and Mycology Biostatistical and Operations Unit and the Bacteriology and Mycology Study Group initiatives, which support clinical trials against fungal and resistant bacterial infections.

- NIAID continues to support research on the prevention of group B streptococcal disease through a contract awarded to researchers at Brigham and Women's Hospital. This collaborative multidisciplinary effort is focused on clinical studies in selected populations to further understand GBS infection and on studies of the host immune response.

- In FY 2003, NIAID supported several clinical trials of group B streptococcal vaccines. Researchers at Baylor College of Medicine are conducting a trial to evaluate the safety and immunogenicity of a booster dose of a group B streptococcal type vaccine in 50-64-year-old healthy adults. In addition, researchers at the Magee-Women's Hospital are conducting a Phase II clinical trial of a group B streptococcal vaccine in 18-30 year old women to evaluate prevention of vaginal acquisition of GBS type III.

- A RFA, Partnerships for Vaccines and Diagnostic Development, was announced in FY 2003, and awards will be made in FY 2004. This RFA focuses on the development of vaccines against Group A Streptococci (GAS), Group B Streptococci, and *Helicobacter pylori.*

- For over 30 years, NIAID has supported two helminth (parasitic worm) resources that serve the research community. The Schistosome Resource Center is maintained by

Biomedical Research Institute and the Filaria Resource Center is maintained by University of Georgia. Both contracts were renewed in FY 2003.

- NIAID has continued to actively test new candidate compounds for efficacy against infectious complications of AIDS in culture and in animals through its anti-infective drug development contracts. These contracts have been awarded for research on several rare diseases caused by these microorganisms *Mycobacterium avium, Pneumocystis, Cryptosporidium, Cryptococcus* and Microsporidium.

- In FY 2003, NIAID continued its support of research into the fundamental mechanisms of TSE disease and transmission as well as the development of diagnostic tests and effective therapies. NIAID awarded a contract to Colorado State University to establish an emerging disease research center focused on the TSE Chronic Wasting Disease (CWD), which will investigate the mechanics of CWD infection in deer and elk. In addition, NIAID-supported scientists are evaluating potential anti-TSE compounds in animal models. Through expansion of an NIAID contract with Utah State University, candidate compounds are evaluated for efficacy in animals.

- In FY 2003, NIAID awarded a contract to TIGR to support a Microbial Genome Sequencing Center to allow for rapid and cost-efficient production of high-quality, microbial genome sequences. This center has the capacity to respond to national needs and Federal agencies' priorities for genome sequencing by providing genome sequencing data for multiple usages, including forensic strain identification and the identification of targets for drugs, vaccines, and diagnostics.

- In FY 2003, NIAID supported approximately 36 large scale DNA sequencing genome projects for microbial pathogens and invertebrate vectors of infectious diseases, including new projects for different strains and clinical isolates of *Bacillus anthracis* and another strain of *Clostridium perfringens*. Genome sequencing projects for the bacteria *Burkholderia mallei, Clostridium perfringens, Escherichia coli (K1 RS218), Streptococcus agalactiae, Rickettsia rickettsii, Rickettsia typhi, Salmonella typhi*, and *Wolbachia* were completed in FY 2003.

- NIAID has continued its support for the Pathogen Functional Genomics Resource Center at The Institute for Genomic Research (TIGR). The center was established to provide and distribute to the broader research community a wide range of genomic and related resources and technologies for the functional analysis of microbial pathogens and invertebrate vectors of infectious diseases. In FY2003, additional organism-specific resources were generated and distributed to the scientific community, including SARS-related resources.

- NIAID has continued to provide support for databases of genomic and post-genomic information and analysis tools on sexually transmitted pathogens and poxviruses. Genomic information for thirteen bacteria and viruses are now included in STDGEN, a database designed to accelerate research on sexually transmitted diseases. The Poxvirus Bioinformatics Resource Center is a web-based resource for scientists that facilitates

basic research on poxviruses as well as research into new therapies and vaccines against them.

- NIAID staff continues to participate in the Microbe Project Interagency Working Group, which previously developed a coordinated, interagency five-year action plan on microbial genomics. In FY 2003, the Microbe Project Interagency Working Group developed a document on the subject of data sharing of pre-publication DNA sequencing data.

- NIAID has continued to participate in a coordinated Federal effort in biodefense genomics and is a major participant in the National Inter-Agency Genomics Sciences Coordinating Committee that includes many Federal agencies. In FY 2003, the committee focused on category A agents and provided the CDC with new technological approaches for sequencing additional smallpox viral strains.

Immune-System Mediated Rare Diseases

- NIAID continues to support demonstration and education research projects aimed at increasing minority involvement in organ donor registries. The Legacy Donor Registry in Louisiana endeavors to increase organ donation by using new and non-traditional approaches to organ donor recruitment, improving the consent process to enhance organ donations, and facilitating the medical community's access to donor registry information.

- NIAID continues to support The Minority Community Outreach on Organ Donation and Transplantation at the Hope Heart Institute in Seattle, WA. This community-based outreach network is dedicated to increasing organ donation among minority populations in Seattle and Tacoma, Washington. A second research project at the Hope Heart Institute is directed at increasing organ donation among rural Alaskan Natives. Culturally sensitive educational materials and community health education programs are being developed on transplant options, and living and cadaveric organ donation for this population.

- In FY 2003, NIAID and NCRR made an award under the RFA National Swine Research and Resource Center to establish a facility for depositing, maintaining, preserving, and distributing swine research resources for studies of human diseases. Swine are a useful model for transplantation research because of their reproductive capacity, anatomical and physiological similarities to humans, and ability to be genetically modified.

- NIAID awarded a multi-year, cooperative agreement titled Systems Approaches to Innate Immunity, Inflammation and Sepsis to a multidisciplinary team of researchers at the Scripps Research institute. These researchers are employing a systems biology approach to create a comprehensive picture of innate immunity, an essential first line of defense against bacterial, viral, and fungal diseases.

- NIAID, NIDDK, and ORWH continued to co-sponsor the Autoimmunity Centers of Excellence (ACEs), a cooperative program which supports collaborative basic and clinical research on autoimmune diseases, including single-site or multisite pilot clinical

trials of immunomodulatory therapies. In FY 2003, this initiative was renewed and expanded to include 9 separate institutions. In addition, these Centers began enrolling participants in three trials.

- The Autoimmune Disease Prevention Centers conduct basic research on the development of new targets and approaches to prevent autoimmune diseases and to evaluate these approaches in pilot and clinical studies. In FY 2003, the Prevention Centers supported 14 pilot projects to test innovative approaches, which may lead to the development of novel targets for disease prevention or assays for biomarkers of disease progression. The Prevention Centers are co-sponsored by NIAID, NIDDK, NICHD, ORWH, and Juvenile Diabetes Research Foundation International (JDRF).

- Two new grants were awarded in FY 2003 under the Hyperaccelerated Awards for Mechanisms in Immunomodulation Trials RFA. This initiative supports immune-based mechanistic studies associated with clinical trials of infectious disease vaccines and immunotherapies for immune-mediated diseases. Applications are abbreviated, submitted and reviewed monthly, and awarded as early as 13 weeks after submission. This program is co-sponsored by NIAID and other NIH Institutes, Centers, and Offices.

- NIAID supports the Immune Epitope Database and Analysis Program, which supports the development and maintenance of an integrated, web-based, searchable database of antibody binding sites (antibody epitopes) and antigenic MHC-binding peptides (T cell epitopes) for a wide variety of infectious agents and immune-mediated diseases. It is anticipated that the information contained within the database and the availability of analysis tools will facilitate identification of novel vaccine candidates and immunotherapeutic strategies.

- NIAID, NIDDK, and JDRF co-sponsor the Immune Tolerance Network (ITN), an international consortium of scientists and clinicians dedicated to the clinical evaluation of promising tolerance induction therapies in four areas: autoimmune disorders, kidney transplantation, islet transplantation for type 1 diabetes, and asthma and allergic diseases. The network is also developing assays and biomarkers to measure the induction, maintenance, and loss of immune tolerance in humans and is studying underlying mechanisms as an integral part of all clinical trials. The ITN includes basic scientists and physicians at more than 40 institutions in the United States, Canada, and Europe.

- NIAID supports the Multiple Autoimmune Diseases Genetics Consortium (MADGC), a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. This repository provides well-characterized material for use in research aimed at identifying the genes involved in autoimmune diseases. MADGC began enrolling families in May 2000 and aims to have 400 enrolled in 2004. To date, 162 families have been fully enrolled, and 125 families are in the process of being enrolled.

- NIAID, in conjunction with NIAMS, NINDS, ORWH, and the National Multiple Sclerosis Society, continues to support the Sex Based Differences in the Immune

Response research initiative. Differences in the immune response of males and females have been documented, including the increased incidence of autoimmune diseases in women. The cause of pregnancy-induced changes in immune mediated diseases and differences in the rate and severity of disease are unclear. An increased understanding of the mechanisms underlying the differences in the immune response in males and females should allow more targeted approaches for the prevention and treatment of immune-mediated disease.

- Through the Stem Cell Transplantation for Autoimmune Diseases Consortium, NIAID is supporting clinical trials to assess the efficacy of hematopoietic stem cell transplantation to treat several severe autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, and scleroderma. Trials involving patients with systemic lupus erythematosus and scleroderma are expected to begin in 2004.

- NIAID chairs the NIH Autoimmune Diseases Coordinating Committee (ADCC). The ADCC was established in FY 1998, at the request of Congress, to increase collaboration and facilitate coordination of research among NIH Institutes and Centers, other federal agencies, and private groups interested in these diseases. The ADCC Autoimmune Diseases Research Plan, which was mandated in the Children's Health Act of 2000 (P.L. 106-310), was presented to Congress in FY 2003.

CRADAs

- NIAID and GenVec, Inc. negotiated a CRADA to develop a recombinant SARS vaccine.

- NIAID and Vical, Inc. negotiated a CRADA to develop WNV DNA vaccines for use as prophylactic vaccines in human and veterinary applications.

Rare Disease-Specific Conferences, Symposia, and Meetings

- On October 22-23, 2002, NIAID convened the Blue Ribbon Panel on Bioterrorism and its Implications for Biomedical Research, focusing on CDC Category B and C agents. This group of experts from academia, industry, and government provided expert advice, which led to the development of *The Counter-Bioterrorism Research Agenda of the National Institute of Allergy and Infectious Diseases (NIAID) for CDC Category B and C Agents*.

- In November, 2002, NIAID, in collaboration with the NIH Office of Rare Diseases, sponsored an international conference on the current status of vaccines against plague and tularemia. Experts from throughout the world participated in this conference, which also stimulated productive interactions between various groups of investigators.

- NIAID and the NIH Clinical Center convened a meeting on November 20-21, 2002, to discuss therapeutic options for individuals who suffer from West Nile Meningoencephalitis. The meeting provided a forum for experts from government, academia, pharmaceutical industry, and private clinical practice to discuss the recent

outbreaks in the United States, focusing on epidemiology, disease, and potential therapeutics, and included identification of gaps in current knowledge and recommendations for courses of action.

- Along with other funding agencies, NIAID organized two meetings (February, 2003 and September 2003) to assess progress and future directions for the three trypanosomatid genome projects: *Leishmania major, Trypanosoma brucei, and Trypanosoma cruzi*. These three genomes are nearing completion and plans are being made for publication.

- NIAID, in cooperation with NIEHS, NIAMS, the NIH Office of Rare Diseases, the NIH Office of Research on Women's Health, the American Autoimmune Related Disease Association, and the U.S. Environmental Protection Agency, sponsored a workshop which was held on February 4-5, 2003, to discuss recent progress in and potential future directions for research related to environmental influences on autoimmunity and autoimmune diseases.

- NIAID organized the Imaging Technology and Study of Immune Function workshop, which was held April 8-9, 2003, to discuss recent progress in programs funded under the RFA New Imaging Technologies for Autoimmune Diseases and to advise the NIAID on future directions and opportunities to utilize imaging technologies to advance the understanding of immune system function.

- On April 23-24, 2003, NIAID and the NIH Office of Rare Diseases co-sponsored a conference on Humoral Rejection in Solid Organ Transplantation, in Bethesda, MD. The goal of this conference was to evaluate the state of the science in diagnosing and treating humoral rejection. Additional co-sponsors were The American Society of Transplantation, American Society of Transplant Surgeons, National Kidney Foundation, International Society of Heart and Lung Transplantation, American Society of Histocompatibility and Immunogenetics, and the Division of Transplantation at the DHHS Health Resources and Services Administration.

- On April 30 - May 1, 2003, NIAID sponsored the Genomics of Transplantation workshop. An expert panel addressed the state-of-the-science in complex trait disease and transplantation genomics; identified gaps in knowledge; and advised NIAID on immediate and long-term research opportunities in transplantation genomics.

- On May 30, 2003, NIAID convened an international meeting on SARS and its implications for the biomedical research community. Experts in coronavirus biology, vaccine and drug development, diagnostics, epidemiology, and clinical management were asked to develop a robust research agenda leading to the development of effective products to control this disease.

- NIAID scientists participated in a joint meeting of the U.S.-Japan Cooperative Medical Sciences Program's TB and Leprosy Panels, which was held in Newark, NJ, on July 21-22, 2003. The goal of the meeting was to foster an exchange of ideas and stimulate

international collaborations among U.S., Japanese, and other Asian Pacific Rim mycobacterial researchers.

- On September 14-15, 2003, NIAID co-sponsored a conference on pediatric organ transplantation. The goals of this conference were to: identify critical organ-specific areas of research facing the pediatric transplant population; identify obstacles to initiation of, participation in, and completion of clinical trials and develop strategies to overcome these obstacles; and develop concepts for organ-specific and all-organ research proposals that are feasible within the constraints of the study population. In the plenary sessions, participants discussed overviews of mechanistic studies in transplantation, existing registries, clinical study design, and the role of industry in clinical trials. Breakout sessions were devoted to establishing research priorities in thoracic, liver and small bowel, and kidney transplantation, as well as infectious diseases and mechanistic studies. Co-sponsors included the Office of Rare Diseases at the National Institutes of Health, the American Society of Transplant Surgeons, the American Society of Transplantation, the International Society of Heart and Lung Transplantation; the National Kidney Foundation; and the North American Pediatric Renal Transplant Cooperative Study.

- On September 16, 2003, NIAID sponsored a conference on post-transplant lymphoproliferative disease (PTLD). The goals of this meeting were to: bring together experts in the field to enhance communication between transplant physicians, surgeons, oncologists, infectious disease specialists, pathologists, and basic scientists interested in PTLD; identify the priority areas for clinical trials and mechanistic studies in PTLD following solid organ transplantation; discuss how to overcome the problems of performing studies in heterogeneous patient populations involving a wide range of ages and solid organ transplants; and develop strategies for moving forward with multi-center studies of the priority areas identified by the conference participants. The multi-disciplinary group of experts addressed a range of topics, including: prevention of PTLD, biological and pharmacological therapies, and strategies to monitor and predict outcomes of therapy. This conference was co-sponsored by the National Cancer Institute and the Office of Rare Diseases at the National Institutes of Health.

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES (NIAMS)

Overview of Rare Diseases Research Activities

The mission of the National Institute of Arthritis and Musculoskeletal and Skin Diseases is to support research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases, the training of basic and clinical scientists to carry out this research, and the dissemination of information on research progress in these diseases. NIAMS-supported researchers have made significant progress in broadening the base of knowledge related to many of the rare diseases within the Institute's scope. Many of our new and ongoing basic and clinical research studies are aimed at reducing the burden associated with disease as well as the development of new treatment options.

Recent Scientific Advances in Rare Diseases Research

Epidermolysis Bullosa

Epidermolysis Bullosa (EB) is a group of severe hereditary blistering skin diseases. A new method of nonviral transfer of normal genes to correct the EB defect has been investigated by NIAMS-supported researchers. They have been able to demonstrate sustained correction of the abnormality in affected cells with the defect. Thus, this potentially safer form of gene transfer may eventually result in genetically based treatments for these affected individuals. Another research group was also able to demonstrate the use of genetically corrected cells to facilitate the healing of wounds in one form of EB (recessive dystrophic EB) that usually results in severe deformity and death in early adulthood. This methodology potentially provides a better way to heal the wounds of EB of this type, although it is not a permanent or long lasting cure. The NIAMS has also recently released a new question and answer booklet on EB which provides an overview of EB, treatment options, and current research.

Juvenile Arthritis

Juvenile arthritis is one of the most prevalent chronic diseases in children in the United States. Scientists studying children with juvenile arthritis have found that increased pain and fatigue are linked to reduced participation in school and social activity. In addition, the researchers noted that anxiety is also significantly associated with increased pain and fatigue. The study, supported by NIAMS, the NIH Office of Research on Women's Health and the private sector suggests that improved treatment protocols for children with juvenile arthritis, including behavioral therapy, should be developed.

Melanoma

Melanoma is the most severe skin disease with regard to mortality, accounting for approximately half of all deaths from skin disease. Scientists are striving to understand the molecular events involved in the transformation of normal pigment cells of the skin to melanoma cells and the

early progression of melanoma. A group of investigators, recognizing that certain atypical moles predisposed individuals to the development of melanoma, studied these cells in culture and added genes to turn on a particular protein (MAPK). The introduction of this activated gene resulted in the development of factors involved in melanoma invasion and metastasis, indicating that this pathway is probably important in melanoma development. This new understanding may facilitate the design of therapeutic interventions to suppress this pathway.

Muscular Dystrophies

The broad fields of muscle biology and muscle diseases are active areas of research, and there are many exciting advances to highlight in these areas. One example is the recent report from scientists who have discovered how to reverse muscle degeneration in a mouse model of Duchenne muscular dystrophy. Researchers devised a way to revitalize wasting muscle by using a special carrier to introduce the missing dystrophin gene into the diseased muscle tissue. Using a strain of mouse that lacks the dystrophin gene, researchers injected affected muscles with the missing gene, using a special adenovirus vector, or carrier. The muscles became more able to resist injury and muscle function was restored. Such techniques could eventually lead to gene therapies for patients with Duchenne muscular dystrophy once it is possible to provide gene delivery to all of the muscles in the body.

NIAMS-supported scientists have found that people with facioscapulohumeral muscular dystrophy (FSHD) have an exclusive association with one of the two different forms, or alleles, of the chromosomal region linked to the disease. Scientists examined the alleles 4qA and 4qB in people with FSHD and in controls. The alleles occurred with roughly equal frequency in the control group, but in the FSHD group, the affected allele was always of the 4qA type. This research may lead to a better understanding of the role of genetics in people with FSHD.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (lupus) is an autoimmune disease that can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. Several recent NIAMS-funded research discoveries have significant implications for the clinical assessment and treatment of lupus. For example, a team of scientists supported by NIAMS and other parts of the NIH discovered a genetic "signature" present in some patients with lupus who develop life-threatening complications such as blood disorders, central nervous system damage, and kidney failure. After analyzing thousands of genes in the blood of patients with lupus, researchers found 14 of those genes were linked to a subset of lupus patients with severe disease. These findings provide strong support for developing new therapies to block the affected pathways in patients with severe lupus, as well as for identifying patients most likely to benefit from new therapies. NIAMS-supported researchers have also found different genetic regions linked to lupus in African Americans and European Americans. These researchers identified a region on chromosome 1 associated with the development of lupus in African American families. They also identified two regions on chromosome 11 associated with lupus in subsets of the African American families. In European American families, they found a genetic linkage to chromosome 4 that contributes to lupus. These results suggest that genetic origins of lupus may differ in African Americans and European Americans.

Another research highlight was the recent discovery that people diagnosed with lupus have autoantibodies (proteins that attach to the body's healthy tissue by mistake) in their blood years before the symptoms of lupus appear. Early detection of autoantibodies may help in predicting who will develop this disease, allowing physicians to monitor patients earlier in the disease process. NIAMS-supported researchers have also recently reported that people with lupus may develop carotid atherosclerosis at an accelerated rate and independently of many risk factors normally associated with cardiovascular disease. The scientists also found that people with lupus who had the disease longer, had more damage from the disease, and had used less of the immunosuppressive drug cyclophosphamide to treat it were more likely to develop fatty deposits in their arteries.

In addition to basic and clinical research activities, the NIAMS is committed to providing culturally appropriate material to those individuals who may have lupus. As one example of this, the NIAMS created a bilingual booklet in Spanish and English titled "¿Tengo Lupus?/Do I Have Lupus?".

Vitiligo

Generalized vitiligo is an autoimmune disorder characterized by loss of pigment in patches on the skin and hair. It often clusters in families allowing for genetic analysis. A group of investigators studied families gathered from both the United States and the United Kingdom, and analyzed multiple family members who were affected by vitiligo. Linkage to a particular location on chromosome 1 established this as the major susceptibility site for vitiligo. The same investigators also used their large population base to look at the coexistence of other autoimmune diseases and vitiligo in these families. They demonstrated that within the same family there were likely to be multiple members with vitiligo as well as other individuals with autoimmune thyroid disease, pernicious anemia, Addison's disease, systemic lupus erythematosus, and inflammatory bowel disease. Many of these autoimmune diseases can be severe both in terms of the general health of the individual and in terms of psychological and social impact. Understanding the genetic basis as well as the environmental triggers that may lead to the development of vitiligo is important in prevention and treatment.

New/Planned Extramural and Intramural Research Initiatives

Juvenile Arthritis

NIAMS has recently provided support for a state-of-the-art genomics project to uncover gene expression patterns that contribute to the development of pediatric arthritis. By using DNA microarrays—small silicon chips that contain tiny amounts of thousands of known genes—to carry out a technique called gene expression profiling, NIAMS-supported researchers will analyze thousands of genes in the blood, fluids, and tissues of children newly diagnosed with various types of pediatric rheumatic diseases such as juvenile rheumatoid arthritis (JRA), juvenile ankylosing spondylitis (spinal arthritis), and related immune disorders. Identifying gene expression patterns—groups of genes that are "turned on"—for different types of childhood arthritis will help to improve diagnosis and to predict disease severity for affected children.

Scleroderma

A new NIAMS funded project is using a unique sample set–lung tissue from scleroderma patients undergoing lung transplant surgery, as well as lung tissue from unused donor lungs–to facilitate investigation into the cellular changes that cause the hardening of the lungs. Another new NIAMS-funded study is uncovering the cellular activities inside the blood vessels in scleroderma patients.

Systemic Lupus Erythematosus

In the area of childhood lupus, the NIAMS recently initiated a large, controlled study to assess the ability of statins (cholesterol-lowering agents) in preventing or delaying progression of cardiovascular disease in children with lupus. This research study involves 20 centers from the Pediatric Rheumatology Research Network in establishing the largest cohort of pediatric lupus patients ever prospectively studied.

Significant Ongoing Rare Diseases Research Initiatives

Heritable Disorders of Connective Tissue

Eight, recently awarded research grants funded by the NIAMS will shed light on heritable diseases of connective tissue. Disorders of connective tissue (the material between cells that gives tissues form and strength) include such conditions as osteogenesis imperfecta, Marfan syndrome, and Ehlers-Danlos syndrome, and, in total, may affect as many as a million people in the United States. The grant awards support individual research projects as well as collaborative exploratory and developmental grants that investigate the cause of one or more of these disorders and novel treatment pathways. These grants will complement ongoing research within the Intramural Research and Extramural Programs at NIAMS.

Paget's Disease of Bone

Current research in Paget's disease and other areas across bone research will facilitate the development of cell- and gene-based treatments for many disorders. For example, NIAMS continues to support a number of projects investigating the viral and genetic factors contributing to Paget's disease, including a multi-component research program aimed at understanding the causes of Paget's disease. Four related projects, integrated within a single program, will examine several factors that contribute to the development of the disease. A key component is the creation of a new strain of mice, based on the long-suspected role of measles virus infection in Paget's disease, that exhibits bone abnormalities resembling the human disease.

Scleroderma

The NIAMS supports several projects which focus on new and innovative treatment options for patients with scleroderma including: a multicenter trial to test type 1 collagen as a treatment for localized forms of scleroderma; ultraviolet phototherapy; and stem cell transplantation. In

addition, behavioral scientists supported by the Institute have found that managing pain and depression may lead to improved functioning and quality of life for patients with scleroderma.

Rare Disease-Specific Conferences, Symposia, and Meetings

Immunomodulatory Drugs and Treatment of Skin Diseases

In September 2003, the NIAMS, in conjunction with the NIH Office of Rare Diseases, held a conference on immunomodulatory drugs in the treatment of skin diseases. The conference explored what we can learn about the pathophysiology of skin diseases by looking at how new, immunomodulatory drugs work. Several rare skin diseases were discussed at this meeting. We anticipate that the recommendations from this conference will help identify scientific opportunities that may promote a better understanding of various skin diseases and how best to treat them.

Osteopetrosis

In October 2003, the NIAMS collaborated with the NIH Office of Rare Diseases and the National Institute of Diabetes and Digestive and Kidney Diseases, as well as a number of private organizations, to sponsor the First International Symposium on Osteopetrosis: Biology and Therapy. At this Symposium, recent findings were presented, identifying the genetic defects that cause most instances of this disease. Such information will be crucial in developing new cell- and gene-based therapies for osteopetrosis, which arises from defects in the cells that normally remove old cartilage and bone as skeleton grows.

Activities with Voluntary Rare Diseases Organizations to Stimulate Research

Health Partnership Program

The NIAMS Health Partnership Program (HPP) has made significant steps in achieving the mission of understanding health disparities in minority populations and providing direction for improving the health status and health outcomes of those communities affected. The HPP is a community-based research initiative which operates through a collaborative effort between NIAMS and Washington, D.C., area community partners. Through this partnership, initiated in February 2000 with the program, the HPP has established the NIAMS Community Health Center (CHC) which is located in a medically underserved minority community in Washington, D.C. This site serves as a focal point for many of the program's activities, including the clinical study, *Natural History of Rheumatic Diseases in Minority Communities.* The CHC has received tremendous praise from the HPP community partners, and from July 2001 to December 2003, 803 patients have been enrolled in this study. In order to extend services to other communities the NIAMS has recently started providing consultation services for patients with rheumatic disease in a separate clinic in southeast Washington, D.C.

Muscular Dystrophy

The NIAMS, the National Institute of Child Health and Human Development (NICHD), and the National Institute of Neurological Disorders and Stroke (NINDS) recently provided funding for the establishment of three new muscular dystrophy cooperative research centers. Each Institute will fund one center at up to $1 million in direct costs per center per year for 5 years. The centers are based at the University of Pittsburgh (funded by NIAMS); the University of Washington, Seattle (funded by NICHD); and the University of Rochester, New York (funded by NINDS). Researchers at the three centers will conduct studies on Duchenne, myotonic, and facioscapulohumeral muscular dystrophies, and will investigate therapeutic approaches, including stem cell and gene therapy. In a novel collaboration, the Muscular Dystrophy Association (MDA) has agreed to commit up to $1.5 million to enhance research activities at each of the three Centers funded by NIH ($500,000 per center per year for 3 years). The NIAMS, NINDS, and NICHD signed a Memorandum of Understanding (MOU) with the MDA in May 2003 to formalize this partnership.

NATIONAL CANCER INSTITUTE (NCI)

Overview of Rare Diseases Research Activities

Cancer is not a rare disease; it is the second leading cause of death in the United States and accounts for one of every four deaths. In 2004, more than 560,000 Americans are expected to die of cancer, an average of more than 1,500 people a day (American Cancer Society, *Cancer Facts and Figures 2004*). Furthermore, despite reductions in age-adjusted rates of cancer death in recent years, the total number of recorded cancer deaths in the United States continues to increase, largely due to an aging and growing population.

Though cancer as a whole is not a rare disease, it is actually many distinct diseases, most of which are still considered rare. Only breast, prostate, lung, skin, and colon cancers can no longer be classified as rare, because they exceed the 200,000 cases per year maximum for inclusion as rare diseases. Unfortunately, incidence and mortality rates have risen for a number of the rare cancers, including cancers of the esophagus, liver, kidney, and brain, as well as melanoma, non-Hodgkin's lymphomas, and multiple myeloma.

NCI's Challenge Goal to the Nation is to eliminate the suffering and death due to cancer by 2015. As the leader of the National Cancer Program, NCI provides vision and direction to the nationwide community of researchers, public health workers, healthcare providers, patients, advocates, and policymakers working to defeat cancer.

The NCI's section of this report discusses selected major research advances, research initiatives within the NCI intramural and extramural programs, and other relevant program activities related to rare cancers.

Recent Advances in Rare Diseases Research

Cancer Biology and Etiology

Basic research studies that explore how cancer develops form the foundation of cancer research. Through these studies, scientists are identifying at the molecular level the fundamental processes that underlie a cell's transformation from normal to malignant. Identifying the processes and pathways that lead to cancer provides attractive targets for new prevention and treatment approaches. Likewise, elucidation of the external and internal factors that cause or contribute to cancer provides avenues for developing behavioral interventions and drugs to prevent cancer.

Novel Targets of Gene Silencing in Oligodendrogliomas

The technologies of restriction landmark genome scanning (RLGS) and array comparative genome hybridization (CGH) were applied to the analysis of oligodendrogliomas, a subtype of primary brain tumors. The investigators showed that aberrant CpG island methylation is the most prevalent alteration in these tumors. Most methylated genes are independent of regions affected by deletion, of which deletions of chromosome 1p and 19q are the most common genetic abnormalities. The expression of a putative zinc finger gene, ZNF342, located in a

commonly deleted region at chromosome 19q13, was specifically decreased in primary oligodendrogliomas and upregulated in glioma cell lines treated with a demethylating agent. The integrated approach taken allows the identification of novel targets of gene silencing and provides a more comprehensive view of the genes and mechanisms underlying the formation of oligodendrogliomas.

Vascular Endothelial Growth Factor and Social Support in Patients with Ovarian Carcinoma

Substantial evidence suggests that psychosocial factors such as stress, depression, and social support are able to modulate many of the immunologic activities relevant to cancer. In addition, a number of studies support a relationship between psychosocial factors and cancer progression. To date, however, there has been only weak evidence that cellular immune factors account for this relationship. Moreover, little is known about other mechanisms through which biobehavioral mechanisms may influence growth and progression of cancer. In a recent report, NCI-supported researchers showed that presurgical ovarian cancer patients with higher levels of social support had lower levels of vascular endothelial growth factor (VEGF), a key factor in tumor angiogenesis and a factor that has been related to survival in ovarian cancer. Patients with higher levels of stress had higher levels of VEGF. This finding, which has since been supported by *in vitro* studies, points to novel pathways by which stress hormones could potentially contribute to tumor progression (e.g., stimulation of angiogenic and tumor growth pathways). This type of finding has the potential to open a new area of inquiry for understanding relationships between psychosocial factors (or stress hormones) and tumor progression.

Prescription Medications Associated with a Decreased Risk of Non-Hodgkin's Lymphoma

Little is known about risk factors for non-Hodgkin's lymphoma. Some studies have suggested that certain medications may have a protective effect against the cancer, but drug exposures were assessed in different ways in the different studies. In new research drawing upon the drug-dispensing records from community pharmacies and hospital records in the Netherlands, scientists report an inverse relationship between occurrence of non-Hodgkin's lymphoma and use of antihistamines (histamine2 blockers) and pain relief medications (analgesics) among women. They also found reductions in risk among women for other drugs studied, but these were not statistically significant and may have been due to chance. However, the inverse associations tended to increase with increasing duration of use of the drugs, suggesting grounds for further study.

Menopausal Hormone Replacement Therapy and Risk of Ovarian Cancer

In a cohort study of 44,241 postmenopausal women in the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program, 329 developed ovarian cancer. Risk was significantly increased among women who used estrogen-only hormone replacement therapy (Relative Risk [RR] = 1.6) and steadily rose with years of use (RR = 3.2 for women who took estrogen for 20+ years). These findings showed that women who used estrogen-only hormone replacement therapy, particularly for 10 or more years, were at significantly increased risk of developing ovarian cancer. Women who used short-term

estrogen-progestin replacement therapy were not at increased risk, but risk associated with short-term and longer-term estrogen-progestin replacement therapy warrants further investigation.

Average Midrange Ultraviolet Radiation Flux and Time Outdoors Predict Melanoma Risk

Sunlight is the major environmental risk factor for melanoma. However, estimates of melanoma risk from sun exposure have varied widely, likely because previous methods for measuring this exposure were varied and often imprecise. In a case-control study of melanoma in Philadelphia and San Francisco, lifetime residential history was coupled with levels of midrange UV radiation (UV flux) to provide a newer and more accurate measure of individual exposure to sunlight. The association between melanoma risk and average annual UV flux was strong and consistent. The study found an association between melanoma risk and total hours outdoors as an adult in both men and women, even in those who are able to develop a deep tan.

Geographic Variations in Penetrance of CDKN2A Mutations for Melanoma

In an international consortium investigating 80 melanoma-prone families with a CDKN2A mutation, which confers a high genetic risk for developing melanoma, the incidence of melanoma varied depending on the families' geographic location. Incidence rates were lowest in Europe, higher in the United States, and highest in Australia. These results suggest that an environmental factor, most likely sunlight exposure, acts to modify the risk of developing melanoma in families that carry the CDKN2A mutation.

A Novel Transcriptional Target in Desmoplastic Small Round-Cell Tumor (DSRCT) is Implicated in Tumor Invasiveness and Contributes to the Malignant Properties of DSRCT

A wide variety of human malignancies is associated with aberrant transcription factors—important components of the cell's machinery that regulate the expression of proteins. Desmoplastic small round-cell tumor (DSRCT) is a highly aggressive primitive tumor arising from the surface of the abdominal peritoneum. Virtually all cases are defined by a chimeric transcription factor that results from fusion of the N-terminal domain of the Ewing's sarcoma gene (EWS) to the transcription factor domain of the Wilms' tumor suppressor (WT1). In each case, the chimeric transcription factor has functionally novel and distinct properties. Multiple lines of evidence demonstrate that the biology of these chimeric transcription factors is central to the development and maintenance of these tumors.

In the case of the DSRCT, the WT1 transcript is alternatively spliced to yield a number of isoforms, the most abundant of which has a 3 amino acid insertion that interrupts the last WT1 zinc finger. The EWS-WT1 fusion protein fails to bind to the known WT1 consensus binding site and does not transactivate known targets of WT1. Using cDNA subtractive hybridization, an NCI-supported research team has identified a novel target gene for EWS-WT1, called LRRC15. They have demonstrated direct binding of EWS-WT1 to a specific DNA sequence upstream of LRRC15 and potent transcriptional activation.

LRRC15 appears to be a protein whose normal role may be linked to placental invasion and which appears to be "misappropriated" by specific types of human cancer. LRRC15 protein is

expressed exclusively at the leading edge of migrating cells. A role for LRRC15 in cellular invasion is suggested by its striking expression solely within the cells of the placenta that invade the uterus during implantation. This is supported by the expression of LRRC15 in primary DSRCT tumor specimens and by data demonstrating reduced invasion of breast cancer cells after specific suppression of LRRC15 expression. Approaches designed to inhibit LRRC15 function may have therapeutic potential in this refractory human cancer.

The Role of CA125 in Ovarian Cancer

CA125 antigen-based serum assays are widely used to monitor patients with ovarian cancer; yet very little is known about the molecular nature or biological significance of CA125. NCI-supported investigators cloned a partial cDNA that codes for a new mucin representing the CA125 antigen; this has been termed MUC16. The researchers confirmed their findings by transfecting a partial MUC16 cDNA into two CA125-negative cell lines and demonstrating the synthesis of CA125 by three different assays. The cloning and expression of CA125 antigen opens the way to an understanding of its function in normal and malignant cells. The long-term hope is that CA125 will be found to play a role in disease initiation or progression and can be utilized as a therapeutic target.

Animal Model for Chronic Lymphocytic Leukemia (CLL)

Several new proto-oncogenes that are over expressed in CLL have been identified. One of these genes, *Tcl1*, was placed under the control of a B-cell promoter/enhancer in transgenic mice. These transgenic mice developed oligoclonal and then monoclonal expansions of CD5 B cells that share biologic, immunologic, and pathophysiologic characteristics with those of CLL in humans. This mouse CLL model may allow investigators to study disease pathogenesis and perform preclinical evaluation of novel therapeutics *in vivo*.

Detection, Diagnosis, and Prognosis

Promotion of research to improve cancer screening and early cancer detection and to develop more accurate diagnostic techniques is of major importance to the NCI. NCI-supported research, conducted at multiple centers throughout the country as well as by intramural scientists, is leading to rapid advances in these areas.

Workshop on Borderline Ovarian Tumor

A two-day workshop organized by Dr. Jules Berman (Cancer Diagnosis Program/NCI) and Dr. Steven Silverberg (University of Maryland Dept. of Pathology) convened borderline ovarian tumor (BOT) experts to identify areas of common agreement and to suggest new research approaches to important unresolved issues in BOT pathology. BOTs are enigmatic neoplasms. Although they do not fall neatly into benign or malignant categories, mounting evidence suggests that surgical excision alone cures the vast majority of BOTs. Recent reports have described a variant of serious BOT, the micropapillary pattern, that may have aggressive behavior, and the clinical and biologic importance of the micropapillary variant of BOT has roused recent controversy. Other BOT-related scientific issues include: 1) the biologic significance of pelvic

implants, and the importance of implant invasion, and 2) the relationship between BOT and serous carcinoma of ovary (i.e. does BOT progress to serous carcinoma?). These and related questions were addressed in the workshop, which was co-sponsored by the National Institutes of Health Office of Rare Diseases, the National Cancer Institute's (NCI) Office of Women's Health, and the NCI Cancer Diagnosis Program. A symposium publication of BOT papers developed from the workshop is expected to be published in late summer/early fall 2004.

Use of Pap and HPV Testing and Risk of Cervical Cancer

A study of nearly 21,000 women in a prepaid health plan evaluated whether simultaneous screening with a Pap test and human papillomavirus (HPV) testing is useful for assessing the risk for cervical intraepithelial neoplasia (CIN) 3 or cervical cancer. Women were followed for up to 122 months to determine their risk for histopathologically confirmed CIN3 or cancer. The study found that negative baseline Pap and HPV tests were associated with a low risk for CIN3 or cancer in the subsequent 45 months, largely because a negative HPV test was associated with a decreased risk of cervical neoplasia. Negative combined test results should provide added reassurance and justification for lengthening the screening interval among low-risk women, whereas positive results identify a relatively small subgroup that requires more frequent surveillance.

Cancer Treatment

NCI has supported research leading to a number of treatment-related advances.

Improved Treatment for Central Nervous System Tumors

Investigators at the Pediatric Brain Tumor Consortium have demonstrated in a pilot study the feasibility of adding intrathecal mafosfamide to an intensive regimen of systemic chemotherapy for infants and young children with intracranial central nervous system tumors. The use of intrathecal therapy should, if successful, reduce the morbidity of therapy by eliminating, reducing, or delaying the need for craniospinal radiotherapy in this setting.

Earlier Treatment for Myelodysplasia and Myeloproliferative Diseases

Because of the toxicity associated with stem cell transplantation (SCT), it is usually postponed until patients have failed other therapies. However, recent studies have shown that for higher-risk patients—particularly those who are younger or have normal genetics—more aggressive therapies, such as acute myelogenous leukemia-type chemotherapy or transplant, should be considered sooner. The increasing use of nonmyeloablative (mini) transplants has allowed patients as old as 75 to receive a transplant.

Enhancing the Immune Response to Chronic Lymphocytic Leukemia (CLL)

Multiple efforts are underway to develop new therapies for CLL, including gene therapy and novel agents. T cells in CLL patients are known to be defective and immune-incompetent. Gene therapy for CLL has been developed whereby neoplastic B cells are infected with Ad-CD154 *ex*

vivo, which renders these transduced B CLL cells to function as proficient antigen-presenting cells. When these transduced cells are administered to patients via intravenous injection, an immune response against CLL cells is induced. Functional T cells are observed in these CLL patients. Data from a Phase I study involving repeated injections of these transduced cells demonstrated that the injections sometimes resulted in the resolution of cervical adenopathy. A Phase II clinical trial is underway to assess the biologic activity and safety of repeated doses of Ad-CD154-transduced leukemia B cells. To date, seven patients have received repeated injections of transduced cells with little or no toxicity.

Rituximab plus Chemotherapy for Aggressive NHL

Results of a study exploring the use of rituximab and Cytoxan, Adriamycin, Oncovin (Vincristine), Prednisone (CHOP) chemotherapy in older patients with aggressive lymphoma have been reported. The study was a collaboration by several of the NCI-sponsored Cooperative Groups and was designed to further explore the benefit provided by this new combination regimen. The findings suggested that more doses of the new drug, rituximab, may provide benefit beyond chemotherapy and that continuing treatment with rituximab after completion of chemotherapy can delay the time to relapse, perhaps preventing it.

More Intensive Chemotherapy for Aggressive NHL

The hypothesis that more intensive therapy for aggressive lymphoma could be safely given and might improve outcome was studied by the Southwest Oncology Group (SWOG). Treatment with dose-intensified CHOP was safely administered and resulted in improved survival. Estimated overall survival at 5 years was 14 percent better than that of patients treated with standard-dose CHOP in an earlier SWOG study. This more intensive chemotherapy regimen is being tested in a Phase III randomized clinical trial, and combinations with novel drugs are being evaluated.

Defining Standard of Care for First Treatment of Hodgkin's Disease

While Hodgkin's disease is curable in the majority of patients, a significant number still succumb to the disease, and the chemotherapy and radiation necessary for treatment cause significant side effects. Research continues to identify more effective and less toxic therapies and to determine what current treatment regimens offer the best balance of activity and toxicity. A large NCI-sponsored randomized Phase III study performed by the Cancer and Leukemia Group B intergroup (CALGB-8952) was reported in 2003. The comparison of two frequently used chemotherapy regimens (ABVD and MOPP/ABV hybrid) included 856 patients. It showed that the two regimens were very similar in their ability to control the disease but that the more intensive regimen caused more toxicity. These results established ABVD as the standard of care in this country, showing it to be a preferable first-line regimen for patients since it provides good clinical effects for most patients with a better safety profile.

Rituximab in HIV-Associated Lymphoma

Results from a large Phase III trial were reported in 2003 showing that the addition of rituximab to standard chemotherapy (CHOP) does not add significantly to the activity of CHOP and may add significant immune suppression, resulting in increased infectious complications. This contrasts with the results from studies in non-HIV-associated lymphoma where rituximab appears to significantly improve results from standard chemotherapy. This information provides significant insight into the impact of rituximab on the immune system and its functioning when compromised by HIV infection. Future use of rituximab in HIV-infected patients will require a more cautious approach, with prophylaxis for possible infectious complications.

Chemotherapy plus Radioimmunotherapy for Indolent NHL

Advanced follicular lymphoma is incurable with conventional chemotherapy and radiotherapy. A Phase II trial of 90 patients tested a novel regimen of six cycles of CHOP chemotherapy followed 4 to 8 weeks later by a radioactive lymphoma-targeted antibody. Treatment was well tolerated. This study has established the feasibility, tolerability, and activity of this regimen for patients with advanced follicular lymphoma. This novel treatment appears promising compared to historical experience using CHOP alone and is currently being compared with CHOP plus rituximab in a randomized Phase III trial.

Long-Term Toxicity Following Radiation Treatment

Radiation therapy is very effective against lymphoid malignancies and has been a mainstay of treatment for lymphoma. As newer systemic therapies have been tested, studies have shown that there is no need for radiation therapy in the majority of patients. In addition, research from the Radiation Therapy Oncology Group (RTOG) investigators has improved the techniques used to give radiation therapy in order to limit exposure of normal tissues to radiation. These combined efforts have markedly decreased patients' exposure and will result in fewer neurologic complications and secondary malignancies.

State-of-the-Science Meeting on Myelodysplasia and Myeloproliferative Diseases

Myeloproliferative disease (MPD) and myelodysplastic syndrome (MDS) are similar in that both are premalignant blood stem cell diseases; they affect relatively small numbers of patients; and the severe forms of the disease are often fatal. There is no treatment known to produce responses in the great majority of patients in either group. Hence, NCI is working with patient-oriented advocacy groups such as the Aplastic Anemia and MDS International Foundations and the American Society of Hematology to ensure that priority is given to increasing basic research and developing clinical trials for patients with these diseases. This recognition is exemplified by a State-of-the-Science Implementation Working Group Meeting for Myeloproliferative, Myelodysplastic, and Marrow Failure Syndromes in March 2003 [cosponsored by the NCI and the National Heart, Lung, and Blood Institute (NHLBI)].

Cancer Control and Survivorship

Posttraumatic Stress Among Siblings of Childhood Cancer Survivors

Few would argue that cancer is a major stressor for anyone diagnosed with the disease. A growing body of research is beginning to show us that it is not only the patient who may be traumatized. NCI-supported scientists found that levels of post-traumatic stress (PTS) are elevated for siblings of childhood cancer survivors. Adolescent siblings of pediatric cancer survivors report more PTS symptoms than a reference group of non-affected teens with similar levels of general anxiety. These data serve as a reminder that cancer is often a family disease. As such, identifying family members at risk for PTS and intervening early to reduce emotional distress may be critical to the subsequent health and well-being of both the individual and the family.

Rare Diseases Research Initiatives

Ongoing Activities

Cohort Consortium

NCI has launched the Cohort Consortium, in which parallel and pooled studies of large population cohorts utilize advances in genomic technology to identify inherited susceptibility genes and gene-environment interactions in nonfamilial cancers. The Consortium is a unique public-private partnership that currently includes 23 population cohorts; epidemiologists for each cohort are collaborating not only with genomicists at their own institutions, but also are working formally with three major genome centers: the Whitehead/MIT Center for Genome Research, the *Centre d'Etude du Polymorphisme Humain* (CEPH) in Paris, and the NCI Core Genotyping Facility.

The Cohort Consortium represents a coordinated, interdisciplinary approach that will both accelerate the research process and allow scientists to perform subset analyses and confirmatory studies to examine gene-environment and gene-gene interactions. Investigators work together and pool information, which provides "instantaneous parallel replication" of findings across cohorts. The Cohort Consortium presents the cancer research community, including the NCI, with an extraordinary opportunity to advance research on genes and the environment and to do so economically by using already existing resources. The unique epidemiologic infrastructure also provides an opportunity to partner with other NIH Institutes to investigate a series of complex diseases, including diabetes and cardiovascular and neurological diseases. By involving both the intramural and extramural research communities as well as public-private partnerships, the opportunity exists for NIH to cost-effectively leverage its resources and ensure that the dramatic advances in genomics and other emerging technologies are incorporated into rigorous population-based studies to unravel the determinants and mechanisms underlying cancer and other diseases.

Cooperative Family Registries for Breast/Ovarian and Colon Cancer

Research to identify genetic changes that predispose to breast, ovarian, and colon cancer and to explore gene-gene and gene-environment interactions that may contribute to the development of cancer among families with these cancers are supported by the Cooperative Family Registries for Cancer Studies. These registries provide the tools and resources needed to clarify gene-environment interactions in cancer risk. They have identified thousands of families at high risk for breast, ovarian, and colorectal cancer that have agreed to be part of this research. Of particular interest are potential collaborations aimed at identification and characterization of cancer-susceptibility genes; definition of gene-gene and gene-environment interaction in cancer etiology; and cooperative research on the translational, preventive, and behavioral aspects of such findings. The outcome will be a clearer understanding of the genes that affect the development of cancer and how the environmental factors may modify these genes.

Cancer Care Collaborative

This collaborative effort is one of the dissemination projects generated from the Quality of Cancer Care Committee of the Department of Health and Human Services. Led by the Institute for Healthcare Improvement in collaboration with the Health Resources and Services Administration Bureau of Primary Health Care and the CDC, this innovative initiative works through 20 Bureau of Primary Health Care centers to drive organizational change within health center practices. There continue to be avoidable deaths from breast, colon, and cervical cancers, especially among disadvantaged ethnic and racial groups and those with lower socioeconomic status. The focus of this initiative is to improve the quality of colon, breast, and cervical cancer care by first improving cancer screening and follow-up of positive tests. This includes moving cancer control research into primary care clinics to improve communication among providers and between providers and patients and optimize processes of care. During FY 2004, the Cancer Care Collaborative will build on results from pilot work, with the long-term goal of translating cancer control research into practice to reduce morbidity and mortality due to colon, breast, and cervical cancers.

The CLL Research Consortium (CRC)

The CRC continues to make significant progress in the genetics, biochemistry, immunobiology, pharmacology, and clinical treatment of Chronic Lymphocytic Leukemia. For the past 30 years, families with two or more living cases of CLL have been enrolled in the NCI Familial Cancer Registry. Medical records and biological specimens have been collected for these subjects. Based on these data, NCI intramural researchers have found that age of onset in familial cases is approximately 10 years earlier than in sporadic cases and that there is often a higher percentage of second primary tumors in these patients. These families provide an ideal opportunity to conduct whole-genome searches, study candidate genes, and evaluate other biomarkers in investigating the etiology of this disease. Efforts to recruit new families in order to expand the search for a susceptibility gene are continuing through a newsletter posted on the *CLL Family Registry News* Web site (http://dceg.cancer.gov/hgp/geb/CLL/CLLnewsletter.html).

In order to expand these studies, NCI intramural investigators formed an international consortium of investigators with an interest in familial CLL to collaborate and share data. The consortium will enrich ongoing scientific investigations by bringing together clinical investigators and genetic epidemiologists to pursue linkage studies and candidate gene approaches in order to determine the genetic underpinnings of CLL. The CRC is collaborating with NCI intramural investigators by contributing clinical data and biospecimens from families with multiple cases of CLL. An analysis of the CRC database has shown that individuals with familial CLL do not differ from those with sporadic CLL on the basis of V(H) mutation status, Zap70 expression, IgV(H) expression, or age at diagnosis. The CRC is actively recruiting families and has obtained specimens from 14 families with 2 CLL cases. These families and others that are being accrued will be combined with those recruited by the NCI intramural investigators and other groups in order to conduct new whole-genome mapping and candidate gene studies to identify genetic causes of CLL.

Clinical Trials for Treating Lymphomas

The proliferation of potential treatment targets and identification of novel agents directed at those targets facilitate NCI's development of novel treatments for patients with lymphomas. These trials include novel agents of many kinds, including molecularly targeted small molecules, monoclonal antibodies, and antisense oligonucleotides. Agents already in development or in the planning stages include the following: Hu1D10 antibody, Campath-1H antibody, rituximab, IDEC-Y2B8 (anti-CD20 radioimmunoconjugate), LMB-2 antibody, triapine (small molecule ribnonucleotide reductase inhibitor), GTI-2040 (antisense ribonucleotide reductase oligonucleotide), flavopiridol (CDK inhibitor), MLN 518 (tyrosine kinase inhibitor), BMS-247550 (epothilone B analogue), CCI-779 (rapamycin analogue), UCN-01 (CDK inhibitor), bryostatin (CDK inhibitor), arsenic trioxide, bortezimib (proteosome inhibitor), tipifarnib (FTI inhibitor), interleukin-12, oxaliplatin, 506U78 (AraG prodrug), thalidomide, depsipeptide (histone deacetylase inhibitor), SAHA (histone deacetylase inhibitor), HeFi-1 (anti-CD30 antibody), and G3139 (antisense Bcl-2 oligonucleotide). There are currently 101 clinical trials for patients with lymphoma using agents under NCI's Investigational New Drug (IND) program, including 14 Phase I trials, 55 Phase II trials, 8 Phase I/II trials, and 17 Phase III trials.

Clinical Trials for Preventing Orphan Cancers

NCI has an active agent development program to identify and evaluate potential new cancer prevention agents using animal models and test systems, support chemical synthesis and regulatory management of the drug development process, and move agents into early phase clinical trials. At this time there are 7 phase I trials and 11 phase II trials either active or approved within DCP directed at orphan diseases. A new clinical trials consortium to conduct these early phase trials was awarded in October 2003; new studies in this system are expected to begin in September 2004.

Clinical Trials for Treating Myelodysplasia and Myeloproliferative Diseases

The NCI currently supports a broad assortment of studies addressing the treatment of MPD and MDS. These can be grouped into biologically targeted therapies, leukemia-type chemotherapy,

and allogeneic stem cell transplants (SCT). More than 20 novel agents are being tested in clinical trials, and approximately 10 different studies exploring variations of allogeneic bone marrow transplantation are ongoing at multiple centers. Drug targets within abnormal cells include cell growth, proliferation, and death pathways; DNA transcription and replication; cell-surface signaling molecules; and metabolic functions. Targets outside of the malignant cell include growth-signaling molecules, immune-effector mechanisms, and blood vessels. A partial list of drugs, biologics, and vaccines in development includes Campath-1H antibody, MLN 518, bortezimib, thalidomide, CC-5013, flavopiridol, UCN-01, Gleevec, bryostatin, arsenic trioxide, tipifarnib, triapine, depsipeptide, SAHA, Gemtuzumab, ozogamycin, G3139, MDX-010, phenylbutyrate, Azacitidine, R115777, and Atrovastatin.

Clinical Trials for Treating Tuberous Sclerosis Complex (TSC), Lymphangioleiomyomatosis (LAM), and Hepatocellular Carcinoma

NCI recently funded a clinical trial using Rapamycin to treat TSC and LAM. This trial takes advantage of the fact that Rapamycin targets a novel kinase (mTOR kinase) that is involved in regulating cell-cycle control and cell growth. Thirty patients will be treated with Rapamycin in a dose-adjusting schedule for one year. In addition, imaging methods will be used to monitor and validate Rapamycin's therapeutic effects.

The proteasome 26S inhibitor PS-341 has been used to treat hepatocellular carcinoma patients. PS-341 acts by preventing the activation of nuclear factor kB (NF-kB), which is critical to the development, growth, and spread of hepatocellular carcinoma. A total of 27 patients will be evaluated in this trial.

Etiology of Barrett Esophagus, Gastroesophageal Reflux Disease, and Adenocarcinoma of the Esophagus

Incidence rates for adenocarcinoma of the esophagus have risen more rapidly than any other cancer and as much as 350 percent for white males. The only known premalignant condition that signals risk for this cancer is Barrett Esophagus (BE). NCI awarded four projects in FY 2003 to address the problem of BE through the following aims:

- Determine whether there are at least two susceptibility genes predisposing to BE and to esophageal cancer and how these may affect familial and sporadic cases of the disease.

- Quantify the risks associated with exposure to epidemiologic and genetic risk factors for reflux esophagitis, BE, and esophageal cancer. Molecular subtypes of BE and cancer will be sought using microarray gene expression.

- Determine the role of smoking, alcohol use, body size, and other risk factors for esophageal cancer using methylation profiles from tissue samples.

- Look for changes in DNA copy number in stages of BE using cDNA microarray-based comparative genomic hybridization and to perform global epigenetic profiling using microarrays.

New Approaches to Brain Tumor Therapy Consortium (NABTT)

The NCI has funded a consortium that is dedicated to the study of innovative therapies for CNS malignancies, including primary CNS lymphoma. Participants include investigators with specific expertise in CNS malignancy and access to relatively large numbers of patients who can be entered into clinical research. This Consortium is currently performing a series of Phase II studies designed to evaluate newer treatment regimens. Current regimens under study explore the use of dose-intensified methotrexate and thiotepa without brain radiation and include the use of immunotherapy with rituximab, an antibody that targets a specific lymphocyte marker on the malignant cells. In addition to these Consortium studies, the NCI is sponsoring multiple ongoing Phase I studies that are testing novel agents and will include patients with primary CNS lymphoma. If these initial experiences suggest that these new agents have activity against CNS lymphomas, more extensive studies will be done.

Rapid Access to Intervention Development (RAID) Program

To expedite the movement of academic discoveries from the laboratory to proof of principle clinical trials, NCI initiated the program Rapid Access to Intervention Development (RAID) in 1998. RAID makes resources available, on a competitive basis, to the academic research community that are necessary to convert a new molecule into a drug candidate suitable for clinical testing and are generally not available to academic investigators who lack a corporate partner. These resources include 1) GMP synthesis, formulation, range finding, and IND-directed toxicology and pharmacology; 2) clinical trial planning; and 3) regulatory assistance so that FDA requirements may be satisfied by any investigator who seeks to put a new molecule into the clinic. As of December 2003, 245 applications have been received, 91 of which were approved for NCI support. A description of the successful applicants and the projects can be found at dtp.nci.nih.gov/docs/raid/raid_index.html.

Other Drug Development Activities

NCI continues to screen new synthetic and natural compounds for antitumor activity using the automated cancer cell line screen. Over 80,000 defined chemical structures have been evaluated since the screen became operational in April 1990. More than 7,500 compounds have demonstrated in vitro antitumor activity, of which more than 4,000 agents have been selected for in vivo evaluation for assessment of therapeutic activity. Obviously, there are more compounds to test/develop than current resources would allow. The Drug Development Group (DDG) oversees the decision-making process regarding the development of new drugs and relies on extramural review of proposed activities. A complete description of this process is available on NCI's Developmental Therapeutics Program Web site (http://dtp.nci.nih.gov). Including vaccines and other biologicals, as well as chemotherapeutic agents, 7 agents are in DDG level 1B (early preclinical testing), 15 are in DDG level 2A (GMP production and late preclinical testing), 3 are in DDG level 2B (IND directed toxicology), and a number of agents are ready for human testing subject to obtaining an IND. Table 1 lists the agents in the DDG process. As the agents move through the different levels of the decision process, the level of NCI's financial commitment increases.

Tissue Resource Initiatives

The NCI currently supports several human tissue resources, including the Cooperative Human Tissue Network, Clinical Trials Cooperative Groups, Cancer Family Registries, and tissue banks located at individual Specialized Programs Of Research Excellence (SPOREs). The National Dialogue on Cancer's Research Team has collaborated with the NCI and more than 100 experts from various sectors to develop the National Biospecimen Network (NBN) blueprint, which proposes to standardize most of the key aspects of tissue collection, processing, annotation, access, and distribution to allow comparison of genomic and proteomic data from biospecimens collected at different institutions. This blueprint describes best practices for all aspects of biospecimen management. The report recommends that some pilot projects be initiated to test the new concept.

Initiatives Planned for FY 2005

Understudied Cancers of High Lethality

When certain cancers, such as pancreatic, esophageal, and liver cancers, are found, relatively little prolonging of life or quality of life follows. Understanding gene-environment interactions is important in learning who is at elevated risk and how that risk is regulated. Discoveries in these areas will be needed if more accurate and cost-effective public health interventions aimed at eliminating mortality are to be developed. The purpose of this initiative is to stimulate epidemiologic etiologic research on three understudied, highly fatal cancers of the pancreas, esophagus, and liver. It is important to note that several of these cancers disproportionately impact minority populations. For example, squamous cell esophageal cancer is three times more common among African Americans than whites. Liver cancer rates are elevated among Asian/Pacific Islanders, Hispanics, and African Americans compared to U.S. whites. Also, Hispanics and African American men experience incidence and mortality rates for pancreatic cancer that are 50 percent higher than those for U.S. whites.

Academic-Public-Private Partnership Program

In July 2003, the NCI published the Request for Applications (RFA) titled "Academic-Public-Private Partnership Program" (AP4). This RFA responded to the recommendation by the Leukemia, Lymphoma, and Multiple Myeloma Progress Review Group to foster partnerships among industry, nonprofits, and the academic sector to expedite drug development and availability of therapies. AP4 will support the discovery of new cancer agents and their rapid translation to human clinical trials. With this program, the NCI promotes collaborations among universities, pharmaceutical companies, biotech companies, and nonprofit organizations. Because of its rather unique funding mechanism, AP4 represents a new paradigm in drug discovery, development, and delivery. Applications for planning grants have been received and are undergoing peer review.

Rare Disease-Specific Conferences, Symposia, and Meetings

In FY 2003, NCI cosponsored ten workshops with NIH's Office of Rare Diseases. These workshops were:

- *UICC International Conference on Familial Cancer*
- *First International Symposium on Childhood and Adolescent Non-Hodgkin's Lymphoma (NHL)*
- *Etiology of the Observed Regional Differences in Rare Cancers in India*
- *Improving Outreach and Communication of the NCI Scientific Program With Ataxia-Telangiectasia Families*
- *International Conference on DNA Repair and Mutagenesis: From Molecular Structure to Biological Consequences*
- *International Workshop on Biliary Tract Cancers: Current Perspectives and Future Directions*
- *Inflammatory Breast Cancer Case-Control Study Collaborators' Meeting*
- *Integrating Research on Spirituality and Health and Well-Being Into Service Delivery: A Research Conference*
- *Model Systems in Plasma Cell Neoplasia*
- *Pathology Workshop on Borderline Ovarian Tumors*

TABLE I: COMPOUNDS THAT PASSED DRUG DEVELOPMENT GROUP
(as of December 2003)

Drug Development Group 1B	Drug Development Group 2A
NSC Number 721381 *2-Methoxy antimycin A1 719239 Discreet 713713 Discreet 713719 Discreet 713721 Discreet 725088 Discreet 728930 Discreet	NSC Number 281612 Dimethane sulfonate 309132 Zebularine 680410 Adaphostin 656240 Dithiophene and derivatives 682994 Dithiophene and derivatives 701315 Anti-HER2 immunoliposomes 703939 RFB4-onconase 711193 CDDO 727038 CDDO-Im 711516 Chimeric antiamyloidosis MAb 716976 BNP7787 722333 Transferrin-doxorubicin conjugate 724910 Discreet 726293 MLN 608 721782 1-methyltryptophan
Drug Development Group 2B	**Drug Development Group 3**
NSC Number 710464 Aminoflavone 713205 Halofuginone 729746 HA22	NSC Number 716976 BNP7787 371331+112907 Cytochlor + Tetrahydrouridine 724770 VEGF-Trap 724636 Biricodar (VX-710) 724772 BAY 43-9006 663249 Triapine 726292 MLN 518 727990 SB-715992 727989 GW-572016 707545 17-DMAG 701852 SAHA 728876 90Y-DOTA-Hpam4 729968 Reolysin 694501 Pyrrolobenzodiazepine (SJG136) 720735 Discreet (PPI-2458-[Fumagillin Analog] 703813 CC-5013

Table II: Active Research and Development Agreements
(as of January 9, 2004)

The NCI cooperates on the development of novel anticancer therapies with commercial as well as institutional entities ranging from fresh startups to the multinational biopharmaceutical firms. NCI currently holds 36 Cooperative Research and Development Agreements (CRADAs), 52 Clinical Trials Agreements (CTAs), 12 Clinical Supply Agreements (CSAs), and 203 Material Transfer Agreements (MTAs) with its collaborators.

Agent	Industry Collaborator	Agreement Type
17-AAG	KOSAN BIOSCIENCES	CRADA
17-DMAG	KOSAN BIOSCIENCES	CRADA
280-446	NOVARTIS	CTA
2-METHOXYESTRADIOL	ENTREMED, INC.	CRADA
506U78	GLAXOSMITHKLINE	CTA
5-AZACYTIDINE	PHARMION CORP.	CTA
AE-941	AETERNA	CTA
ALL-TRANS RETINOIC ACID	HOFFMANN-LAROCHE	CTA
ANTI-CTLA4 ANTIBODY	MEDAREX	CTA
ANTIGEN GENES FORMULATED FOR DELIVERY IN A DERMAL POWDERJECT XR GENE DELIVERY DEVICE	POWDERJECT	CTA
ARSENIC TRIOXIDE	CELL THERAPEUTICS INC.	CRADA
BAY 43-9006	BAYER CORPORATION	CTA
BENZOYLPHENYLUREA	ISHIHARA SANGYO KAISHA	CTA
BEVACIZUMAB (Avastin)	GENENTECH	CRADA
BMS 214662	BRISTOL-MYERS SQUIBB	CTA
BMS 247550	BRISTOL-MYERS SQUIBB	CTA
BMS 275291 (MMPI)	BRISTOL-MYERS SQUIBB	CTA

Agent	Industry Collaborator	Agreement Type
BNP7787	BIONUMERIK PHARMACEUTICALS	CTA
BRYOSTATIN-1	GPC BIOTECH	CTA
CAMPATH 1H	BERLEX LABORATORIES	CTA
CARBOXYPEPTIDASE G2	PROTHERICS, INC.	CTA
CCI-779	WYETH PHARMACEUTICALS, INC.	CRADA
CILENGITIDE	MERCK KGAA	CRADA
CLODRONATE	SCHERING OY	M-CRADA
COL-3	COLLAGENEX	CRADA
CYTOCHLOR + THU	HALOGENETICS, INC	CTA
DECITABINE	SUPERGEN, INC.	CRADA
E7389	EISAI RESEARCH INSTITUTE	CRADA
FK228	FUJISAWA	CRADA
FLAVOPIRIDOL	AVENTIS PHARMACEUTICALS	CRADA
G3139	GENTA	CRADA
GADOLINIUM TEXAPHYRIN	PHARMACYCLICS	CRADA
GM-CSF	BERLEX	CTA
GTI-2040	LORUS THERAPEUTICS	CTA
GW-572016	GLAXOSMITHKLINE	CTA
HALOFUGINONE	COLLGARD PHARMACEUTICALS	CRADA
HERCEPTIN	GENENTECH	CRADA
HOMOHARRINGTONINE	AMERICAN BIOSCIENCE INC.	CRADA
HSP-E7	STRESSGEN BIOTECHNOLOGIES	CTA
ID-KLH LYMPHOMA VACCINE	BIOVEST INTERNATIONAL	CRADA
ING201	INTROGEN	CTA

Agent	Industry Collaborator	Agreement Type
IRESSA (ZD1839)	ASTRAZENECA	CTA
IRINOTECAN	PFIZER	CTA
KRN5500	KIRIN	CTA
LUTETIUM TEXAPHYRIN	PHARMACYCLICS	CRADA
MEDI-522	MEDIMMUNE	CRADA
MGI 114	MGI PHARMA	CTA
MLN 518	MILLENNIUM PHARMACEUTICALS	CRADA-LOI
MS-275	NIHON SCHERING K.K.	CRADA
O6-BG	AOI PHARMACEUTICALS	CRADA
OSI-774	OSI PHARMACEUTICALS, INC.	CTA
OXALIPLATIN	SANOFI-SYNTHELABO	CRADA
PERIFOSINE	AOI PHARMACEUTICALS	CRADA
PPI 2458	PRAECIS PHARMACEUTICALS	CTA
PROTEIN D1/3-MAGE3-HIS	GLAXOSMITHKLINE BIOLOGICALS S.A.	CTA
PS-341 (Velcade)	MILLENNIUM PHARMACEUTICALS	CRADA
PSC-833	NOVARTIS	CTA
PV701	WELLSTAT	CRADA
R115777 (Zarnestra)	JOHNSON & JOHNSON PHARMACEUTICAL R&D	CTA
REBECCAMYCIN ANALOG	EXELIXIS	CTA
REOLYSIN	ONCOLYTICS BIOTECH	CTA
rF-TRICOM, rF-CEA-TRICOM	THERION	IntMurl-CRADA
RITUXAN	IDEC PHARMACEUTICALS	CRADA
rV-B7.1	THERION	IntMurl-CRADA

Agent	Industry Collaborator	Agreement Type
SAHA	ATON PHARMA	CTA
SB-715992	GLAXOSMITHKLINE	CTA
SC-55494	SEARLE	CTA
STI571	NOVARTIS	CRADA
THALIDOMIDE	CELGENE CORPORATION	CTA
TIRAPAZAMINE	SANOFI-SYNTHELABO	CTA
TOPOTECAN HYDROCHLORIDE	GLAXOSMITHKLINE	CTA
TRIAPINE	VION PHARMACEUTICALS	CTA
UCN-01	KYOWA HAKKO KOGYO	CTA
VX710	VERTEX PHARMACEUTICALS	CTA
ZEVALIN	IDEC PHARMACEUTICALS	CTA

Table III: Investigational New Anticancer Agents in Early Clinical Trials (as of January 2004)

Biologic Agents	
Phase I	**Phase II**
Adenovirus p53 (Advexin)	Adenovirus p53 (Advexin)
ALVAC-hB7.1/StemSep Vaccine	Anti-idiotype-KLH Lymphoma Vaccine
Anti-idiotype-KLH Myeloma Vaccine	Anti-idiotype-KLH Myeloma Vaccine
Antisense GTI-2040	Antisense GTI-2040
Apolizumab (MoAb: Hu1D10)	Apolizumab (MoAb: Hu1D10)
Apolizumab + Rituxan	Apolizumab + Rituxan
Avastin™ (bevacizumab, MoAb: anti-VEGF)	Avastin™ (bevacizumab, MoAb: anti-VEGF)
BL22 Immunotoxin	Avastin™ PAP-pulsed Dendritic Cells
DNA/IL-12 Vaccine	BL22 Immunotoxin
G3139	CAP-1 Vaccine
gp 100 IVS Cells Vaccine	D1/3 MAGE-His Fusion Vaccine
gp100 Protein (184V) Vaccine	ESO-1:157-165 (165V) Peptide Vaccine
Herceptin® (trastuzumab; MoAb: humanized Her2)	G3139
HPV E6 & E7 Peptide Vaccine	gp100 IVS Cells Vaccine
IL-12	gp100 Peptides A,C,F Vaccine
IL-12 + IL-2	gp100 Protein (184V) Vaccine
LBM 2 Immunotoxin	Herceptin® (trastuzumab; MoAb: humanized Her2)
MDX-010 (Human Anti-CTLA4 MoAb)	HPV E6 & E7 Peptide Vaccine
MEDI-522	IL-12
MoAb: 3A1, 95-5-49, 95-6-22 (Anti-T cell)	LMB-2 Immunotoxin
MoAb: CAMPATH-1H (Anti-CD52)	MDX-010 (Human Anti-CTLA4 mAb)
MoAb: HeFi-1 (Anti-CD30)	MoAb: 3A1, 95-5-49, 95-6-22 (Anti-T cell)
MoAb: I-131 HuCC49 Delta CH2	MoAb: CAMPATH-1H (Anti-CD52)
MOV-18 Chimeric T cell Receptor	MoAb: I-131 HuCC49 Delta CH2
MS275	Mutated VHL Peptides Vaccine
PG13/LNc8 Retrovirus Transduced Cloned T-Cells	PAX3/FKHR/EWS/FLI1&2 Vaccine
PR-1 Peptide Vaccine	PG13/LNc8 RetrovirusTransduced T cells
PSA Tricom Vaccine	PR-1 Peptide Vaccine
PV701	PSA Tricom Vaccine
ras/p53 Vaccine	ras/p53 Vaccine
Recombinant Fowlpox GM-CSF Vaccine	Recombinant Fowlpox-CEA(6D)/TRICOM + Vaccinia-CEA(6D)/TRICOM Vaccine
Recombinant Fowlpox- CEA(6D)/TRICOM + Vaccinia- CEA(6D)/TRICOM Vaccine	Recombinant Fowlpox-gp100:ES209-217(210M) Vaccine

Recombinant Fowlpox-TRICOM and Vaccinia-TRICOM Vaccine	Recombinant Fowlpox-PSA Vaccine
SGN-00101 (HspE7) Vaccine	Recombinant Fowlpox-TRICOM and Vaccinia-TRICOM Vaccine
Sodium Phenylbutyrate (IV)	Recombinant Vaccinia- and Fowlpox-Tyrosinase Vaccine
SS1(dsFv) PE38	Rituxan® (rituximab, MoAb: IDEC-C2B8)/Chemotherapy
Thalidomide	SGN-00101 (HspE7) Vaccine
Zevalin®(MoAb: Y2B8)	Sodium Phenylbutyrate (IV)
	Telomerase:540-548 Peptide Vaccine
	Thalidomide
	Zevalin® (MoAb: Y2B8)
Chemotherapeutic Agents	
Phase I	**Phase II**
17-AAG	17-AAG
2-ME	Arsenic Trioxide
Arsenic Trioxide	BMS 247550 (Epothilone B Analog)
BMS 214662 (FTI)	BMS 275291 (MMPI)
BMS 247550 (Epothilone B Analog))	Bryostatin 1
BPU	CAI
Bryostatin 1	Camptosar® (Irinotecan, CPT-11)
CAI	CCI-779 (Rapamycin Analog)
Camptosar® (Irinotecan, CPT-11)	COL-3
CCI-779 (Rapamycin Analog)	Compound 506U78
COL-3	Decitibine
Cytochlor + Tetrahydrouridine	Depsipeptide
Decitibine	Dolastatin 10
Depsipeptide	EF5
E7389 (Halichondrin B Analog)	Fenretinide
EF5	Flavopiridol
EMD 121974	Gleevec® (Imatinib Mesylate, STI571)
Fenretinide	Halofuginone (Topical)
Flavopiridol	Iressa (ZD1839)
Gadolinium Texaphyrin	Irofulven (MGI-114)
Gleevec® (Imatinib Mesylate, STI571)	O^6-BG
Iressa (ZD1839)	OSI-774
Irofulven (MGI-114)	Oxaliplatin
KRN5500	Perifosine
Lutetium Texaphyrin	Pyrazoloacridine
O^6-BG	R115777

OSI-774	Rebeccamycin Analog
Oxaliplatin	SarCNU
Perifosine	Suramin
Pyrazoloacridine	Taxotere® (Docetaxel)
R115777	Tirapazamine
Rebeccamycin Analog	Topotecan (Hycamtin®)
SarCNU	UCN-01
Suramin	Velcade® (Bortezomib, PS341)
Taxotere® (Docetaxel)	
Tirapazamine	
Topotecan (Hycamtin®)	
Triapine®	
UCN-01	
Velcade™ (Bortezomib, PS341)	
XK469	

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)

Overview of Rare Diseases Research Activities

The National Institute of Child Health and Human Development mission is to ensure that babies are born healthy and develop, through childhood and adolescence, into productive adults. The Institute works to achieve this mission in part by conducting and supporting a broad range of innovative research activities that address rare diseases and conditions. Some of the Institute's activities have recently resulted in significant scientific advances. In addition, to spur further discoveries and advances, the Institute is leading and supporting a variety of initiatives and workshops to fill research gaps and to better understand rare diseases and conditions. Highlighted below are some of the NICHD's activities related to treating and preventing rare diseases and conditions as they affect children, women, and families.

Recent Scientific Advances in Rare Diseases and Conditions Research

Modifiable Risk Factors Associated with the High Rate of Sudden Infant Death Syndrome Among Northern Plains Indians

The sudden infant death syndrome (SIDS) rate among American Indians (AIs) is the highest of any population group in the United States and overall is slightly more than double that of whites. The disparity is most acute in the Aberdeen Area of the Indian Health Service (AAIHS), where the SIDS rate is four times greater than that of the U.S. population. The NICHD collaborated with the AAIHS, Centers for Disease Control and Prevention, and the Aberdeen Area Tribal Chairman's Health Boards to study infant mortality among AIs and to identify prenatal and postnatal modifiable risk factors that would reduce SIDS risk. Researchers found that even one visit by a public health nurse during pregnancy or after birth reduced the infant death rate due to SIDS by one-fifth compared to homes never visited. Furthermore, a mother's binge drinking (five or more drinks at a time) during the first trimester of pregnancy was associated with an eight-fold increased likelihood that her infant would die of SIDS. Finally, infants usually wearing two or more layers of clothing at night, not including the diaper, were six times more likely to die of SIDS. These findings highlight several key SIDS risk factors that can be targeted in future intervention programs for the AI population.

Discovering How an Embryo Attaches to the Uterus: Implications for Preeclampsia and Endometriosis

In addition to conducting research to reduce infant mortality, the NICHD supports research to help women overcome conditions that interfere with their ability to become pregnant and carry their pregnancies successfully to term. Last year, researchers provided new insight into the events that must take place before a pregnancy can be established. This scientific advance may lead to answers on how to prevent or treat preeclampsia and endometriosis. Preeclampsia is life-threatening and complicates 5 to 10 percent of pregnancies. Also, endometriosis is a major cause of infertility in women who have difficulty becoming pregnant and affects 10 to 15 percent of women of reproductive age.

A recent NICHD-supported study sheds new light on understanding the first biological steps needed to establish a successful pregnancy. About six days after fertilization, the embryo, or blastocyst, is shaped like a sphere. Its surface is composed of a layer of specialized cells called the trophoblast, which later gives rise to cells that form the fetus' part of the placenta (the placenta is made up of both maternal and fetal tissue). The trophoblast is coated with a protein known as L-selectin, while the wall of the uterus is coated with carbohydrate molecules. Researchers uncovered evidence that, as the blastocyst travels along the uterine wall, L-selectin on its surface binds to carbohydrates on the uterine wall, until the blastocyst gradually slows to a complete stop. The process is similar to a tennis ball coming to a stop after rolling across a syrup-covered table. Only after the binding takes place, can the fetus implant itself in the uterine wall and a pregnancy begin. This finding may lead to insights about preeclampsia, which may result from failures of the embryo to attach properly to the uterine wall.

Moreover, the finding may lead to a better understanding of some cases of endometriosis-associated infertility. Endometriosis is a disorder in which endometrial tissue–tissue that normally lines the inside of the uterus–begins growing in other parts of the abdomen, such as the outside of the uterus, ovaries, or intestines. Another NICHD-supported research team found that women with infertility due to endometriosis have very low levels of the enzyme that makes the ligand for L-selectin. The ligand is a rubber-band like molecule that tethers L-selectin to the uterine wall. Researchers believe that without this enzyme, the embryo cannot attach to the uterine wall and a pregnancy cannot begin. The finding may lead to new therapies to treat women with endometriosis-related infertility.

Compounds Prevent Alcohol from Damaging the Fetus

To improve pregnancy outcomes, the Institute continues to support research activities to address fetal alcohol syndrome. As many as 12,000 babies are born each year with fetal alcohol syndrome. It is considered the most common non-hereditary form of mental retardation. Currently, however, no medication exists that can prevent alcohol's harmful effects on the developing fetus. This may change now that scientists from the NICHD and National Institute on Alcohol Abuse and Alcoholism (NIAAA) recently found that NAP and SAL, the active peptides from two brain proteins known to protect nerve cells against a variety of toxins, also protect mouse embryos from ethanol-induced fetal death and growth abnormalities. The researchers also discovered that these peptides interfere with the way ethanol disrupts the chemical ties that hold cells together. NAP protected cells to a greater degree than did SAL, completely preventing ethanol from breaking these chemical ties, even in the presence of ethanol concentrations that kill cells. These discoveries strengthen the case that ethanol causes birth defects by interfering with cell adhesion. Understanding this process may help researchers design drugs to prevent some of the effects of fetal alcohol syndrome.

Ongoing and Future Initiatives

Prenatal Alcohol Exposure Among High-Risk Populations: Relationship to Sudden Infant Death Syndrome

In collaboration with the NIAAA, the NICHD is encouraging researchers to develop community-linked studies to examine the role of prenatal alcohol exposure in the risk for SIDS and adverse pregnancy outcomes such as stillbirth and fetal alcohol syndrome. The study plans will enable researchers to launch multidisciplinary research projects in communities at high risk for prenatal maternal alcohol consumption. Overall, the goal is to decrease fetal and infant mortality and improve child health in these communities.

Mental Retardation and Developmental Disabilities Research Centers

The NICHD continues to support the Mental Retardation and Developmental Disabilities Research Centers program to advance diagnosis, prevention, treatment, and amelioration of mental retardation and developmental disabilities. The purpose of the program is to provide core support and facilities for cohesive, interdisciplinary research, and research training. Research projects may include genetic, molecular, and behavioral research to develop new treatment approaches for conditions such as Rett syndrome, which affects approximately 1 in 10,000 to 15,000 baby girls, and Fragile X, which affects approximately 1 in 3,600 boys and 1 in 4,000 to 6,000 girls.

Innovative Methods of Newborn Screening

Nationwide, newborns are screened routinely for only two disorders: phenylketonuria (PKU) and congenital hypothyroidism. Screening and initiating treatment before symptoms develop prevents severe mental retardation that can result from these disorders. Some states screen for other conditions using techniques such as tandem mass spectrometry that allows about 40 conditions to be detected at birth. Application of new microchip technologies that analyze DNA and proteins hold the potential to identify hundreds more. A panel convened by the Secretary of the Department of Health and Human Services recommended that the Nation expand and standardize its approach to newborn screening. Given its mission, the NICHD will embark upon a major new initiative to address this need. As a first step, the Institute will support development of new microarray chip technologies for newborn screening that can be expanded to screen for many disorders. The goal is to screen newborns for a wide range of genetic diseases that cause mental retardation, immunodeficiency, muscular dystrophy, cystic fibrosis, blood-clotting disorders, and other conditions more inexpensively and effectively, with just one major step, at birth, when chances for treating them successfully are greatest. Large numbers of infants with disorders lacking effective treatments will also be identified so that these children can be enrolled in clinical trials, and eventually effective new therapies can be developed. Thus, this newborn screening initiative will go beyond just providing innovative methods to diagnose disorders and will become an essential tool for preventing their adverse consequences.

Rare Disease-Specific Conferences, Symposia and Meetings

The NICHD co-sponsored several meetings, conferences, and symposia with the NIH Office of Rare Diseases.

Vulvodynia: Towards Understanding a Pain Syndrome (April 14-15, 2003)

In collaboration with the Office of Rare Diseases (ORD) and other NIH Institutes and Centers (ICs), the NICHD held a workshop to stimulate innovative approaches to future research projects that would help scientists better understand the causes of vulvodynia. Vulvodynia is a condition characterized by burning, stinging, irritation, or rawness of the female genital area when there is no apparent infection or skin disease that could cause these symptoms. In addition, for many women this condition remains undiagnosed. Workshop participants discussed existing knowledge of this condition, basic mechanisms that lead to pain, and approaches to treatment. In addition, participants identified future research directions needed to better understand the fundamental and basic mechanisms of vulvodynia and to develop clinical strategies for appropriate and evidence-based methods to alleviate vulvar pain.

Pediatric Critical Care: Focus on the Differential Diagnosis and Management of Critically Ill Children with Rare Diseases (June 8-12, 2003)

The NICHD organized an international symposium held at the Pediatric Intensive Care World Congress. The purpose of the symposium was to highlight the current state-of-the-art medical care in pediatric intensive care units (PICUs) for children with rare diseases, anomalies, and injuries. In addition, the symposium promoted cross-disciplinary collaborations among scientists and caregivers. Septic shock, cardiovascular collapse, respiratory failure, status epilepticus, hepatic and renal deficiency, overwhelming acidosis, brain injury, and coma are common conditions that bring children to the intensive care unit. Often, however, these emergency medical conditions are related to an undiagnosed rare disease or injury. To optimize health outcomes for critically ill infants and children, pediatric critical care professionals must be able to identify and treat any underlying rare disease or injury.

Physical Disabilities Through the Lifespan (July 21-22, 2003)

With improvements in health care, developed nations face an unprecedented increase in the number of individuals living longer and more productive lives. At the same time, there is an increasing number of aging individuals with disabilities or rare conditions. To address the special problems that people with disabilities face as they age, the NICHD held a conference to discuss these issues. The ORD and many other NIH ICs supported the conference. The conference goals were to 1) understand the relationship between the aging process and its effect on disabilities, 2) identify effective strategies for coping with disabilities and maintaining productive lives, 3) set an agenda for integrating research and policy issues, and 4) provide policymakers with key information on aging with disabilities. The summary slides of the

meeting presentations are currently available on the National Center for Medical Rehabilitation Research Web site, http://www.nichd.nih.gov/about/ncmrr/disabilities/index.htm.

From Bench-to-Bedside: Preventing Bilirubin Induced Brain Injury in the Newborn and Kernicterus in the 21st Century (July 21-22, 2003)

Left untreated, bilirubin-induced brain injury (BIBI) can lead to kernicterus, which is a type of brain damage that may cause mental retardation. Most experts agree that such injury is preventable; however, the incidence of BIBI has increased over the past decade. To begin addressing this problem, the NICHD, with support from the ORD, held a conference to encourage multidisciplinary research activities that will help reduce the risk of BIBI and kernicterus. The conference aimed to identify critical research gaps that need to be examined and to identify biological and social factors that might lead to BIBI. The overall goal is to develop practical strategies that will not only curb the increase in BIBI incidence, but also minimize its occurrence and the risk of mental retardation in newborns.

NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE (NCCAM)

Overview of Rare Diseases Research Activities

Congress endowed NCCAM with a broad statutory mandate to conduct and support complementary and alternative medicine (CAM) research, support research training, disseminate information, and facilitate integration of CAM and conventional healthcare delivery to move the CAM field forward. To fulfill its mandate, NCCAM is undertaking a number of challenges and supporting a broad portfolio of research to expand basic and clinical research, including the prevention, evaluation, and treatment of many rare diseases. The research projects supported by NCCAM also test hypotheses for which minimal preliminary data or lack of a conventional biological rationale exists.

Recent Scientific Advances in Rare Diseases Research

1. Cancers

Ovarian Cancer

In order to assess care options for patients with end-stage cancer, investigators are evaluating acupuncture as a complementary treatment for women who are receiving conventional palliative care for ovarian and other advanced cancers. These researchers will be determine whether acupuncture can relieve pain and nausea symptoms and improve quality of life in ambulatory ovarian cancer patients. In a separate study, investigators will apply acupuncture as an adjunct therapy to ovarian cancer patients with chemotherapy-induced neutropenia and to adolescent and young women with endometriosis who experience chronic pelvic pain.

Non-Hodgkin's Lymphoma

Previous research has indicated that guided imagery and music therapy show promise as intervention techniques to improve mood in patients with cancer. A currently funded study on music imagery integration with standard cancer care explores the effect of music imagery therapy on patients receiving intense chemotherapy for acute leukemia or high-grade non-Hodgkin's lymphoma. Outcomes will include measures of general anxiety, depression, and fatigue.

Liver Neoplasms

S-adenosylmethionine (SAMe) is a naturally occurring compound that is also available in supplement form. Previous research in animal model studies has shown that SAMe is anti-apoptotic in normal hepatocytes and pro-apoptotic in hepatoma cells, and that a fall in hepatic SAMe levels may eventually lead to liver injury and liver cancer. Scientists presently are using additional animal model studies to enhance the understanding of the role of S-

adenosylmethionine (SAMe) in liver biology and pathology and its role in serving as a therapeutic agent. Steps towards this goal include examining SAMe's effect on hepatocyte cell cycle progression in normal and cancerous hepatocytes; elucidating SAMe's effects on apoptosis in normal versus cancerous liver cells; investigating how SAMe deficiency leads to oxidative stress; and examining whether chronic hepatic SAMe deficiency predisposes to liver fibrosis.

Glioblastoma

Qi Gong is an ancient Chinese Taoist health exercise for rejuvenating the body's "internal energy systems." Previous in vitro model studies have shown that Qi Gong treatment may stimulate the growth of cultured human brain cells (astrocytes). In a currently funded study, researchers are working to replicate these results, in addition to assessing cell growth and cell death in order to determine the effects of Qi Gong administered at a distance on normal astrocytes and on cancerous brain cells. In a separate study, researchers are performing a double-blind randomized controlled clinical trial in order to investigate whether distance healing (a "mental intention on behalf of one person, to benefit another at a distance") may have an effect on the survival time and loss of function of patients with the most common form of brain cancer, glioblastoma. The Qi Gong sessions are complementary to standard radiation therapy. The healing intervention is performed at a distance, such that patients and healers never meet and patients are unaware if they are in the healing group.

Sarcoma

Researchers have initiated a randomized, controlled study to determine whether electroacupuncture is effective in the treatment of chemotherapy-induced delayed nausea and vomiting in patients with pediatric-type sarcomas, resulting in improved management of these symptoms and enhanced quality of life. They also are working to determine if acupuncture reduces the psychological stress associated with chemotherapy treatment and thus reverses the negative effects of stress on the neuro-endocrine and immune systems.

2. Neurological Disorders

Amyotrophic Lateral Sclerosis

Scientists are using cell culture studies and relevant animal models to investigate the molecular and cellular mechanisms of action of antioxidants such as alpha-lipoic acid, ethylenediamine tetra-acetic acid (EDTA), desferrioxamine, and uric acid, and their safety and efficacy in treating amyotrophic lateral sclerosis (ALS) and other disorders. These studies will provide essential knowledge about dose-response effects, methodologies for advancing CAM therapies to human trials, and problematic side effects. In a separate study, researchers are evaluating the nutritional supplement creatine in a Phase III clinical trial to determine if it may safely improve the arm muscle strength and slow the deterioration of motor and pulmonary function of patients with ALS.

Huntington's Disease

Creatine is a widely used dietary supplement principally taken to enhance athletic performance. Scientists are investigating whether creatine can effectively act as a neuroprotectant by preventing oxidative stress, which is conventionally associated with neuronal death in Huntington's disease (HD). Previous research has shown that creatine can improve behavioral and neuropathological phenotypes in HD animal models. Additional preliminary studies have shown that creatine can reduce metabolic stress in humans with HD. The investigators have since initiated a study to definitively determine the potential mechanisms of creatine neuroprotection, test its safety and tolerability in HD patients, and examine how it impacts HD symptoms (e.g., weakness and muscle mass loss) and progression.

3. Other Rare Diseases

Sickle Cell Anemia

Investigators are evaluating in-home massage therapy and in-home relaxation training to alleviate pain in African American adolescents and adults with sickle cell disease. The randomized clinical trial will measure pain, physical functioning, depression, anxiety, and health care utilization, such as physician and emergency department visits, hospitalizations, and medicine use.

Crohn's Diseases

Reiki is a subtle energy healing approach in which a practitioner transmits the "Universal Life Force Energy" to the recipient. In placebo-controlled animal model study, researchers are determining if Reiki can diminish the adverse effects of noise stress-induced intestinal damage, a condition that may be a precursor to immune system disorders. Measurements of intestinal impairment, including excess reactive oxygen species generation, epithelial damage, increased microvascular permeability, and increased foreign particle uptake by intestinal cells involved in the immune system process (M cells) following Reiki treatment are being performed.

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS (NIDCD)

Overview of Rare Diseases Research Activities

NIDCD conducts and supports research and research training on normal mechanisms and diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. This mission is achieved through a wide range of research performed in its own laboratories, a program of research grants, individual and institutional research training awards, career development awards, center grants, cooperative clinical trials, and contracts to public and private research institutions and organizations. The Institute also conducts and supports research and research training that is related to disease prevention and health promotion. NIDCD addresses special biomedical and behavioral problems associated with individuals who have communication impairments or disorders. NIDCD also supports efforts to create devices that substitute for lost and impaired sensory and communication functions.

Recent Scientific Advances in Rare Diseases Research

Mitochondrial Genes and Deafness

Mitochondria are specialized structures within cells that play a crucial role in metabolism and energy production. Mitochondria contain their own genes, which replicate during cell division. All of the mitochondria present in individuals are derived from the mother's egg. Therefore, diseases that appear to be passed exclusively through the maternal lineage are often linked to defective mitochondrial genes.

NIDCD-supported scientists have identified several specific mitochondrial mutations that predispose an individual to hearing damage resulting from toxicity from the aminoglycoside class of antibiotics to the inner ear hair cells. These investigators have determined that genetic loci in the nucleus of the cell act to modify the effects of the mitochondrial mutations. Most recently, a specific gene was identified in mice, which modulates the severity of mitochondrial deafness and is also implicated in age-related hearing loss. This mouse model will be extremely valuable for detailed studies of the molecular mechanisms by which mitochondrial mutations contribute to deafness. These findings could be used to develop genetic tests to determine whether an individual has an increased risk for aminoglycoside-induced hearing damage.

Usher Syndrome

Usher syndrome (USH) is characterized by hearing loss and retinitis pigmentosa (RP). About 5 percent of individuals who are deaf have USH, and more than half of the deaf and blind individuals (>10,000) in the United States have USH. The severity of the hearing loss and the presence of vestibular dysfunction distinguish two major clinical subtypes of USH, types 1 and 2. Individuals who have USH type 1 are congenitally deaf, and have a balance deficiency at birth, while RP has an onset at about the time of puberty. Individuals with USH type 2 are distinguished from USH type 1 in having a less severe hearing loss. A third form of USH (type 3) is characterized by progressive loss of hearing and retinal function. There are more than

eleven different genes in which mutations can cause USH. NIDCD intramural scientists have identified and characterized some of the genes responsible for USH and two common mutations that cause USH in the Ashkenazi Jewish population. They have discovered that the genes for Usher syndrome type 1D and type 1F, both encode cell adhesion proteins cadherin 23 and protocadherin 15, respectively. In addition, several NIDCD-supported scientists reported cloning the gene for Usher syndrome type 2A. The *USH2A* gene encodes a protein, Usherin, that has structures similar to other proteins involved in assembling cells and tissues into functional organs. NIDCD-supported scientists also have identified the genes responsible for Usher type 1C. These advances are critical steps towards developing strategies to treat this devastating disease that causes deafness and blindness.

Waardenburg Syndrome (WS)

WS is an autosomal dominant disorder which is characterized by pigmentary disturbances and deafness. NIDCD-supported scientists are seeking to determine the loci for WS type 2 by utilizing a high-density genome scan coupled with linkage analysis to identify candidate genes mutations that could be the cause of this disorder in three large, multigenerational families and several smaller families with WS2. Other scientists are studying the Dalmatian as an animal model for understanding the genetics of pigment-associated deafness in the dog and human. The relationship between pigmentation and deafness is not unique in Dalmatians and this model offers a unique opportunity to conduct genetic analysis of hereditary deafness.

Auditory Neuropathy

A small but substantial number of individuals with bilateral hearing loss have normal cochlear function. These individuals have severely abnormal central neural processing of auditor sensory input as evidenced by poor or absent auditory brainstem responses. Standard treatment strategies for bilateral hearing loss, such as hearing aids, are of little use to these individuals. When this disorder strikes young children or infants, it can cause severe disruption of normal language and speech development. The most likely cause of hearing loss is a disorder of the auditory nerve, hence the term "auditory neuropathy." This disorder is rare but more common than previously expected. Investigation of the physiologic mechanisms, the genetic basis, and possible treatments for this disorder is ongoing.

Endolymphatic Sac Tumors (ELSTs) in von Hippel-Lindau (VHL) Disease

NIDCD intramural scientists are studying individuals affected by VHL disease and tumors of the inner ear. These ELSTs have been found to develop in approximately 10 percent of individuals carrying mutations of the *VHL* gene. Hearing loss, balance disturbances, and tinnitus represent the primary clinical manifestations of this disease. Recent molecular genetic studies have confirmed the phenotypic association of ELST with VHL disease by demonstrating loss of heterozygosity at the *VHL* locus in tumor cells obtained from surgical specimens. In a clinical trial to preserve hearing in individuals with early stage ELST, preliminary results have revealed that these tumors can be safely removed while preserving hearing at preoperative levels and maintaining or improving vestibular function.

Prospective studies of this population of individuals should provide insight into the natural history of hearing and balance disturbances associated with ELST, while basic investigations will focus on the mechanisms by which ELSTs cause dysfunction of hearing and balance.

Enlarged Vestibular Aqueduct (EVA)

EVA is characterized by progressive childhood sensorineural hearing loss in association with enlarged vestibular aqueducts. Recent data indicate that at least some cases are associated with mutations in the Pendred syndrome gene (*PDS*). Individuals with Pendred syndrome have sensorineural deafness and goiter. NIDCD intramural scientists are working to identify the genetic basis of EVA, including several cases where it is clearly not caused by mutations in *PDS*. In addition, the role of congenital cytomegalovirus infection in this form of hearing loss is also being studied.

Stickler Syndrome

Stickler syndrome is a genetic disease affecting the connective tissues of organs throughout the body. Stickler syndrome can affect the inner ears, resulting in permanent sensorineural hearing loss. Studies on inner ears of normal mice, as well as a mouse model for Stickler syndrome (the *chondrodysplasia* mouse), have been completed by NIDCD intramural scientists and reveal how and where mutations in fibrillar collagen genes cause hearing loss in Stickler syndrome. The mutations act to disrupt the functions of normal genes and their corresponding protein products in the tectorial or basilar membranes of the cochlea, where these genes are specifically expressed. This disruption of gene function likely causes hearing loss by disrupting the biomechanical properties of sound wave propagation within the cochlea.

Nonsyndromic Deafness

Isolated deafness affects approximately 1 in 1000 newborns and infants. Mutations in any one of nearly 100 genes can cause childhood deafness. NIDCD intramural scientists have recently identified several novel deafness genes through genetic mapping studies of large families with hereditary deafness from Pakistan and India. Identification of these genes increases our ability to diagnose hereditary deafness with molecular tests, and studies of their function in normal and pathologic states provide fundamental insights into normal hearing and the pathogenesis of hearing loss.

Pendred Syndrome

Pendred syndrome is a genetic disorder causing deafness in combination with, in some cases, enlargement (goiter) of the thyroid gland. Pendred syndrome is caused by mutations in the *SLC26A4* gene. NIDCD intramural scientists have studied the genetic epidemiology of deafness (and thus Pendred syndrome) caused by *SLC26A4* mutations in east and south Asia, which contain approximately one half of the global population. In some populations, such as Koreans, *SLC26A4* mutations are the most common known cause of deafness. In all studied populations, *SLC26A4* mutations account for approximately 10 percent of all genetic deafness in childhood. This is a significant proportion, given that there are dozens of genes in which mutations can

cause genetic deafness. This study also demonstrated that ethnic groups each have their own distinctive spectrum of mutations, with one or a few most prevalent mutations. These results have significant implications for the design and implementation of molecular genetic tests for childhood deafness.

Resistance to Thyroid Hormone (RTH)

Resistance to thyroid hormone (RTH) is a genetic disease causing resistance of target tissues to the actions of circulating thyroid hormone. RTH is caused by dominant mutations in the gene encoding the thyroid hormone receptor beta subunit. Intramural scientists from NIDCD and the National Institute of Diabetes and Digestive and Kidney Diseases have demonstrated that some individuals with RTH develop permanent sensorineural hearing loss. A mouse model for RTH was generated at the NCI and used for studies of auditory function and structure by NIDCD scientists. The results indicate that RTH mutations cause hearing loss through dominant negative effects upon one or more other genes. Other studies by NIDCD-sponsored scientists revealed that this other affected gene likely encodes the thyroid hormone receptor alpha subunit. The disruption of the functions of the thyroid hormone receptor alpha and beta genes by RTH mutations results in hearing loss due to retarded development of the neurosensory tissue of the inner ear, which are dependent upon thyroid hormone for normal development and function.

Acoustic Neuroma

Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder that occurs in about 1 out of every 40,000 Americans. This mutation on chromosome 22 is strongly associated with the development of bilateral vestibular schwannomas, which then results in damage to both auditory nerves. Treatment of these acoustic neuromas often requires bilateral removal of the auditory nerves, which usually renders the individual deaf. Electrical stimulation of the residual neural pathways within the cochlear nucleus can provide a sense of hearing after this surgery. NIDCD-supported scientists are working to optimize the design of a neural implant used for electrical stimulation of the cochlear nucleus in these individuals, with the goal of providing a device equal in performance to the cochlear implant used in individuals with profound hearing loss.

Hereditary Cerebellar Ataxia Syndrome of Early Onset

Several abnormal genes that are associated with inherited cerebellar syndromes that cause disorders of balance and coordination have been identified. Relatively little is known about how different mutations lead to specific types of the disorder. There are typically great differences in the clinical signs and symptoms within families that segregate the same mutation and across families with mutations in the same gene. NIDCD-supported scientists have previously demonstrated linkage to chromosome 19p in four families with episodic vertigo and the inability to coordinate muscle movement (ataxia). The scientists have identified a missense mutation in the calcium channel gene on chromosome 19p in a family with severe progressive cerebellar ataxia of early onset involving the trunk, the limbs, and speech function.

Olfactory Function

NIDCD-supported scientists are investigating relationships between decreased olfactory function and a number of rare diseases. Studies have shown that olfactory loss appears to be among the first signs of such common neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Recent psychophysical studies have evaluated the prevalence and magnitude of olfactory loss in subtypes of Parkinson's disease, Down syndrome, schizophrenia, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and the rare amyotrophic lateral sclerosis/Parkinsonism/dementia complex of Guam. Better understanding of the associations between olfactory function and rare diseases may lead to earlier diagnosis and improvement in monitoring of these rare diseases.

Kallmann Syndrome

Kallmann syndrome is a rare genetic disorder with two main symptoms: an absence of the ability to smell and failure of the gonads to mature. There is a five- to seven-fold chance that this syndrome occurs in males in comparison to females, suggesting that the X-linked form of the disease is the most frequent. NIDCD-supported research has led to the identification of a common developmental defect in nerve migration, which links the two major disease symptoms. A unique family of proteins and their receptors that regulate nerve migration and direction during development are under investigation by NIDCD-supported scientists. Additional research is focused on isolating and cloning an X-linked gene responsible for Kallmann syndrome.

Carcinoma of the Vocal Tract

Cancers that occur in the mouth, throat, and vocal tract are less common than breast, prostate, or lung cancer, but have a significant impact on voice, speech, and swallowing. There are approximately 40,000 new cases and 12,000 deaths each year, and more than 320,000 survivors of head and neck cancer living in the U.S. Approximately 80 percent of these cancers occur in persons who use tobacco and alcohol. A subset of tumors occurring in the tonsillar and adenoid areas have been associated with Human Papilloma Viruses that also cause cervical cancer and Epstein Barr Virus that also causes mononucleosis. There is also an increased risk of this type of cancer in persons with Fanconi's Anemia, a rare inherited disorder in which there is increased susceptibility to DNA damage, anemia, and cancer. NIDCD intramural scientists are collaborating with molecular biologists and clinicians from the National Cancer Institute to address the molecular basis for the disease and possible new treatments. These tumors show an increased response to growth factors when compared to other cells. Specific intracellular signaling molecules that mediate this effect have been identified. In addition, these tumors produce factors that stimulate the blood supply and immune cells in ways that help promote tumor growth and spread. Drugs that block the effects of these signaling pathways and factors may provide new approaches for prevention and therapy of these cancers.

Velo-Cardio-Facial Syndrome (VCFS) /DiGeorge Syndrome

VCFS is a disorder that has been associated with more than 30 different features, the most common being cleft palate, heart defects, characteristic facial features, minor learning problems,

and speech and feeding problems. VCFS is also known as Shprintzen, DiGeorge, cardiofacial, or conotruncal anomaly unusual face syndrome. These syndromes result from a large deletion at chromosome 22q11. VCFS is inherited in only about 10 percent to 15 percent of cases, however, in most instances, neither parent has the syndrome or carries the defective gene, and the cause of the deletion in the affected child is unknown. NIDCD-supported scientists have completed a detailed sequence analysis of the DiGeorge chromosomal region (DGCR) of chromosome 22q11. The 22q11.2 deletion occurs more frequently than originally anticipated, and the endpoints of the deletions occur in clusters. There is considerable variability in the abnormalities associated with deletions of similar size. The presence of a deletion is not always sufficient to cause cleft palate, strongly suggesting that modifier genes interact with the genes of the deletion region. Recent research has shown that the Clathrin heavy chain-like gene is a strong candidate gene for VCFS.

Rare Disease-Specific Conferences, Symposia, and Meetings

On June 16-17, 2003, the NIDCD conducted a workshop on *"Neurological Motor Speech Disorders in Adults: Research Needs and Opportunities,"* to discuss neuroimaging in speech production disorders, central neural control of speech production, and how speech can be better assessed in neurological disease. The NIH Office of Rare co-sponsored the workshop.

NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH (NIDCR)

Overview of Rare Diseases Research Activities

The mission of the National Institute of Dental and Craniofacial Research is to improve oral, dental, and craniofacial health through research, research training, and the dissemination of health information. NIDCR's programs encompass basic, translational, and clinical studies of the broad range of diseases, disorders, conditions, and syndromes involving the oral cavity and craniofacial structures. NIDCR's section of this report highlights selected scientific advances within the Institute's intramural and extramural programs and other related program activities relevant to rare diseases that fall within NIDCR's mission.

Recent Scientific Advances in Rare Diseases Research

Amelogenesis and Dentinogenesis Imperfecta

Amelogenesis Imperfecta (AI) and Dentinogenesis Imperfecta (DI) are the most common hereditary diseases affecting tooth enamel and dentin, respectively. A lack of suitable animal models in the past has hampered detailed studies of the molecular mechanisms leading to defects in enamel and dentin formation. A team led by NIDCR researchers has been able to disrupt the amelogenin gene to generate an AI mouse model. These mice display tooth defects similar to AI patients, including enamel discoloration, hypoplasia, and attrition. Genetically altered mice in which the dentin sialophosphoprotein gene has been disrupted, mimic the DI phenotype and display abnormally thin and defective dentin. Both of these mouse models are being further characterized to determine the function of these tooth specific genes.

Cleft Lip/Cleft Palate

Scientists have discovered the gene that causes Van der Woude syndrome, the most common of the syndromic forms of cleft lip and palate. The term "syndromic" means babies are born with cleft lip and palate, in addition to other birth defects. The discovery could very possibly direct them to genes involved in "nonsyndromic" cleft lip and palate. The gene, called IRF6, seems to play a key role in the normal formation of the lips, palate, skin, and genitalia. Further study of the gene should provide precise molecular clues into normal human development and suggest specific biological strategies to prevent birth defects, such as cleft lip and palate. Children with the syndrome are born with any of four characteristic birth defects: pits, or small indentations, in the lower lip, cleft lip, cleft palate, and undeveloped tooth buds.

Craniosynostosis

Growth and expansion of the brain continues well into postnatal life and requires growth of the overlying calvarial bones of the skull. Premature fusion of the cranial sutures, or craniosynostosis, impedes this growth and results in an abnormal shape of the skull and defects such as blindness and mental retardation. Gain-of-function mutations in fibroblast growth factor receptors (*fgfr*) have been associated with several syndromic forms of craniosynostosis. An NIDCR-supported team of investigators has demonstrated that *noggin*, an antagonist of bone

morphogenetic proteins, is expressed in the suture mesenchyme of patent, but not fusing, cranial sutures. *Noggin* misexpression prevents cranial suture fusion both in vitro and in vivo. This research suggests that syndromic *fgfr*-mediated craniosynostosis may be the result of inappropriate down regulation of *noggin* expression. Since *noggin* expression prevents the fusion of cranial sutures, it may provide a therapeutic intervention to mediate syndromic disorders of skull fusion.

Dyssegmental Dysplasia--Silverman-Handmaker Type

Dyssegmental dysplasia, Silverman-Handmaker type (DDSH) is a rare autosomal recessive skeletal dysplasia characterized by abnormally shaped vertebral bodies and short limbs. Individuals with DDSH also have a flat face, abnormally small jaws, cleft palate, and reduced joint mobility. NIDCR researchers and collaborators have identified mutations of the perlecan gene (*HSPG2*) in patients with DDSH and demonstrated that DDSH is caused by functional null mutations of the perlecan gene similar to the perlecan gene knockout mice. These results indicate that perlecan is essential for cartilage development. Future work will examine the role of perlecan in cartilage development by identifying more mutations of DDSH and animal models.

Fabry Disease

Fabry disease is a familial sex-liked disorder of lipid metabolism in which glycolipid accumulates in many tissues. NIDCR researchers previously had generated a Fabry mouse model by disrupting alpha-galactosidase a gene in the mouse genome. These mice show a subclinical Fabry phenotype-accumulation of uncatabolized lipid substrates in the target organs. Since a significant number of Fabry patients complain of dry mouth syndrome, scientists have begun to analyze the condition of teeth and salivary glands in these mice.

Growth Hormone (GHD) Deficiency (Adult)

GHD is a disorder with a prevalence of approximately 1/10,000. The most common etiology is frank pituitary disease, often the presence of nonfunctional pituitary adenomas, or as a result of surgery or radiotherapy for pituitary adenomas. NIDCR scientists recently submitted a proposal to the FDA for a clinical study based on the hypothesis that a replication deficient recombinant serotype 5 adenovirus (Ad5) vector is capable of safely transferring the normal human growth hormone (hGH) gene to adult patients with GHD, resulting in transiently elevated serum levels of normal hGH after oral administration of Plaquenil. The targeted tissue site for this Ad5 vector is a single parotid gland. The proposed Phase 1 / 2 study evaluates safety using conventional clinical and immunological parameters and efficacy using levels of insulin-like growth factor-I in serum.

Kaposi Sarcoma

Kaposi Sarcoma (KS) is the most common cancer arising in HIV-infected patients and the most frequent oral neoplasm in immunosuppressed patients. It affects, among other sites in the body, the oral cavity and salivary glands. The Kaposi Sarcoma Associated Herpes virus (KSHV; HHV-8) has been recently identified as the infectious cause of Kaposi Sarcoma. Compelling

evidence now supports a critical role for the oral cavity as the primary source of infectious HHV-8 in both immunocompetent and immunosuppressed patients.

- The molecular characterization of the KSHV genome has revealed the presence of numerous potential oncogenes. Scientists at the NIDCR have developed a novel transgenic animal model enabling endothelial cell-specific retroviral infection *in vivo* using candidate KSHV oncogenes. One gene, v*GPCR,* was sufficient to induce angioproliferative tumors that strikingly resemble human KS, and provided evidence suggesting a critical role for *vGPCR* in initiating KS tumor development. As this gene encodes a cell surface receptor, this research may lead to the development of novel therapies against this AIDS-associated malignancy.

- NIDCR supported scientists are using sophisticated molecular biology systems to detect the virus associated with Kaposi sarcoma. The techniques allow the investigators to identify virus particles and virus specific nucleic acids that cannot be routinely detected by conventional laboratory techniques and are frequently missed in clinical laboratories. They are currently collecting samples from high-risk susceptible individuals to validate their novel approaches. Other studies are looking at the mechanisms by which HHV-8 manipulates genetic expression of cellular factors and cell signaling networks to induce this kind of cancer.

Localized Juvenile Periodontitis

Localized juvenile periodontitis (LJP, also called early onset periodontitis, EOP) is a rare but aggressive infection of the gingiva that can lead to bone destruction and loss of teeth in young adults. Researchers supported by NIDCR have developed a new assay to identify unique antigens associated with a bacterium, called Aa, that may cause LJP. The technique uses information about antibodies produced to unique antigens that are only expressed when the bacterium is grown in the host. This may provide important information about the critical immune responses that either prevent or enhance the oral pathology seen in LJP patients.

McCune-Albright Syndrome and Fibrous Dysplasia of Bone

The McCune-Albright syndrome is defined by the triad of fibrous dysplasia of bone (FD), café-au-lait skin spots, and endocrine gland hyperfunction. Some patients may have only a single focus of bone affected, and others may have severe disease affecting multiple endocrine glands and virtually the entire skeleton. Previous studies have indicated that FD is the functional outcome of the mutation on skeletal stem cells that are present in bone marrow. NIDCR scientists have underway five clinical research protocols studying various aspects of the disease, ranging from a study of the natural history of the disease, to treatment studies for the bone and endocrine disorders. The molecular and cellular defects underlying the observation of impaired mineralization have been identified as an excess of the newly identified phosphaturic hormone FGF-23, as well as the response of the abnormal FD cells to alterations in the mineral and hormonal milieu. Ongoing clinical drug trials are likely to improve care for patients with this rare disease.

Noma

Noma is a highly lethal orofacial infection of severely malnourished children. NIDCR funded researchers at Forsyth Institute in Boston are using sophisticated microbial detection systems to identify the bacteria associated with Noma. The techniques allow the investigators to identify bacteria that cannot be routinely cultured and, thus, are frequently missed in clinical laboratories. The collection of clinical materials is underway in Nigeria with the aid of researchers in that country. An emphasis has been placed on trying to identify the microorganisms associated with the earliest stages of disease in hopes that prevention, diagnosis, and treatment can be advanced**.**

Squamous Cell Carcinomas of the Head and Neck

Squamous cell carcinomas of the head and neck, which include oral squamous cell carcinomas result in approximately 11,000 deaths per year in the U.S. Although the incidence is rare compared to other cancers, these cancers remain among the most fatal and morbid of malignancies of any anatomic site.

- NIDCR has established a research program to identify the nature of the genes expressed during oral cancer development. Using laser capture microdissection techniques to isolate normal and cancerous cells, and techniques to extract, amplify, and label their messenger RNAs for the subsequent hybridization to gene arrays, it is now possible for researchers to identify genes that are differentially expressed between normal and tumor tissues. These efforts, together with other multi-institutional genomic and proteomic initiatives are expected to contribute to the understanding of the molecular pathogenesis of oral cancer, thus helping to identify new markers for early detection and novel targets for drug therapy.

- Oral squamous cell carcinoma (OSCC) invasion and metastasis occur through a discrete set of signals between the tumor and stromal cells. A group of scientists funded by NIDCR have analyzed the signaling pathway of integrin αvβ6 in OSCC cells. They showed that αvβ6 receptor complex associates with Fyn, a member of the Src family kinases. This binding further activates certain pathways that directly result in matrix metalloproteinase-3 (MMP-3) gene activation, which in turn, results in ECM component degradation, further promoting cell migration. These data suggest that signaling molecules such as Fyn and MMP-3 may serve as potential therapeutic targets for prevention of the OSCC metastatic phenotype.

- One of the applications of cancer biomarkers is to assess and monitor cancer progression and to predict a tumor's biological behavior and responsiveness to treatment. Researchers supported by NIDCR are using gene expression profiling in search of biomarkers that can be linked to a specific phenotype required for head and neck cancer progression. In doing so, they identified plasminogen activator inhibitor 2 (PAI-2), a gene whose expression is linked to inhibition of extracellular matrix degradation and tumor cell invasion, which may be useful as a biomarker to predict the progression to invasive head and neck cancer.

- NIDCR researchers have engineered a mouse model lacking TGF-ß receptor expression. The mouse displays a novel phenotype that results in squamous cell carcinomas in the head

and neck region as well as in the distal colorectal area. By six months of age, more than 30 percent of the mice exhibit tumor growth. Interestingly, one out of three tumor bearing mice also show increased expression of interleukin (IL)-13receptor. These tumors were successfully transplanted into recipient nude mice. Currently, the molecular pathology underlying the tumor formation is under investigation.

- Human papillomaviruses (HPVs) have been established as a risk factor for oral and pharyngeal cancers; however, it is unclear whether this viral infection affects survival from head and neck malignancies. NIDCR-funded investigators have detected HPVs in 21 percent of tumors among 139 newly diagnosed cases of oral cancers. HPV infected patients were found to have slightly better overall survival than those with HPV-negative tumors. There was an interaction between gender and HPV overall and disease-specific survival that suggested that HPV infected males had better prognosis than HPV-negative males; the same relationship was not found among females. This finding suggests the need to further study the relation of HPV infection and gender on survival.

- Many pre-cancers do not progress to advanced stage, suggesting that host factors, such as the immune system, can interfere with this progression. Attempts to develop immunotherapy for cancer patients are currently in progress and appear promising. NIDCR-funded researchers are using novel vaccination strategies for human oral cancer. One of the vaccine strategies involves transferring of DNA from cancer cells into a highly immunogenic cell line in which genes specifying tumor associated antigens are expressed. In other vaccine approaches, researchers are determining the relevance of antigen presenting cells such as dendritic cells (DC) in the induction of anticancer activity that may lead to the development of potent DC-based vaccines and therapy for head and neck cancer.

Temporomandibular Muscle and Joint Disorders

Temporomandibular muscle and joint disorders (TMJDs) are a group of conditions causing pain and dysfunction in the temporomandibular joint and surrounding muscles. While there are no firm data on how many people are affected by TMJDs, orofacial pain, by itself or as a symptom of an untreated oral problem, is a major cause of poor quality of life. There is tremendous variability in how people respond to pain. One of the many possible explanations is the subtle variation written into genes encoding proteins that process pain signals. An excellent example is the COMT gene, which produces a substance that metabolizes catecholamines, a modulator of certain nerve chemicals that signal pain. NIDCR supported researchers have found that a subtle variation of the COMT gene influences how people respond to masseter muscle pain. They also showed that the gene might underlie individual differences in adaptability or tolerance to pain. Such detailed information is critical to design targeted drugs to help people efficiently manage pain and their susceptibility to it.

Trigeminal Neuralgia

A variety of rare diseases produce the symptom of pain, which can be chronic and frequently is intractable to conventional medicinal and interventional therapies. These include trigeminal

neuralgia and other neuropathic pain conditions, and severe, refractory cancer pain seen with advanced disease. In many cases, the mechanisms underlying these conditions are not well understood nor are new, highly effective treatments available. Using animal models, NIDCR researchers demonstrated that an ultra-potent analog of capsaicin (an active ingredient in hot chili pepper) called resiniferatoxin (RTX) results in literally killing the pain neurons rendering the animal analgesic to inflammatory pain but still sensitive to warm and very hot temperatures and mechanical pinch. The NIDCR research team showed that application of RTX into the trigeminal ganglion or cerebrospinal fluid around the spinal ganglion blocked experimental pain in rodents and naturally occurring arthritic pain and cancer pain in veterinary canine patients. The effect required only one application and was permanent. These studies form the basis for use in humans, preparations for which are a current focus of attention.

Rare Diseases Program Activities

- In response to the Request for Applications (RFA) titled *Pathobiology of Temporomandibular Joint Disorders,* the NIDCR funded 10 new grants in FY 2003 that will explore the etiology and pathology of TMJ Disorders. These include studies on TMJ tissue inflammation and inflammatory cytokines, abnormal biomechanics of the TMJ, central plasticity in nociceptive pathways, and the role of genotype in the susceptibility to TMJ Disorders.

- During FY 2003, NIDCR released two RFAs related to head and neck cancer. The first RFA invites applications to design, implement and evaluate interventions based on a needs assessment regarding oral cancer. The needs assessment can include: (a) the level of oral cancer within the state; (b) the level of public and health professional knowledge of oral cancer risk factors; (c) diagnostic practices; and (d) whether adults are receiving an oral cancer examination/screening annually. Based on the findings from the needs assessment, applicants will design, implement, and evaluate interventions to raise awareness about risk factors and to promote the early detection of oral cancers. The second RFA invites applications that foster basic and translational research aimed at deciphering the complex molecular networks involved in the development of squamous cell carcinomas of the head and neck.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES (NIDDK)

Overview of Rare Diseases Research Activities

The National Institute of Diabetes and Digestive and Kidney Diseases supports research on many rare diseases. Although diseases such as type 1 diabetes and type 2 diabetes are not rare, there are rare single gene defects that cause diabetes such as Maturity Onset Diabetes of the Young (MODY) and lipodystrophy. In addition, the NIDDK supports research on both common and rare causes of kidney and liver diseases. Every year, 20,000 babies are born with kidney problems, 2,000 of which will die and 1,000 will begin treatment for renal failure. The Institute also supports research on genetic metabolic diseases such as cystic fibrosis and Alagille syndrome; lysosomal storage diseases, including Niemann-Pick disease and mucopolysaccharidoses; disorders of copper transport, including Menkes and Wilson disease; and hematologic diseases such as Cooley's anemia and sickle cell disease.

Recent Scientific Advances in Rare Diseases Research

Cystic Fibrosis (CF)

Cystic fibrosis is the most common fatal genetic disease in Caucasians, affecting approximately one in 3,000 newborns. Patients are diagnosed in early childhood due to symptoms of the disease such as failure to thrive. With management of the nutritional problems and infections, the life expectance for CF has been increased to 30 years. Newborn screening for CF has been conducted as a pilot study in several states in the U.S. as well as in Australia and several European countries. Based of the experiences from these studies, including a randomized control screening project in the state of Wisconsin supported for the last 20 years by the NIDDK, a CDC convened panel has found the evidence for newborn screening compelling. Early diagnosis will be particularly important as new methods to treat the pathology of CF are identified. Since the cloning of the CF gene and identification of its protein product, CFTR, as a cAMP-regulated chloride channel, there has been impressive progress in the molecular understanding of this disorder. The most common defect in the CFTR gene is the deletion of the codon for the amino acid, phenylalanine, at position 508. This defective protein is not folded correctly and is retained in the ER rather than exported to the cell membrane. This year several compounds have been identified that appear to increase the ability of mutant CFTR to traffic to the cell surface in cultured cells. These molecules could be a potential treatment for many patients with CF.

Mucopolysaccharidosis (MPS)

Mucopolysaccharidosis are a group of disorders that result from a defect in enzymes needed to degrade mucopolysaccharides. These undegraded molecules become trapped in the lysosomes of the cell. Years of basic science research, much of it conducted in the NIDDK intramural program, has lead to the first treatment available for MPS. Genzyme has introduced Aldurazyme, an enzyme replacement therapy (ERT) for MPSI, which is given intravenously every week. The treatment reduces storage of mucopolysaccharides in the peripheral organs,

including the liver, spleen, and joints. Recently the gene for multiple sulfatase deficiency, a disorder which includes five types of MPS, has been identified. This gene is responsible for activation of sulfatase enzymes and may help in the ability to produce large amounts of active MPS enzymes for ERT. Several groups have studied the use of gene therapy to introduce a corrected copy of the mutated gene. Recently, retroviral gene therapy used to introduce the gene for the enzyme beta-glucuronidase into the liver of the dog model of MSPVII has shown a dramatic improvement. A single administration of vector has resulted in long-term correction of many problems of this disorder, including clearing storage from the liver and spleen and improvement of the bone disease. However, both the ERT and systemic gene therapy do little to get enzyme into the brain. Researchers are investigating methods to allow genes or enzymes to penetrate the blood-brain barrier. NIDDK-supported researchers used mannitol to open the blood-brain barrier and allow a new self-complementary AAV vector to penetrate the brain. They have shown global distribution of a marker gene in the mouse. These encouraging studies are the first steps to developing a treatment for the forms of mucopolysaccharidosis that include significant brain pathology.

Niemann-Pick Disease Type C (NPC)

Niemann-Pick disease type C (NPC) is an autosomal recessive lipid storage disorder characterized by progressive deterioration of the central nervous system resulting in death in early childhood. This disorder affects an estimated 500 children in the U.S. The disease is autosomal recessive and is inherited when a child receives two mutant genes, one from each parent. In NPC, cholesterol derived from low-density lipoprotein accumulates in cells of the brain, liver, spleen, lungs, and bone marrow. This leads to an enlarged spleen and liver, poor muscle control, impaired eye movements, slurred speech, and dementia. Two recent studies have identified molecules that decrease the cholesterol accumulation in cultured cells from NPC patients. One group of investigators has developed a high throughput screening assay for compounds that induce cholesterol transport. Using this screening assay, they have identified a molecule, NP-27, that stimulates cholesterol transport and LDL stimulation of cholesterol esterification in NPC cells. Another research group has studied the relationship between the NPC proteins and the sterol regulatory machinery. They discovered that NPC mutants cannot synthesize oxysterols and that treatment of NPC cells with oxysterols reduces cholesterol accumulation. These two studies provide new clues for the development of drugs to treat NPC.

Alagille Syndrome

Alagille syndrome is an autosomal dominant disorder that is characterized by liver disease, cardiac disease, and ocular, skeletal, and facial abnormalities. Alagille syndrome is caused by mutations of Jagged 1 gene which encodes a ligand in the Notch signaling pathway. Researchers have studies relatives of patients who also have mutations in JAG1 to see if there is a relationship between the genetic mutation and the severity of the disease. Twenty-five percent of these relatives with the same JAG1 mutations as the patients did not meet the diagnostic criteria for Alagille syndrome. The frequency of cardiac and liver disease was lower in the relatives with mutations. This study shows that factors other than mutations in the JAG1 gene are responsible for the variable clinical symptoms. Researchers also studied a missense mutation at G274D, which has been found in 13 individuals in a pedigree exhibiting cardiac disease in the

absence of liver disease. This mutation result in abnormal glycosylation of the JAG1 protein and reduced trafficking to the cell surface. The cardiac-specific phenotype associated with this mutation suggests that the developing heart is more sensitive than the liver to reduced JAG1 at the cell surface.

Rare Diseases Research Initiatives

NIDDK joined with ORD and NCRR as well as other ICs to sponsor the RFA, RR-03-008, for the Rare Disease Clinical Research Network. Each of these Centers coordinate research on a group of related rare disorders. NIDDK was able to co-fund the Center proposing to study Urea Cycle Disorders, a group of rare genetic metabolic diseases that leads to life-threatening episodes of acute hyperammonemia.

The NIDDK is collaborating with the VA on a study to test if intensive renal support in critically ill patients with acute renal failure will decrease mortality as compared to conventional management strategies. Patients will receive intermittent dialysis if hemodynamically stable; more critically ill patients will receive continuous renal replacement. The study will enroll 1,164 patients over 3 years. Patients will be recruited at 16 Veterans Affairs sites and 9 NIDDK sites.

The Division of Digestive Diseases and Nutrition, NIDDK has just funded a cooperative agreement titled, "Peginterferon and Ribavirin for Pediatric Patients with Chronic Hepatitis C (Peds-C)." Peds-C is a prospective, randomized controlled trial of peginterferon therapy with or without ribavirin in children with chronic hepatitis C. Eleven clinical centers with expertise in pediatric liver disease and hepatitis C and a central coordinating center will conduct a prospective trial of antiviral therapy in children with chronic hepatitis C. Approximately 120 children will be randomly assigned to receive peginterferon alfa-2a alone or peginterferon with ribavirin for 48 weeks. Children will be carefully monitored for serum markers of liver disease and hepatitis C virus levels as well as side effects of therapy, growth and development, and quality of life. A long-term follow up study is planned. Children will undergo liver biopsy before initiating therapy. Samples of blood, genomic DNA, and liver tissue will be stored in a central repository. The final protocol is expected to be available by early 2004 and children enrolled by mid 2004. The study is being co-funded by the Food and Drug Administration's Office of Orphan Products Development and has considerable industry support.

In 2003, the NIDDK issued a Request for Application titled "Genetic Modifiers of Mendelian Diseases of Interest to NIDDK" for research applications to identify and characterize genetic modifiers for Mendelian diseases. Striking variations are seen in clinical expression of genetic diseases, presumably due to differences in the genetic makeup and environmental exposure of the individual. Even though a mutation in a single gene may play a predominant role in the development of a Mendelian disorder, individuals with identical genotypes at that locus may display considerable variation in the prevalence, severity, and clinical symptoms of the disorder. To understand this variation and to exploit it as a target for therapy, it is important to identify genes or other factors that contribute to this variation. The NIDDK was able to fund eight applications in response to this RFA. These applications included studies on cystic fibrosis, hemochromatosis, polycystic kidney disease, Alagille syndrome, and tuberous sclerosis syndrome.

Rare Diseases-Related Program Activities

On September 13 -15, 2003, the NIDDK, NCI and ORD co-sponsored *The Sixth International Workshop on Resistance to Thyroid Hormone* at Ocean Point Resort and Club in Miami Beach, Florida. The conference was cosponsored by the Interthyr Research Foundation, Abbott Pharmaceuticals, and Quest Diagnostics. The chairmen of the organizing Committee were Paul M. Yen, M.D., NIDDK, and Sheue-Yann Cheng, Ph.D., National Cancer Institute. Other members of the international organizing Committee were Paolo Beck-Peccoz, M.D., University of Milan, Italy; Geraldo Medeiros-Neto, M.D., Sao Paolo, Brazil; Yoshiharu Murata, M.D., Ph.D., Nagoya University, Nagoya, Japan; Samuel Refetoff, University of Chicago, Chicago, IL; and Roy Weiss, M.D., Ph.D., University of Chicago, Chicago, IL. A total of 29 lectures were given by senior and junior investigators and covered the following topics: clinical aspects of RTH: thyroid hormone receptor (TR)-structure and genomics; modulators of TR actions by co-regulators/chromatin structure; animal models of RTH and development; and TR effects in specific tissues. Additionally, 16 posters were presented. Approximately 80 investigators, clinicians, and trainees from the U.S., Canada, South America, Europe, and Japan attended the workshop. The workshop featured much new research that was unpublished. Several especially noteworthy reports were of mutations in a thyroid hormone transporter that could cause a RTH and neurological dysfunction by Theo Visser, Erasmus University, Rotterdam, Holland; natural thyroid hormone analogs that had non-genomic effects by Thomas Scanlan, University of California, San Francisco, San Francisco, CA; and a knock-in mouse model of a TR mutation that cannot bind DNA to probe non-DNA-binding functions of TR by Frederic Wondisford, University of Chicago, Chicago, IL. These and other talks provided new insights into thyroid hormone action and the syndrome of RTH. At the adjournment of the workshop, participants agreed to meet again in 2 years time in Lyon, France.

On January 13-14, 2003, the NIDDK, ORD and the Crohn's and Colitis Foundation sponsored a workshop on the *"Conduct of Clinical Trials for Crohn's Disease."* Crohn's disease has many different manifestations and variable responses to existing medical and surgical therapies, resulting in a continued search for new and improved therapies. Fortunately, new research advances have led to the development of many novel therapies which have the potential for improving the life of patients with Crohn's disease. However, rapid translation of research advances from the bench to the bedside may be hampered by the lack of accepted guidelines on the design of clinical trials in this complex disease. To address this problem, multiple working groups, each composed of an international group of experts, have addressed many of the specific problems of clinical trial design. Among the many issues analyzed by these working groups are specific definitions, measurement instruments, clinically relevant outcomes, duration of therapy, unique issues of design and data interpretation, specific problems in pediatric investigation, current ethical and safety requirements, and gaps in present knowledge that present new research opportunities. The specific purpose of this meeting was for the working groups to present their reports for public discussion. A final report is being developed and will be made available on the NIDDK website.

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

Overview of Rare Diseases Research Activities

The National Institute on Drug Abuse (NIDA) provides national leadership and conducts and supports biomedical and behavioral research, health services research, research training, and health information dissemination with respect to the prevention of drug abuse and treatment of drug abusers. NIDA plans, conducts, fosters, and supports a comprehensive program of research and research training relating to the causes, prevention, treatment, patterns, and consequences of drug abuse and addiction through research performed in its own laboratories and through contracts and grants to scientific institutions and to individuals. NIDA supports training in fundamental sciences and clinical disciplines relating to drug abuse by individual and institutional research training awards and coordinates with other research institutes and with other federal health and other agencies on activities relevant to drug abuse and addiction. NIDA conducts and fosters health information dissemination activities, including the collection and dissemination of research findings and related educational materials for health professionals, educators, and the lay public. In addition, NIDA coordinates with institutions and professional associations and with international, national, state, and voluntary agencies working in these areas, including collaboration with the Substance Abuse and Mental Health Services Administration (SAMHSA) on services research issues as well as on other programmatic issues.

Incidence and prevalence figures for dependence on controlled substances (not alcohol or nicotine) are always difficult to estimate, as they vary from type of drug, community, and supply availability (generally a function of supply interdiction/law enforcement). Unlike other disease conditions, illicit marketers have a reason (profit) to introduce and infect the population with abusable and/or dependence producing substances. Illicit drugs utilized in some communities are not always available or in vogue in other communities. Thus, there may be various drug dependence indications that, in and of themselves, may affect less than 200,000 persons in the United States (U.S.). It is very clear, however, that abuse of opiates such as heroin and other narcotics exceeds 1 million persons and stimulants such as cocaine and "crack cocaine" exceeds 2 million are endemic in the U.S. (The White House Office of National Drug Control Policy). Even the lowest estimates from any source put dependence levels of these substances at figures well above the 200,000 threshold generally used for defining orphan products. The total disease burden of drug abuse and addiction in the U.S. has been estimated to exceed $160 billion per year.

Additionally, injection drug use and sexual contact among users is a highly correlated vector in the spread of HIV, hepatitis, and tuberculosis. This creates a public health problem of enormous magnitude. However, it is a historical fact that drug addiction is treated as an orphan disease or at least an area of low return on investment by the pharmaceutical industry.

Despite the enormous public health burden of this disease state, there exists little or no incentive for pharmaceutical companies to pursue research and development of new treatment medications for this population. Although total numbers of persons afflicted may seem sufficient in the aggregate, unlike other disease states, many of these persons are not treatment seeking upon diagnosis. Therefore, the actual population who may be a potential market for a medication is

actually less than the total number who could benefit. Additionally, many of these persons will be treated in publicly funded clinics where companies perceive reimbursement as modest or inadequate and perhaps subject to artificial cost controls. Finally, much of the treatment system existing in the U.S. is based on nonpharmacological treatment modalities.

A further complication is that some treatment agents may themselves be abusable and will be strictly controlled (witness methadone, classified as a Schedule II controlled substance for use in opiate maintenance therapy—some 900 U.S. clinics are licensed to dispense methadone and serve approximately 190,000 persons per year with a pharmaceutical market value of approximately $30 million per year). This is simply not an attractive market to most manufacturers based on projected return on investment when compared to nearly any other indication they could pursue. Each of these points is well documented in the Institute of Medicine (*Report on the Development of Medications for the Treatment of Opiate and Cocaine Addiction, 1995*) and are well known to the pharmaceutical and market research industries. Therefore, while de jure opiate and cocaine dependence do not fit the definition of orphan products, de facto they certainly do. As an instructive example, consider the development and approval of levomethadyl acetate hydrochloride (trade name ORLAAM), an alternative to methadone. Despite the fact that human data on 6,000 subjects from government-sponsored studies was available for ORLAAM, despite the fact that the compound was off-patent, and despite the fact that the government had a large supply of the compound available for anyone interested in obtaining a New Drug Application (NDA), no private sector entity attempted to finish the development of this compound until NIDA paid a contractor to do so. Similarly, the development of naltrexone was largely a NIDA-funded effort. Therefore, these products should be viewed as entirely "orphan-like" insofar as their ability to attract private sector sponsors.

Due to the lack of pharmaceutical industry interest in developing new medications to treat addiction to controlled substances, NIDA has been substantially involved in the development of nearly all such medications since the Institute's inception in 1972.

History of Rare Diseases Research

Currently there are four medications for the treatment of opiate addiction that have received orphan product designation. Each of these products was developed with substantial involvement by NIDA. These drugs are ORLAAM, naltrexone, buprenorphine, and buprenorphine combined with naloxone. ORLAAM, an alternative to methadone used for opiate maintenance therapy, received NDA approval in 1993. Naltrexone, an opiate antagonist for use in detoxified patients, was approved in 1985. Currently, orphan exclusivity for ORLAAM and naltrexone has expired. Additionally, ORLAAM's distributor has notified physicians that it will discontinue distribution of the product in 2004, due to poor sales in the U.S. and its withdrawal from European markets. ORLAAM's orphan product designation expired in 2000 and thus there is no legal requirement for a manufacturer to maintain the product in the U.S. market.

The opiate partial agonist buprenorphine and a combination of buprenorphine plus naloxone have also received orphan designation (see details below) and were approved for marketing in the U.S. on October 8, 2003. These products represent a major success as the FDA designated them both as orphan products. Buprenorphine became the first product to receive an orphan

designation based on an economic, rather than a population-based rationale (i.e., the product would not recoup their developmental expenses in 7 years of exclusivity in the U.S. market).

Recent Scientific Advances in Rare Diseases Research

The discovery of opiate receptors by NIDA-funded scientists in the 1970s opened a new era of neurobiological research that is ongoing today. Scientists continue to map brain receptor system types and subtypes, continuously gaining understanding of their structure and function. This information will allow the design of interventions (behavioral, chemical, and genetic) that may be useful in the treatment of a huge number of disorders of mankind, all of which are mediated in the brain.

A generation of research has shown that drug addiction is a complex biomedical and behavioral disease that has its roots in those parts of the brain that underlie, mediate, and allow us to have the emotions that make us human. Just as we have learned that depression is a brain disease that can be treated with medicine, so too have we learned that drug addiction is a brain disease that can and often should be treated with medicine.

The role of a medication is to reestablish normality to brain function and behavior so that the addicted patient has the opportunity for rehabilitation through counseling, psychotherapy, vocational training, and other therapeutic services. While the mechanisms of many central nervous system disorders are still to be elucidated, scientists working in the field of drug abuse have now identified and cloned the putative site of action in the brain for every major drug of abuse. Thus, the potential to develop new treatments is enormous. For example, having cloned the dopamine transporter mechanism where cocaine exerts its action, NIDA scientists are now designing molecules that will block cocaine's effects at this site without disrupting essential neurotransmitter functions of dopamine.

Rare Diseases Research Initiatives

As described in the history section above, NIDA considers medications for the treatment of dependence on controlled substances to be de facto orphans. Thus, the development of medications for the treatment of these conditions may well be considered as rare disease research within the context of an urgent public health need with a wholly inadequate private sector response. Therefore, NIDA's medications development program effort may (until facts prove otherwise) be considered as part of a rare disease research initiative.

In 1990, the Medications Development Division (MDD) was established in NIDA. In 1999, MDD became part of the Division of Treatment Research and Development (DTR&D). The functions of MDD within the new division remained the same; namely, DTR&D conducts studies necessary to identify, develop, and obtain FDA marketing approval for new medications for treatment of drug addiction and other brain and behavior disorders; develops and administers a national program of basic and clinical pharmacological research designed to develop innovative biological and pharmacological treatment approaches; supports training in fundamental sciences and clinical disciplines related to the pharmacotherapeutic treatment of drug abuse; collaborates with (a) the pharmaceutical and chemical industry in the U.S. and other

nations, and (b) the Federal medications development programs of other institutes and entities; and works closely with the FDA in assuring that research designed to show the clinical efficacy of new compounds is evaluated and approved in the most expeditious manner possible.

The Division operates within the larger context of a NIDA-wide Medications Development Program that incorporates basic research discoveries from other divisions (intramural and extramural) in the quest to develop new pharmacological treatments. Application of research results from the intramural and extramural community allows the Division to have access to the latest theoretical bases and an opportunity to test new hypotheses in controlled clinical settings. As physicians now have a choice of several different FDA-approved products for treating opiate addiction (methadone, buprenorphine, buprenorphine/naloxone, and naltrexone) and no FDA-approved products for treating addictions to stimulants (e.g., cocaine or methamphetamine), NIDA's efforts are currently shifting toward a greater emphasis on discovery and development of medications for treating stimulant dependence (cocaine, methamphetamine, nicotine), and, as of 2003, cannabis dependence. Clinical trials in this area have focused on medications that are already marketed for other indications, and substantial efforts are also being devoted to the discovery and development of novel compounds that may specifically address the problem of stimulant dependence through attempts to collaborate with the pharmaceutical industry. Efforts are also directed toward supporting, through grants and contracts, synthesis of novel compounds for screening and pharmacological testing.

Significant areas of research and development are summarized below:

1. Opiate Addiction Treatment

Buprenorphine/Buprenorphine-Naloxone Combination

A major milestone and achievement for NIDA's Medications Development Program and for Reckitt Benckiser Pharmaceuticals, Inc. (NIDA's collaborator in a Cooperative Research and Development Agreement) was the October 8, 2002, approval by the FDA for the marketing of two new products for the treatment of opiate addiction. These two new products, known under the trade names Subutex and Suboxone, represent new tools in the arsenal of anti-addiction medications. Both have been designated as orphans, based on the expectation that these products will not recoup their developmental expense during their period of U.S. marketing exclusivity. Marketing of these products began in January 2003, but are subject to certain restrictions imposed by U.S. law and regulations. Nevertheless, these products may, under the conditions specified in law and regulations, be prescribed in a variety of settings, including physician's offices.

Subutex and Suboxone now join methadone as medications that will be available for the treatment of heroin and other opiate addiction. They offer a broader array of options to physicians and patients, and should expand treatment availability.

These products represent the culmination of several years of research and development between NIDA and Reckitt Benckiser Pharmaceuticals, Inc. The unique pharmacology of Subutex (buprenorphine) and Suboxone (buprenorphine combined with naloxone) and

the statutory changes enacted by the Drug Addiction Treatment Act of 2000, as contained in P.L. 107-273, "The Children's Health Act of 2000," permits these products to be prescribed by appropriately trained physicians in settings other than the existing, but limited, Opiate Treatment Programs (OTPs). It is hoped that this will translate into an increase in treatment availability across the U.S. A wider dispersal of new treatment settings should follow the introduction of these products to the market. Additionally, patients who either have no OTP programs available, or who cannot avail themselves of these programs will have another option for treatment. As of the date of this report, SAMHSA reports that 3,188 physicians have taken the training required by law to prescribe these two medications and 2,170 have registered as potential providers.

Depot Naltrexone

Naltrexone, a marketed long-acting, orally effective opioid antagonist, was approved in 1983 for the indication of blocking the pharmacological effects of exogenously administered opiates. It is an adjunct to the maintenance of the opioid-free state in detoxified, formerly opioid-dependent individuals.

One of the major obstacles to the success of naltrexone has been patient compliance with therapy. Naltrexone must be taken at least 3 times per week and has no effect other than to block the effects of heroin, a drug that the patient is not supposed to use. Because of this, many patients forget to take or stop taking their medication. Therefore, the greatest success with naltrexone has been in the limited population of highly motivated formerly opiate-dependent patients.

During 1999, NIDA completed, via a Small Business Innovative Research (SBIR) grant to Biotek, Inc., the production and preclinical testing of a batch of 120 doses of depot naltrexone. These doses are designed to last 30 days when administered subcutaneously in humans and to produce a blood level of about 2-3 ng/ml (which will be relatively constant over this period). This product has been shown, in an inpatient clinical study, to block subjective responses to heroin challenges at 12-25 mg. This study was completed in 2000 and showed that it was possible to block 25 mg heroin challenges up to 5 weeks after depot injection. A 2-site outpatient double-blind study was designed to test the product in a real world setting. This outpatient study began in November 2000 and was completed in 2003. Results are pending publication.

Additionally, another investigational formulation of a sustained release formulation of naltrexone supplied by Alkermes, Inc. has undergone clinical trials at NIDA's Intramural Research Program. This study provided information on the safety and duration of effect of this potential treatment product. The oral form of naltrexone was approved in 1994 for the treatment of alcohol abuse; the depot preparation may also be of value for the treatment of that disease. Alkermes has reported that their dosage form of depot naltrexone reduces heavy drinking behavior in males (but not females) and that the company intends to pursue further development of their dosage form.

Thus, the feasibility of a sustained release formulation of naltrexone for the treatment of opiate and alcohol addiction is moving rapidly from concept and clinical testing toward potential regulatory approval and marketing.

2. Cocaine Addiction Treatment

Compounds in Advanced Clinical Testing

Several small studies of potential cocaine addiction treatment agents have been completed and are in various stages of data analysis. Clinically significant findings will be followed up in larger controlled trials as warranted.

Disulfiram

There is a growing body of evidence generated by NIDA grantees concerning the potential use of disulfiram in the treatment of cocaine dependence. Disulfiram (Antabuse), marketed as aversive therapy for treating alcoholism, is also showing promise in the treatment of cocaine dependence. Several NIDA sponsored studies conducted at Yale University documented interaction of disulfiram with cocaine in humans. Pharmacokinetics studies showed that disulfiram increases plasma concentrations of cocaine and potentiates physiological-cardiovascular responses to cocaine. Three efficacy trials conducted with different populations of cocaine-dependent individuals suggest that disulfiram in combination with each of three different therapeutic interventions (cognitive behavioral treatment, 12 step facilitation, or clinical management) might be effective in treating cocaine dependence. In cocaine-alcohol abusers disulfiram treatment showed sustained effect on reduced cocaine and alcohol use 1 year after cessation of the therapy. Disulfiram treatment of cocaine abusing opioid-dependent patients maintained on methadone resulted in significant decrease of the amount and frequency of cocaine use. A preliminary study showed that disulfiram also decreases cocaine use in cocaine-opioid dependent addicts maintained on buprenorphine.

NIDA is currently sponsoring three large outpatient clinical trials with disulfiram as the treatment for cocaine dependence: 1) study on 160 opioid-cocaine dependent patients maintained on methadone conducted at Yale University; 2) study on 180 opioid-cocaine dependent patients maintained on buprenorphine conducted at Yale University; and 3) study evaluating disulfiram and naltrexone alone and in combination in the treatment of 208 alcohol-cocaine dependent individuals conducted at the University of Pennsylvania. All these studies include some forms of behavioral or cognitive therapy and drug counseling. They are monitoring not only use of cocaine, but also opiates or alcohol. Finally, NIDA is planning a clinical pharmacology/safety study of the interactions between disulfiram and intravenous-administered cocaine, prior to launching large-scale phase III multi-center trial with this medication.

GBR 12909 (Vanoxerine)

Major neurochemical effects of cocaine include release of dopamine (DA), serotonin, and noradrenaline via a transporter mediated exchange mechanism. There is considerable evidence

that the initiation and continuation of cocaine use is associated with the effects of the drug on the dopaminergic, serotonergic, and noradrenergic modulation of the central nervous system (CNS) function. Animal studies suggest that the mesocorticolimbic dopaminergic pathways are important mediators of cocaine's reinforcing and addictive properties. Cocaine binds to these transporters and blocks the removal of these neurotransmitters from the synaptic gap. The neurobiological mechanisms underlying the effects of cocaine are not well understood. Preclinical studies indicate that cocaine's blockade of the DA transporter plays a key role in producing cocaine's addictive and reinforcing effects. Primate and nonprimate studies have shown that GBR 12909 has a strong affinity for the DA transporter. GBR 12909 is a high affinity, selective, and long-acting inhibitor of DA uptake that produces a persistent and noncompetitive blockade of DA transporters and substantially reduces cocaine-induced increases in extracellular mesolimbic DA. In addition, GBR 12909 has a higher affinity than cocaine for the DA transporter. Ongoing research is searching for a dopamine sparing cocaine antagonist that might be developed as a pharmacological treatment to block cocaine from acting at the transporter level to produce its reinforcing effects. GBR has been postulated to act by binding only to precise sites on the dopamine transporter that are required for cocaine binding and making available the sites where DA binds to the transporter.

A Phase I clinical study was conducted in support of an Investigational New Drug (IND) application filed by NIDA. The main objectives of this study were to determine the safety, tolerance, and pharmacokinetics of multiple escalating dosages of oral GBR 12909 in healthy volunteers. In addition, PET scans measuring the occupancy of the DA transporter by GBR 12909 were obtained. The occupancy scan results are being correlated with the safety data to determine an optimal oral dose of GBR 12909.

The study report from the Phase I (healthy volunteer) showed 30-40 percent dopamine transporter occupancy at the 100 mg dose level. Based on primate data showing equivalent levels of occupancy at doses reducing cocaine self-administration, this may be clinically meaningful in cocaine treatment. Consultants reviewed the study in October 2001. The consultants recommended a follow-up study in cocaine dependent patients to address the safety and other metabolic issues that were raised in the first study, in planning for a cocaine interaction study. Phase I studies in cocaine dependent subjects have begun.

Dopamine Agonists

The activation of the dopaminergic reward system in the brain appears to be the principal neurochemical mechanism involved in the addiction to stimulants such as cocaine and amphetamine. Chronic abuse of these drugs results in dopamine deficiency in the brain, which has been hypothesized to lead to craving for stimulants, depression, anhedonia, and dysphoria.

Most recently, studies in rodents, and to a lesser extent in monkeys, have differentiated the roles of D1 and D3 receptors with regard to cocaine. The D1 system may inhibit the effects of cocaine, while the D3 system may block conditioned cues. Compounds that affect both systems are under study.

Kappa Opioids

Recent studies have shown that kappa opioid compounds exhibit effects opposite to that of cocaine in terms of dopamine release and neuron firing patterns. In animal studies, kappa opioids block drug discrimination and self-administration of cocaine and also prevent context-independent sensitization to cocaine. NIDA and NIDA grantees are testing compounds of this class in clinical studies.

Glucocorticoid Antagonists

Studies have shown that cocaine causes the release of stress hormones known as glucocorticoids in both rats and humans. There is some evidence from rat studies that glucocorticoid antagonists and CRF antagonists reduce cocaine self-administration in a dose-related manner. NIDA will follow up on these basic research findings with additional studies aimed at developing a potential treatment for cocaine addiction. DTR&D is attempting to obtain CRF antagonist compounds from pharmaceutical company sources.

Immunology

During 1998, NIDA sponsored a meeting on the potential of utilizing peripheral blockers for prevention and treatment of cocaine addiction. The ability to block cocaine's entry into the brain or decrease its rate of entry (and thus attenuate the "high" produced) was discussed. Several approaches (active and passive immunization, catalytic antibodies) were actively explored. One of these theoretical constructs has now been translated into actual therapeutic entities that are currently at various stages of research and development as listed below.

Researchers funded by NIDA's DTR&D reported that they have successfully immunized rats against many of the stimulant effects of cocaine. Cocaine was prevented from entering the brain when rats were "vaccinated" with a substance that triggers the body to produce antibodies to cocaine. These antibodies then acted as biological "sponges" to which cocaine binds, thereby reducing the amount available in the blood to reach the brain. The results of this research are presented in "Suppression of Psychoactive Effects of Cocaine by Active Immunization" in the December 14, 1995, issue of *Nature*.

Researchers Kim Janda, Ph.D., Rocio Carrera, M.A., George Koob, Ph.D., and colleagues at The Scripps Research Institute demonstrated a greater than 70 percent reduction in cocaine uptake in the brains of rats inoculated with the antibody-producing compound as compared to a group which was not inoculated. Researchers designed the compound so that the antibodies produced would respond specifically to the cocaine molecule yet not affect normal brain chemistry.

In the study, Dr. Janda and colleagues used an "active immunization" approach by developing a substance that when administered to rats would trigger the immune system to produce antibodies that are specific for the cocaine molecule. The researchers inoculated the rats over a 35-day period and then tested their responses to cocaine. The immunized animals showed significantly lower responses to the stimulant effects of cocaine than control animals because the

immunization prevented much of the cocaine from getting to the brain. Cocaine concentrations in the brain tissue of the immunized animals were found to be dramatically less than the concentrations of cocaine in brain tissue of controls.

Other immunotherapy research for drug abuse treatment has explored the use of catalytic antibodies and other external agents that can be used to treat cocaine dependence. The research reported in *Nature* differs by inducing the production of antibodies that remain in the bloodstream for an extended period of time and block cocaine's effects after it is used.

Another vaccine, currently owned by Xenova, a United Kingdom company, links a protein to cocaine, resulting in a molecule that induces antibody formulation. Once titers reach a certain level, cocaine's ability to cross the blood brain barrier is impeded. NIDA has supported this research via a SPIRCAP grant and an SBIR grant. Thirty-four subjects completed the initial Phase I study in the U.S. Specific antibody titers for cocaine were developed in the vaccine-challenged subjects. Under the SPIRCAP award, two additional studies were funded (an inpatient study examining the extent to which the antibody can block the effects of administered cocaine and an outpatient study.) To date, no adverse events have been reported, and the company plans to continue development of the vaccine. A Phase II safety and immunogenicity study started in 2002.

Dr. Michael Owens, at the University of Arkansas for Medical Sciences in Little Rock, presently receives NIDA funding to develop a new generation of monoclonal antibody-based medications for treating drug abuse ("Immuno-Therapy for Drug Abuse" R01 DA07610, and "Antibody-Based Therapy for Methamphetamine Abuse" R01 DA11560). This research is focused on treatments for methamphetamine, ecstasy (MDMA), and phencyclidine (PCP) abuse. These medications function as pharmacokinetic antagonists and are designed to reverse the effects of drug overdose and/or help blunt the reinforcing effects of drugs of abuse. Because of the unique pharmacological profile of these new medications, they would be well suited for use with other more conventional chemically based medications and treatments, such as behavioral modification to aid in the long-term recovery from drug addiction.

Cocaine "Receptor": Imaging Studies

In addition to the categories of compounds being tested as described above, a new and potentially useful technology is being investigated as to its value for predicting efficacy of potential cocaine treatment medications. Research in the field of structure-activity relationships have revealed highly selective and potent binding ligands for the DA transporter. NIDA intramural researchers have identified three "generations" of such compounds, with each succeeding generation being more selective and potent than the previous one. RTI-55, the first potent compound, was shown to be an effective in vivo labeling agent in animal studies and was subsequently examined in human imaging studies by SPECT. A second compound, RTI-121, was found to be more selective for the DA transporter but had a higher apparent lipid solubility and exhibited lower specific to nonspecific binding in vivo. NIDA researchers are testing new compounds and are also utilizing some older compounds (e.g., WIN-35,428) in brain imaging studies. Procedures have been developed for estimating the occupancy of transporter sites in vivo. DA transporter imaging studies of cocaine abusers have been completed (see section on

GBR 12909). This technology may make it possible to estimate the effectiveness of a potential treatment compound or regimen by correlating receptor occupancy (as shown in imaging studies) with actual clinical results. NIDA will continue to follow this line of research.

Additionally, NIDA is participating in an effort with NIMH, NINDS, and NIAAA to develop appropriate imaging ligands that will be essential to the study of many brain and CNS conditions, as well as the effects of various treatments.

3. Methamphetamine Treatment Discovery Efforts and Program Activities

Methamphetamine is a potent psychomotor stimulant that has gone through episodic periods of widespread use and abuse in the U.S. Cocaine abuse and addiction surpassed use of methamphetamine in the 1970s and 1980s, but methamphetamine abuse and addiction has been reappearing in some regions of the U.S. and is widespread in Western U.S. cities such as San Francisco, Denver, Phoenix, and Los Angeles. In 1994, according to the National Household Survey on Drug Abuse, an estimated 3.8 million people had tried methamphetamine; and by 1999, the total number had increased to 9.4 million. The epidemic is spreading to rural areas, and nationwide there were approximately 11,000 acute hospital admissions related to amphetamine toxicity in 1999.

There are no accepted treatment medications for methamphetamine addiction or abuse. As a result, NIDA has developed a Medication Discovery Program for methamphetamine and is funding a number of extramural and intramural studies to develop medications to treat methamphetamine abuse.

Preclinical Methamphetamine Program

A Methamphetamine Think Tank meeting was held on January 10, 2000, in order to gather a group of consultants to consider the direction of a methamphetamine treatment development program. Based upon recommendations of these consultants, several types of methamphetamine-specific screening assays are being developed to evaluate and characterize compounds for their potential usefulness in the treatment of methamphetamine dependence. Some of the assays recommended are similar to those used in the Cocaine Treatment Discovery Program, and there will be substantial overlap between the two programs. Existing contract protocols are being used to test compounds for their interactions with dopamine transporters, but additional assays will be utilized to measure dopamine release in vitro, which is an effect of methamphetamine that is not shared by cocaine. In addition, behavioral assays are being set up to assess a compound's ability to block the locomotor stimulant effects of methamphetamine, to block the discriminative stimulus effects of methamphetamine, and to determine effects on methamphetamine self-administration. In addition, assays to measure effects of potential treatment compounds on the cardiovascular system, both alone and in combination with methamphetamine, are being developed. Finally, methods for assessing the neurotoxic effects of methamphetamine are under development, and these assays may be useful in assessment of potential treatment medications.

Clinical Methamphetamine Program

To implement the recommendations of the Methamphetamine Addiction Treatment Think Tank (MATTT) meeting held in January 2000, a process was started to establish a group of sites to conduct clinical trials for methamphetamine dependent patients. Six sites were selected where the epidemic is currently concentrated, two in the Midwest (Des Moines, IA and Kansas City, KS); the other four are Los Angeles and San Diego, CA, San Antonio, TX, and Honolulu, HI. Currently ondansetron, bupropion, and modafinil are in either Phase I or Phase II clinical trials at these sites. Plans are underway to obtain lobeline from a pharmaceutical manufacturer to study its safety profile with methamphetamine and, if warranted, advance it to outpatient studies.

In addition to the U.S., methamphetamine abuse and addiction is becoming an international problem. The Ministry of Public Health, Kingdom of Thailand, requested and received technical assistance from the NIDA Medications Development Program. Personnel from the MDP and UCLA have provided substantial amounts of time providing technical assistance to help the Government of Thailand prepare an infrastructure capable of undertaking research studies of methamphetamine dependence and psychosis.

4. Medications Development for Cannabis-Related Disorders

The treatment of cannabis-related disorders (CRDs) is an issue of great public health concern. Currently, marijuana is the most commonly used illicit drug in the U.S., with recent estimates from SAMHSA of 14.6 million users in the past month, and particularly heavy use occurring in adolescent populations (over 20 percent of all high school seniors). Approximately 2.4 million people use marijuana for the first time every year and 2/3 of them are between 12 and 17 years of age. In addition, of the 3.5 million people who met criteria for past-year cannabis abuse or dependence in 2001, more than 2/3 were between the ages of 12 and 25 years. An estimated 852,000 individuals reported marijuana as the specific substance for which they received their last or current treatment among persons who received treatments in the past year and approximately 1/2 of those individuals were 25 years old or younger.

Sufficient research has been carried out to confirm that the use of cannabis can produce serious physical and psychological consequences. The consequences of cannabis use may be due to the acute effects of the drug or due to the chronic exposure that may ultimately produce abuse or dependence. The use of a large amount in a short period of time may induce hallucinations, delirium, and other perceptual manifestations compatible with a psychotic episode. Chronic users of cannabis may experience difficulty in stopping or controlling drug use, develop tolerance to the subjective and cardiovascular effects, and eventually present withdrawal symptoms after sudden discontinuation of use.

Unfortunately, there is currently no effective pharmacological treatment for CRDs, and there is very limited research focused on the identification and development of medications to treat these disorders. Drug abuse treatment research as a whole has rarely focused on the treatment of CRDs. One indicator is the fact that there are no published randomized controlled clinical trials to evaluate pharmacotherapies for CRD as the primary outcome.

There are multiple reasons why it is timely to develop medications to treat CRDs. First, there are newly marketed medications available whose mechanisms of actions may have potential therapeutic effects on the clinical manifestations of CRD. Second, the recent discovery of an endogenous cannabinoid system with specific receptors and endogenous ligands, the availability of genetically engineered knockout mice that lack functional cannabinoid receptors to study genetic predispositions to the effects of cannabinoids, and the subsequent development of reliable preclinical models to study the rewarding and dependence-producing effects of THC, all provide understanding of the basic therapeutic mechanisms. Lastly, there is the discovery and development of new chemical entities, some of them already being investigated at the clinical level, which target the cannabinoid system and have the potential for therapeutic benefit. All these factors are setting the stage for the development of medications to treat CRDs.

New Request for Applications for Medications Development for Cannabis Related Disorders

Based on the needs as described above, NIDA has recently (December 1, 2003) published a Request for Application (RFA) with the goal of developing safe and effective medications for the treatment of CRDs. Studies may focus on the treatment of marijuana, hashish, or other cannabis derivatives. Medications studied under this RFA may aim to treat cannabis-use disorders, such as abuse and dependence, or cannabis-induced disorders, such as intoxication, delirium, psychosis, and anxiety. They may also focus on the specific symptoms of the disorder such as withdrawal, craving, or relapse; complications such as cognitive impairment, sleep disorders/disruption of normal rhythms; or the clinical surrogates of their use such as depression and other mood disorders.

The rationale for choosing the medication(s) to be investigated can be based on a top-down approach, a bottom-up approach, or both approaches combined. The top-down approach would be the testing of marketed medications that are available for other indications and which may be promising candidates for the treatment of CRDs. For example, an FDA approved antidepressant may be chosen as a target medication. The bottom-up approach involves the identification and testing of new chemical entities that, because of their chemical characteristics and mechanism of action, could be candidates to be developed specifically for CRDs.

Applications are due to NIDA by March 23, 2004. NIDA intends to commit approximately $3 million in fiscal year 2004 for this RFA.

Information on this RFA or NIDA's Medications Development Program may be obtained on NIDA's website www.nih.nida.gov or by calling at (301) 443-6173.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS)

Overview of Rare Diseases Research Activities

NIEHS supports basic research into the fundamental mechanisms of how environmental exposures interact with the human body to produce disease and dysfunction. This research on molecular pathways and environmental interaction has also yielded insights into the basic mechanisms involved in the pathogenesis of rare diseases and conditions. This report includes highlights of NIEHS-supported rare diseases research.

Highlights of Rare Diseases Research

Role of Somatic mtDNA Mutations in Neurodegeneration
(Beth Israel Deaconess Medical Center)

This research study is looking at the mechanisms responsible for the slow progression of late-onset neurodegenerative diseases. The understanding of these mechanisms may help to find ways to make these processes even slower, thus moving the onset of these debilitating diseases outside the normal human lifespan. Specifically, researchers will test the hypothesis that accumulation of somatic mutations in mtDNA of critical cell types in the brain is one of the conditions necessary for the progression of at least some neurodegenerative processes. One of the possibilities is that once the fraction of mutated mtDNA in specific cells exceeds a certain threshold, these cells become sensitive to biochemical insults associated with some diseases. This hypothesis has arisen from the preliminary finding that individual pigmented neurons in substantia nigra accumulate very high levels of mtDNA deletions, which are highly likely to compromise cell's resistance to various stresses. Moreover, there are indications that cells with a heavy mutational load are the first to die in Parkinson's brain. It is also possible that progression of the disease accelerates accumulation of mutations thus creating a positive feedback. The efforts will be focused first on Parkinson's disease patients and pigmented neurons of substantia nigra. Then research will be extended to Alzheimer's disease, Huntington's disease, and the various corresponding brain areas and critical cell types.

Possible Cause of Progressive External Opthalmoplegia Identified (Intramural)

NIEHS scientists have discovered an active site point mutation in the gene for the mitochondrial DNA polymerase gamma that is associated with the human genetic disease Progressive External Opthalmoplegia, which results from mitochondrial dysfunction. This mutated gene encodes a polymerase with reduced catalytic efficiency and reduced DNA replication fidelity, features that are implicated as causative for this disease.

Molecular Modeling of Human DNA Repair Protein Gives Insight into
Three Human Diseases (Intramural)

Structural studies of human proteins often give insights into disease processes. However, it is sometimes difficult or impossible to obtain sufficient human protein in high enough purity to obtain crystals that yield atomic resolution information. Therefore, molecular modeling is an

extremely useful complementary approach when direct structural information is lacking. Scientists at the NIEHS have built a detailed molecular model of a human DNA repair protein, XPD using the crystal structure of UvrB, a homologous repair protein from bacteria. Mutations in the XPD gene can lead to one of three human diseases: xeroderma pigmentosum, trichothiodystrophy, and Cockayne's syndrome. XPD, as part of a nine protein complex, functions in a variety of cellular functions including, DNA repair, transcription, and cell cycle control. The validity of the model was tested in two ways. First, mutations associated with these human diseases were introduced in the bacterial UvrB protein and these mutant proteins was tested in a series of biochemical DNA repair assays. Second, specific mutations were introduced into XPD and its activity tested in DNA repair and transcriptional assays. Mutations in specific regions of the protein were found to affect repair producing xeroderma pigmentosum, while other sites in the protein affect transcription, producing either trichothiodystrophy or Cockayne's syndrome.

Global Ultraviolet Light May Alter Autoimmune Muscle Disease (Intramural)

NIEHS clinical researchers coordinated a study that produced the first global findings from a group of international experts organized to utilize the natural genetic and environmental variations around the world to begin to understand differences in the clinical expression of, and genetic and environmental risk factors for, the autoimmune muscle disease, myositis. Myositis occurs in two major forms, dermatomyositis and polymyositis. Of the geoclimatic variables studied, surface ultraviolet radiation intensity most strongly predicted the relative proportion of dermatomyositis and was strongly related to the proportion of the dermatomyositis autoantibodies at 15 locations on four continents. The striking differences in the proportion of dermatomyositis and dermatomyositis-specific autoantibodies observed around the world do not appear to be the result of inherent global variations in known genetic risk factors. These data suggest that ultraviolet light exposure modulates the expression of an autoimmune disease in different populations around the world. These findings have important preventative implications, may affect studies of other immune-mediated diseases, and suggest new avenues of investigation for such disorders.

Immunotoxicology of a Heavy Metal (Scripps Research Institute)

Exposure to toxins and chemicals can produce aberrant immune reactions that may include autoimmunity. The observation that eludes explanation is the restriction of the autoantibody response to a single, or a limited number of intracellular antigens the specificity of which appears dependent in part upon the toxin or chemical involved. NIEHS supported researchers have shown that the heavy metal mercury induces a genetically restricted autoantibody response in mice that targets the nucleolar protein fibrillarin. Mercury-induced cell death results in modification of the molecular properties of fibrillarin, however mercury-modified fibrillarin is a poor antigen for HgCI2-induced antifibrillarin autoantibodies. These observations suggest that mercury-modified fibrillarin might be a source of (cryptic) T cell determinants. Immunization studies with bacterial recombinant fibrillarin, modified by mercury, were not successful in eliciting the same spectrum of antifibrillarin antibodies as HgC12-treatment. Alternative antigen sources appear more promising, including fragments of fibrillarin produced following cell death associated proteolysis, and eukaryotic cellular material resulting from HgCI2-induced cell death.

Investigators will continue to examine the immunogenicity of fibrillarin by using eukaryotic expression systems to determine if the nature of the antigen is a limiting factor in autoantibody production. This will be achieved by examination of the fine specificity of anti-fibrillarin antibodies produced by immunization, or HgCI2-treatment.

NATIONAL EYE INSTITUTE (NEI)

Overview of Rare Diseases Research Activities

The National Eye Institute was created on August 16, 1968, by Public Law 90-489 for the purpose of supporting and conducting research for improving the prevention, diagnosis, and treatment of diseases that affect the eye and vision. Eye diseases and blindness cost the Nation an estimated $38.4 billion per year. More than 12 million people in the United States suffer some significant impairment of vision. Over the years, vision researchers supported by the NEI have conducted many pioneering studies that have greatly advanced our understanding of eye diseases, including those classified as rare, and provided eye care professionals with new tools and methods to prevent or cure many sight-threatening conditions. In October of 2003, the NEI released its strategic plan for vision research National Plan for Eye and Vision Research. This plan is the seventh in the series that dates back to the publication of Vision Research Program Planning in 1975. The development and publication of the aforementioned plans address the visual health needs, including rare diseases of the eye and visual pathways, of the Nation.

Recent Scientific Advances in Rare Diseases Research

Retinitis Pigmentosa and Related Disorders

Retinitis pigmentosa (RP) is a group of blinding hereditary retinal degenerative diseases characterized by a progressive loss of vision due to the degeneration of photoreceptor cells. RP patients frequently report night blindness and loss of mid-peripheral vision during adolescence, and they are usually legally blind by the age of 40. Photoreceptor cells of the retina (the rods and cones) are responsible for the capture of light and the initiation of an electrical signal to the brain in the process of vision. The study of signaling in photoreceptor cells, termed the visual phototransduction cascade, has provided a detailed molecular description of this pathway.

The NEI is committed to supporting and conducting research that will identify genes involved in both inherited and retinal degenerative diseases (including RP), determine the pathophysiological mechanisms underlying these mutations, and determine new potential therapeutic strategies for treatment such as gene transfer, tissue and cell transplantation, growth factor therapy, and pharmacological interventions.

NEI-supported scientists have identified the receptors for the binding and ingestion of spent rod outer segments by the RPE. It has long been suspected that dysfunction in outer segment phagocytosis by the RPE causes retinal degeneration and blindness. The identified receptors are also utilized for the uptake of apoptotic cells by other phagocytes. Therefore, the phagocytic mechanism of the RPE belongs to a group of related clearance mechanisms that share common elements. This is a major conceptual advance.

NEI-supported research has shown that disruption of a number of enzymes and binding proteins involved in the metabolism and transport of retinoids to cause visual dysfunction. The gene RPE65 has been demonstrated to play a critical role in retinoid metabolism and to be essential for the production of 11-cis-retinol, the precursor for the photopigment 11-cis-retinal. Mutations

in this gene were discovered in humans and dogs. This then culminated in a dramatic and successful, adeno-associated virus-vectored gene replacement therapy. The NEI has capitalized on this event by funding additional preclinical investigations intended to take this gene-based therapy into human clinical trials.

More than 130 genes causing inherited retinopathies in humans have been found. This makes it possible to identify the cause of RP in approximately 50 percent of patients and the cause of Usher syndrome in 75 percent of patients. Sophisticated analytical techniques such as serial analysis of gene expression (SAGE) have been used to identify over 80 genes that are retina specific or are enriched in the human retina. This genomic information will be useful in identifying candidate genes involved in retinal disease.

Dry Eye (Sjögren's Syndrome)

Recent studies, funded by NEI, of the causes and mechanisms involved in tear deficiency have led to the suggestion that dry eye syndromes may involve inflammatory processes. Translational research has led to the development of therapeutic strategies that target ocular inflammatory responses and increase tear production as a means of managing dry eye diseases. The importance of hormonal influences in maintaining lacrimal and meibomian gland function is emerging. Studies of altered protein trafficking in the lacrimal gland suggest that dry eye in Sjögren syndrome may involve autoantigens misdirected to the plasma membrane from intracellular sites where they are attacked by regulatory lymphocytes.

Corneal Dystrophies

Knowledge about inherited corneal diseases has increased considerably in recent years and will lead to better diagnosis and therapy. The NEI-funded Collaborative Longitudinal Evaluation of Keratoconus Study established that keratoconus is a slowly progressing, asymmetric disease, but when patients are treated with rigid contact lenses, surprisingly good vision is achieved. Along with the discovery of new corneal dystrophies, molecular genetic studies have identified gene loci for more than 30 of these disorders and a variety of gene mutations are associated with distinctive clinical and histopathological characteristics. For example, more than 20 mutations of the TGFBI (BIGH3) gene have been found in 14 clinically distinct disorders, including various types of granular and lattice corneal dystrophies. Similarly, a number of phenotypes of macular corneal dystrophy have been attributed to over 70 distinct mutations in the CHST6 gene. Defects in this sulfotransferase gene alter the processing of proteoglycans in the stroma, such as lumican and keratocan, which are essential for optical clarity.

Rare Diseases-Related Program Activities

The National Advisory Eye Council and the NEI have established the following goals for rare disease research in the National Plan for Eye and Vision Research.

- Understand the pathogenesis of inherited retinal diseases.
- Continue to develop models and a coordinated system to share animal model data and resources in the vision community.

- Characterize the genes and proteins expressed in tissues of the ocular surface; determine the functional consequences of changes in expression and molecular interactions and determine the epigenetic, hormonal, neural, and environmental influences under both normal and pathological conditions.

Rare Diseases–Specific Conferences, Symposia, and Meetings

In fiscal year 2003, the NEI co-funded with other NIH ICs (NHGRI, NIDDK, and ORD) a conference titled *"Genetics of Rare Disease Conference: Window to Common Disorders"* on March 25, 2003 in Washington, DC. The conference was conducted under the auspices of the National Disease Research Interchange.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES (NIGMS)

Overview of Rare Diseases Research Activities

The National Institute of General Medical Sciences (NIGMS) supports broad-based fundamental research that is not targeted to any specific organ system or disease. Examples include studies on the structure and function of organelles and membranes at the cellular and molecular level; investigations into the organization and function of the genome in organisms ranging from bacteria to man; development of new and improved instrumentation and technology for application to biological problems; studies on basic biorelated organic chemistry for the elucidation of biosynthetic pathways and the development of new synthetic strategies for molecules of biological interest; and investigations of basic pharmacological mechanisms at levels ranging from the receptor to the molecular. In general, support of investigations related to specific diseases, unless of wide applicability across disease or organ system lines, is not the responsibility of the NIGMS, but rather would be assigned to one of the categorical Institutes.

Human Genetic Cell Repository

The NIGMS Human Genetic Cell Repository provides a valuable resource for investigators studying genetic disorders. The Repository, located at the Coriell Institute for Medical Research in Camden, NJ, collects, characterizes, maintains, and distributes cell lines and DNA samples from patients and families with a wide variety of genetic disorders and from normal persons whose tissues serve as controls. More than 8,700 unique cell lines, representing over 600 different diseases, and 3,700 DNA samples are available to qualified investigators. The Repository stimulates research on rare diseases by providing access to cell lines and DNA samples derived from these cell lines, that otherwise are not readily available. Among the cell lines requested most frequently in the last year are those from patients with rare diseases such as xeroderma pigmentosum, ataxia-telangiectasia, cystic fibrosis, Fragile X-linked mental retardation, Niemann-Pick disease, Nijmegen breakage syndrome, Friedreich ataxia, Fanconi anemia, Bloom syndrome, glycogen storage disease, and morbid obesity. Recent acquisitions to the collection include samples from patients with the following rare disorders: adrenoleukodystrophy, Alexander disease, Apert syndrome, ATP synthase deficiency, Canavan disease, fascioscapulohumeral muscular dystrophy, RETT syndrome, and osteogenesis imperfecta. These cell lines, as well as those previously acquired, are used for biochemical, cellular, and molecular studies to help elucidate the causes of genetic defects. The Repository has a growing collection of cell lines in which the mutation has been characterized at the molecular level. These include the newly acquired samples from patients with adrenoleukodystrophy, Alexander disease, Bloom syndrome, galactosemia, and osteogenesis imperfecta, as well cell lines with recently characterized mutations from patients with cystinuria, familial dysautonomia, Emery-Dreifuss muscular dystrophy, and neuraminidase deficiency.

In addition, the Repository supplies DNA isolated from two complete panels of well-characterized human-rodent somatic cell hybrids and from chromosome-specific somatic cell hybrid panels for nearly every human chromosome. The hybrids are a valuable resource to investigators interested in mapping the location of disease-related genes, frequently the first step in characterizing the etiology of the disease.

The Repository also houses sets of cell lines (and DNAs derived from them) that represent the National Human Genome Research Institute's DNA Polymorphism Discovery Resource, the CEPH family collection, and other identified populations that represent the genetic diversity of humans. These samples will help researchers map and identify genes that are involved in the etiology of complex genetic diseases.

Recent Scientific Advances in Rare Diseases Research

Drosophila Model of Bloom Syndrome

Bloom syndrome is a rare genetic disorder in humans characterized by several developmental abnormalities and a predisposition to the early development of cancer. The disorder is correlated with mutations in the BLM gene, a homolog to the bacterial RecQ enzyme, which is involved in homologous recombination and DNA repair activities. While implicated in similar activities in humans, the precise role of the BLM gene is unclear.

The Drosophila homolog of BLM (DmBlm) is encoded by the mus309 gene. Mutations in this gene result in genetic abnormalities similar to those observed in humans, including non-disjunction and chromosome loss. Recent work supported by NIGMS has shown that DmBlm is likely to play an important role in the repair of double-strand breaks in chromosomal DNA. Using a clever genetic assay, researchers have shown that flies that carry a mutant mus309 allele are severely impaired in their ability to repair DNA double-strand breaks by a homologous recombination pathway termed synthesis-dependent strand annealing. Instead, mus309 mutant flies attempt to repair these breaks by an error-prone pathway that is subject to creation of large, often lethal deletions. It is likely that human Bloom syndrome cells may have similar deficiencies in double-strand break repair that result in the chromosomal instabilities seen in Bloom syndrome patients. This Drosophila model will provide important contributions to our understanding of Bloom syndrome in humans and should lead to the development of useful interventions.

Hairpin Formation Underlies Triplet Repeat Expansion in Friedreich's Ataxia

Expansion of trinucleotide repeat sequences (triplet repeats) in specific genes in the human genome is known to be the basis of more than a dozen hereditary neuromuscular diseases, including several rare diseases such as Huntington's disease, Myotonic Dystrophy, Fragile X syndrome, and Friedreich's Ataxia. The precise mechanism of triplet repeat expansion is unknown. However, a role for DNA secondary structure in the form of self-annealed single-stranded DNA hairpins has been proposed as an intermediate. While most triplet repeat sequences associated with human disease have been shown to self-anneal in vitro, the repeat tracts found in Friedreich's Ataxia (GAA/TTC) have been previously reported not to undergo self-annealing. Consequently, the mechanism of repeat expansion in this disease has been a mystery.

To address this issue, NIGMS-supported researchers developed a DNA replication system that mimics the expansion of Friedreich's Ataxia triplet repeats in vitro. The system duplicates

discontinuous lagging strand DNA synthesis, which is thought to be primarily responsible for expansion of repeat tracts, and generates massive expansions of (GAA)n and (TTC)n triplets during DNA replication. The products of the reaction were shown to be authentic, self-annealed DNA hairpin structures by electron microscopic examination and by sensitivity to restriction endonuclease digestion. These results provide strong evidence that DNA hairpin formation underlies all of the disease-associated triplet repeat expansions. In addition, the development of an in vitro system that duplicates the expansion process will be a powerful tool for exploring the molecular mechanisms of these events.

Defects in Three Human Genetic Diseases Involve a Single Cell Pathway

The findings from NIGMS-supported research on the basic mechanisms that control cell growth and development indicate that defects in the pathway that involves the growth regulatory gene, TSC2, can result in three different human genetic diseases.

Defects in either the TSC2 or TSC1 genes are known to be the cause of tuberous sclerosis complex (TSC), in which tumors grow in the brain and nervous system throughout a person's life. The severity TSC can range from learning disabilities and epilepsy to mental retardation and uncontrollable seizures. Researchers have discovered that cellular energy levels regulate the activity of the TSC1/TSC2 protein complex in determining the growth rate and final size of cells. When cells are starved for energy, such as when glucose or ATP levels are low, the TSC proteins are activated and the complex acts to slow the cell growth rate and protect cells from energy deprivation-induced apoptosis. They also showed that the mechanism by which energy levels manifest this effect involves the phosphorylation of TSC2 by the enzyme AMPK.

Defects in the gene for AMPK have been implicated in Wolf-Parkinson-White syndrome (WPW), a condition that involves heart rhythm defects and heart muscle overgrowth. AMPK activity is directly influenced by cellular ATP levels and by interaction with the protein LKB1. Defects in LKB1 are associated with the Peutz-Jeghers syndrome, in which benign tumors develop in the stomach and intestines and dark pigmentation appears around the mouth and nostrils of young children.

The cellular pathway that involves LKB1, AMPK, and TSC2 also includes mTOR, a molecule that is pivotal in cell growth, protein synthesis, and cell viability. These insights combined with the demonstration in other laboratories that Rapamycin, an anti-rejection drug used in organ transplants, regulates mTOR activity raise the possibility that there may be a drug treatment for the multiple genetic disorders involving this pathway.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

Overview of Rare Diseases Research Activities

The NHLBI provides leadership for a national program in the causes, diagnosis, treatment, and prevention of diseases of the heart, blood vessels, lungs, and blood; in sleep disorders; and in the uses of blood and the management of blood resources. Through research in its own laboratories and through extramural research grants and contracts, it conducts and supports an integrated program that includes basic research, clinical trials, epidemiological studies, and demonstration and education projects.

Although the major part of the research supported by the NHLBI addresses common conditions such as hypertension, coronary heart disease, and chronic obstructive pulmonary disease, a significant amount of research is devoted to rare diseases in children and adults. NHLBI activities related to rare diseases research in FY 2003 are described below.

Recent Scientific Advances in Rare Diseases Research

Heart and Vascular Diseases Programs

Abetalipoproteinemia

Abetalipoproteinemia is a recessive disorder of lipid metabolism characterized by the absence of apoprotein B-containing lipoproteins from the plasma. Fat malabsorption is severe and triglyceride accumulation occurs. Acanthocytosis, a rare condition in which the majority of red blood cells have multiple spiny cytoplasmic projections, is common. Additional symptoms all appear to be secondary to defects in the transport of vitamin E in the blood. This disease appears to be related to abnormal processing of apolipoprotein B (apo B) due to the absence of microsomal triglyceride transfer protein (MTP). Researchers supported by the NHLBI have found that cells lacking MTP are unable to assemble and secrete apo B-containing lipoproteins and have identified a possible repressor protein that may regulate MTP levels under normal circumstances.

Antiphospholipid Syndrome (APS)

APS is characterized by the presence of circulating autoantibodies to certain phospholipids (lipids containing phosphorous). It is clinically manifested by recurrent blood clotting disorders, a history of spontaneous loss of pregnancy, and autoimmune diseases such as thrombocytopenia. The circulating autoantibodies characteristic of the disease correlate with the presence of isoprostanes, strong biomarkers for atherogenesis. Autoantibody genes cloned on the basis of their ability to bind to oxidized phospholipids play an important role in atherogenesis and confer protection against certain bacterial infections. Some researchers have suggested that oxidized phospholipids play a crucial role in mediating macrophage recognition of damaged structures and cells. Recently, researchers have characterized some of the structural features of oxidized phospholipids that are necessary for determining reactivity to a specific monoclonal autoantibody (EO6). Many patients with APS also have the autoimmune disorder systemic lupus

erythematosus. Researchers are investigating a lipid carrier protein, apolipoprotein H, found in SLE patients for a link between SLE and the production of APS antibodies. Other research is underway to determine whether genetic factors predispose individuals to developing APS antibodies. Efforts are also being made to develop reliable, standardized immunoassays to detect individual antiphospholipid antibodies.

Arrhythmogenic Right Ventricular Dysplasia (ARVD)

ARVD is a family of rare cardiomyopathies that result in sudden cardiac death and abnormal heart rhythm, including ventricular fibrillation. Most forms are believed to be due to the inheritance of autosomal dominant mutations in genes, most of which have yet to be identified, but that clearly affect myocardial integrity. ARVD is characterized by marked, selective, right ventricular dilatation, myocardial cell death, and cell replacement with fat cells and fibrous tissue. Expression in gene carriers is variable but, in those who display symptoms, the disease is frequently fatal. The NHLBI supports the Multidisciplinary Study of Right Ventricular Dysplasia, an integrated network of three separate groups, to investigate genotype-phenotype relationships in familial forms of ARVD. Additional clinical centers are being added to the study in order to establish a national registry of patients with newly-diagnosed ARVD and their family members. Research in other laboratories is focused on determining the genetics of arrhythmogenic right ventricular cardiomyopathy to improve subclassification of the various forms of the disease. For example, investigators have recently confirmed locus assignment and performed mutation screening of four candidate genes for arrhythmogenic right ventricular cardiomyopathy type 1 (ARVD1). Other recent studies have focused on characterizing magnetic resonance imaging findings in patients with arrhythmogenic right ventricular dysplasia.

Bartter Syndrome

Bartter syndrome, a rare autosomal recessive disease, typically manifests itself through salt imbalance and low blood pressure. Researchers at an NHLBI-supported Molecular Genetics of Hypertension Center have discovered that a mutation in a potassium channel can lead to Bartter syndrome. Their results demonstrate that this channel is an important regulator of blood pressure and ion and fluid balance. Mutations associated with Bartter syndrome have also been identified in genes for chloride channels and researchers think that additional Bartter syndrome genes may be discovered. The hypotensive state of Bartter syndrome suggests that the mutated genes may protect against the development of high blood pressure.

Beta-Sitosterolemia

Beta-sitosterolemia is a rare inborn error of metabolism characterized by increased absorption of dietary cholesterol and sterols from plants and shellfish. People with beta-sitosterolemia have a markedly increased risk of premature cardiovascular disease. Effective treatment is not available at present, although a number of drugs are under development. One NHLBI-supported investigator is studying patients with beta-sitosterolemia. This work may eventually lead to the development of pharmacologic and dietary treatments for patients with the disorder. Another NHLBI-supported researcher is exploring beta-sitosterolemia, the basic mechanisms of sterol absorption, and related disorders of sterol metabolism.

Brugada's Syndrome

Brugada's syndrome is a rare inherited disorder characterized by cardiac electrophysiological abnormalities (right bundle branch block and ST elevation in the precordial leads) and associated with a high occurrence of sudden cardiac death (SCD). The NHLBI supports a Program Project Grant and a small portfolio of research that address the molecular and genetic bases of Brugada's syndrome. NHLBI-supported investigators have demonstrated a novel genetic and biophysical mechanism responsible for SCD in infants, children, and young adults that is caused by mutations in the gene, KCNH2. The recent occurrence of SCD in the first 12 months of life in two patients suggests the possibility of a link between Brugada's syndrome and sudden infant death syndrome. In a brief review, NHLBI grantees have chronicled historical highlights in research on Brugada's syndrome, while other NHLBI-supported investigators have published a review of genetics and arrhythmias that highlights work on Brugada's syndrome.

Congenital Heart Disease

Congenital heart disease encompasses a constellation of abnormalities in the heart that occur during embryonic development. It is the most common birth defect, occurring in up to one percent of live births, and is an important cause of infant mortality, pediatric and adult morbidity, and shortened adult life expectancy. About one-third of affected infants and children require open heart surgery or interventional cardiac catheterization to repair or ameliorate their defects. Approximately the same proportion has associated extracardiac anomalies, such as chromosomal abnormalities and syndromes involving other organ systems.

The NHLBI has supported research in pediatric cardiovascular medicine since it first funded heart research grants in 1949. Researchers supported by the NHLBI have been instrumental in developing diagnostic fetal imaging techniques, surgical techniques, and medical therapies now used to ensure healthy survival for most affected children. They have also made significant contributions to the epidemiology of congenital heart disease and to understanding the molecular and genetic basis of normal and abnormal heart development. Currently, an NHLBI-supported congenital heart surgeon is using robotics to help perform delicate surgery on children with congenital heart disease. In the area of basic research, investigators are unraveling the complexities of transcription factor NKX2.5, which is implicated in several types of congenital heart disease and also in some heart rhythm abnormalities. Understanding the role of NKX2.5 will lay the foundation for more accurate genetic counseling and potential risk-stratification of affected patients.

DiGeorge Syndrome

DiGeorge syndrome occurs in about 1 in 4,000 live births. It is characterized by many abnormalities, including cardiac outflow tract anomalies, hypoplasia of the thymus and parathyroid glands, cleft palate, facial dysmorphogenesis, learning difficulties, and other neurodevelopmental deficits. It is usually sporadic, but may be inherited, and is caused by deletion of a segment of chromosome 22. The NHLBI supports both human and animal studies of DiGeorge syndrome in several grants, including two Specialized Centers of Research in

Pediatric Cardiovascular Disease. One Center has been instrumental in developing a team approach that has changed the way pediatric cardiologists treat children with DiGeorge syndrome. Much of the basic science research in congenital heart disease supported by the NHLBI also contributes to understanding DiGeorge syndrome because several of the most frequent cardiac malformations occur in conjunction with DiGeorge syndrome. In FY 2003, researchers identified a genetic mutation associated with DiGeorge syndrome that is present in a large proportion of children with the disease. Now that a gene has been identified, researchers can begin to understand how it is regulated by other genetic and environmental factors. This will improve diagnosis and the ability to counsel affected families.

Dysbetalipoproteinemia

Dysbetalipoproteinemia is a disorder with a strong heritable component that is characterized by the presence of beta-migrating very-low-density lipoprotein (VLDL). The disorder leads to the formation of characteristic yellow skin plaques (xanthomas) and predisposes to early ischemic heart disease and peripheral vascular disease. Researchers are investigating the biochemical events underlying its etiology and pathophysiology. A mutant form (apo-E2) of a protein (apo E) has been identified as the chief molecular defect that causes the disease. In 2003, a truncated version of apoE was found to ameliorate hyperlipidemia in an animal model (apoE2 transgenic mice) for dyslipidemia. Truncated apoE normalized the cholesterol levels of apoE-deficient mice without induction of hypertriglyceridemia.

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is an inherited disorder characterized by elevated concentrations of low-density lipoproteins (LDL). The homozygous form of FH is rare (one in a million) but people who have it are very prone to premature coronary heart disease. Cholesterol derived from LDL, when deposited in arteries, leads to heart attacks and, when deposited in tendons and skin, causes xanthomas. FH is caused by a mutation in a gene specifying the receptor for plasma LDL. LDL receptors facilitate the removal of LDL and, when they are deficient or absent, the rate of LDL removal declines, and the level of LDL in the plasma rises. Several grants support studies on the biochemistry, genetics, and potential treatment of the disease. The NHLBI supports research on the many aspects of LDL receptor regulation and on the regulation of cholesterol levels in the blood. Two new proteins, INSIG-1 and INSIG-2, which regulate cholesterol and lipid levels, have been discovered. Their discovery is an important step towards better clinical management of hypercholesterolemic patients who are susceptible to statins. Research on the proteins also may aid in the discovery of key steps that are suitable for targeted interventions.

Familial Hypobetalipoproteinemia

Familial hypobetalipoproteinemia (FHBL) is a disorder of lipid metabolism characterized by greatly reduced levels of apoprotein B-containing lipoprotein cholesterol. Several different types of FHBL have been found, each resulting from a different mutation. It is thought that fatty livers (which have a five-fold increase in fat compared to normal livers) may be present in up to 80 percent of people with a form of FHBL resulting from apo B truncation. In one group of patients

with FHBL, an associated gene mutation on chromosome 2 (resulting in apo B truncation) has been identified and characterized. However, in another group, the truncation mutation is not present. A genome-wide search is underway to look for other genes that may be involved and a likely candidate is believed to be located on chromosome 3. A third group of eight families has been identified that may have a third form of FHBL; in that form, a different region of chromosome 2 is implicated. The NHLBI funds two grants to study the genetic, biochemical, and metabolic aspects of this disease.

Klippel-Trenaunay-Weber Syndrome (KTWS)

KTWS is a very rare vascular deformation disease involving capillary, lymphatic, and venous channels. It usually manifests as three symptoms present together: cutaneous port-wine capillary malformations, varicose veins, and enlargement of soft tissues and bone in one limb. KTWS symptoms are usually present at birth, with 75 percent of patients having symptoms before the age of ten. One NHLBI grant supports molecular research on characterizing the gene(s) responsible for KTWS. The researchers are investigating the hypothesis that KTWS pathogenesis involves the disruption of key genes for vascular morphogenesis during embryonic development. Their research implicates chromosomes 5 and 11 in KTWS. In addition, they have identified a novel vascular gene, VEG5Q (Vascular Endothelial Gene on chromosome 5q), as the first candidate gene for KTWS susceptibility. Additional results suggest that KTWS pathogenesis is caused by increased angiogenesis. The findings may prove useful in developing new treatments for KTWS, cardiovascular disease, and cancers that depend on angiogenesis.

Liddle Syndrome

Liddle syndrome is characterized by increased renal reabsorption of sodium resulting in hyperaldosteronism (overproduction of the hormone aldosterone from the outer portion of the adrenal gland). The hyperaldosteronism of Liddle syndrome results in low potassium levels (hypokalemia), reduced acidity of the body (alkalosis), muscle weakness, excessive thirst (polydipsia), increased urination (polyuria), and severe hypertension. Research on Liddle syndrome is currently being pursued as part of the NHLBI Specialized Centers of Research on Molecular Genetics of Hypertension. Previous studies showed that a mutation in the gene encoding part of an epithelial sodium channel is responsible for the disorder. Recently, researchers have developed a diagnostic test for the syndrome. Scientists supported by the NHLBI have also developed a mouse model that displays features similar to those seen in people with either Liddle syndrome or salt-sensitive hypertension. This mouse model exhibits both sodium channel and renin locus dependency for blood pressure control, as recently described in the normal healthy human. This represents the first potential digenic (reproduced in alternate generations) model for hypertension.

Long QT Syndrome (LQTS)

LQTS is identified by a prolonged QT segment on an electrocardiogram and is associated with fainting (syncope), ventricular arrhythmias, and, frequently, sudden cardiac death. Studies have found that LQTS is often an inherited disorder. It is believed to be caused by alterations in cellular cardiac action potential repolarization induced by mutations in at least six cardiac ion

channel genes. In some forms of the disease, affected individuals may inherit other abnormalities, such as deafness, and have varied clinical outcomes depending on their specific mutational patterns. About 70 percent of diagnosed cases are in women.

The NHLBI currently supports research on LQTS through a Specialized Center of Research on Sudden Cardiac Death (SCD) as well as through other grants. In FY 2003, the NHLBI supported an investigator-initiated grant comprising an international LQTS registry and related research. Researchers are using data collected in the registry to assess genotype-phenotype correlations related to the long-term course of the disease. Researchers continue to identify previously described as well as new genetic variants in affected registry members. Some of the newly identified LQTS genetic variants appear to be associated with recurrent coronary events. Several other NHLBI-supported studies have also reported advances in the understanding of LQTS. One study showed that factors other than the location of mutation influence clinical phenotype in patients with one type of LQTS (LQT1). Other researchers demonstrated that long-term oral potassium intake could safely increase serum potassium in patients with LQT2, resulting in improved repolarization of cardiac cells. In another study, computer modeling was used to propose a mechanism for drug-induced changes in potassium movement in and out of cardiac cells. Other investigators created a transgenic mouse with an abnormal LQTS phenotype (Kv1DN) and demonstrated that direct manipulation of abnormal channel protein expression tended to normalize cardiac cellular action potential repolarization.

Marfan Syndrome

Marfan syndrome is an inherited connective tissue disorder associated with potentially severe cardiovascular complications such as aortic aneurysms and mitral valve prolapse, as well as noncardiac complications such as dislocation of the lens of the eye. It occurs in about 1 per 10,000 persons and in all races. The NHLBI supports animal research on the assembly of microfibrils and their effects on cardiovascular development as well as a significant research portfolio on aortic aneurysm development and its treatment in the atherosclerotic population. This research may have implications for treating aneurysms in people with Marfan syndrome.

Niemann-Pick Type C Disease (NPC)

There are several types of Niemann-Pick disease: types A (NPA), B (NPB), C (NPC), and D (NPD). NP disease is a lipid storage disorder usually characterized by excessive accumulation of cholesterol in the liver, spleen, and other vital organs. Patients have cardiovascular disease, enlargement of the liver and spleen (hepatosplenomegaly), and severe progressive neurological dysfunction. The gene deficiency in NP disease types A and B affects sphingomyelinase, a protein that breaks down the lipid sphingomyelin. The gene deficiency in NP disease types C and D affects the NPC-1 protein. Animal studies and basic research show that mutations in NPC-1 interfere with lipid metabolism, cholesterol homeostasis, and intracellular cholesterol trafficking. The defect in intracellular cholesterol movement leads to abnormal accumulation of cholesterol in a cellular compartment called the lysosome. Two NHLBI grants support research on regulation of intracellular cholesterol movement. Although dysfunctions associated with NPC cause severe damage to the nervous system, bone marrow, and other tissues and organs, they also appear to stabilize atherosclerotic plaques against rupture. Thus, they may protect

adults who carry the NPC mutation from cardiovascular events such as heart attack, angina, and stroke.

Smith-Lemli-Opitz Syndrome (SLOS)

SLOS is an inherited disorder caused by a defect in an enzyme active in the last step of cholesterol biosynthesis. In SLOS, endogenous cholesterol synthesis is inadequate to meet biological demands for functions such as maintaining membrane structure and synthesizing bile acid. As a result, the precursor 7-dehydrocholesterol and its derivatives accumulate. Newborns with SLOS have a distinctive facial dysmorphism; suffer from multiple congenital anomalies, including cleft palate, congenital heart disease, genitourinary abnormalities, and malformed limbs; and exhibit severe developmental delays, digestive difficulties, and behavioral problems. SLOS is thought to account for many previously unexplained cases of mental retardation. During FY 2003, the NHLBI supported two investigator-initiated grants relevant to SLOS. One is investigating sterol balance and lipid metabolism in infants with SLOS, the effectiveness of cholesterol-supplemented baby formula in ameliorating symptoms of SLOS, and the effectiveness of simvastatin therapy in lowering the plasma concentrations of toxic forms of cholesterol precursor compounds. The other is using transgenic animal models of SLOS to gain a better understanding of the basic pathophysiology of the condition and the normal role of cholesterol in fetal development and to develop improved molecular therapeutic approaches to SLOS.

Supravalvular Aortic Stenosis (SVAS)

SVAS is a vascular proliferative obstructive disease that is believed to be caused by a mutation in the gene for elastin, an extracellular matrix protein accounting for about 50 percent of the dry weight of the vascular wall. Studies suggest that native elastin maintains the contractile phenotype of vascular smooth muscle cells, whereas a mutation in the gene for elastin activates the migratory and proliferative phenotype. The disorder, which affects the aorta and coronary, carotid, and peripheral arteries, is thought to comprise less than five percent of all congenital heart defects. The NHLBI supports two active grants that focus on SVAS.

Tangier Disease

Tangier disease is a rare syndrome characterized by a deficiency of high-density lipoprotein (HDL), mild hypertriglyceridemia, neurologic abnormalities, and massive cholesterol ester deposits in various tissues such as the tonsils. The disease is inherited and appears to be due to excessive breakdown of HDL rather than to a fault in synthesis. Tangier disease patients have defective intracellular lipid trafficking that prevents removal of cholesterol from cells. A member of the ATP-binding cassette (ABC) transporter family (human ABCA1) located on chromosome 9 has been identified as the defective gene in Tangier disease. ABCA1 is thought to be the gatekeeper for eliminating excess cholesterol from tissues and, therefore, key in determining cholesterol accumulation in arterial walls. The NHLBI funds six grants to investigate the cell biology and biochemistry of human ABCA1 and its role in Tangier disease. In 2003, much progress was achieved toward understanding ABCA1 at the genetic and

biochemical level. To date, four families with low HDL who have novel variants of ABCA1 have been identified.

Trimethylaminuria (TMAU)

Trimethylaminuria (TMAU) is caused, most often, by genetic mutations that inactivate specific liver enzymes, leading to defects in the body's ability to break down trimethylamines (TMAs). TMAs are volatile compounds that are produced by the action of gastrointestinal bacteria on choline and related substances derived from the diet. TMAU occasionally occurs with some liver and kidney diseases and with other genetic syndromes such as Prader-Willi syndrome. In people with TMAU, excess TMA is excreted in sweat and exhaled into the air causing offensive odors and leading to severe social isolation. Neurologic and psychiatric symptoms, such as seizures and depression, may also be present. Case reports suggest that symptoms in many TMAU patients can be ameliorated by diets low in choline, lecithin, carnitine, lysine, other dietary amines, and vegetables from the cabbage family. Progress in nutritional management offers one of the most promising therapeutic options for TMAU patients, but cannot be made without accurate information on the choline content of foods. In 2003, the results of the Food Choline Database analyses were published in the *Journal of Nutrition*. Food choline data should prove useful for conducting research on the efficacy of dietary treatment and on the mechanisms whereby diet affects clinical outcomes.

Lung Diseases Programs

Advanced Sleep Phase Syndrome (ASPS)

ASPS is a rare, genetically based sleep disorder characterized by an early evening onset of sleep, normal sleep duration, and spontaneous early awakening. The NHLBI supports basic research to elucidate the neural pathways through which the biological clock mechanism regulates sleep; clinical research to elucidate genetic risk factors; and applied research on the role of the biological clock in disturbed sleep and alertness of shift workers, school-age children, and drowsy drivers.

Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin (AAT) deficiency is an inherited deficiency of a circulating protein inhibitor that is manufactured primarily in the liver. Deficiency states (circulating serum AAT levels below 0.6 mg/ml) are associated with emphysema, presumably from inadequate protection against enzymatic destruction of lung elastic fibers by neutrophil elastase. Fifteen percent of the AAT-deficient population also develops liver disease. NHLBI-supported investigators are defining the abnormalities and degradation pathways of the AAT protein, characterizing the inflammation that leads to disease, and evaluating the possibility of treating the disease with drugs that enhance the release of partially active mutant protein from liver cells. A study of families is seeking to identify other genes that may modify the nature and severity of AAT. A gene therapy clinical trial is also being conducted. In addition to research that specifically focuses on AAT, the NHLBI supports related studies addressing lung transplantation; the general causation of emphysema; enzymes that are inhibited by AAT; and animal models of other

enzyme inhibitor deficiencies. Recent studies of genetically engineered mice demonstrated the importance of both neutrophil elastase (NE) and matrix metalloproteinase (MMP)-12 in the development of cigarette smoke-induced emphysema and resolved an apparent discrepancy between findings from studies based on patients with AAT deficiency and those from more recent studies in animals.

Asbestosis

Asbestosis is an occupational lung disease that results from exposure to inhaled asbestos fibers. It is characterized by interstitial pneumonitis and fibrosis. In response to the deposition of asbestos fibers, macrophages and lymphocytes accumulate, type II alveolar epithelial cells and smooth muscle cells proliferate, fibrosis appears in the adjacent walls of respiratory airways, and alveolar septa thicken. NHLBI-supported researchers are investigating the molecular and cellular events that trigger the accumulation and proliferation of cells in response to asbestos exposure. They are also studying the regulation of the asbestos-induced lung tissue remodeling that leads to fibrotic lesions. A mouse model has been helpful in understanding mechanisms of injury and cellular proliferation of lung epithelial cells.

Bronchopulmonary Dysplasia (BPD)

BPD is a chronic lung disease characterized by disordered lung growth; specifically, by changes in cell size and shape and a reduction in the number of alveolar structures available for gas exchange. It affects at least 10,000 very-low-birth-weight (VLBW) infants each year and is associated with high neonatal intensive care costs. The incidence of BPD has increased in recent years due to the increased survival of smaller premature infants. One of the participating Centers of the NHLBI SCOR Program in Pathobiology of Lung Development identified nitric oxide (NO) as an important regulator of lung circulation during development. Two clinical trials investigating the role of NO in preventing and treating chronic lung disease in VLBW premature infants are expected to yield definitive information about the utility of and "window of therapeutic opportunity" for using NO to prevent of chronic lung disease. The Collaborative Program for Research in BPD provides a well-characterized primate model of BPD to facilitate multidisciplinary research on the disease. Recent research showed that the capillary deficient alveolar beds in the baboon BPD model correlate with the histology of the lungs of human infants with BPD who died with a low level of a vascular growth factor, VEGF. Another recent study, based on a previous study using the baboon model, showed that an elevated level of bombesin-like-peptide in the urine of premature human infants is associated with a 10-fold greater risk of developing BPD.

Congenital Central Hypoventilation Syndrome (CCHS)

CCHS is a rare disorder characterized by normal breathing while awake, but shallow breathing during sleep (hypopnea) that is not effective in moving fresh air into the lungs. In severe cases, breathing is also ineffective in affected individuals who are awake. The NHLBI supports a basic research program to elucidate the anatomical and physiological organization responsible for neural rhythm generation and translation into breathing. Research is focused on obtaining a better understanding of how breathing is regulated and the conditions under which reflexive

generation of respiratory rhythm is abolished. Identification of the neuronal pathways producing respiratory rhythm and pattern is a prerequisite for a full understanding of a variety of respiratory sleep disorders such as CCHS. Genetic and pathological studies of CCHS patients are now leading to identification of candidate genes and to specific areas of the brain stem involved in autonomic regulation including respiration.

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a developmental disorder that occurs once in every 2,400 births. Often CDH occurs in isolated fashion, i.e., it is not associated with any other life-threatening anomalies or chromosomal aberrations. Without surgical intervention, neonates with CDH usually die soon after birth due to inadequately developed lung tissue, pulmonary hypertension, or persistent fetal circulation syndrome. As a result of recent advances in ultrasonography, CDH is now diagnosed before birth with increasing frequency. Enrollment in an investigator-initiated NHLBI-sponsored study of the efficacy of an *in utero* surgical technique (fetal endoscopic tracheal occlusion) to correct lung hypoplasia in human fetuses with the most severe form of CDH was terminated due to the unexpectedly high survival rate with standard care. Members of the study's data safety and monitoring board concluded that further recruitment would not result in significant differences between the two groups.

Cystic Fibrosis

Cystic fibrosis (CF) is a multisystem disease that affects a variety of epithelial tissues. It is characterized by defective transport of chloride and sodium across the cell membrane. Although it affects multiple systems, lung disease is the major cause of morbidity and mortality in people with CF. CF is the nation's number one genetic cause of death among children and young adults; more than 25,000 Americans have CF and disease incidence is about 1 in 3,300 among Caucasians. Defects in a single gene, the CF transmembrane conductance regulator (CFTR), give rise to CF. However, evidence suggests that this disease gene does not function alone in determining disease outcome. Recent exploration showed a striking correlation between the survival of CF patients and genetic variation in mannose binding lectin (MBL), a genetic determinant of host innate immunity. Distinct genetic subgroups of MBL are associated with increased disease severity, a higher risk of infection, poor prognosis, and early death. The NHLBI supports a vigorous program of basic, clinical, and behavioral research in CF. Renewals of two investigator-initiated program project grants that are focused on overcoming the barriers to gene therapy for CF will be awarded in 2004.

Early in life CF patients become persistently colonized with the bacterium *Pseudomonas aeruginosa* (PA). As PA infections become chronic, airways are destroyed and lung function declines, which eventually results in death. Although an aerobic organism, PA adapts well to the anaerobic conditions in the lungs of CF patients. Under these conditions, PA acquires features that form biofilms, thereby allowing PA to evade host defenses. The discovery that PA, normally an aerobic bacterium, adapts to anaerobic conditions in the airways has led to a new strategy for the care of CF patients and will likely influence the treatment of infections in other bronchitic conditions. Although generally believed to be ineffective against PA (based on drug sensitivity testing under aerobic conditions), macrolide antibiotics (erythromycin, azithromycin,

and clarithromycin) have been found to be clinically effective against biofilm-grown PA adapted to the anaerobic conditions in the lung.

Idiopathic Pulmonary Fibrosis (IPF)

IPF is a rare, chronic, lung disease that is initiated by unknown causes. In people with IPF, normal lung tissue is replaced by nonfunctional connective (scar) tissue that contains fibroblasts, myofibroblasts, and collagen. IPF is commonly treated with corticosteroids, sometimes in combination with other immunosuppressant drugs, and less commonly with lung transplantation. Therapy is rarely effective and the disease progresses, resulting in death over a relatively short time in most patients (about 50 percent 5-year mortality from diagnosis). Recent estimates put the prevalence at 150,000 and the incidence at 80,000. NHLBI-supported researchers are continuing to investigate the molecular and cellular events that trigger the injury of alveoli which occurs in the early stage of IPF and then progresses to the irreversible, fibrotic, end stage of the disease. It has been hypothesized that alteration of alveolar macrophage (AM) gene expression may contribute to the development and progression of lung fibrosis. To test this hypothesis, researchers compared large-scale gene expression of AM from IPF patients with that of AM from age- and gender-matched volunteers without lung disease. The data demonstrated that total mRNA was lower in IPF patients than in normal volunteers.

Other recent studies have focused on determining disease outcome in patients with IPF. A recent study suggests that identifying the presence of usual interstitial pneumonitis (UIP) is important when assessing the prognosis of patients with IPF. UIP is associated with alveolitis, progressive injury, and the worst prognosis. Another study measuring blood oxygen desaturation during a six-minute walk test showed that IPF patients with exercise-induced hypoxia had a four-fold higher risk of dying than patients who did not exhibit exercise-induced hypoxia.

Lymphangioleiomyomatosis (LAM)

LAM is a rare lung disease that affects women, usually during their reproductive years. Symptoms develop as the result of proliferation of atypical, nonmalignant, smooth muscle cells. Common symptoms include shortness of breath, cough, and sometimes coughing up blood. Patients often develop spontaneous pneumothorax or chylous pleural effusion (collapse of the lung or collection of milky looking fluid around the lung). The clinical course of LAM is quite variable, but is usually slowly progressive, eventually resulting in death from respiratory failure. Although no treatment has been proven effective in halting or reversing LAM, lung transplantation is a valuable treatment for patients with end-stage lung disease. Some patients with Tuberous Sclerosis Complex (TSC) develop lung lesions identical to those seen in LAM. The underlying genetic mechanisms leading to smooth muscle proliferation in LAM and TSC are controlled by abnormalities in the same genes, but TSC is inherited and LAM is a disease that occurs sporadically (does not appear to run in families).

As part of its intramural program, the Institute has established a research laboratory at the NIH Clinical Center to learn more about the cause and progression of LAM. The NHLBI extramural program supports a national LAM Patient Registry, co-funded by the Office of Research on Women's Health, and coordinated by the Cleveland Clinic Foundation. Recently researchers

have shown that treatment of LAM cells with an immunosuppressant, rapamycin, restores the ability of the cells to regulate growth. In a rat model of TSC, rapamycin successfully reduced the size of the multiple tumors. Rapamycin, which is already FDA approved to prevent graft rejection following kidney transplant, is currently being used in a phase II clinical trial in patients with TSC. The recent finding that LAM cells are able to migrate although they appear to be benign may help determine how metastases occur in LAM and other conditions characterized by benign looking cells. Other experiments using lung tissue from LAM patients show that tissue inhibitor of metalloproteinase is present in normal-appearing areas of their lungs but absent from the LAM lesions. Interestingly, mice unable to make this inhibitor of metalloproteinase spontaneously develop cysts in their lungs suggesting that the destructive cysts characteristic of LAM may be related to the unopposed activity of metalloproteinases in the vicinity of the LAM cells. Intramural investigators have hypothesized that modifier genes may be important in disease susceptibility and progression. Studies support a role for proteinases and surfactants, in particular surfactant B, as modifiers in this disease. In the case of surfactant B, the protein may promote lung function in patients with severe disease, enabling them to postpone transplantation.

Recently, intramural investigators have developed two antibodies that positively identified LAM cells in greater than 99 percent of cases. They have also developed a procedure for isolating LAM cells from blood, thus facilitating diagnosis without the need for an invasive surgical procedure. In addition, intramural investigators using cardiopulmonary exercise testing with LAM patients found that maximal oxygen uptake is useful in grading the severity of the disease.

Narcolepsy

Narcolepsy is a disabling sleep disorder affecting over 100,000 people in the United States. It is characterized by excessive daytime sleepiness and rapid onset of deep (REM) sleep. Other symptoms involve abnormalities of dreaming sleep, such as dream-like hallucinations and transient periods of physical weakness or paralysis (cataplexy). Low cerebrospinal fluid levels of hypocretin, a neurochemical messenger linking sleep with the regulation of muscle tone, are highly specific to narcolepsy. Through programs such as the SCOR in Neurobiology of Sleep and Sleep Apnea, the NHLBI supports research on the regulation of sleep and wakefulness, the regulation of muscle tone during sleep, and the genetic basis of narcolepsy in humans and animals.

Persistent Pulmonary Hypertension of the Newborn (PPHN)

PPHN affects approximately 1 in 1,250 live births. Due to inappropriate muscularization of fetal pulmonary vessels, the lung arteries of affected newborns fail to dilate after birth to allow for normal blood flow to the lung. Infants with PPHN are poorly oxygenated and require costly and prolonged medical care, including intubation of the airway, inhalation of 100 percent oxygen, mechanical ventilation and, often, heart/lung bypass (extracorporeal membrane oxygenation). One of the NHLBI-funded Specialized Centers of Research on the Pathobiology of Lung Development is focused on the unique vascular response of a developing fetus to injurious stimuli. Recent studies point to a critical role for endogenous nitric oxide as a modulator of the levels of endogenous vasoactive mediators that determine pulmonary vascular tone and reactivity.

Primary Ciliary Dyskinesia (PCD)

PCD, also known as Kartegener syndrome or immobile ciliary syndrome, is an inherited disease characterized by defects in the cilia lining the respiratory tract. Patients with PCD have impaired ciliary function, reduced or absent mucous clearance, and susceptibility to chronic, recurrent respiratory infections, including sinusitis, bronchitis, pneumonia, and otitis media. The disease typically affects children ages 0 to 18 years, but the defect associated with it has a variable clinical impact on disease progression in adults as well. Many patients experience hearing loss and, in males, infertility is common. Another symptom, situs inversus (having organs on the opposite side from usual), occurs in approximately 50 percent of PCD patients. Clinical progression of the disease is variable with lung transplantation required in severe cases. For most patients, aggressive measures to enhance clearance of mucus, prevent respiratory infections, and treat bacterial superinfections are recommended. Although the true incidence of the disease is unknown, it is estimated to be 1 in 32,000 or higher.

NHLBI-supported researchers are working to identify defects in the cilia of PCD patients at the level of individual proteins, and ultimately at the level of mutations responsible for PCD. Other researchers are identifying and characterizing a regulatory protein, Foxj1, expressed in ciliated epithelial cells. Preliminary findings with a mutant mouse lacking Foxj1 suggest that this transcription factor is involved in regulation of ciliogenesis in early development and that cilia function may be critical in left-right body axis symmetry. An investigator-initiated project is seeking to establish a mammalian ciliated cell bank to facilitate investigations and screening for therapeutic agents in a high throughput format. In a recent study, researchers interested in identifying the major clinical and biological markers of disease undertook a rigorous evaluation of a large cohort of PCD patients. Their results showed that clinical and ciliary phenotyping is useful in diagnosing PCD. Moreover, measures of other biologic markers such as nasal nitric oxide also were found to be useful as an adjunct to diagnosis.

Primary Pulmonary Hypertension

Primary pulmonary hypertension (PPH) is a rare condition characterized by structural changes in small pulmonary arteries that lead to increased resistance to blood flow in the lungs and to heart failure. PPH is an aggressive disease with poor short-term outcome. The average untreated survival time is 3-5 years after initial diagnosis. PPH has a mortality of 30 percent over 4 years, even with current best therapy. The incidence of PPH is estimated to be between 1 and 2 cases per million, with women being predominantly affected. Recent developments in treatment are likely to improve survival and quality of life for many patients, but it remains a devastating disease. The NHLBI supports an active program of basic research that seeks to identify the cause or causes of PPH and to suggest new therapeutic approaches.

Results from a small clinical trial of Bosentan (Traceleer) suggested that the drug increases exercise capacity and improves heart function in patients with PH. A more recent study extended these findings and reported that the benefits persist after 1 year of treatment. The effectiveness of adding sildenafil, a phosphodiesterase inhibitor, to the medical regimen of patients with PPH has been recently studied in a small cohort of 13 patients. The results suggest

that sildenafil significantly increases cardiac output and decreases pulmonary artery pressure. A third new treatment option, beraprost, an orally active prosatcyclin analog, was also evaluated in a clinical trial. Compared to patients treated with placebo, patients who received beraprost showed improvements in exercise capacity and less evidence of disease progression at 6 months, but these benefits were not seen at 9 or 12 months of treatment. Interesting new findings reported this year suggest that infection with a virus may be associated with the pathogenesis of PPH. Investigators examined lung tissue samples from patients with sporadic PPH and tissue from patients with secondary PH for evidence of infection with human herpes virus 8 (HHV-8). Sixty-two percent (10 of 16) of PPH patients were HHV-8 positive as compared to none of the 10 patients with secondary PH. These results suggest that the virus plays some role in the pathogenic process underlying PPH.

Sarcoidosis

Sarcoidosis is a disease involving organ systems throughout the body in which normal tissue is invaded by pockets of inflammatory cells called granuloma. Most sarcoidosis patients have granuloma in their lungs. The disease can exist in a mild form that disappears spontaneously or in a severe form that results in a life-long condition. Estimates of the number of Americans with sarcoidosis range from 13,000 to 134,000, and between 2,600 and 27,000 new cases appear each year. Up to 5 percent of individuals with pulmonary sarcoidosis die of causes directly related to the disease. The morbidity associated with the disease can be severe, resulting in significant loss of function and decrease in quality of life. The causes of sarcoidosis are presently unknown, but disease development is thought to involve both a genetic predisposition and the immune system.

The NHLBI supports research on sarcoidosis in both its extramural and intramural programs. Results from the NHLBI multi-center study, A Case Control Etiologic Study of Sarcoidosis (ACCESS), showed differences in the way that sarcoidosis presents in different subgroups of the study population. Researchers conducting the study concluded that the initial presentation is related to sex, race, and age. Information from the study should help physicians diagnose sarcoidosis. Results from genetic studies that were also part of ACCESS indicate that certain genes that help regulate immunity (HLA class II alleles) may be markers for different manifestations of sarcoidosis. Another multi-center study, the U.S. Sarcoidosis Genetic Analysis Consortium (SAGA), is performing a linkage analysis of 360 African American families with affected siblings. The focus is on African Americans because they are more likely to report a family history of sarcoidosis. Other NHLBI grants support research to identify the etiologic agent in sarcoidosis. NHLBI intramural investigators are conducting a clinical trial to evaluate pentoxifylline as a treatment for pulmonary sarcoidosis.

Blood Diseases and Resources Programs

Cooley's Anemia

Cooley's Anemia (CA), also called beta-thalassemia, thalassemia major, or Mediterranean anemia, is a genetic blood disease that results in inadequate production of hemoglobin. Individuals affected with CA require frequent and lifelong blood transfusions to sustain life. Because the body has no natural means to eliminate iron, the iron contained in transfused red

blood cells builds up over many years and eventually becomes toxic to tissues and organ systems. Many children with CA have acquired other diseases such as hepatitis through years of transfusion exposure.

Extramural research efforts include identifying mutations in the globin gene cluster that lead to CA, understanding naturally occurring mutations that significantly increase levels of fetal hemoglobin (Hb F) in adult red blood cells, studying iron chelation, identifying therapies and drugs for the disorder, and developing gene therapy strategies to treat it. NHLBI grantees have used several vectors to optimize gene transfer and expression in mouse models. Recently, grantees have for the first time demonstrated high-level, long-term, somatic human beta-globin gene transfer into the hematopoietic stem cell of an animal. These results suggest that a retroviral gene therapy approach to treating CA and sickle cell disease may be feasible. Researchers studying Hb F induction have described several compounds that increase Hb F. They include not only hydroxyurea, a compound routinely used to treat sickle cell disease, but also a number of butyrate based compounds as well as 5-azacytidine and decitabine.

Creutzfeldt-Jakob Disease (CJD)

CJD is a slow degenerative disease of the central nervous system that is characterized by motor dysfunction, progressive dementia, and vacuolar degeneration of the brain. The disease is rare, but invariably fatal, and has been associated with a transmissible agent. A protease-resistant protein or prion is the hallmark of all transmissible spongiform encephalopathies (TSE), including CJD. This group of neurodegenerative illnesses—collectively referred to as prion diseases—includes bovine spongiform encephalopathy (BSE) or "mad cow disease," scrapie in sheep, and chronic wasting disease in deer and elk. Prion diseases may cross the species barrier, the most notable example being the recent cases of variant CJD (vCJD) in humans caused by consumption of beef contaminated with BSE. Classical CJD occurs worldwide at a rate of 1-2 cases per million per year. Although it is believed that BSE is spread from cattle to man and manifested in humans as vCJD, very little is known about how this process occurs. To gain a better understanding of how diseases like BSE are transmitted between species, researchers at the NIH examined the process by which scrapie transfers from hamsters to mice. The investigators found that the transfer is a prolonged and subtle process and that the early stages are very difficult to detect. Based on these results, the investigators recommended that the medical, veterinary, and scientific communities be more vigilant in monitoring the spread of TSE diseases.

Fanconi Anemia (FA)

Fanconi Anemia (FA) is an autosomal recessive bone marrow failure syndrome characterized by a decrease in blood cells and platelets (pancytopenia), developmental defects, and cancer susceptibility. Many FA patients can be identified at birth because of congenital anomalies, although approximately 25 percent do not have birth defects. FA is a clinically heterogeneous disorder; it can currently be divided into at least eight complementation groups designated A through G. Recent studies have identified a new FA complementation group designated L. The NHLBI supports a multidisciplinary program to determine the causes of FA at the molecular and cellular level. Investigators representing the clinical disciplines of medicine, pediatrics, medical

genetics, hematology, and oncology are working on protocols to identify and target hematopoietic stem cells, to discover how *ex vivo* manipulation of stem cells alters their biologic properties, and to improve vectors. Rejection after allogeneic bone marrow transplantation for FA remains a complication with a high risk of mortality. Recently, treatment with antilymphocyte globulin has shown promising results for preventing rejection. With the indications for bone marrow transplant for FA patients growing, and with new data emerging regarding the benefits of cord blood, cord blood banking promises to be a realistic approach of great potential benefit for hemoglobinopathy families. The NHLBI is currently supporting an investigator-initiated cooperative agreement to conduct sibling donor cord blood banking and transplantation.

Hemophilia

Hemophilia is a hereditary bleeding disorder that results from a deficiency in either blood coagulation factor VIII or factor IX. About 20,000 individuals in the United States with hemophilia are dependent on lifelong treatment to control periodic bleeding episodes. The NHLBI supports a broad spectrum of activities on blood coagulation and its disorders. Hemophilia research includes studies of viral and nonviral approaches for gene therapy, mechanisms of antibody inhibitor formation, modification of factors for improved therapeutics, safety of plasma derived products, and infections associated with blood products. In addition, basic genetic, molecular biology, and protein biochemistry studies of factors VIII and IX are supported to improve understanding of their mechanism and regulation. Two NHLBI-funded grants support the development of gene-based therapies for hemophilia A and B and of new therapies with a focus on treatment in the presence of inhibitory antibodies. NHLBI-supported investigators are working on gene transfer of factor IX into skeletal muscle in patients with hemophilia B using an adeno-associated viral vector. In 2003, the researchers reported that this method is safe at the doses tested in a Phase I clinical trial. Other researchers are developing an innovative, nonviral, gene transfer method that has the potential to reduce the risk of genetic mutations. The method has been used to insert factor IX into a specific site in the mouse chromosome. Another group of investigators is using nonviral, liver-specific gene transfer vectors to achieve high-level, persistent expression of factor VIII in mice.

Hereditary Hemorrhagic Telangiectasia (HHT)

Hereditary hemorrhagic telangiectasia (or Osler-Weber-Rendu disease) is a bleeding disorder caused by weakness of the vascular support structure. Its most common manifestations are red spots on the lips and bleeding from mucosal membranes such as in the nose. In an advanced stage, arterio-venous malformations often develop in the lung, brain, gut, and liver. Two gene defects have been identified in patients with HHT. One is in a gene associated with the protein endoglin. This defect results in HHT type 1 disease. The other is in a gene associated with the activin receptor-like kinase 1 protein and results in HHT type 2 disease. A correlation may exist between the gene defect and organ susceptibility to the disease. An important development in research on HHT is the generation of a mouse model of HHT type 2. This animal model and the concepts generated from it are providing insights into HHT as well as other syndromes involving disruption of normal vascular morphogenesis.

Lymphedema

The lymphatic system regulates the flow of fluid that surrounds cells. Lymphedema results when the system becomes unbalanced. There are two major types of lymphedema: primary (congenital) and secondary (caused by tissue injury, scarring, cancer, lymph node removal, or infection). The incidence of primary lymphedema has been estimated to be between 1 in 300 and 1 in 6000 live births. The NHLBI is interested in finding the developmental, molecular, and cellular causes of lymphedema as well as designing better therapies for both primary and secondary lymphedemas. Relevant NHLB-funded projects include Regulation of Angiogenesis by SLP-76 Signaling; Genes for Vascular Morphogenesis: A Genetic Approach; Influences of Lymph Flow on the Lymphatic Pump; Physiology of Systemic and Pulmonary Microangiectasias; Molecular Regulation of Vascular Development; Lymph vs. Blood Angiogenesis: Functional Differences; Prox1 in Mammalian Lymphangiogenesis; FOXC2 in Hereditary Lymphedema; Control of Lymphatic Endothelial Differentiation Program; and Molecular Characterization of Familial Lymphedema.

Sickle Cell Disease

Sickle cell disease (SCD) is an inherited blood disorder that is most common among people whose ancestors come from Africa, the Middle East, the Mediterranean basin, and India. In the United States, it affects primarily African Americans, about 72,000 of whom have the disease. Sickle cell disease is the most common genetic blood disorder in the U.S., affecting approximately 1 in 400 African American and 1 in 1000 Hispanic newborns each year. It occurs when an infant inherits the gene for sickle hemoglobin from both parents or the gene for sickle hemoglobin from one parent and the gene for another abnormal hemoglobin (e.g., beta-thalassemia) from the other parent. In patients with the disease, the abnormal hemoglobin molecules in the red blood cells tend to damage the red blood cells, causing them to stick to blood vessel walls. This leads to the acute painful episodes that are the hallmark of the disease. Chronic end-organ damage occurs to the vital organs and leads to premature death. The median age at death for severely affected individuals is 42 to 48 years.

The current NHLBI sickle cell disease research portfolio includes research on the following topic areas: (a) development of methods for gene addition to the hematopoietic stem cell, (b) characterization of interactions between sickle cells and the vascular endothelium, (c) improved understanding of hemoglobin gene switching to allow increased production of fetal hemoglobin (Hb F), (d) a Phase III clinical trial (STOP II) to evaluate the use of blood transfusion to prevent strokes in children with abnormal blood velocities, (e) a Phase III clinical trial (BABY HUG) of hydroxyurea (HU) to determine if HU can prevent the onset of chronic end-organ damage in very young children with SCD, (f) an epidemiologic study of the incidence of parvovirus B19 seroconversion in children with SCD, and (g) an epidemiologic study of the adult patients who participated in the Multicenter Study of Hydroxyurea (MSH) Trial.

The original MSH trial was designed to test whether HU reduced symptoms of SCD compared to placebo in severely affected patients. Results from the MSH showed that over 2.5 years, HU diminished the morbidity of SCD in adults by reducing the incidence of painful episodes and

acute chest syndrome by nearly half. In 2003, results from a follow-up study of patients from the MSH trial were published. The follow-up study showed that patients who took HU over a 9-year period experienced a 40 percent reduction in mortality. Another study, the Cooperative Study of Sickle Cell Disease, showed that severely affected SCD patients who experience 3 or more crises per year die 10 to 15 years earlier consume more medical resources than patients who suffer fewer crises per year. Researchers hope that HU treatment will significantly decrease mortality, morbidity, and health care costs of the severely affected SCD patient population.

Systemic Lupus Erythematosus (SLE)

Lupus is an autoimmune disorder in which the body produces antibodies that harm its own cells and tissues. Typical symptoms of lupus include fatigue, arthritis, fever, skin rashes, and kidney problems. Lupus affects more women than men. The risk of coronary heart disease in women with SLE is up to 50 times higher than in the general population. SLE patients have a higher incidence of blood clot formation (thrombosis) and spontaneous loss of pregnancy. Although its cause remains unknown and there is no known cure, its symptoms can be controlled with appropriate treatment and most patients can lead an active life. The NHLBI supports two major areas of research that are relevant to SLE. The first area concerns components of the blood that regulate bleeding and blood clotting disorders (hemostasis and thrombosis), including the biology of platelet molecules, the mechanisms of blood clotting, and the interaction of blood components with blood vessel surfaces. The second area concerns the cardiovascular complications of SLE, including risk factors that may help explain the elevated incidence of premature cardiovascular disease in women with SLE. Such risk factors include the presence of antiphospholipid antibodies, which are present in 50 percent of SLE patients versus only 1-5 percent of healthy individuals. The NHLBI co-funded two major studies, published in 2003 in the *New England Journal of Medicine,* which showed that (1) atherosclerosis occurs prematurely in patients with SLE and is independent of traditional risk factors for cardiovascular disease and (2) in patients with SLE the prevalence of coronary-artery atherosclerosis is elevated and the age at onset is reduced.

Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic thrombocytopenic is a potentially fatal disease characterized by low blood platelet levels and widespread platelet thrombi in arterioles and capillaries. Both endothelial cell damage and intravascular platelet aggregation have been implicated in the pathogenesis of TTP. Microscopic examination of the thrombi has revealed an abundance of the plasma protein von Willebrand factor (VWF). VWF is synthesized as large polymers and is then cleaved into smaller units by a plasma protease, ADAMTS 13. NHLBI-supported grantees have confirmed the presence of inhibitory antibodies to ADAMTS 13 in the plasma of some patients with familial TTP. Inhibition of ADAMTS 13 allows individual VWF molecules to bind together forming large VWF "multimers" in the plasma. Once assembled into multimers, VWF molecules can spontaneously aggregate platelets. Researchers believe that techniques to increase availability of ADAMTS 13 could be a promising approach for the treatment of patients with TTP. Currently, efforts also are being directed toward large scale production of recombinant ADAMTS 13. A major achievement of NHLBI grantees is the development of

advanced technology for the direct visualization of cleavage of newly synthesized VWF multimers by ADAMTS 13 as well as quantitation of the physical forces involved.

Rare Diseases Research Initiatives

Ongoing Initiatives

- Animal Models of Antigen-Specific Tolerance for Heart and Lung Transplantation Beryllium-Induced Diseases
- Biology of Iron Overload and New Approaches to Therapy
- Blood and Marrow Transplant Clinical Research Network
- Cell-Based Therapies for Heart, Lung, Blood, and Sleep Disorders and Diseases
- Cellular and Molecular Mechanisms of Primary Pulmonary Hypertension Clinical Research on Cooley's Anemia
- Comprehensive Sickle Cell Centers
- Coordination of Vascularization and Lung Development
- Creutzfeldt-Jakob Disease (CJD) Assay Methods Development
- Developmental Processes in Differential Expression of Globin Genes
- Diamond-Blackfan Anemia and Other Congenital Bone Marrow Failure Syndromes: Underlying Molecular Mechanisms
- Exploratory and Developmental Research Grants for Investigations in Rare Diseases (R21)
- Functional Heterogeneity of the Peripheral, Pulmonary, and Lymphatic Vessels
- Genelink
- Genetic and Cellular Discovery in Myelodysplastic Syndromes (MDS)
- Genetic Aspects of Tuberculosis in the Lung
- Genetic Modifiers of Single Gene Defect Diseases
- Granulomatous Lung Inflammation in Sarcoidosis
- Heritable Disorders of Connective Tissue
- Hutchinson-Gilford Progeria Syndrome: Exploratory/Developmental (R21) Grants
- International Cooperative Biodiversity Groups (ICBG)
- Interstitial Lung Fibrosis Clinical Research Network
- Mechanisms of Fetal Hemoglobin Gene Silencing for Treatment of Sickle Cell Diseases and Cooley's Anemia
- Mesenchymal Stem Cell Biology
- Molecular Mechanisms of Mucous Cell Metaplasia and Excess Mucous Secretion in Human Airway Diseases
- Molecular Targets and Interventions in Pulmonary Fibrosis
- Multicenter Study of Hydroxyurea in Sickle Cell Disease: Patient Follow-Up Extension I
- National Registry of Patients with Marfan Syndrome
- NHLBI Lung Tissue Resource
- Oxygen Sensing During Intermittent Hypoxia
- Pathogenesis and Treatment of Lymphedema
- Pediatric Heart Disease Clinical Research Network

- Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG)
- Pediatric Mechanical Circulatory Support
- Plasticity of Human Stem Cells in the Nervous System
- Programs for Genomic Applications (PGAs) for Heart, Lung, and Blood Research
- Programs of Excellence in Gene Therapy (PEGT)
- Pulmonary Complications of Sickle Cell Disease
- Somatic Cell Therapy Processing Facilities
- Specialized Centers of Research (SCOR) in Hematopoietic Stem Cell Biology
- Specialized Centers of Research (SCOR) in (a) Neurobiology of Sleep and Sleep Apnea and (b) Airway Biology and Pathogenesis of Cystic Fibrosis
- Specialized Centers of Research (SCOR) in Pediatric Cardiovascular Disease
- Stem Cell Plasticity in Hematopoietic and Non-Hematopoietic Tissue
- Stem Cell Transplantation to Establish Allochimerism
- Strategies to Augment Alveolization
- Thalassemia (Cooley's Anemia) Clinical Research Network
- Thrombocytopenia: Pathogenesis and Treatment
- Transactivation of Fetal Hemoglobin Genes for Treatment of Sickle Cell Disease and Cooley's Anemia
- Transfusion Medicine/Hemostasis Clinical Research Network
- Treatment of HIV and Associated Complications in Hemophiliacs
- Tuberculosis Curriculum Coordinating Center

Initiatives Started in 2003

Cell-Based Therapies for Heart, Lung, Blood, and Sleep Disorders and Diseases

A new Request for Applications (RFA), initiated by the NHLBI, stimulates basic research on stem cell biology and on the use of stem cells in cellular therapies for cardiovascular, lung, blood, and sleep disorders and diseases. Areas supported include the basic biology and characterization of embryonic, fetal, and adult stem cells and progenitor cells; the use and differentiation of stem and progenitor cells for cell transplantation; stem cell homing to sites of tissue injury or specific tissue or organ sites; and tissue engineering using stem or progenitor cells.

Chemical Screens for New Inducers of Fetal Hemoglobin

A new NHLBI-initiated Program Announcement (PA) supports high-throughput chemical activity screens for new pharmacologic inducers of fetal hemoglobin. The long-term objective is to develop better drugs to treat sickle cell disease and Cooley's Anemia. Promising compounds identified through these Small Business Innovation Research (SBIR) grants will later be subjected to toxicology and pharmacokinetic testing in primates.

Comprehensive Sickle Cell Centers

A renewal of an NHLBI-initiated RFA operates a nationwide network of collaborative, comprehensive centers in basic and translational research focused on the development of cures or significantly improved treatments for sickle cell disease. The network of ten centers and a statistics and data management core will conduct basic research, inter-center collaborative clinical research, and local clinical research focused on the most promising biomedical and behavioral therapies. The centers will support the career development of young investigators in sickle cell disease research. They also will support services, including patient education, patient counseling, community outreach, and hemoglobin diagnosis.

Coordination of Vascularization and Lung Development

A new RFA, initiated by the NHLBI, fosters investigation of the fundamental relationships between vasculogenesis, angiogenesis modulation, and lung development in order to select rational therapeutic interventions for correcting aberrant lung development. Information on the temporo-spatial expression of the regulatory genes, growth factors, and receptors involved in the processes of vasculogenesis and angiogenesis would have the potential for broad clinical utility in forms of pathological angiogenesis such as primary pulmonary hypertension, diabetic retinopathy, and retinopathy of prematurity. Identification of agents that inhibit negative modulators of vascularization might provide opportunities to reverse arrested alveolization, which is a feature of the chronic lung disease observed in very-low-birth-weight premature infants.

Functional Heterogeneity of the Peripheral, Pulmonary and Lymphatic Vessels

A new NHLBI-initiated RFA encourages characterization of the structural and functional heterogeneity of arteries, veins, and lymphatics within the adult vasculature. A more complete understanding of the underlying regional, tissue, cellular, and molecular factors that contribute to the heterogeneity of the pulmonary and peripheral vascular beds will provide much needed insights into the presentation of vascular diseases and will lead to new and more effective treatments.

Genelink

A new Request for Proposals (RFP), initiated by the NHLBI, promotes a collaborative approach to gene finding in NHLBI-funded family studies. The goal is to use existing data to increase the yield and reliability of linkage results for pursuing fine mapping, gene identification, and characterization. The initiative will support an interactive website and a series of meetings involving investigators in 15 to 20 NHLBI genetic linkage studies.

Hutchinson-Gilford Progeria Syndrome: Exploratory/Developmental (R21) Grants

A new PA, co-sponsored by the NHLBI, the NIA, the NIDCR, and the NICHD encourages research on the molecular and mechanistic bases of Hutchinson-Gilford progeria syndrome (HGPS), an incurable and terminal premature aging disorder, characterized by short stature, abnormal skeletal and tooth development, scleroderma-like skin changes, and cardiovascular disease. Children with the disorder usually die of heart attacks or strokes at an average age of 13

years. Fibroblast and lymphoblastoid cell lines from HGPS patients from ten different families are available to awardees. A better understanding of the mode of inheritance, molecular basis, and pathomechanisms of HGPS could lead to new insights into the mechanisms of vascular occlusive diseases.

Hutchinson-Gilford Syndrome: Relationship to Mutations in the Lamin A/C Gene (LMNA) and to Other Known Laminopathies

A new PA, co-sponsored by NIA and NHLBI, focuses on understanding how mutations in the gene that codes developmentally for the lamin A/C nuclear protein leads to dysfunction of the nuclear envelope and, depending on the mutation, Hutchinson-Gilford syndrome (HGS) in humans. Understanding the biology of lamin may provide insights into how disturbances in lamin function could contribute to the pathogenesis of cardiovascular disease, possibly leading to new treatment paradigms.

International Cooperative Biodiversity Groups (ICBG)

A renewal in 2003 of an RFA co-sponsored by the NSF, the USDA, and several NIH institutes, including the NHLBI, addresses the interdependent issues of biodiversity conservation, economic capacity, and human health. The RFA encourages the discovery and development of therapeutic agents for diseases that are important to both developing countries and developed countries. Innovative, integrated approaches to access resources and to share benefits with host country stakeholders and participants are an important component of the overall program. Particularly relevant disease areas and health needs include cancer, HIV-AIDS and its opportunistic infections, tuberculosis, malaria and other emerging diseases, mental disorders of adults and children, drug abuse, and cardiovascular and pulmonary diseases.

Mechanisms of Fetal Hemoglobin Gene Silencing for Treatment of Sickle Cell Disease and Cooley's Anemia

A new RFA, initiated by the NHLBI, encourages research on the mechanisms involved in fetal hemoglobin (gamma-globin) gene silencing during normal human development and on developing therapeutic approaches to inhibit silencing. Both cis- and trans-acting elements important in gamma-globin gene silencing will be identified and their mechanisms of action determined. Pharmacologic or gene-based approaches to interfere with silencing may ultimately be pursued. Increased understanding of the molecular basis of fetal hemoglobin silencing will facilitate the development of new gene-based therapeutic approaches to increase fetal hemoglobin in red blood cells and thereby cure beta-chain hemoglobinopathies such as sickle cell disease and Cooley's Anemia.

Mesenchymal Stem Cell Biology

A new RFA, initiated by the NHIBI and cosponsored by the NIA, supports basic research on mesenchymal cell biology in order to provide the basis for clinical application of mesenchymal stem cells (MSCs) to hematopoietic and nonhematopoietic stem cell transplantation. MSCs are pluripotent progenitor cells located in bone marrow that can differentiate into a variety of

nonhematopoietic tissues, including bone, cartilage, tendon, fat, muscle, and early progenitors of neural cells. Preclinical studies suggest MSCs facilitate hematopoietic stem cell transplantation while decreasing immune rejection of allogeneic transplants. To realize the therapeutic potential of these results, the initiative supports the identification of population and assay methods to characterize the clinical potential of candidate human MSCs. Another goal of the RFA is to develop standards for isolating and characterizing MSCs to enable comparison of results from different studies.

Molecular Mechanisms of Mucous Metaplasia and Excess Mucin Secretion in Human Airway Diseases

A new NHLBI-initiated RFA promotes research to elucidate the molecular and cellular mechanisms of mucous metaplasia (the forming of an emergency blanket of mucus to trap and clear contaminants) and the pathways involved in the excess mucin secretion in airway diseases such as infections, chronic bronchitis, asthma, COPD, and sinusitis. The primary emphasis will be on investigations using in vitro systems and animal models. Investigators will be encouraged to apply their results in companion studies of the expression of specific regulatory molecules, the activities of specific mucous pathways, and the location, character, and extent of mucous metaplasia in the airways of humans with airway diseases.

Novel Approaches to Enhance Animal Stem Cell Research

A renewal of a PA, co-sponsored by 11 institutes, including the NHLBI, supports research to isolate, characterize, and identify totipotent and multipotent stem cells from nonhuman biomedical animal models. The PA also encourages researchers to generate reagents and techniques for characterizing and separating stem cells from other cell types. This trans-NIH announcement stresses innovative approaches to the problems of making multipotent stem cells available from a variety of nonhuman sources and to creating reagents that will identify multipotent stem cells across species allowing for their separation from differentiated cell types.

Pulmonary Fibrosis: Molecular Targets and Interventions

A new RFA, initiated by the NHLBI, will promote research to discover molecular targets for interfering with fibrogenesis in pulmonary fibrosis in humans and to identify agonists or antagonists that interact with previously or newly identified targets to attenuate, halt, or reverse the fibrotic process.

Somatic Cell Therapy Processing Facilities

A new Broad Agency Announcement (BAA) initiated by the NHLBI establishes centralized facilities for the development of cellular therapies that would provide support in areas ranging from basic science to animal studies to proof-of-principle and eventually human trials. Activities supported by the facilities will include, but not be limited to, primary *ex vivo* cell culture under Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) conditions, high throughput cell sorting, *ex vivo* expansion of desired cell subsets, and *ex vivo*-genetic

modification of cells with genes that will allow subsequent cell expansion or elimination under *in vivo* pharmacologic control.

Specialized Centers of Research (SCOR) in (a) Neurobiology of Sleep and Sleep Apnea and (b) Airway Biology and Pathogenesis of Cystic Fibrosis

A renewal of a NHLBI-initiated RFA will foster multidisciplinary basic and clinical research enabling accelerated application of basic science findings to clinical problems of sleep and cystic fibrosis (CF). The objective of the sleep SCOR is to integrate clinical research on the etiology and pathogenesis of sleep disorders, particularly sleep apnea, with molecular, cellular, and genetic approaches to the study of sleep. The objective of the CF SCOR is to use current knowledge of the CF transmembrane conductance regulator (CFTR) as a focus to promote advances in research on the pathogenesis of CF, the role of CFTR in airway biology, and the development of new treatment strategies.

Tuberculosis Curriculum Coordinating Center

A new NHLBI-initiated BAA strengthens, expands, and increases access to the best national tuberculosis (TB) educational and training curricula products developed under the NHLBI Tuberculosis Academic Award (TBAA) program. In the first phase of the award, medical and health professional school faculty members who are TB media and educational experts will: (1) develop survey instruments to assess student knowledge, (2) analyze current educational materials, (3) eliminate outdated materials, and (4) select materials appropriate for different educational levels. In the second phase of the award, high-level faculty members at medical schools without TBAA awards will work with a newly established Tuberculosis Curriculum Coordinating Center to implement the best TB curricula in their institutions. The program is designed to expand the impact of the TBAA program from the 25 medical schools with TBAA awards to all 125 medical schools in the U.S.

Zebrafish: Tools for Genetic Studies

A new Trans-NIH PA, co-sponsored by the NHLBI, exploits the power of mutagenesis screening in zebrafish in order to detect and characterize genes, pathways, and phenotypes of interest in development and aging, organ formation, behavior, and disease processes. A secondary goal of the announcement is to ensure that tools developed under it are made widely available to the research community.

Initiatives Planned for the Future

Diamond-Blackfan Anemia and Other Congenital Bone Marrow Failure Syndromes: Underlying Molecular Mechanisms

A new RFA will be initiated by the NHLBI in FY 2004 to promote research on the genetics and biochemical mechanisms of Diamond-Blackfan Anemia and other rare inherited bone marrow failure syndromes. An understanding of the molecular pathways disrupted in the syndromes would facilitate development of targeted therapies and stimulate research on the molecular

mechanisms underlying defective hematopoiesis, congenital anomalies, and cancer development in marrow failure diseases. Other diseases that are related to this initiative include dyskeratosis congenita, Pearson syndrome, severe congenital neutropenia (Kostmann syndrome), Shwachman-Diamond syndrome, and congenital amegakaryocytic thrombocytopenia.

Exploratory and Developmental Research Grants for Investigations in Rare Diseases (R21)

A new PA, which will be initiated by the NHLBI and co-sponsored by the ORD in FY 2004, encourages research on understanding, treating, and preventing rare diseases in the areas of heart, lung, and blood disease as well as sleep disorders. Such diseases are often referred to as "orphan" diseases since there is a general lack of interest among industries to invest resources in diseases that in aggregate affect too few people to guarantee a reasonable return on investment.

Granulomatous Lung Inflammation in Sarcoidosis

A new RFA will be initiated by the NHLBI in FY 2004 to support research on the immunopathogenic mechanisms that lead to the nontuberculous granulomatous inflammation in the lungs seen in sarcoidosis. In addition to seeking the etiology of sarcoidosis and determining its susceptibility factors, research will focus on identifying the components in the innate and/or adaptive immune pathways that affect lung lymph nodes and tissue.

NHLBI Lung Tissue Resource

A new BAA will be initiated by the NHLBI in FY 2004 to facilitate studies of pulmonary diseases by establishing and supporting a program for the standardized processing, storage, and distribution of lung tissues and their associated clinical data. The resource will enable investigators to perform studies correlating molecular histopathology of the lung with pulmonary function and clinical status. Tissues will be procured and processed from 500 smoking and nonsmoking subjects with essentially normal lungs and from 2,000 subjects with pulmonary disease. The majority of those with disease will have COPD and will be extensively characterized with respect to airflow limitation and CT measures of emphysema. Lung specimens will also be obtained when possible from individuals with pulmonary fibrosis, sarcoidosis, asthma, primary pulmonary hypertension, and other serious chronic diseases that affect the lungs.

Pediatric Mechanical Circulatory Support

A new BAA to be initiated by NHLBI in FY 2004 will develop mechanical assist devices, including extracorporeal membrane oxygenation (ECMO) systems, left ventricular assist devices (LVADs), and other bioengineered systems for children with congenital and acquired cardiovascular disease. The program will provide basic physiological and bioengineering data necessary for the design of effective pediatric assist and replacement devices while also supporting Phase I studies to explore innovative strategies to meet the clinical needs of the pediatric patient population.

Programs for Genomic Applications (PGAs) for Heart, Lung, and Blood Research

A renewal in FY 2004 of an NHLBI-initiated RFA will link the genomic resources and tools of the Human Genome Project (HGP) to major biological processes and systems involved in cardiovascular, pulmonary, hematologic, and sleep function and dysfunction through the establishment of 11 Programs for Genomic Applications (PGAs) for Heart, Lung, and Blood Research. The PGAs will identify subsets of genes that are particularly relevant to the biology, diagnosis, management, treatment, and prevention of heart, lung, blood, and sleep-related disorders and prioritize the information for further focused study. The generation and interpretation of data from the PGAs will enable a broad range of investigators to exploit the unique opportunities provided by the information coming from the HGP and related technologies. In addition, the PGAs will continue training and education programs for NHLBI-supported investigators in the use of genomic information and technologies. The 11 PGAs are expected to continue to collaborate to develop common protocols, standard procedures, and nonredundant education and training efforts.

Genetic and Cellular Discovery in Myelodysplastic Syndromes (MDS)

A new RFA to be initiated by the NHLBI in FY 2005 and co-sponsored by the NCI will investigate the causes and progression of myelodysplastic syndromes (MDS) in order to discover new therapeutic approaches. MDS is a collection of disorders in which the bone marrow does not produce enough blood cells. The disease can develop due to exposure to certain chemicals or radiation, e.g., those used for the treatment of cancer. A rare, familial form may also develop in patients who have family members with MDS. Through basic stem cell biology experiments, the mechanisms of disease can be studied. The use of gene expression analysis and/or identification of gene products or cellular molecular expression may be instrumental in discovering pathways of disease development and evolution.

Interstitial Lung Fibrosis Clinical Research Network

In FY 2005, the NHLBI will initiate a new RFA to establish a network of clinical centers to conduct multiple treatment trials on patients with established idiopathic pulmonary fibrosis (IPF), a disease of inflammation that results in scarring, or fibrosis, of the lungs, and eventually interference with oxygen transport. Researchers believe that IPF may result from either an autoimmune disorder or the after effects of an infection, most likely a virus. The network will consist of eight clinical centers and a data coordinating center. Each of the clinical centers is expected to enroll 40 to 50 patients per center per year for a 2-year interval of treatment and 2 years of follow-up. For patients who require an open lung biopsy for diagnosis, living lung tissue and blood will be stored for future studies on cellular genomic and immunopathogenic changes.

National Registry of Patients with Marfan Syndrome

A new RFA will be initiated by the NHLBI and co-sponsored by the NIAMS in FY 2005 to establish a registry to collect and analyze clinical data and samples (e.g., blood and tissue) of Marfan patients and improve understanding of cardiovascular complications and therapies for the disorder. Ultimately, the registry will provide an essential resource to improve clinical care for patients afflicted with Marfan syndrome.

Pulmonary Complications of Sickle Cell Disease

In FY 2005, a new RFA will be initiated by the NHLBI to conduct basic and clinical research on the pulmonary complications of sickle cell disease (SCD). Acute sickle cell chest syndrome, the second most common acute clinical complication of SCD, is characterized by infiltrates in the lungs, and sometimes by fever, pneumonia, and thromboembolism of peripheral blood clots and/or fat emboli. The less common chronic form of sickle cell lung disease is characterized by pulmonary perfusion and diffusion defects, pulmonary hypertension, changes in the vessel walls such as intramural and perivascular connective tissue deposition, hyperplasia/hypertrophy of smooth muscle cells, and, in some cases, by intramural thrombosis. Further elucidation of the acute and chronic lung syndromes is required in order to develop more adequate therapies.

Thalassemia Clinical Research Network

In FY 2005, the NHLBI will renew an RFA to continue operation of a cooperative network of five clinical centers and a data coordinating center conducting clinical trials to evaluate existing and future therapies for the treatment of thalassemia major (Cooley's Anemia). The network enhances progress in moving effective therapies, e.g., fetal hemoglobin enhancing agents, gene therapy, or iron chelation, from the laboratory to the bedside through rapid and systematic collaborative testing in phase II and phase III clinical trials. A registry of thalassemia patients has also been developed and will be used to identify patients available for future trials.

Rare Diseases-Related Program Activities

The five NHLBI Specialized Centers of Research in Pediatric Cardiovascular Disease held their annual meeting in FY 2003. The discussion at the meeting focused on basic and clinical advances in understanding normal and abnormal heart development.

In September 2002, the NHLBI and the Alpha One Foundation co-sponsored a meeting titled *"Models of Emphysema: Speeding the Pace of Progress."* Participants discussed the utility of animal models in studies of Alpha-1-antitrypsin deficiency and chronic obstructive pulmonary disease.

In September 2003, the NHLBI and Office of Rare Diseases co-sponsored a meeting titled *"Macro-Molecular Interactions and Ion Transport in Cystic Fibrosis."* The meeting highlighted the multiple pathways and interacting proteins involved in CFTR folding, biosynthesis, processing, and trafficking.

The NHLBI and the LAM Foundation co-sponsored the *LAM Research Conference* in Cincinnati, Ohio, in April 2003.

The NHLBI and the Office of Rare Diseases co-sponsored a workshop called *Translational Research in Primary Pulmonary Hypertension: Future Directions* in March 2003. Recommendations were discussed in three areas: 1) genetic studies; 2) receptors, mediators, ion channels, and signaling studies; and 3) clinical studies.

The Pulmonary Hypertension Association is collaborating with the NHLBI to support new career award (K series) investigators who are conducting research projects on PPH.

An NHLBI-sponsored working group, titled *Future Directions in Sarcoidosis Research,* was held in August of 2002 in Bethesda, Maryland. The summary of this meeting was submitted to the *American Journal of Respiratory and Critical Care Medicine* and is now being revised.

The annual meeting of the reconstituted *Collaborative Program for Research in Bronchopulmonary Dysplasia* took place in September 2003 in San Antonio.

In June 2003, the NHLBI sponsored a *Working Group on Stem Cell Therapies.*

In April 2003, the NHLBI held a meeting on progress related to an RFA titled *"Stem Cell Transplantation and Biology."*

In April 2003, the NHLBI sponsored a meeting on progress related to an RFA titled *"Clinical Research for Cooley's Anemia and Biology of Iron Overload."*

In October 2003, the NHLBI participated in the *fifteenth Annual Fanconi Anemia Research Fund Scientific Symposium* sponsored by the Fanconi Anemia Research Foundation and held in Houston, Texas.

The Comprehensive Sickle Cell Center Steering Committee met for the first time in December of 2002. This group, which for the first time contains a collaborative clinical research component, presented, discussed, and ranked proposals for collaborative multicenter clinical research protocols.

A meeting titled *"Bone Marrow Transplantation for Hemoglobinopathies"* was held in August 2003. The goal of the meeting was to foster cooperation between the various small and large bone marrow transplantation consortia so that morbidity and mortality from the therapy can be decreased. Investigators in the fields of bone marrow transplantation and sickle cell disease clinical care discussed current transplant protocols and U.S. database information.

At the *BABY HUG Steering Committee Meeting* held in August of 2003, investigators finalized plans for protocol development and subject recruitment for the BABY HUG clinical trial. The objective of the trial is to determine if hydroxyurea therapy is effective in the prevention of chronic end-organ damage in pediatric patients with sickle cell disease.

The Multicenter Study of Hydroxurea Patients' Follow-up Steering Committee Meeting was held in August 2003. At the meeting, investigators discussed follow-up of the cohort for the next 5 years.

The STOP II Trial Steering Committee met in August of 2003 to discuss the STOP II Trial protocol and subject recruitment. The STOP II Trial will attempt to ascertain if it is safe to stop transfusing children with sickle cell disease who have already suffered a stroke after 30 months.

A Nursing Outcomes workshop was held in August 2003. Nurses and physicians who care for patients with sickle cell disease met to discuss clinical practice care and nursing outcome guidelines. Updates were provided for usage of hydroxyurea and care for patients with acute chest syndrome.

An Adult Providers Network meeting was held in August 2003. Adult hematologists who care for patients with sickle cell disease met to discuss improving care by providing consultation services for patients who live in parts of the U.S. that are not served by a Comprehensive Sickle Cell Disease Center.

A workshop titled *"New Therapies for Sickle Cell Disease in the Genome Era"* was held in November 2003. Approximately 120 SCD researchers were invited to deliberate on gaps in the current federal SCD research program and future directions. Major recommendations from the meeting were to: (1) increase clinical research infrastructure that will allow linking of DNA resources to clinical phenotypes, (2) standardize definitions of SCD complications used in research, and (3) maintain training of new researchers.

A meeting titled *"Lupus Today: Research into Action"* was held in September 2003. The meeting was co-sponsored by the NHLBI, 13 other DHHS components (NIH Institutes, CDC, FDA, HRSA, and several offices within the Office of the Secretary, DHHS), and eight voluntary organizations involved in lupus, autoimmune-related diseases, and arthritis research. Scientists and physicians shared information about ongoing clinical trials. Panel discussions included planned future clinical trials, enhancement of patient participation in trials, and potential new therapeutic agents for lupus.

Problem Areas Related to Rare Diseases

Alpha-1 Antitrypsin Deficiency

Research needs include better animal models of the disease, identification of biomarkers, development of chemical chaperones that could specifically enhance the secretion of mutant alpha-1 antitrypsin protein, and improvements in approaches to gene therapy.

Bronchopulmonary Dysplasia (BPD)

The incidence of BPD has increased in recent years due to the increased survival of smaller and smaller premature infants. At least 10,000 very-low-birth-weight infants suffer from BPD each year. The associated neonatal intensive care costs are approximately $30,000 - $60,000 per

individual. Basic research on the etiology of BPD continues to be required to inform clinical intervention and, thereby, to reduce the high costs of clinical care.

Brugada's Syndrome

The challenge is to use knowledge of the basis of the disease to develop effective therapies.

Congenital Diaphragmatic Hernia (CDH)

There is no evidence that fetal surgical intervention represents an advance for CDH. Accurate counseling regarding the expected outcome is crucial. Scientific information on alternative treatments for CDH must be provided to assist affected families in making decisions about appropriate management of the disorder.

Congenital Heart Disease

With the improvements in surgery made during the past 30 years, many children with congenital heart disease can now grow into adulthood. However, little systematic research has addressed the management of adults with congenital heart disease, or the interaction between congenital heart disease and adult cardiovascular disease. A related concern is that many children need multiple open-heart operations to replace valves that they outgrow. Researchers using bioengineering techniques hope eventually to develop valves that would grow with a child. In addition, better understanding of heart development is needed. It is especially important to increase understanding of: (1) the development of coronary arteries, (2) the process by which the heart develops from a symmetric tube to a complex folded structure with a distinct left and right side, and (3) regulation of heart muscle cell division.

Cooley's Anemia (CA)

Growth and development in patients with thalassemia remains a problem. Cardiac morbidity and mortality in CA patients is still a major concern. A number of co-morbidities are associated with the chronic transfusions required by people with CA, including infectious diseases (e.g., HIV and hepatitis C) and iron overload. The nature of iron toxicities and their tissue specificities require further study and new approaches to chelation therapy are needed. The morbidity and mortality associated with transplantation of hematopoietic stem cells remain unacceptably high. The potential for gene therapy remains untapped and untested in clinical studies.

Creutzfeldt-Jakob Disease (CJD)

Recently, the British Government reported a possible case of transmission of vCJD to a blood transfusion recipient, the first report that the disease might be transmitted to people through blood transfusion. The British are considering this a presumptive case of transfusion-transmitted vCJD because, statistically, it is highly unlikely that the recipient developed the infection by another mode of transmission. The potential for blood transmission of vCJD underscores the need for a sensitive screening assay to detect vCJD. A screening assay could form the basis of a blood/tissue donor screening test and could provide a diagnostic test for neurologists. Currently,

there is no way of detecting disease in the pre-clinical stage. These assays could also be useful in testing for TSE in animals, especially in domestic animals used for human consumption.

Cystic Fibrosis

A large animal model is needed that replicates the human disease. Many questions, related to both clinical and basic research problems, remain to be answered about gene therapy for cystic fibrosis. Additional information is needed about the basic biology of CFTR. An important goal is to provide an integrative understanding of the impact of mutant CFTR on the pathological processes of CF and to determine whether repairing mutant CFTR with various agents will reverse these processes.

Fanconi Anemia (FA)

Defects in any one of no less than eight different genes can cause FA. The process of identifying the mutations responsible for a particular case of FA is complicated and cumbersome because each of the eight potential genes must be examined for mutations.

Hemophilia

Approximately 20 percent of severe hemophilia patients develop antibody inhibitors that specifically neutralize the activity of the replacement factor (e.g., factor VIII) and complicate treatment. The adult hemophilia population has been severely affected by blood-borne infectious agents in plasma derived replacement products. Over 80 percent have been infected with hepatitis virus and approximately 20 percent are infected with HIV.

Hereditary Hemorrhagic Telangiectasia (HHT)

Diagnosis of patients with vascular malformations, particularly at an early age, is difficult because multiple organs are affected. Establishment of a genetic linkage may allow earlier diagnosis and improved treatment.

Homozygous Familial Hypercholesterolemia

Very few people have homozygous familial hypercholesterolemia, making it difficult to study.

Idiopathic Pulmonary Fibrosis (IPF)

Because IPF is a rare disease, it is difficult to recruit enough patients for studies. All clinical trials require a multicenter effort, hence the need to create a clinical research network. The natural course of the disease is poorly understood and no animal models exactly replicate the human disease. Only one effective treatment, lung transplantation (if successful), exists.

Klippel-Trenaunay-Weber Syndrome (KTWS)

Very few people have KTWS, making it difficult to study.

Long QT Syndrome (LQTS)

The number of patients with well-defined Long QT mutations is insufficient to permit clinical studies of interventions. Investigators continue to work to increase the visibility of the LQTS registry in the African American medical community. It is not known whether LQTS is less common among African Americans, or if they are referred to the registry with less frequency compared to the Caucasian population.

Lymphangioleiomyomatosis (LAM)

LAM tissue is scarce and cell lines are difficult to establish and maintain. In addition, more work is needed to establish relevant animal models of LAM.

Lymphedema

It is difficult to get biotech and pharmaceutical companies interested in working on lymphedema due to a general lack of interest among industries in investing resources in diseases that do not guarantee a reasonable return on investment.

Persistent Pulmonary Hypertension of the Newborn (PPHN)

Even with complex and high-risk interventions such as extracorporeal membrane oxygenation, PPHN currently results in substantial mortality and morbidity.

Primary Pulmonary Hypertension (PPH)

Many approved therapies for PPH are expensive and as yet offer relatively minor benefits to exercise capacity. Aggressive efforts to launch Phase I and Phase II trials to evaluate new treatments for PPH are needed. Because PPH is a rare disease collaborative efforts are required in order to conduct meaningful clinical trials. Development of animal models that mimic PPH in humans is a high priority for future research. Noninvasive methods and biomarkers to monitor pulmonary artery pressure and the course of PPH are not yet available. Better efforts are needed to boost collaborations between basic researchers and clinical investigators.

Sarcoidosis

Human tissue and animal models are needed to advance basic research on sarcoidosis. In spite of efforts by many researchers over the last half century, no etiologic agent has been identified. Better diagnostic markers and better treatments are needed.

Supravalvular Aortic Stenosis (SVAS)

Very few people have SVAS, making it difficult to study.

Systemic Lupus Erythematosus (SLE)

The fear of miscarriage is of great concern for many women with SLE. The use of antibodies to phospholipids to prevent blood clots in high risk pregnant women needs evaluation. Trials of more focused and effective anti-inflammatory therapies are needed. More research is needed to elucidate the factors contributing to accelerated cardiovascular disease in patients with SLE.

Thrombotic Thrombocytopenic Purpura (TTP)

Plasmapheresis has improved the survival of patients with TTP, but it remains an expensive and laborious procedure. The metalloprotease ADAMTS 13 could be useful for specific therapy of familial TTP. The expression and yield of the recombinant product has limited large scale production of the protease, which will be needed for clinical studies.

NATIONAL HUMAN GENOME RESEARCH INSTITUTE (NHGRI)

Overview of Rare Diseases Research Activities

The National Human Genome Research Institute led the National Institutes of Health's (NIH) contribution to the International Human Genome Project, which had as its primary goal the sequencing of the human genome. This project was successfully completed in April 2003, ahead of schedule and under budget. April 2003 also witnessed the 50th anniversary of James Watson and Francis Crick's Nobel Prize winning description of the DNA double helix. To mark these achievements in the history of science and medicine, the NHGRI, the NIH, and the Department of Energy held a month-long series of scientific, educational, cultural, and celebratory events across the United States. Furthermore, in April 2003 NHGRI published a landmark scientific report describing the future of the field of genomics and the role of NHGRI in realizing that future.

NHGRI's mission has now expanded to encompass a broad range of studies aimed at understanding the structure and function of the human genome and its role in health and disease. After completing a more than year-long planning effort, the NHGRI has created a vision document to guide the institute into a new era of genomic research. The vision, formulated into the major themes of genomics to biology, genomics to health, and genomics to society, includes six crosscutting elements (resources, technology development, computational biology, training, ethical, legal and social implications, and education) relevant to all three themes. Both NHGRI intramural scientists and scientists in the broader biomedical research community will develop resources and technology to accelerate scientists' understanding of the molecular basis of common and rare diseases and ultimately lead to improved diagnostic, prevention, and treatment strategies.

Inherited Disorders of the Immune System

The NHGRI Genetics and Molecular Biology Branch is conducting a research program to find the causes and develop better treatments for inherited disorders of the immune system. These include immunodeficiencies, in which gene defects impair the ability of the immune system to fight infections, and also disorders of immune cell regulation, in which autoimmunity may be seen. Current areas of investigation include severe combined immunodeficiency, mucocutaneous candidiasis, hyper-IgE syndrome, certain inherited autoimmune diseases, including variants of autoimmune lymphoproliferative disease, and genetic determinants of susceptibility to HIV/AIDS.

Severe Combined Immunodeficiency (SCID)

SCID is a rare, but devastating complete lack of T cell and B cell immunity, also known as the Bubble Boy disease. The gene for the most common form of SCID was discovered by NHGRI scientists to be the IL2RG gene, which encodes the common gamma chain of receptors for several lymphocyte growth factors or cytokines. When this gene is defective, lymphocytes cannot develop normally, and affected infants therefore have frequent, severe infections that are ultimately fatal unless the immune system can be restored. Scientists are analyzing the

expression and function of the common gamma chain protein. Carrier testing and genetic counseling can then be provided, as well as prenatal diagnosis, which makes affected infants eligible for improved early treatments.

In addition, scientists have developed and tested methods for correcting the genetic defect in X-linked SCID by gene transfer. Bone marrow transplant is often life saving and gene transfer is a promising treatment. Clinical trials of human gene transfer are planned to treat patients with X-linked SCID who were not helped by bone marrow transplant.

Hyper IgE Syndrome (Job's Syndrome)

Hyper IgE syndrome is an enigmatic, rare condition characterized by recurrent skin abscesses, recurrent pneumonia with development of lung cysts, and extreme elevations of serum IgE. The specific immune defect has not been discovered; however, NHGRI scientists have found that the syndrome can be inherited as an autosomal dominant disorder and therefore genetic studies may help find the cause. NHGRI and NIAID scientists have arrived at a new clinical understanding of the condition as a multi-system disorder with immune, dental, and skeletal abnormalities. It has variable expressivity and penetrance. Genome-wide linkage studies show at least 3 loci in the human genome that may be associated with hyper-IgE syndrome. Scientists have also mapped dominant mucocutaneous candidiasis to human chromosome 2p.

Autoimmune Lymphoproliferative Syndrome (ALPS)

ALPS is a newly discovered syndrome in which patients have large lymph nodes and spleens, autoimmune disease, increased numbers of a rare type of lymphocyte called CD4-/CD8- T cells, and defects in programmed cell death of their lymphocytes. NIH research has shown that people with ALPS have a high risk of lymphoma. NHGRI and NIAID scientists have discovered that most patients with this condition have inherited defects in the apoptosis mediator Fas. The position of mutations within the Fas gene influences how severe the case of ALPS is and whether family members with the same mutation are likely to have symptoms. Mouse models for ALPS combined with studies of family members can show how varying genetic background influences the disease manifestations.

Developmental Disorders

Hutchinson-Gilford Progeria Syndrome (HGPS)

HGPS is the most dramatic human syndrome of premature aging. Children with this rare condition usually appear normal at birth; however, within a year, their growth rate slows and their appearance begins to change. Affected children typically become bald with aged-looking skin and pinched noses. They often suffer from symptoms typically seen in elderly people, especially severe cardiovascular disease. Death occurs on average at age 13, usually from heart attack or stroke. Taking advantage of an array of genomic technologies–from whole-genome scans to high-throughput sequencing of targeted DNA regions–researchers at NHGRI determined the most common cause of progeria is a single-letter "misspelling" in a gene on chromosome 1 that codes for lamin A, a protein that is a key component of the membrane surrounding the cell's

nucleus. Specifically, the researchers found that 18 out of 20 children with classic progeria harbored exactly the same misspelling in the lamin A (LMNA) gene, a substitution of just a single DNA base among the gene's 25,000 base pairs. In addition, one of the remaining progeria patients had a different single base substitution just two bases upstream. In every instance, the parents were found to be normal, indicating that the misspelling was a new, or "de novo," mutation in the child. The research team believes this work may extend far beyond progeria to tell us much more about the molecular basis of this model of premature aging may provide us with a better understanding of what occurs in the body as we all grow older.

Polydactyly Syndromes

A group of syndromes that include polydactyly with other malformations is the subject of a clinical-molecular study. These disorders include Pallister-Hall Syndrome (PHS), Greig cephalopolysyndactyly syndrome (GCPS), McKusick-Kaufman syndrome (MKS), and Bardet-Biedl syndrome (BBS). The manifestations of these disorders include polydactyly, central nervous system malformations (with or without mental retardation and seizures), craniofacial malformations, and visceral malformations such as renal malformations or congenital heart defects. Researchers are studying these disorders using a translational approach that begins in the clinic with careful clinical evaluation of the phenotypes by physical examination, imaging studies that include radiographs, ultrasound, MRI, and CT scanning. This work has demonstrated the cause of PHS and also that BBS and MKS can both be caused by mutations in the same gene. In addition, researchers have shown that in GCPS, patients with large deletions are more likely to have developmental delay or delayed speech.

Lowe Syndrome

Lowe syndrome (OCRL) is a rare X-linked metabolic disorder characterized by congenital cataracts, developmental delay, and Fanconi syndrome of the renal tubules. The defect is a deficiency in an enzyme, a phosphatidylinositol 4,5 bisphosphate 5-phosphatase localized in the golgi complex, particularly the trans-Golgi network. NHGRI scientists are investigating the relationship between this enzyme deficiency and the clinical phenotype through cellular and animal models. NHGRI is also hosting a major clinical conference this year in cooperation with the Office for Rare Diseases, the Lowe Syndrome Association (U.S.A.), and the Lowe Syndrome Trust (U.K.) to address problems in management and treatment of complications of Lowe syndrome.

Hirschsprung Disease

Animals heterozygous for mutations in the SOX10 transcription factor exhibit multiple defects in neural crest development, including reduced numbers of melanocytes in the skin, an absence of myenteric ganglion in the colon, and deafness. A human congenital disorder, Hirschsprung disease, also exhibits rectocolic aganglionosis and hypopigmentation caused by SOX10 mutations. Thus SOX10 mice, as well as other neural crest mutant mice, serve as mouse models for this disease. Investigation of the involvement of SOX10 in Hirschsprung disease and other neural crest related disorders is being explored.

Microphthalmia Syndromes

Researchers at NHGRI seek to understand the clinical and molecular basis of syndromic forms of microphthalmia, including the Lenz microphthalmia syndrome, a rare disorder causing small or absent eyes, mental retardation, and skeletal anomalies. Researchers have identified a large family affected by this disorder and have mapped the gene to the short arm of the X chromosome. The results show that Lenz microphthalmia is an amalgam of two disorders due to another family with this disorder mapping to the long arm of the X chromosome. Researchers have isolated the gene that is altered in the condition and found that Lenz syndrome is related to another disorder of eye development called the Oculofaciocardiodental syndrome. The results of this research should allow development of accurate diagnostic tests for microphthalmia and improved understanding of eye development.

Molecular Genetics of Anabaptist Diseases

The Old Order Amish and Mennonites represent a cultural and genetic isolate and are subject to a number of extremely rare and perhaps unique genetic diseases. The diseases under study in the past year include Amish microcephaly, a disease that affects fewer than 75 persons and causes severe prenatal brain maldevelopment and hypoplasia. The disorder is lethal and patients usually die within six months. Progress has been made in the genetic and physical mapping of this disease and collaborative efforts are underway to characterize the CNS pathology.

Proteus Syndrome

Proteus syndrome is a rare, sporadic syndrome that causes progressive, patchy overgrowth, bony distortion or deformation, tumor predisposition, and mental retardation. The purpose of this project is to determine the natural history and etiology of Proteus syndrome. The natural history and the phenotypic range will be determined by clinical assessment and longitudinal follow-up of a cohort of patients. Very little is known about the natural history and the range of the phenotype of Proteus syndrome. Some diagnostic confusion should be expected for patients affected by a disorder that is hypothesized to be due to somatic mosaicism, as this mosaicism is inherently variable among patients. To address this issue, NHGRI researchers have accrued a cohort of nearly 40 patients with Proteus syndrome and overlapping phenotypes and are following them over time. As the disorder is usually apparent at or soon after birth and appears to evolve at least into the twenties, it will be necessary to have long-term follow-up. The etiology has been studied using various comparative molecular biology techniques, including representational difference analysis, cDNA arrays, and other techniques.

Alagille Syndrome (AGS)

Scientists at NHGRI have shown that mutations in the Jagged1 (JAG1) gene are responsible for AGS, a developmental disorder affecting multiple organ systems, including liver, heart, eye, face, and vertebrae. In order to understand the role of Jaggeds in vertebrate development and to understand how alterations in their function lead to AGS in humans, scientists have isolated and characterized Jagged genes from zebrafish. There are 3 Jaggeds in zebrafish and they exhibit

distinct expression patterns during development. Blocking expression of Jaggeds with antisense oligonucleotides are being carried out to evaluate the function(s) of the Jagged proteins in vertebrate development.

Left-Right (L-R) Axis Malformations

A study of the complex genetics of L-R axis malformations has been undertaken with an emphasis on genes that are associated with common phenotypes of L-R disorders, including situs inversus, heterotaxia, and organ isomerism. L-R defects can result from either environmental or genetic causes. Investigators at NHGRI aim to determine the genes responsible for both normal and abnormal L-R axis formation through the study of patients with these disorders. Mutations in genes such as ZIC3, LEFTY A, and ACVR2B have been shown to be responsible for several familial and sporadic cases of heterotaxia. It is anticipated that many additional genes important for L-R development will be identified in the search for genetic causes of laterality disorders. Recently, NHGRI scientists have identified the human CFC1 gene as causing laterality defects and are studying this and other genes in individuals with cardiac anomalies.

Congenital Disorders of Glycosylation (CDG)

CDG is a group of metabolic disorders characterized by a wide range of phenotypic presentations from severe developmental delay and systemic manifestations to only gastrointestinal symptoms and normal development. CDG results from defective N-linked oligosaccharide synthesis; a pathway with approximately 200 steps, with different types of CDG resulting from a disruption in any individual step. NHGRI scientists are identifying new patients with CDG and conducting studies to determine the pathogenic basis for novel cases of CDG and to define the relationship between genotype and phenotype in CDG patients. As an outcome of the proposed investigations, NHGRI scientists expect to elucidate the correlation between the phenotype, the glycobiology, and the genes involved.

Neurological Disorders

Friedreich's Ataxia

Friedreich's ataxia is an inherited disease that causes progressive damage to the nervous system resulting in symptoms ranging from muscle weakness and speech problems to heart disease. Researchers at NHGRI are studying the perceptions of adults with Friedreich's ataxia regarding transitional events were described. Across the lifespan, key transitional events mark important points when one's life course is significantly altered. Transitional events were either a direct outcome of Friedreich's ataxia or a developmental task altered by having the condition. Events were a reflection of the individual's experience with Friedreich's ataxia and often corresponded to clinical progression. One's awareness of symptoms changes in mobility status and concern about falling were the most salient themes from the experience of living with Friedreich's ataxia. Developmental events influenced by the condition were one's primary relationships and life's work. Both Friedreich's- and developmentally-related transitions affected self-image, life activities, and future planning. The severity of the condition and age contributed to the nature of each identified event. Participants reported using both emotion and problem-based coping

strategies during transitional events. These results, as well as data obtained from participants about experiences with health care providers, help to alert professionals of potentially challenging times in patients' lives, which are subtly or profoundly influenced by chronic illness or disability and suggest areas for further research. Implications for developmental counseling approaches, which emphasize key transitional events, were suggested for genetic counseling.

Hyperparathyroidism-Jaw Tumor (HPT-JT) Syndrome

HPT–JT syndrome is an autosomal dominant, multiple neoplasia syndrome primarily characterized by hyperparathyroidism due to parathyroid tumors. Researchers at NHGRI aim to narrow the region on chromosome 1 where a locus for HPT-JT had been mapped by several previous linkage studies and to eventually clone and characterize this gene. The gene has been localized and characterized within the region indicated by our fine-mapping analyses. Researchers plan to use these data to examine questions about haplotype sharing method and its uses in localizing disease genes. Future research is being planned on studies of the penetrance of various mutations at this locus and of possible gene-environment interactions between susceptibility alleles at this locus and various environmental risk factors.

Familial Encephalopathy with Neuronal Inclusion Bodies (FENIB)

NHGRI researchers continue to explore the clinical, laboratory, neuropsyche, and imaging features of at-risk members of families with Familial Presenile Dementia with Neuroserpin Storage. The clinical facet of this project continues to be a long-term exploration of the natural history of family members at risk. The protocol was extended to the pediatric population, which will increase insight into the pathophysiology and clinical presentation of FENIB. These families provide not only rich clinical insight but also the opportunity to understand the controversy surrounding presymptomatic testing in late onset neurodegenerative disorders. Further clinical delineation and assessment of counseling needs remain the clinical goals for this project. A parallel laboratory project includes the development of a mouse model for FENIB, which will further help to elucidate the phenotype and genotypic variation.

Endocrine Disorders

Multiple Endocrine Neoplasia Type 1 (MEN1)

MEN1 is characterized by multiple tumors of the parathyroid, anterior pituitary, and GI endocrine tissues. Researchers at NHGRI have shown earlier that mutations in the MEN1 gene are responsible for the MEN1 syndrome, and the MEN1 encoded nuclear protein, Menin, binds the transcription factors JunD and NFkB and can repress JunD and NFkB-induced transcription. Researchers have developed both conventional and conditional mouse knockout models, which yield phenotypes that are remarkably similar to the human MEN1 disease, which has allowed them to delineate the stages in tumor development. In addition, researchers developed tissue specific menin-inducible transgenic mouse models. Gene expression changes associated with the presence or absence of menin in mouse fibroblast cell lines and in islet cells at various stages of tumor formation are being studied. A model to re-express menin in knockout mice and to monitor the tumor growth/regression by a combination of histological analysis and noninvasive

imaging methods is being developed. Efforts are underway to explore the role of menin on differentiation, if any, by inducing menin-null ES cells to differentiate into pancreatic islet cells. In addition, tissue specific transgenic expression and knockout models for MEN1 are also being developed in Drosophila. These models should help to understand the functional role of menin.

Disorders of Vision

Cataract and Craniofacial Anomalies Syndrome

A new rare syndrome involving congenital cataracts and craniofacial anomalies in an inbred Saudi Arabian family has been identified. The most prominent feature is a failure of closure of the fontanels and sutures; and, at birth, the anterior fontanel is large due to open sagittal and metopic sutures. The second major feature is posterior Y-shaped structural cataracts that are congenital or develop over time. Chromosomal and biochemical studies were normal. A genome-wide screen was performed using 387 markers at the Center for Inherited Disease Research on 21 DNA samples. Efforts to fine map the gene were completed with a single candidate gene identified. A search for candidate loci is underway and tests for association will be used in an attempt to narrow the region and to subsequently clone the gene.

Rieger Syndrome

A continuing area of interest of researchers at NHGRI involves the homeodomain family of proteins, which play a fundamental role in a diverse set of functions that include body plan specification, pattern formation, and cell fate determination during metazoan development. Members of this family are characterized by a helix-turn-helix DNA-binding motif known as the homeodomain. Homeodomain proteins regulate various cellular processes by specifically binding to the transcriptional control region of a target gene. These proteins have been conserved across a diverse range of species, from yeast to human. A number of inherited human disorders are caused by mutations in homeodomain-containing proteins. One specific homeodomain protein, FOXC1, is implicated in Axenfeld-Rieger malformations. Patients with Axenfeld-Rieger malformations typically show a spectrum of ocular findings, including iris hypoplasia, a prominent Schwalbe line, iris adhesions, and goniodysgenesis. The most severe cases show elevated intraocular pressure, leading to the development of glaucoma. Work is continuing in this area to better understand these eye related mutations and their net effect on vision.

Rare Diseases-Specific Meetings and Workshops

"Lowe Syndrome: Clinical Challenges and Solutions" Conference

Lowe (oculocerebrorenal) syndrome is a rare genetic disorder that affects multiple organ systems and presents complex clinical challenges. Most individuals with Lowe syndrome must be followed by specialists in many different areas, including ophthalmology, nephrology, neurology, genetics/metabolism, orthopedics, endocrinology, and specialized dentistry. Because of the complex and fragmented nature of these medical services, patients with Lowe syndrome may not receive the maximum benefit available from these various specialties. Also, because Lowe syndrome is rare, clinicians often find it difficult to locate sources of accurate and

comprehensive information on appropriate care. Finally, because the various clinical features result from the same underlying metabolic error (lack of a specific enzyme), areas of commonalities may exist between the different disciplines that have not yet been identified. Knowledge gained from clinical experience in one area may be relevant to understanding and treating complications in another area.

The Lowe Syndrome Research Workshop brought together knowledgeable and experienced physicians to exchange ideas about appropriate treatments and suggest hypotheses for future clinical trials. The meeting could lead to increased interest in clinical research projects in order to develop more effective treatments. Approximately 30 physicians from about eight different medical specialties were invited to participate in a 2-day meeting in the fall of 2002. These physicians were chosen based on their first-hand knowledge treating patients with Lowe syndrome and/or their experience and expertise in clinical research in various areas of medicine pertinent to Lowe syndrome. One participant in each specialized area made a brief presentation on the complications of Lowe syndrome in that area. Following each presentation, all participants were invited to comment based upon their experience and knowledge regarding the clinical features and effective care. At the end of the meeting, a 1-2 hour summary session included a discussion of future plans, a listing of medical questions that need to be answered, and the identification of potentially promising areas for clinical research. The Lowe Syndrome Association arranged for the entire meeting to be audio taped.

Bringing the Genome to You

In April 2003, NHGRI celebrated the historic culmination of sequencing of the human genome, the 50th anniversary of James Watson and Francis Crick's Nobel Prize winning description of the DNA double helix, and the publication of a landmark scientific report that describes the future of the field of genomics and the role the National Human Genome Research Institute (NHGRI), parts of the National Institutes of Health (NIH), and other government agencies will play in enabling that future. To mark these achievements in the history of science and medicine, the NHGRI, the NIH and the Department of Energy (DOE) held a month-long series of scientific, educational, cultural, and celebratory events across the United States. Among the events, NHGRI, the Office of Rare Diseases, NIH, and DOE co-sponsored a symposium for the public, "Bringing the Genome to You," held at the National Museum of Natural History in Washington, DC. This symposium was designed to provide a stimulating look at the impact of the Human Genome Project on society.

Additional Activities

Genetic and Rare Diseases Information Center

In order to respond to the public's need for information on genetic and rare disorders, NHGRI and the Office of Rare Diseases, NIH, launched the NHGRI/ORD Genetic and Rare Diseases Information Center in 2002. The Information Center focuses on meeting the information needs of the general public, including patients and their families, health care professionals, and biomedical researchers. The purposes of the Information Center are to: 1) serve as a central, national repository of information materials and resources on genetic and rare diseases,

conditions, and disorders; 2) collect, produce, update, and disseminate information on the diagnosis, treatment, and prevention of genetic and rare disorders; and 3) coordinate with organizations and associations interested in genetic and rare disorders to explore networking capabilities, avoid duplication of effort, and identify information gaps.

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)

Overview of Rare Diseases Research Activities

The mission of the National Institute of Mental Health is to reduce the burden of mental illness and behavioral disorders through research on mind, brain, and behavior. As reported in the World Health Organization's Global Burden of Disease study, mental disorders comprise four of the top five sources of premature death and disability in 15-44-year-olds in the Western world. Serious mental illnesses such as schizophrenia, depression, bipolar disorder, and anxiety disorders are the primary foci of research that NIMH supports and conducts. Other research areas of significance to NIMH that can be classified as rare diseases include anorexia nervosa (AN) and bulimia nervosa (BN), suicide, prepubertal and adolescent bipolar disorder, pediatric and geriatric HIV/AIDS, progressive multifocal leucoencephalopathy, childhood-onset schizophrenia, Sydenham chorea, and Gaucher disease.

Recent Scientific Advances in Rare Diseases Research

Anorexia Nervosa and Bulimia Nervosa

Eating disorders are often chronic, relapsing disorders that have some of the highest death rates of any mental illness. Females are more likely to develop eating disorders than males, and these disorders frequently co-occur with other mental illnesses such as depression, substance abuse, and anxiety disorders. Several family and twin studies suggest a high heritability of anorexia and bulimia, and scientists are searching for genes that confer susceptibility to these disorders. Researchers are investigating the interaction between multiple genes with environmental and other factors to increase the risk of developing these illnesses. Other studies are investigating the etiological and pathophysiological causes of eating disorders.

One NIMH-supported project involves collaborative preclinical and clinical studies related to normal and abnormal regulation of eating behavior, with particular emphasis on the pathophysiology of AN and BN. The experiments integrate findings from animal and human studies to explore potentially significant parallels between the pathophysiology of these disorders and those of substance abuse and addiction. In 2003, data on 16 patients were collected to examine the interaction between anorexia and exercise. Findings from the animal studies support the notion that the serotonin receptor in the vagal system mediates food-related signals in the negative feedback control of ingestion. Further, palatable food releases endogenous opioids that can lead to behavioral sensitization, craving, receptor adaptation, and naloxone-induced withdrawal, which are characteristics of dependency. Opioid-mediation of addiction to a substance like sugar may be induced by alternating dietary restriction and hyperphagia (abnormally increased appetite for and consumption of food). These findings have important implications for development of more targeted interventions for eating disorders.

Suicide Deaths

Suicide is rare, accounting for 1.3 percent of total deaths in 2001. Nearly 90 percent of the time, fatal self-injuries occur in the context of a mental and/or substance abuse disorder. Statistics for 2001 indicate that 30,622 Americans took their own lives; however, for every suicide death, there are an estimated 8 to 25 suicide attempts. Individuals who die by suicide have overlapping, but quite distinct, characteristics from persons who attempt suicide. For example, estimates of attempted suicide indicate that twice as many women attempt suicide as men; however, five times as many men as women actually die by suicide.

NIMH-supported research on biological risk factors and interventions for persons at high risk for suicidality both provide evidence that suicidality is not simply epiphenomena of mental or substance use disorders. Biological research focusing on post-mortem tissue suggests a neurobiological risk factor for suicide that is independent from major depressive illness and other mood disorders. From intervention research—both pharmacologic and psychosocial approaches—it appears that targeting suicidal behavior per se may be more efficient for reducing risk for future suicide attempts and deaths than treating symptoms from mental disorders.

Intervention research has also demonstrated that particular settings or health care systems can be successfully modified to reduce the risk of suicidal behavior. A post-hoc evaluation of the Air Force suicide prevention program strongly suggested that a system-wide approach was effective in reducing not only suicide deaths but accidents as well. A multi-site study focused on treating depressed, older adults seen in primary care settings indicated that depression and suicide ideation could be reduced substantially and sooner using a collaborative care model (including an on-site depression specialist) of monitoring depression treatment adherence, compared to usual care practice.

Prepubertal and Adolescent Bipolar Disorder

NIMH-supported researchers are conducting the first phenomenology and longitudinal study of a prepubertal and early adolescent bipolar disorder phenotype. Data from studies of approximately 100 children with intake episode mania, assessed at 6, 12, 18, 21, 36 and 48 months, validate the existence, long episode durations, and chronicity of child mania. The participants were recruited from psychiatric and pediatric sites by consecutive new case ascertainment. Their mean age at intake was 10.8 years, and their mean age at onset of baseline episode was 7.4 years. The study will also address the controversy over whether this phenotype can be differentiated from attention deficit hyperactivity disorder (ADHD) by demonstrating that these subjects had persistent mania.

Childhood-Onset Schizophrenia

Childhood schizophrenia, defined as onset of psychosis by age 12, is a severe and unremitting form of the disorder. Patients with this rare, severe illness have profound impairment in development and resemble adult patients with poor-outcome schizophrenia. Several advances have been made in the study of childhood-onset schizophrenia this year at NIMH.

Recent brain imaging studies have shown that childhood-onset schizophrenia is associated with significant progressive loss of both cerebral and cerebellar volume during adolescence. The siblings of patients with childhood-onset schizophrenia also exhibit decreases in cerebral tissue volume. This excessive loss of brain tissue suggests a generalized abnormal process in childhood-onset schizophrenia that impacts normal brain development and might be used as a trait marker for schizophrenia.

Family, twin, and adoption studies have demonstrated that the development of schizophrenia is heavily influenced by genetic components. Recent studies show that this genetic influence may exert itself most strongly in cases of childhood-onset schizophrenia. Parents of patients with childhood-onset schizophrenia have a higher rate of schizophrenia spectrum disorders than parents of patients with the adult-onset form of schizophrenia, which would suggest a very early onset of the disorder is associated with greater familial vulnerability. Genetic studies of these patients and their families may be particularly helpful in finding genes involved in schizophrenia.

Sydenham Chorea: A Childhood Autoimmune Disorder

Sydenham chorea is a rare childhood disorder that may follow a streptococcal infection such as rheumatic fever. It is characterized by involuntary movements and neuropsychiatric disturbances, including obsessive-compulsive symptoms, hyperactivity, and emotional instability. Sydenham chorea can develop in 10-30 percent of rheumatic fever cases, with symptoms emerging as late as 6 months after the strep infection. A resurgence of strep has been seen in the United States since 1985 and continues to be a problem in developing nations. Whereas the postinfectious immune responses leading to inflammatory heart disease in strep have been characterized, the mechanisms of strep-induced central nervous system dysfunction in Sydenham chorea have not been defined. Past research has suggested that the strep infection induces an immune response that also acts against specific molecules in the brain, but the identity of these molecules is unknown. In research conducted in part in NIMH labs in Bethesda, researchers used antibodies collected from a patient with Sydenham chorea to identify the targets of these strep-induced molecules in the brain and the mechanism by which these molecules have a role in the disorder. These antibodies targeted the surface of human neuronal cells, causing an activation of an enzyme called CaM kinase II, which affects the transmission of signals within the cell. This activation of CaM kinase II may function to affect the release of excitatory neurotransmitters, which could give rise to the clinical symptoms of Sydenham chorea. The results of the study suggest that neuron-specific antibodies might alter neuronal cell function through signal transduction to produce the neurologic dysfunction that characterizes Sydenham chorea.

Gaucher Disease

Gaucher disease is a rare, inherited metabolic disorder in which deficiency of the enzyme glucocerebrosidase results in the accumulation of harmful quantities of certain lipids throughout the body, particularly within the bone marrow, spleen, and liver. The symptoms associated with Gaucher disease vary greatly. There are three general classifications of Gaucher, each defined by the extent of neurological complications. Type 1 Gaucher disease involves essentially the peripheral organs and has no primary neuropathy. An association between type 1 Gaucher

disease and Parkinson's disease has been described in very rare case reports. Genetic studies done in collaboration with NIMH scientists in Bethesda suggest that the enzyme deficiency itself may predispose the patient to be vulnerable to other genetic or environmental triggers of parkinsonism. While the occurrence of these two phenotypes could be a coincidence, the shared clinical characteristics and neuropathology of the patients described in this study suggest a related etiology. The studies also suggested that the atypical phenotype of Gaucher disease with parkinsonism may be influenced by modifier genes, which are becoming increasingly implicated in a host of Mendelian disorders.

New/Planned Extramural or Intramural Research Initiatives

Geriatric HIV/AIDS

In April 2002, NIMH, NIA, NIDA, and the NIH ORD co-sponsored a workshop titled *"Mental Health Research Issues in HIV/AIDS and Aging."* The workshop formed the basis of: (1) RFA-MH-03-004, "HIV/AIDS and Aging: Basic and Clinical Research" and (2) a special supplement issue in the journal AIDS on "HIV/AIDS and Aging" to be published in early 2004. These activities helped to build a NIMH grant research portfolio on HIV/AIDS and aging covering basic, intervention, and treatment studies. This is expected to form the core for further development of the field and creation of an expanded research grant portfolio both within NIMH and across other relevant ICs.

FY 2003 Rare Diseases-Specific Program Announcement

Suicide

NIMH, NIDA, NIAAA, NCI, and NIA issued the program announcement (PA) "Research on the Reduction and Prevention of Suicidality." The intent of the PA is to intensify investigator-initiated research on this topic, attract new investigators to the field, and increase interdisciplinary approaches to developing effective strategies to reduce suicidality. For this PA, mental disorders, along with alcohol use disorders (AUDs) and substance use disorders (SUDs) and their respective trajectories, are of particular interest as they pertain to risk and protective factors and treatment efficacy and effectiveness for suicidality.

FY 2003 Rare Diseases-Specific Request for Applications

Eating Disorders

NIMH issued the request for applications (RFA) "Research on Interventions for Anorexia Nervosa (RIAN)," subsequent to a workshop co-sponsored by NIMH and ORD in late September 2002. The purpose of the RFA is to develop a network of institutions (i.e., infrastructure) to conduct research on the treatment of anorexia nervosa. Specifically, this RFA is intended to address the dearth of studies with sufficient power to provide an adequate test of an intervention for this disorder. The infrastructure developed through this network will have the capacity to conduct a moderate to large-scale evaluation of promising interventions, including a

long-term follow-up of study participants. In addition, it will serve as a resource for future ancillary studies.

Suicide

NIMH, NIDA, and NIAAA issued the RFA "Developing Centers on Interventions for the Prevention of Suicide (DCIPS)." The purpose of this initiative is to establish core support for building research infrastructure for the study of preventive and treatment interventions for suicidality (severe ideation, attempts, deaths) related to mental health, SUDs and AUDs. This RFA supports an early phase of infrastructure building to be utilized by qualified institutions with active research programs but without the existing capacity to mount the extensive and highly integrated research effort expected of an advanced center. Fifteen applications have been received.

Significant Ongoing Rare Diseases Research Initiatives

Suicide

NIMH continues to encourage the inclusion of more diverse samples of patients, including suicidal patients, in treatment research protocols. In order to help protect these patients and to encourage more researchers to include suicidal patients in research, NIMH conducted a workshop in June 2001, co-sponsored by ORD and the American Foundation for Suicide Prevention (AFSP), that involved experts in bioethics, law, and suicide treatment research. The purpose was to develop several documents describing approaches to considering the ethical issues in treating suicidal patients, and ways to increase the safety and monitoring of suicidal patients in clinical trials. One summary of this workshop was published in 2002 in the journal *IRB: A Review of Human Subjects Research*. A second document is currently under being developed for publication review.

Healthy People 2010 has as one of its developmental goals to increase the proportion of juvenile justice facilities that screen new admissions for mental health problems. An ORD supplement to one NIMH-supported researcher has allowed for the assessment of suicidality among a very large sample of juvenile detainees, and follow-ups of these youth have indicated that they are at increased risk for death by suicide after incarceration. The implications from these findings suggest that screening and adequate treatment of juveniles in detention could be life saving.

Through a supplement from ORD and additional funding from NIDA and CDC, one investigator is conducting a meta-analyses of numerous NIMH, NIDA, and CDC prevention trials to determine whether active interventions focused on reducing risk factors (aggression) and increasing protective factors (problem solving, improved peer interactions) in childhood and adolescents reduce the risk for suicide in young adulthood. By examining multiple prevention trials and looking at their combined populations and intervention effects, the researcher is developing a methodology that will, for the first time, be able to determine whether such efforts reduce rare outcomes such as suicide. This methodology has important implications for other rare disease outcomes (psychoses) and conditions (homicides, accidental deaths).

Prepubertal and Adolescent Bipolar Disorder

NIMH-supported researchers have been conducting a longitudinal study of bipolar disorder in children and early adolescents since 1995. During the past year, NIMH awarded funding for a second longitudinal study of pediatric bipolar disorder, with follow-up of children and adolescents with first-degree relatives. The course and persistence of the disorder will be assessed at 1-year intervals. Data on unaffected siblings will provide complementary information on a sample at high risk for bipolar disorder. Funding was also awarded for the development of validation of an effective screening instrument for bipolar spectrum disorder in 5- to 17-year-olds. It is an effort to refine and evaluate assessment procedures for juvenile bipolar disorder in community health as well as clinical settings. As part of this effort, the researchers will examine developmental changes in symptom occurrence and presentation across the age span from 5 to 17 years. In addition, a career development award is supporting a validation study of pediatric bipolar disorder in 11 extant data sets consisting of comparable case control studies of clinically referred children and adults. The study will define subtypes of pediatric bipolar disorder, validate subtypes, examine developmental trajectories, and identify risk factors for pediatric bipolar disorder.

Pediatric HIV/AIDS

A follow-up effort initiated as a result of a meeting supported by ORD in 2001 has partnered NIMH with NICHD to fund a study to better understand the impact of HIV on the development of psychiatric symptomatology in youth perinatally infected with HIV. This study will be conducted in cooperation with the Pediatric AIDS Clinical Trial Group (PACT-G). The PACT-G is one of the largest clinical research programs in the United States focused on the care of HIV-infected children and is funded by NIAID and NICHD. NIMH will fund this sub-study to identify psychiatric consequences of living with HIV from birth to develop an understanding of the issues and to ultimately develop interventions to prevent or lessen the psychiatric consequences of living with HIV in children and adolescents, both with and without early antiretroviral treatment. This information will become of great importance in developing countries as antiretroviral therapy becomes more available and children and adults live longer.

Rare Diseases-Specific Conferences, Symposia, and Meetings

Eating Disorders

In late September 2002, NIMH and ORD co-sponsored a workshop the *"Development of Research Priorities for the Treatment of Anorexia Nervosa: Overcoming Existing Barriers."* A group of scientists and NIH staff were convened to provide an update of what is known about the treatment of AN, address barriers to conducting research in this area, and propose recommendations about how to overcome these problems and facilitate the development and implementation of improved interventions. A summary is available on the NIMH Web page (http://www.nimh.nih.gov/events/ansummary.cfm), and a full report of the workshop is in press in the *International Journal of Eating Disorders*.

Suicide

NIMH awarded a conference grant (R13) to the University of Rochester in FY 2000 to conduct five annual meetings to review and develop scientific consensus on suicide risk factors and prevention strategies for a number of at-risk groups. There are multiple NIH and other agency co-sponsors. The first of these meetings focused on suicide prevention in adolescents and young adults. The third meeting, held in June 2003, focused on men in their middle years, and a fourth, scheduled for the summer of 2004, will focus on risk and protective factors for women. The University of Rochester was also awarded an R25 training institute grant to begin training young investigators in suicide prevention research in the summer of 2004.

In May 2003, ORD provided funding for the NIMH and the AFSP workshop *"Research on Survivors of Suicide."* A panel of scientists and clinicians from multidisciplinary backgrounds assessed existing research on suicide survivors and identified needed areas of research to effectively and appropriately serve this population. A summary of the workshop is available on the NIMH and AFSP websites, and a special section of the journal Suicide and Life Threatening Behavior will include a longer summary and some key articles based on the workshop.

Progressive Multifocal Leuceoencephalopathy (PML)

NIMH, NINDS, and the ORD jointly organized a workshop, *"Basic, Clinical and Epidemiologic Studies of Progressive Multifocal Leucoencephalopathy: Implications for Therapy,"* in July 2002. The purpose was to facilitate the development of potential strategies to translate current basic research on the biology of JC virus into therapeutic approaches. An important outcome of the meeting was a decision to develop consensus on terminology to define patient groups affected by HIV-associated PML following the profound disease changes resulting from highly active antiretroviral therapy (HAART). This consensus terminology and the research presentations were published in 2003 in a *Journal of NeuroVirology* supplement (Vol. 9, Suppl 1) devoted to the workshop proceedings.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS)

Overview of Rare Diseases Research Activities

The mission of NINDS is to reduce the burden of neurological disease—a burden borne by every age group and every segment of society worldwide. The brain, spinal cord, and nerves are vulnerable to hundreds of disorders, most of which can be considered rare. Even diseases such as stroke, epilepsy, and Parkinson's disease, include rare subtypes. The NINDS supports research to uncover the causes of, and develop treatments for, individual rare disorders, while also promoting cross-cutting research on stem cells, gene therapy, and neuroimaging that will impact many neurological disorders.

The NINDS supports research on rare diseases through its extramural and intramural programs. The NINDS collaborates with ORD and voluntary rare disease organizations to stimulate specific research areas via workshops, grant solicitations, and strategic planning efforts, although the Institute's primary support of research is through unsolicited, investigator-initiated grant awards, as investigators often have the greatest insight into the critical questions facing a particular field of research. New rare disease grants in FY 2003 include ones focused on prion diseases; lysosomal storage disorders, including Batten disease and ML4; Niemann-Pick C; Huntington's disease; muscular dystrophy; tuberous sclerosis; Rett syndrome; Fragile X; spinal muscular atrophy; myasthenia gravis; Joubert syndrome; Tourette syndrome; and Friedreich's Ataxia.

Recent Scientific Advances in Rare Diseases Research

Amyotrophic Lateral Sclerosis (ALS)

ALS, or Lou Gehrig's disease, progressively destroys the nerve cells that control voluntary movement, ultimately leading to paralysis and death. Why these cells die remains a mystery. Researchers genetically engineered mice to carry the ALS-causing mutation only in certain cell types and got results suggesting that the disease might not begin with abnormalities in the motor neurons themselves, but rather in the neighboring glial, or supporting cells. Further work is necessary to confirm this evidence, but, if replicated, there are important implications for developing treatments for ALS. For example, it had been thought that stem cells might not be feasible for treating ALS—replacing lost motor neurons could be especially difficult because the new cells would have to grow long axons that would need to find and connect to appropriate muscles of the body. However, it might be plausible to use stem cell technology to replace the supporting glial cells, which stay within the spinal cord and do not require such specific connectivity.

Fabry Disease

NINDS intramural researchers have made strides in developing therapies for Fabry disease, a hereditary disorder characterized by recurrent episodes of severe pain in the hands and feet, skin lesions, damage to the cornea, kidneys, heart, or blood vessels of the brain, and death in the fourth or fifth decade of life. Fabry disease is caused by a faulty enzyme, α-galactosidase, which

allows certain substances to accumulate in cells to harmful levels. The FDA recently approved an enzyme replacement therapy for Fabry disease based on positive results in NINDS intramural trials. As enzyme replacement therapy may have limitations for long-term use, intramural researchers are also exploring the potential of gene therapy to treat Fabry disease. A recent study demonstrated that Fabry mice injected with virus containing the α-galactoside gene were able to express the enzyme for over six months, and they reduced their levels of the substances responsible for the Fabry symptoms. These results suggest a new strategy for treating Fabry patients.

Huntington's Disease

Huntington's disease is an inherited disorder that causes cognitive and motor difficulties, including chorea–uncontrollable and irregular muscle movements. Symptoms usually begin in early to mid-adulthood and progressively worsen, leading to death. An inherited defect in a protein called huntingtin causes the disorder. Researchers have found that the mutant huntingtin protein allows too much calcium into brain cells, thereby contributing to brain damage. Furthermore, normal huntingtin, which appears to protect brain cells, is depleted not only in Huntington's disease, but also in brain trauma and stroke, which also involve calcium-associated brain damage. These results suggest that similar molecular and cellular activities are at play in disparate neurological disorders.

Muscular Dystrophy

The muscular dystrophies are inherited diseases in which the muscles that enable voluntary movements progressively weaken and waste away. There are many different forms of muscular dystrophy, varying in severity, age of onset, pattern of muscles involved, and the extent to which other bodily systems are affected. This year, two research teams reported their development of improved diagnostic tests for specific types of muscular dystrophy. One group developed a simple and affordable blood test that detects Duchenne, the most common form of muscular dystrophy, in more than 95 percent of cases. In a separate effort, researchers developed a genetic test that detects myotonic muscular dystrophy type 2 with 99 percent accuracy. Initial use of this test indicates that myotonic dystrophy type 2 is much more common than previously thought. Both of these new tests not only eliminate the need for painful muscle biopsy in many children and allow for earlier diagnosis, but they will also enable researchers to develop and test treatments that are tailored to specific types of muscular dystrophy.

Defects in the protein dysferlin have been implicated in two forms of muscular dystrophy, limb-girdle muscular dystrophy type 2b and Miyoshi myopathy. However, until recently, it was not known how defective dysferlin leads to muscle degeneration. This year, scientists discovered that muscle cells with defective dysferlin are not more easily damaged than normal cells, as was predicted based on studies of other forms of muscular dystrophy. Rather, these muscle cells fail to repair damage that occurs from everyday stresses of muscle use, and the muscles degenerate as a result. This finding is likely to lead to further discoveries about the structure, growth, and repair of muscle cells and to a better understanding of other muscle diseases.

Neurofibromatosis

The neurofibromatoses are genetic disorders that cause tumors to grow on nerves and produce other abnormalities such as skin changes and bone deformities. People who carry a single mutant copy of the neurofibromatosis 1 (NF1) gene develop tumors when the remaining normal gene copy is spontaneously mutated during a round of cell division. Researchers have discovered that cells missing both copies of the NF1 gene must be surrounded by cells that are missing at least one copy in order to generate a tumor in a mouse model system. The results suggest that a particular genetic environment may be essential for tumor development and that altering this environment may prove an effective strategy for preventing tumor growth.

Parkinson's Disease

Scientists investigating a rare familial form of early-onset Parkinson's disease have discovered that too many copies of the normal form of the alpha-synuclein gene, leading to production of excess protein, may cause Parkinson's disease. Abnormal accumulations of the protein alpha-synculein also occur in the brains of people with the common form of Parkinson's disease, as well as in Alzheimer's disease, so following up these findings may add to the growing trail of evidence that improper disposal of proteins by brain cells is somehow involved in several neurological disorders.

Rett Syndrome

Rett syndrome is a progressive neurological disorder, most commonly arising in girls. It is characterized by reduced communication and motor skills and autistic-like behavior. Defects in the MeCP2 protein are known to cause Rett syndrome, and the MeCP2 protein has been implicated in gene regulation. However, major questions remain: what genes are controlled by MeCP2, and how does misregulation of these genes lead to the neurological problems associated with Rett? This year, two research teams may have found part of the answer. They discovered that MeCP2 directly controls expression of brain-derived neurotrophic factor (BDNF), which is essential for neural plasticity, learning, and memory; it is highly active in infants aged 6 to 18 months, the age at which Rett appears. This finding suggests part of a model for how Rett develops: mutations in MeCP2 impair its ability to regulate BDNF, and abnormal BDNF levels alter brain development, contributing to Rett symptoms.

Spinal Muscular Atrophy (SMA)

The spinal muscular atrophies are genetic disorders that cause degeneration of motor neurons in the spinal cord and brainstem, leading to muscle weakness and, in the severe forms of the disease, death. SMA is caused by mutations in the SMN1 gene that prevent SMN protein from being expressed at sufficient levels. NINDS intramural researchers recently found that valproic acid, a compound that is FDA-approved for treating epilepsy, can increase SMN protein levels in cell lines derived from SMA patients, and they are developing a clinical trial to test the safety and efficacy of valproic acid in SMA patients. Recent discoveries by NIH extramural researchers suggest that it may be possible to trick a gene called SMN2 into compensating for

defective forms of SMN1. The SMN2 gene is almost identical to SMN1, except that SMN2 produces an mRNA readout with an additional sequence that makes it unstable. Scientists have been able to modify expression of SMN2 to "skip" the destabilizing sequence in cell culture, thereby elevating SMN protein levels.

New/Planned Research Initiatives

The NINDS has funded research related to rare disease under the following FY 2003 solicitations, some of which were issued in collaboration with other Institutes and patient voluntary organizations:

- Announcement of NINDS High Throughput Drug Screening Service and Call for Assay Proposals (includes ALS and Ataxia Telangiectasia)
- Collaborative Programs to Accelerate SMA Therapeutics Development
- Rare Disease Clinical Research Network (with NCRR, ORD, NICHD, NIAMS, and NIDDK)
- NINDS Administrative Supplements: Testing of Candidate Drug Treatments for Neurodegeneration in Rodent Models (includes ALS, Huntington Disease, and Spinocerebellar Atrophy)
- Gene Discovery for Complex Neurological and Neurobehavioral Disorders (with NIA, NIDA, and NIEHS; includes Tourette Syndrome, ALS)
- Basic and Clinical Research on Rett Syndrome and MECP2 (with NICHD)
- The Etiology, Pathogenesis and Treatment of ALS (with Department of Veteran's Affairs and The Amyotrophic Lateral Sclerosis Association)
- Interactions Between Stem Cells and the Microenvironment in vivo (with NIDA, NIDCD, NIAAA, and NIA)
- NINDS Administrative Supplements for Research on Human Stem Cells

Among the FY 2004 solicitations are:

- National Centers for Neurofibromatosis Research (with NIDCD)
- Announcement of Request for Proposals: Inducible Mouse Models of Spinal Muscular Atrophy

New NINDS intramural clinical studies begun in FY 2003 include a trial to test the safety and effectiveness of the drug Rituximab in treating the autoimmune peripheral neuropathy MGUS and a study to determine whether histone deacetylase inhibitor drugs can increase SMN levels in SMA patients. The results of this latter study may support the use of such drugs in a clinical trial for SMA patients.

Significant Ongoing Rare Diseases Activities

The NINDS, together with NIAMS and NICHD, has been actively implementing the provisions of the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 ("MD-CARE Act;" P.L. 107-84). In September 2002, NIH issued a Request for Applications (RFA) to establish Muscular Dystrophy Cooperative Research Centers and awarded

three grants in October 2003. The NINDS funds a Center at the University of Rochester, which focuses on the myotonic and facioscapulohumeral forms of muscular dystrophy. Also in compliance with the MD-CARE Act, the Muscular Dystrophy Coordinating Committee (MDCC), composed of representatives from government agencies with an interest in muscular dystrophy (including NINDS, NIAMS, and NICHD) and public members, was formed and held its first meeting in July 2003. The MDCC is in the process of developing a research and education plan for muscular dystrophy, which will be submitted to Congress in the summer of 2004.

In July 2003, the NIH released a Research Plan for Tuberous Sclerosis. Developed by NINDS, in collaboration with ORD, NIDDK, NICHD, NLHBI, NIMH, NIAMS, NCI, and the Tuberous Sclerosis Alliance, this Plan defines the key challenges in tuberous sclerosis research and strategies to address them. The NIH and the broader research community will use this plan to guide and develop tuberous sclerosis research activities.

In an effort to enhance translational research in SMA, the NINDS awarded a contract in September 2003 for a milestone-driven SMA therapeutics development program and established a steering committee (which includes NINDS program staff) to oversee the program. With the ongoing consultation of the steering committee, the contractor will solicit and coordinate individual research projects in areas such as drug development, gene therapy, and stem cell therapy. This contract-based SMA translational program is the first of its kind at NINDS, and may eventually serve as a model for other diseases.

Rare Diseases-Specific Conferences, Symposia, and Meetings

In FY 2003, the NINDS led or participated in several workshops relevant to rare diseases. In most cases, the Institute collaborated with ORD or other appropriate components of NIH and often with patient voluntary groups.

- *Hereditary Dysautonomias: Current Knowledge and Collaborations for the Future*
- *9th International Congress on Neuronal Ceroid Lipofuscinosis (Batten Disease)*
- *Workshop on Friedreich Ataxia (FRDA)*
- *The NNFF International Consortium for the Molecular Biology of NF1 and NF2*
- *ALS Clinical Trials-The Challenge of the Next Century*
- *2003 Gordon Conference on CAG Triplet Repeat Disorders*
- *Hereditary Inclusion Body Myopathy and Sialuria Due to GNE Gene Mutations: Genetics, Biochemistry and Implications for Therapy*

For FY 2004, NINDS is working with ORD on several meetings, including ones focused on lysosomal storage diseases, ideomotor apraxia, rare neuroimmunologic disorders, peroxisomal disorders, frontotemporal dementia, and Tourette syndrome.

NATIONAL INSTITUTE OF NURSING RESEARCH (NINR)

Overview of Rare Diseases Research Activities

NINR supports clinical and basic research to establish a scientific basis for the care of individuals across the life span: from management of patients during illness and recovery to the reduction of risks for disease and disability, the promotion of healthy lifestyles, promoting quality of life in those with chronic illness, and care for individuals at the end of life. Using an interdisciplinary approach, NINR's rare diseases research portfolio investigates strategies to control, manage, and prevent biobehavioral complications of such pathologies.

Recent Scientific Advances in Rare Diseases Research

Childhood Acute Lymphoblastic Leukemia (ALL)

NINR-funded researchers, as part of an ongoing study, reported that children and adolescents with ALL who receive therapy for at least one year, experience specific behavioral adjustment problems and may require ongoing assessments and interventions that target at-risk areas such as somatization, anxiety, adaptability, and attention and learning problems. Further, central nervous system (CNS) treatment-related cognitive and academic deficits appear to be associated with specific behavioral adjustment problems. The researchers cautioned that, although the findings are based on a relatively small sample (N'47) and are preliminary, there is a need for interventions to improve outcomes for youths diagnosed with cancer who are receiving CNS treatments.

Acute Respiratory Distress Syndrome (ARDS)

NINR researchers are studying optimum ways to wean patients diagnosed with ARDS from mechanical ventilation and have published some of their findings. One study evaluated heart rate variability (HRV) and thermodynamics to determine the effect of HRV on weaning from mechanical ventilation. A canine model was used, with control animals having normal cardiac function during baseline controlled mechanical ventilation. The experimental group was exposed to high mechanical ventilator pressure settings to simulate parameters required when treating patients with ARDS. Hemodynamic responses measured in both groups included cardiac output, heart rate, and right-ventricular end-diastolic volume. NINR-funded investigators anticipate that the conclusions of this study will provide insight into methods of optimizing cardiovascular and respiratory function to modulate HRV in ARDS patients and improve success in weaning from mechanical ventilation.

Another NINR-funded prospective randomized study is investigating the effect of early and repeated prone positioning on clinical outcomes in pediatric ARDS patients who require mechanical ventilation. Early reports indicate improvements in oxygenation without serious iatrogenic injury after prone positioning.

Multiple Sclerosis (MS

NINR researchers surveyed 621 MS sufferers taking part in a larger, long-term descriptive study about their use of complementary and alternative therapies (CATs) to treat the discomfort and functional decline associated with their disease. The average age of the respondents was 50 years, 93 percent were White, and 83 percent were female. While most were well-educated, 32 percent reported being unemployed as a result or their condition. Over 85 percent described their disease course as either relapsing/remitting or progressive, and 38 percent were taking one of the three available medications to modify the course of the disease. Almost half reported having tried some form of CAT, and 33 percent were using one currently. The CATs reported as most helpful in alleviating symptoms were massage, nutritional supplements, yoga, herbal treatment, and special diets, while those most often reported to have no effect or to be harmful included acupuncture, bee venom, and homeopathy. Of those who had tried chiropractic treatment, over one half found it helpful, but over one third found it useless or harmful. Use of CATs was related to other positive health promotion activities, including nutrition, activity, and maintaining relationships. Researchers have recommended that clinicians need to ask MS patients about their use of CATs, and be prepared to offer informed and nonjudgmental advice about the possible risks and benefits.

Irritable Bowel Syndrome (IBS)

NINR researchers recruited 149 women with IBS to complete a 5-day symptom diary around the time of their menses. The average age of the women was 32 years, 89 percent were White, 66 percent had completed college, 37 percent were using oral contraceptives, and 56 percent worked jobs that paid more than $20,000 per year. An initial questionnaire revealed different primary symptom patterns: 41 women reported constipation, 58 reported diarrhea, 46 reported an alternating pattern, and 4 were unclassifiable. Of women with IBS, those on oral contraceptives reported lower severity of cognitive, anxiety, and depressive symptoms. Menstrual disturbances, sleep disruption, and cognitive symptoms were strongest in the IBS sufferers with alternating constipation/diarrhea bowel patterns. Compared to a control group of 42 women with normal GI function, all three groups of women with IBS reported greater severity of menstrual, somatic, and sleep symptoms.

Epilepsy

NINR researchers assessed 175 epileptic children for symptoms of Attention Deficit Hyperactivity Disorder (ADHD). The sample was evenly divided between males and females, with an average age of almost 12 years, and all the children had been treated for epilepsy for at least 6 months. Parents completed the Child Behavior Checklist (CBCL) and either the Child Symptom Inventory (CSI), for children 12 and under, or the Adolescent Symptom Inventory (ASI), for children 13 and up. From the CBCL attention subscale, 37 percent of younger children and 25 percent of adolescents scored in the clinical range for ADHD. From the CSI/ASI scores, 24 percent were at risk for ADHD-inattentive type, 2 percent for ADHD-hyperactivity/impulsivity type, and 11 percent for the combined type. Overall, the prevalence of ADHD among children with epilepsy was higher than reported rates in the general population,

especially for the inattentive type. Girls were more affected than boys, suggesting a different pathway of ADHD among these children.

Fibromyalgia (FM)

NINR researchers compared the sleep quality and daytime fatigue in 22 women with FM against a control group of 23 women without FM. The two groups were close in age, ethnicity, body mass index, and physical activity levels. Before entering the study, all women were screened for depression or psychiatric conditions, and all were weaned from any medications or herbal supplements that might affect sleep. The women maintained daily logs of their perceived sleep quality at night and level of fatigue during the day. In addition, they wore an actigraph for three nights to record motion and activity, as a measure of sleep quantity and quality. The women with FM reported poorer quality of sleep and more fatigue than the control group, although actigraph results were not significantly different. In addition, the self-reports of sleep quality and fatigue for women with FM correlated with actigraph indicators of total sleep time and sleep fragmentation. Sleep quality indicators by self-report and actigraphy can help in the assessment of sleep disturbances for FM patients.

Rare Diseases Research Initiatives

Program Activities (Completed)

The National Institute of Nursing Research (NINR) and the Office of the Director/Office of Rare Diseases (ORD) at the National Institutes of Health (NIH) convened the workshop *"Moving the Research Agenda Forward For Children with Cancer"* on August 5-6, 2003, in Bethesda, Maryland. This workshop brought together 13 experts from diverse fields such as nursing science, pediatric oncology, psychology, medical anthropology, and communication sciences among others. These experts discussed issues related to diagnosis, treatment, quality of life, survivorship, relapse and end of life care in order to develop and move the research agenda forward for children with cancer in the 21st century. There was consensus among participants that biobehavioral and sociocultural aspects of the pediatric cancer experience are understudied areas. Despite great advances, cancer is the leading cause of death, from disease, in children outside of the immediate newborn period. Therefore, it is understandable that research has focused more on survival and cure than on the biobehavioral/sociocultural issues faced by pediatric cancer patients. A paradigm shift may be necessary to view the whole life course as a continuum in order to effect further progress in prevention, treatment, palliation, and long-term survival, involving the full range of the child's experience as a member of a family and society. *The Journal of Pediatric Oncology Nursing* has agreed to publish the proceedings.

The National Institute of Nursing Research (NINR), National Institutes of Health (NIH), convened the workgroup *"Optimizing Pregnancy Outcomes in Minority Populations"* on March 3-4, 2003, in Bethesda, Maryland. This workgroup brought together researchers in the fields of nursing, epidemiology, psychology, and clinical and basic sciences in a collaborative, multidisciplinary approach to address this issue and formulate future research strategies. Nine white papers on the following topics were presented and discussed: Psychosocial and Biological Influences on Pregnancy in Minority Populations; Stress and Neuroendocrine Mechanisms in

Prematurity and LBW Outcomes; Behavioral Influences and Maternal Health During Pregnancy; Defining Risk and Risk Factors; Environmental Exposure and Biological Mechanisms Affecting Pregnancy Outcomes; Identification of Physiological Pathways and Biochemical Markers; Measurement of Psychosocial Constructs; and Methodological Considerations in Designing Multidisciplinary Biobehavioral Research on Prematurity and LBW.

With partial funding from the Office of Rare Diseases, these papers, along with an additional paper highlighting research gaps and recommendations for future directions, are currently being published as a group in the *American Journal of Obstetrics and Gynecology*.

Rare Diseases Research Initiatives

Program Activities (New)

Developing the Capacity for End of Life and Palliative Care Research

Although the field of palliative care has developed a substantial body of knowledge that addresses the needs of such patients and their families, there continues to be a dearth of persons with expertise in end of life and palliative care who are able to organize and conduct biomedical, clinical, and behavioral research in this field. A two-day workshop is proposed for the spring of 2004 in Bethesda, Maryland, whereby experts in end of life and palliative care from across the NIH, DHHS, and from major universities will convene to formalize a plan of action to develop a research training program. Sessions will be held to: determine the most effective framework for developing a summer institute; develop content that is unique to this area of research; determine the profile of participants who would benefit from this course; develop a profile of mentors to be recruited; and identify strategies for program evaluation.

Improving Patient Health Through Improved Mental Functioning

The prevalence of nondementing brain disorders (ND-BD, e.g., multiple sclerosis, epilepsy, Parkinson's disease, cerebral palsy) is undefined; however, it is thought that as much as 5 percent of the American population may live with these "most common" brain diseases. In assessing the burden of these chronic primary diseases, little or no research has addressed the secondary effects, decreased cognitive and affective function, on physical health and quality of life (QOL). Even less is known of effective cognitive-behavioral and psychosocial interventions that may improve the health maintenance and QOL in this understudied population. A workshop is planned for the summer of 2004 to examine the cognitive and affective changes observed in some persons with ND-BD and to identify intervention strategies to improve health behaviors, including health decision-making, and QOL in these patients.

Increasing Opportunities in Biobehavioral Research Utilizing Allergic Bronchopulmonary Aspergillosis (ABPA) as a Framework

A meeting will be held in the summer of 2004 with a diverse and multidisciplinary group of biological, behavioral, and rare diseases researchers with expertise related to biobehavioral measurements relevant to allergic bronchopulmonary aspergillosis (ABPA).
Specifically, the goal of the meeting is to bring together a group of biological, behavioral, and immunological experts to examine the existing body of knowledge and develop recommendations on methods and approaches for research. The curriculum will subsequently be utilized for training researchers who do not have the requisite skills to conduct biobehavioral research related to rare diseases. ABPA will be the model condition used to develop this curriculum.

NATIONAL CENTER FOR RESEARCH RESOURCES (NCRR)

Overview of Rare Diseases Research Activities

NCRR develops and supports critical research technologies and resources that facilitate biomedical research to improve the health of citizens of the United States. NCRR supports shared resources, sophisticated instrumentation and technology, animal models for study of human disease, clinical research resources, and research capacity building for underrepresented groups.

Through its support of multidisciplinary research resources, NCRR is uniquely positioned to provide resource support in partnership with other Institutes or Centers to address emerging clinical and basic research needs, such as the study of rare diseases. Expansion of NCRR's efforts in new biotechnologies and instrumentation, development of animal models, and clinical research resources will foster interdisciplinary collaborations and advance NIH's efforts to study rare diseases.

Recent Scientific Advances in Rare Diseases Research

Fabry Disease

In Fabry disease, a rare genetic disease, a deficiency of the enzyme alpha-galactosidase A (α-Gal-A) results in a progressive accumulation of globotriaosylceramide (GL-3) in cells and tissues. Eventually, the small blood vessels of the kidney, heart, and brain are blocked, causing these organs to malfunction. Patients with Fabry disease, who are most frequently males, rarely survive beyond their early 50s. In a multicenter study of 58 patients, supported in part by the General Clinical Research Centers at Mt. Sinai School of Medicine and at Cedars Sinai Medical Center, Fabry patients were treated every 2 weeks for 20 weeks with either a genetically engineered form of the missing enzyme (rα-Gal-A) or with placebo. More than two-thirds of the treatment group–but none of the patients receiving placebo–achieved complete or nearly complete clearance of GL-3 deposits in their kidneys without major side effects. Similar results were observed in skin and heart tissues. This recombinant enzyme (rα-Gal-A; Fabrazyme) is the first FDA-approved treatment for Fabry disease. The availability of a safe effective treatment provides an example of incremental advances in basic science and clinical research ultimately leading to improved diagnosis and treatment of individuals with a devastating rare disease.

Fanconi Syndrome

Fanconi syndrome is a rare hereditary disease of kidney function that results in loss of glucose, bicarbonate, phosphates, uric acid, potassium, sodium, and certain amino acids in the urine. In addition, exposure to heavy metals or chemical agents, vitamin D deficiency, kidney transplantation, multiple myeloma, or amyloidosis may lead to secondary Fanconi syndrome. In the hereditary form, weakness and bone pain accompanied by increased excretion of acidic urine may begin during infancy. High levels of glucose, bicarbonate, phosphates, uric acid, potassium, and sodium in the urine are diagnostic. Fanconi syndrome can be controlled, but not cured, with proper treatment, including sodium bicarbonate, potassium, phosphate, and vitamin D

supplements. The National Gene Vector Laboratory at the Indiana University, through the support of NCRR and the Office of Rare Diseases, is generating clinical-grade lentiviral vector for a Phase I clinical trial designed to correct the genetic mutation in patients afflicted with this disease.

Niemann-Pick Disease Type C (NPC)

Niemann-Pick disease type C is a hereditary lysosomal storage disorder that leads to enlarged organs, jaundice, seizures, delayed mental and motor development, and shortened lifespan. Onset is usually in infancy and childhood. Approximately 1,000 U.S. children are affected. NCRR-supported investigators at Colorado State University have characterized the gene responsible for the most common type of human NPC (NPC1) in a cat model. Research performed explores mitochondrial functions in skin fibroblasts *in vitro* and deposition of abnormal protein in the CNS *in vivo*. Tissues from these cats are available to other investigators for research. The further development and study of the NPC feline model will allow characterization of the disease on a molecular, biological, and physiological level and evaluation of various therapeutic modalities such as the efficacy of a ganglioside synthesis inhibitor.

Mucopolysaccharidosis (MPS)

Mucopolysaccharidosis, an inherited lysosomal storage disease, is characterized by deficiency of several different enzymes (*e.g.*, beta-glucuronidase) and the accumulation of complex carbohydrates in multiple organs leading to their failure. An NCRR-supported research team at the University of Pennsylvania, School of Veterinary Medicine, has discovered a canine model of MPS IIIB. Using this model, researchers injected affected dogs at 2-3 days of age with a modified retroviral vector expressing canine beta-glucuronidase. This treatment caused expansion of liver cells with the introduced enzyme resulting in its stable secretion throughout the observation period. Dogs treated with the retrovirus vector-expressing enzyme showed dramatically improved values on skeletal and cardiac evaluation, corneal exam, and body weight up to 17 months of age, while age-matched, mock-treated animals showed evidence of MPS at 20 weeks of age. These results describe the first successful application of gene therapy in preventing the clinical manifestations of a lysosomal storage disease in a large animal.

Bardet-Biedl Syndrome (BBS)

BBS comprises a group of inherited rare disorders whose major features include mental retardation, obesity, delayed sexual development or underdeveloped reproductive organs, progressive pigmentary degeneration of the retinas of the eyes, abnormalities in kidney structure or function, and/or abnormal or extra fingers and/or toes. BBS expression varies both within and between families, and diagnosis is often difficult. NCRR supported researchers at Ponce School of Medicine have studied 14 families with 34 affected individuals and 321 relatives (68 carriers). All families showed linkage to a chromosome 11 locus and researchers have characterized genetic markers in this region. A strong association between a specific marker and obesity was seen in most individuals. Significant differences were found in the subject's leptin levels and their BMIs (Basal Metabolism Indices). This suggests that this genetic marker on chromosome 11q predisposes to BBS. Future research may lead to a genetic test for BBS.

Chagas Disease

Chagas disease, caused by *Trypanosoma cruzi*, a parasite related to the African trypanosome that causes sleeping sickness, is spread by reduviid bugs. In Central and South America, 20 million people are infected, while approximately 500,000 people in the United States are affected. Acutely, Chagas disease may produce swelling and reddening at the site of infection, swelling of one eye, swollen lymph nodes, fever, fatigue, and an enlarged liver and spleen. The disease goes into remission, with no further symptoms for many years. Late development of cardiac disease (cardiomyopathy) and congestive heart failure are frequently fatal. NCRR supported researchers at Meharry Medical College who are studying the genes that regulate infection in Chagas disease are using retroviruses to generate mammalian cells that are resistant to infection. Examination of these cell lines will allow the identification of the genes involved in development of resistance to *T. cruzi* infection. These studies will be important in the identification of host genes that regulate trypanosome binding and entry and to the development of novel means of molecular intervention in Chagas disease.

Huntington's Disease (HD)

Huntington's disease is an inherited devastating degenerative brain disorder which slowly diminishes the affected individual's ability to walk, think, talk, and reason, resulting in total dependence upon others for his or her care. More than a quarter of a million Americans have HD or are "at risk" of inheriting the disease. In 1993, the HD gene was isolated and a genetic test can accurately determine whether a person carries the HD gene. The test cannot predict when symptoms will begin. Researchers at the University of Delaware are utilizing research techniques they developed for editing and repairing defective genes to study the HD gene with the goal of development of novel therapeutics. Through work with the Hereditary Disease Foundation, the Delaware research team is studying samples from a Venezuelan native tribe devastated by endemic Huntington's disease.

Usher syndrome (US)

Usher syndrome is the most common condition that involves both hearing and vision problems: more than half of the estimated 16,000 deaf-blind people in the United States are believed to have US, for which there is currently no treatment. US is an inherited condition which causes serious hearing loss that is usually present at birth or shortly thereafter, and progressive vision loss caused by retinitis pigmentosa (a group of inherited diseases that cause night-blindness and peripheral (side) vision loss through the progressive degeneration of the retina). Although some of the genes that cause US have been identified, the diagnosis is still based on ocular and clinical testing. Researchers at West Virginia University with funding from the NCRR, are using a wide range of techniques such as genetic analyses and functional brain imaging in order to study sensory disorders that are inherited or that occur during development. Recently, they have identified a cluster of nerve cells in a region of the brain stem that receives both excitatory input from the inner ear and inhibitory input from another region of the brain. This cluster of cells may serve to encode the complex sounds of speech. Identifying the specific

brain cells associated with speech recognition may lead to treatments for defects in this ability due to a variety of pathological conditions, including US.

Research Initiatives

Rare Diseases Clinical Research Network

To address the challenges inherent in the study of rare diseases, NCRR and the NIH Office of Rare Diseases established the Rare Diseases Clinical Research Network. Additional support is provided by NICHD, NIDDK, NIAMS, and NINDS. The network consists of a Data and Technology Coordinating Center (DTCC) and seven Rare Diseases Clinical Research Consortia (RDCRCs). Each Consortium focuses on a subset of related rare diseases and includes multiple sites, both domestic and international. These dispersed investigators and the relevant patient support groups are collaborating on clinical studies, including longitudinal studies, clinical trials, outcomes measures, diagnostics, and identification of biomarkers. This configuration will accelerate recruitment of research subjects in rare diseases. Each Consortium, in addition, has developed specific training programs to create a cadre of clinical investigators interested in rare diseases. The Data and Technology Center develops and enables technology, tools, and services for the network, including electronic data entry, remote direct laboratory transfer, vocabulary and laboratory standards, statistical support, web site development and maintenance, and database querying tools. The Network is developing a web-based resource for patients, families, researchers, clinicians, and the public about rare diseases, including a listing of available clinical studies. The Network will develop resources relevant to all rare diseases, including best practices for studies of small numbers of subjects. NCRR-supported GCRCs provide valuable resources for clinical research to the consortia and sites. Through the Rare Diseases Clinical Research Network, novel and improved approaches to the diagnosis, prevention, and treatment of rare diseases will be developed. The Request for Application (RFA: RR-03-008) titled "Rare Diseases Clinical Research Network" was released on February 27, 2003, and funded in September 2003.

Industry Initiated Rare Diseases Research Supported on GCRCs

The NCRR supported GCRCs host much of the research focused on rare diseases, as there are few large clinics available specifically for these unusual disorders. While most of these studies are investigator initiated, there are industry sponsored phase 1, 2, and 3 trials of new

interventions that utilize the GCRCs. Since the number of affected individuals is small, the expected market is also small, limiting the interests of many pharmaceutical companies. Recognizing the need to advance the development of new agents for these diseases, the Orphan Drug Act provides incentives for companies to develop and license agents for rare diseases. The NCRR, also recognizing the need and benefit from support of new agents for rare diseases, recently modified the guidelines for GCRCs for industry initiated studies and trials. Normally, companies that wish to utilize the resources of the GCRCs in the performance of their studies must pay for those resources. For industry-supported rare diseases studies and trials, the GCRC may approve use of GCRC resources without charge. Several rare diseases studies are already

benefiting from this change, including cystic fibrosis, lysosomal storage diseases, and urea cycle disorders.

Rare Diseases-Specific Conferences, Symposia, and Meetings

In collaboration with the Office of Rare Diseases, NIH, NCRR organized the *"Rare Diseases Clinical Research Network: Developing Collaborative Cyber-Infrastructure for Clinical Research"* workshop on September 29-30, 2003. The invited speakers provided information on those components needed for a cyber-infrastructure to support rare diseases research. These included the use of standard vocabularies for clinical evaluation and laboratory tests, clinical data management systems, including integrated remote electronic data capture, and novel informatics networks to support collaborative research. The Rare Diseases Clinical Research Network investigators discussed the adoption of similar technologies in the new network to facilitate their research.

Activities with Non Profit Organizations

Cystic Fibrosis Foundation (CFF)

In partnership with the Cystic Fibrosis Foundation, NCRR supports a novel approach to development of new therapeutics for cystic fibrosis, a rare genetic disease. The CFF Therapeutics Development Network (TDN) unites investigators focused on cystic fibrosis research to perform clinical trials of promising agents for treatment and cure of this disorder. NCRR-supported General Clinical Research Centers (GCRCs), which provide personnel, resources, and space for the conduct of clinical research, are utilized by many investigators in this network. In addition, NCRR supports a coordinating center, which provides informatics support for the management, conduct, and analysis of the studies. This bioinformatics component includes a secure, interactive Web environment for network communication and data entry, as well as a biostatistical unit. These resources facilitate transfer of new discoveries from bench to bedside.

National Disease Research Interchange (NDRI)

The National Disease Research Interchange is a not-for-profit organization in Philadelphia, PA, founded in 1980. NCRR provides support for approximately one-third of their activities via a cooperative agreement. NDRI personnel obtain commitments from academic pathologists to provide human tissues for basic research and statements of need according to specific protocols from biomedical researchers. These two lists, with very specific clinical details (but without patient identifiers), are kept in NDRI databases. When a tissue becomes available, a researcher is contacted and asked if he/she can accept it. Upon positive reply, the pathologist is notified, prepares the tissue according to the researcher's protocol and sends it, anonymized, to the researcher. The researcher pays a relatively small fee. Through this cooperative agreement, NDRI facilitates laboratory research on a broad variety of rare and common diseases. The agreement is currently co-funded by NCRR, the Office of Rare Diseases, and four other ICs.

NATIONAL LIBRARY OF MEDICINE (NLM)

Overview of Rare Diseases Research Activities

The National Library of Medicine provides information resources useful to rare diseases research and to those seeking information about conditions that affect them or their families.

Database Resources

- Citations to articles on rare diseases have long been available in the MEDLINE database, now accessible to researchers, health professionals, and the public through NLM's free Web-based PubMed system, and also in the TOXNET system. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi and http://toxnet.nlm.nih.gov/.
- MedlinePlus, NLM's consumer health information service, has a general rare diseases page, which has been effective in referring members of the public to the NIH Office of Rare Diseases at http://www.nlm.nih.gov/medlineplus/rarediseases.html, and was accessed 3,137 times for October-December 2003. MedlinePlus also incorporates links on health topic pages to Genetics Home Reference, a new NLM database which includes many rare diseases; current entries include amyotrophic lateral sclerosis, Gaucher disease, and Marfan syndrome. In addition, MedlinePlus has added topics on specific rare diseases requested by consumers, including Fragile X syndrome, Asperger's syndrome, Progressive Supranuclear Palsy, and Tay-Sachs disease.
- Online Multiple Congenital Anomaly/Mental Retardation (MCA/MR) Syndromes, http://www.nlm.nih.gov/mesh/jablonski/syndrome_title.html, a database of structured descriptions of congenital abnormalities (many of them rare) associated with mental retardation. This database was searched nearly ½ million times in 2003.
- ClinicalTrials.gov, NLM's consumer health information system for linking patients to medical research, currently includes approximately 9,000 studies. Of these, about 4,100 represent approximately 800 rare disease conditions. Also, starting in FY 2003, study records in ClinicalTrials.gov, including those investigating rare diseases, were linked to relevant genetic condition summaries in Genetic Home Reference. Such links provide consumers seeking information about clinical trials with additional background about the conditions and the genes responsible for the conditions. http://clinicaltrials.gov/ and http://ghr.nlm.nih.gov/.
- The Genetics Home Reference (GHR) is the NLM's web site for consumer information about genetic conditions and the genes responsible for those conditions. GHR's integrated web-based approach provides brief, consumer-friendly summaries of genetic conditions and related genes. Understanding is enhanced by direct links to glossary definitions and a resource called "Help Me Understand Genetics" that explains the fundamental genetic concepts. Additional links to consumer information from MEDLINEplus, applicable clinical trials, and relevant patient support groups are provided. Each summary also includes links to advanced information from the NLM and other authoritative sources. GHR currently offers summaries on more than 100 genetic conditions, including numerous rare diseases and disorders, and 90 gene summaries. New content for genes and disorders are being added to GHR and it is updated continuously. http://ghr.nlm.nih.gov/

Research Support

- NLM chairs the Communications Working Group of the Multilateral Initiative on Malaria (MIM), which began in 1997. The objective is to support African scientists and the ability of malaria researchers to connect with one another and sources of information through full access to the Internet and the resources of the World Wide Web, as well as create new collaborations and partnerships. http://www.mimcom.net/
- NLM is assisting NCRR in establishing the NIH-funded Rare Disease Clinical Research Network as an early test-bed for the use of standard clinical vocabularies to improve the efficiency of clinical research.
- A Multicenter Clinical Trial Using Next Generation Internet (NGI) Technology. NGI technology was applied to provide the infrastructure of a multicenter clinical trial of new therapies for adrenoleukodystrophy (ALD), a fatal neurologic genetic disorder. This project involved the formation of a worldwide imaging network of clinical institutions to evaluate ALD therapies. This network was required to provide a sufficient number of patients for evaluating ALD therapies. This can serve as a model for many other disorders. Three centers collaborated on this project. The Imaging Science and Information Systems (ISIS) Center at Georgetown University Medical Center, the Kennedy Krieger Institute, and the Department of Radiology at Johns Hopkins University. NGI technology was used to speed the transmission and evaluation of high quality MRI images. Another important feature of this project was to gain insight into procedures that ensure medical data privacy and security. http://www.nlm.nih.gov/research/ngisumphase2.html

Rare Diseases Research Initiatives

The National Center for Biotechnology Information (NCBI), a division of the National Library of Medicine (NLM), serves as a national public resource for molecular biology information. In this capacity, NCBI establishes and maintains various genomic databases and develops software tools for mining and analyzing this data, all of which are freely disseminated to the biomedical community to facilitate a better understanding of the processes affecting human health and disease.

The Human Genetic Map

NCBI is responsible for collecting, managing, and analyzing the growing body of data being generated from the sequencing and mapping initiative of the Human Genome Project. This data is made available without restriction to the scientific community and has expedited the decoding of various human chromosomes. By analyzing the DNA sequence of a chromosome, scientists may begin to understand the causes of certain rare diseases. Scientists can determine the organization of the genes on a chromosome, how these genes are expressed, how changes in a gene's DNA sequence give rise to a disease-causing mutation, and how a chromosome is duplicated and inherited. Scientists have used these strategies to find clues about gene defects on chromosomes 21 and 22 that lead to a variety of rare diseases, including Downs syndrome, Usher syndrome, DiGeorge syndrome, and Ewing's sarcoma—just to name a few. NCBI

investigators have also played an instrumental role in the identification and analysis of other disease genes and genetic loci, including analysis of genetic data leading to scientific advances in several rare diseases and disorders, such as the identification and analysis of the genes for Kallmann syndrome and neurofibromatosis (NF1). Examples of other rare diseases currently being studied by NCBI investigators include ataxia telangiectasia, breast cancer, hyper-IgE syndrome, nemaline myopathy, and obesity.

Genetic Analysis Software

NCBI investigators are working to develop, implement, and disseminate high performance computational tools and application software packages for the analysis and linkage of genetic data.

FASTLINK is a software program designed by NCBI investigators for conducting genetic linkage analyses—a statistical technique used to study the association of genes and genetic markers that lie near each other on a chromosome. Genes and other genetic markers that are linked tend to be inherited together and, therefore, can be used to identify and map the location of a particular disease gene. NCBI investigators have used FASTLINK to study hyper-IgE syndrome, a rare immunodeficiency characterized by recurrent skin abscesses, pneumonia, and highly elevated levels of serum IgE. Using FASTLINK, researchers were able to find evidence linking this syndrome to chromosome 4. FASTLINK has been cited in over 400 other published genetic studies, including studies of macular dystrophy, type 1 hereditary sensory neuropathy, and Alstrom's syndrome.

CASPAR (Computerized Affected Sibling Pair Analyzer and Reporter) is a software program designed by NCBI investigators to study the genetics of complex diseases, or diseases involving the interaction of multiple genes. It allows a user to explore various hypotheses about how different factors may be involved in disease susceptibility. NCBI investigators have used CASPAR to study linkage analysis in patients with a form of diabetes.

The PedHunter software was developed to query genealogical databases to determine a connection between a set of relatives that are afflicted with the same disease and to construct a pedigree suitable for input to genetic linkage analysis. NCBI investigators are using PedHunter to query the Amish Genealogy database to collect information on various genetic diseases, including nemaline myopathy. Nemaline myopathy is a rare genetic neuromuscular disorder that is usually apparent at birth and characterized by extreme muscle weakness. Using PedHunter, in combination with other genetic analysis software, NCBI investigators have demonstrated that, in the Amish, this disorder is caused by a mutation in the gene for the sarcomeric thin-filament protein, slow skeletal muscle troponin T (TNNT1). TNNT1 maps to chromosome 19 and has been previously sequenced. Further analysis resulted in the identification of a stop codon that segregated with the disease. Researchers concluded that Amish nemaline myopathy is a distinct, heritable, myopathic disorder caused by a mutation in TNNT1.

The CGH (comparative genomic hybridization) analysis software package is being used by NCBI investigators for modeling the process of tumor formation in various forms of cancer. The focus of the software is to develop models that relate genetic aberrations with tumor progression.

Investigators have used CGH as part of a larger project to search for and identify possible susceptibility loci involved in both breast and bladder cancer. Investigators have also published the results of a case study in which CGH was used to analyze chromosomal abnormalities in a large collection of ovarian cancer samples.

Three-Dimensional Structure Database

NCBI's Structure Research Group maintains a database of experimentally determined three-dimensional biomolecular structures, as well as tools for visualizing and analyzing these structures. Three-dimensional structures provide a wealth of information on biological function of a molecule, on mechanisms linked to function, and on evolutionary history of and relationships between macromolecules, all valuable clues leading towards better understanding rare diseases.

For example, in 1995, the structure of leptin—the protein coded for by a gene linked to obesity and forms of diabetes—was predicted by NCBI investigators using the structure database. After the discovery of leptin, researchers analyzed the protein's sequence and determined that it exhibited no similarities to other known proteins. NCBI investigators hypothesized that leptin was ancestrally related to at least one other protein whose sequence had diverged such that only a comparison of three-dimensional structures might detect a relationship. Investigators conducted a search of the database to determine whether this protein might adopt a similar fold pattern, or structure, to that of a protein structure already stored in the database. They discovered that leptin's sequence was compatible with the structure of a family of known proteins and predicted a structural model based on these results. Subsequently, this early prediction was confirmed by cloning of the protein's receptor, and more recently, by X-ray structure determination. Now that the structure of leptin has been confirmed, future studies of leptin, as well as other leptin-regulated genes, may reveal the mechanisms by which leptin exerts its effect on the body.

Malaria Genetics and Genomics

Malaria is by far the world's most important tropical parasitic disease. The causative agents in humans are four species of a single-celled parasite from the genus Plasmodium—*P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Of these, *P. falciparum* accounts for the majority of infections and is the most lethal. Malaria is a curable disease if promptly diagnosed and adequately treated. Therefore, much research at the NIH focuses on the treatment and prevention of malaria.

The NCBI, in collaboration with the NIAID, supports the efforts to sequence and analyze the complete genome of *P. falciparum*, thereby providing researchers with access to information relative to all of the genes found in this parasite. Genetic investigations of malaria require a genome-wide, high-resolution linkage map of *Plasmodium falciparum.* A collaborative team of NIH investigators, including researchers from the NCBI, constructed such a map. The markers and map, as well as other parameters, are facilitating genome sequence assembly, localization of determinants for such traits as virulence and drug resistance, and genetic studies of parasite field populations.

NCBI's Malaria Genetics and Genomics Web page serves as a resource for data and information relevant to *Plasmodium* in general and more specifically on *P. falciparum*, *P. vivax* (the second most prevalent form of human malaria), and various forms of rodent malaria. From NCBI's site, researchers may access genome maps, linkage markers, and information about genetic studies. Links are also provided for other malaria sites and for genetic data on related parasites, including NIAID's Malaria Research and Reference Reagent Resource Center (MR4)—a central source for quality controlled malaria-related reagents for the international research community. One may also link to information concerning malaria epidemiology, taxonomy, molecular tools for data analysis, and various malaria research projects being conducted at NIH.

NCBI recently released a new resource for enhancing studies on *Anopheles gambia* (mosquito), the primary vector that transmits human malaria. This information, together with the knowledge gained from the sequences of malaria parasites and the human genome, will provide researchers with a wealth of genomic data necessary for understanding this complex disease as well as for developing malaria control strategies and improved anti-malarial drugs and vaccines.

Additional Human Genome Resources

The NBCI makes available a number of other resources to facilitate the widespread use of human sequence data. The Human Genome Resources Web page serves as an integrated, one-stop, genomic information infrastructure for biomedical researchers from around the world so that they may use this data in their research efforts. From the Human Genome Resources Web page, researchers can access the NCBI Map Viewer, which presents a graphical view of the available human sequence data as well as cytogenetic, genetic, physical, and radiation hybrid maps. Researchers may search for a gene, or a gene marker, of interest by querying against the entire human genome, or by querying one chromosome at a time. Query results link to a graphical display of where the gene or gene marker may be viewed in the context of additional data.

NCBI's Genes and Disease Web page is designed to introduce a visitor to the relationship between genetic factors and human disease. Genes and Disease provides information for greater than 60 genetic diseases, including numerous rare diseases and disorders. The Online Mendelian Inheritance in Man database, or OMIM, is a continuously updated catalog of inherited human disorders and their causal mutations, authored and edited by Dr. Victor A. McKusick and colleagues and developed for the Web by NCBI.

One of the many reasons for sequencing the human genome was to gain an understanding of the role of a gene, or genes, in human disease. By studying the sequence of a disease gene—whether it be from humans or other model organisms, researchers can gain important insights into the genetic and environmental basis of disease. The advances outlined here demonstrate the importance and utility of NCBI's computer databases, data analysis tools, and software algorithms in identifying and understanding human disease genes and pave the way for the development of novel strategies to diagnose, treat, and ultimately, prevent, all forms of disease.

SARS Coronavirus Resource

The Severe Acute Respiratory syndrome (SARS) virus was responsible for an outbreak of severe, atypical pneumonia in Guangdong Province, China, in late 2002. The disease had an extremely high mortality rate (up to 19 percent) and expanded rapidly to other countries. In April 2003, a previously unknown coronavirus was isolated from patients and subsequently shown to be the causative agent in experiments on monkeys. The first complete sequence of SARS coronavirus was produced by the BCCA Genome Sciences Centre, Canada, about 2 weeks after the virus was detected in SARS patients. It was submitted to the NCBI's GenBank sequence database, and the NCBI Viral Genomes Group annotated the sequence and released it the next day. The availability of sequence data and the functional dissection of the SARS-CoV genome at the NCBI site has been a necessary prerequisite for developing diagnostic tests, antiviral agents, and vaccines. The NCBI Web resource includes the complete sequence as well as links to the latest sequence data and publications and results of pre-computed sequence analyses: genomic, protein, and structural.

Database of the Major Histocompatibility Complex

The NCBI dbMHC database provides an open, publicly accessible platform for DNA and clinical data related to the human Major Histocompatibility Complex (MHC). MHC research and clinical data generated at meetings such as the International HLA Workshop and Congress has proven valuable to the international research community. NCBI makes these data available along with tools for submission and analysis of research data linked to the MHC. The dbMHC contains reagent data used for tracing DNA typing and a section with anonymous clinical data from MHC-related research projects related to diseases such as celiac disease, narcolepsy, ankylosing spondylitis, and hemochromatosis.

WARREN GRANT MAGNUSON CLINICAL CENTER (CC)

Overview of Rare Diseases Research Activities

Two Clinical Center investigators currently are conducting significant work on rare diseases. Mark Gladwin, M.D., Critical Care Medicine Department, leads a robust program exploring the prevalence, etiology, and treatment of secondary pulmonary hypertension. This clinical research program is complemented by a basic science program focusing on the pathophysiology and experimental therapeutics of Sickle Cell disease. Margaret Rick, M.D., Department of Laboratory Medicine, continues both clinical and laboratory investigation on von Willebrand factor.

Sickle Cell Disease

Project Title:	Translation Research Program in Sickle Cell Disease
Principal Investigator:	Mark T. Gladwin, M.D., CCMD, CC, NIH
Other Investigators: (Detailed in Appendix)	Frederick P. Ognibene, M.D., CCMD, CC, NIH Richard O. Cannon III, M.D. CB, NHLBI, NIH Alan N. Schechter, M.D.; LCB, NIDDK, NIH Vandana Sachdev, M.D.; CB, NHLBI, NIH Maria Jison, M.D.; CCMD, CC, NIH Griffin P. Rodgers, M.D.; MCHB, NIDDK, NIH Oswaldo Castro, M.D.; Howard University Greg Kato, M.D., CCMD, CC, NIH Stephen Chanock, M.D., Genotyping Facility, NCI Peter J. Munson, Ph.D., CIT, NIH Christopher Reiter, Ph.D., LCB, NIDDK, NIH Wynona A. Coles, RRT; CCMD, CC, NIH James S. Nichols, RN; CCMD, CC, NIH Inez Ernst, RN; CB, NHLBI, NIH Lori A. Hunter, BSN; CCMD, CC, NIH William Blackwelder, Ph.D.; CCMD, CC, NIH

Aims:

- *Scope of sickle cell disease*: In the United States there are 50,000 individuals with sickle cell disease (SS hemoglobin). One of every 650 African Americans (0.15 percent) is born with sickle cell disease, and about 8 percent are heterozygous for the sickle cell gene. According to the United States Census Bureau there were approximately 35,509,000 African Americans in the year 2000 which would indicate that there are approximately 50,000 patients with sickle cell anemia in this country.

- *Mortality and pulmonary disease*: The median age at death for patients with sickle cell disease is 42 years for men and 48 years for women (Platt, 1994). Pulmonary

complications account for a large proportion of deaths among adults with sickle cell anemia. According to the Cooperative Study of Sickle Cell Disease (CSSCD), in a prospective multicenter study of 3,764 patients, over 20 percent of adults likely had fatal pulmonary complications of sickle cell anemia (Platt, 1994). Acute and chronic pulmonary complications of sickle cell anemia, such as pulmonary hypertension, pulmonary fibrosis, and asthma, are common but often under-appreciated by health-care providers.

- *Sickle cell is an orphan disease:* From the pharmaceutical industry's standpoint, this is considered an orphan disease with limited market potential. This fact has severely limited the exploration of potentially beneficial new medications.

- *Scope of current intramural program:* Over the last four years we have created a unified consortium of CC, NIDDK, and NHLBI intramural investigators and created one of the largest sickle cell disease translational research programs in the country and one of the largest minority research programs in the intramural NIH. We have enrolled over 200 patients with sickle cell anemia and over 100 control subjects (48 African Americans) into six studies (see appendix A). The largest study explores the prevalence, etiology, and treatment of secondary pulmonary hypertension, a leading cause of adult mortality in patients with sickle cell disease. This clinical program is complemented by a basic science program, which is extremely well-published in areas of pathophysiology and experimental therapeutics.

Accomplishments:

- Characterize the role of nitric oxide in the pathogenesis and treatment of sickle cell disease

    1. In a series of studies over the last four years we have combined forearm blood flow studies, using endothelium-dependent and independent vasodilators and nitric oxide (NO) synthase inhibitors, with NO inhalational protocols to probe the bioavailability of NO in patients with sickle cell disease and to explore the role of NO in therapeutics. These human forearm blood flow studies revealed five major mechanisms of vascular instability in sickle cell disease:

        -- Basal and stimulated (with acetylcholine) endothelium-dependent vasodilation is markedly increased in patients sickle cell disease, consistent with the low systemic vascular resistance of sickle cell disease.

        -- Mediators other than NO (prostacyclin and carbon monoxide (CO) gas derived from heme-oxygenase) account for most of the increased endothelium-derived vasoactivity.

        -- Gender differences in NO bioavailability are observed, with males demonstrating increased NO scavenging.

        -- The evidence points to the presence of an inhibitor of NO in the vasculature (discussed in detail below).

-- Hydroxyurea is metabolized to nitric oxide in vivo and induces eNOS resulting in improved endothelial function and NO bioavailability.

2. Studies in both transgenic murine models and in humans with sickle cell disease uniformly indicate an impairment in NO-dependent relaxation in the vasculature, and specifically an *inhibition* of NO bioactivity. We have recently found and reported that NO may be scavenged and destroyed by ferrous oxyhemoglobin present in the plasma of patients with sickle cell disease. The plasma from patients with sickle cell disease contains 2-20 μM ferrous (Fe^{II}) oxyhemoglobin, released during steady state hemolysis. The levels of plasma hemoglobin rise during vaso-occlusive crisis and the acute chest syndrome as hemolysis intensifies. This plasma ferrous oxyhemoglobin reacts with NO at nearly diffusion-limited rates to produce methemoglobin and nitrate, a dioxygenation reaction that inactivates NO.

   -- This inhibition of NO will impair important vascular functions of NO such as vasodilation, platelet inhibition, and the tonic down-regulation of VCAM-1 and E-selectin.

   -- Hemoglobin will also scavenge endothelium-derived NO, resulting in a secondary induction of endothelin-1 expression. Endothelin-1, the most potent circulating vasoconstrictor in humans, is induced in vaso-occlusive crisis, and we believe contributes to the vascular instability of sickle cell disease and the development of secondary pulmonary hypertension (discussed below).

   We have proposed a model wherein the production of NO is augmented by increasing NOS expression, the latter driven by tissue hypoxia, increased erythropoietin, and estrogens. However, the bioavailability of NO is limited, particularly in men and, in all likelihood, in all patients during vaso-occlusive crisis and the acute chest syndrome, by inactivation by plasma hemoglobin and superoxide. In this model, the observed reduction in plasma L-arginine levels in patients with sickle cell disease (demonstrable in steady state, vaso-occlusive crisis, and the acute chest syndrome) results from increased utilization of L-arginine by enhanced endothelial NOS, the latter driven by inordinate scavenging of its product, NO. Therapies that target these mechanisms, such as inhalation of NO (which will oxidize and inactivate circulating hemoglobin), and the HMG-Co-enzymeA inhibitors (which induce eNOS expression and reduce inflammation) are currently being evaluated.

- *Identification of therapeutic targets:* In the last two years we have identified three potential novel therapeutic approaches based on our laboratory investigations:

  1. Statins: patients with sickle cell disease have endothelial dysfunction secondary to endothelial nitric oxide (NO) deficiency that will likely respond to HMG-Coenzyme A inhibitors.

2. NO gas inhalation: steady state intravascular hemolysis in sickle cell patients liberates micromolar quantities of plasma hemoglobin which stoichiometrically consumes NO. This effect is inhibited by NO gas inhalation.

3. Sildenafil/L-arginine: we have recently demonstrated that hydroxyurea, the only FDA approved drug for sickle cell disease therapy, induces fetal hemoglobin via a nitric oxide-guanylyl cyclase-cGMP dependent pathway. These data suggest that synergy between hydroxyurea and phosphodiesterase inhibitors (Sildenafil) or L-arginine may increase fetal hemoglobin induction.

- *Characterizing the emerging syndrome of hemolytic anemia-associated secondary pulmonary hypertension*

1. In collaboration with Frederick Ognibene, CCMD, and investigators in the Cardiovascular Division of NHLBI, we performed Doppler echocardiographic assessment of pulmonary artery systolic pressure in 175 consecutive adult patients (males=74, females=101, mean age=37±11) recruited from the greater Washington, D.C., area. Pulmonary hypertension was prospectively defined as a tricuspid regurgitant jet velocity (TRV) ≥ 2.5 m/sec. TRV and right heart catheterization pressures were compared in patients with tricuspid regurgitant velocities exceeding 2.8 m/sec. A right heart catheterization unit has been developed for use in 10D ICU studies. Patients were followed for a mean of 12.3±0.5 months and censored at time of death or loss to follow-up.

   Peak TRV correlated strongly with catheterization-determined pulmonary artery systolic pressure ($r=0.95$; $p<0.001$). Doppler-defined pulmonary hypertension occurred in 33 percent of patients and was unrelated to cardiac output, left ventricular stroke volume, or left ventricular systolic dysfunction (the latter observed in <2 percent of patients). Multiple-logistic regression analysis, using the dichotomous variable TRV ≥ or < 2.5 m/sec, identified higher age, increased levels of plasma markers of hemolysis (lactate dehydrogenase), decreased transferrin, increased alkaline phosphatase, and increased body mass index as statistically significant independent correlates of pulmonary hypertension, while fetal hemoglobin level, white blood cell count, platelet count, and hydroxyurea therapy were not. In univariate analysis, TRV was a strong predictor of mortality (relative risk 8.3; 95 percent CI = 1.7 to 40; $p=0.003$) and, in a multivariate model, was the only significant independent predictor of mortality in this population ($p=0.01$).

   These results suggest that secondary pulmonary hypertension is common in adult patients with sickle cell disease, appears to be resistant to hydroxyurea therapy, and confers a high mortality. These data suggest that a non-invasive Doppler echocardiogram identifies adult sickle cell patients at increased risk of death and that therapeutic trials targeting this population are indicated.

2. Based on these results we have ongoing phase I/II trials evaluating a variety of therapeutic interventions, including NO gas inhalation by pulse delivery system, exchange transfusion designed to induce aplasia and inhibit hemolysis, oral arginine, and oral sildenafil (in women).

Future Goals:

1-3 Year (all projects in progress)

- Pulmonary hypertension screening study (01-DK-0088; n=370)
  --Determine prevalence, etiology, and diagnostic accuracy of echocardiogram
  --Prospectively determine the prognosis of pulmonary hypertension
  --Identify hemoxygenase/VCAM-1 candidate gene polymorphisms

- Pulmonary hypertension treatment study (01-H-0223; n=100)
  --Evaluate acute responses to NO, prostacyclin, and oxygen
  --Evaluate chronic responses to NO and transfusion therapy

- Gene expression project (01-CC-0078; n=50)
  --Identify inflammatory pathways in sickle cell disease using mononuclear cell mRNA expression microarrays

- Fetal hemoglobin induction (03-CC-0127; n=50)
  --Evaluate effects of hydroxyurea treatment combined with sildenafil/arginine in vitro and in vivo
  --Evaluate hydroxyurea analogues

- HMG-Co-enzyme A inhibitors (Pending; n=39)
  --Initiate phase II trial of "statins" for the chronic treatment of patients with sickle cell disease. Evaluate effects on markers of inflammation, endothelial function, and symptoms

- Inhaled NO trial for vaso-occlusive crisis (Pending; n=200)
  --Initiate multicenter phase II placebo-controlled trial of inhaled NO for vaso-occlusive crisis

Protocols:

1. Principal Investigator; NIH Clinical Protocol #98-CC-0129: **Physiologic Effects of Inhaled Nitric Oxide, Nitroglycerin, and Placebo in Patients with Sickle Cell Anemia.**
2. Principal Investigator; NIH Clinical Protocol #01-CC-0078: **Targeted Delivery of Nitric Oxide by Hemoglobin to Improve Regional Blood Flow in Sickle Cell Disease.**

3. Principal Investigator; NIH Clinical Protocol #01-DK-0088: **Determining the Prevalence and Prognosis of Secondary Pulmonary Hypertension in Adults with Sickle Cell Anemia.**
4. Principal Investigator; NIH Clinical Protocol #01-H-0223: **Inhaled Nitric Oxide or Exchange Transfusion for the Therapy of Patients with Sickle Cell Anemia and Secondary Pulmonary Hypertension.**
5. Principal Investigator; NIH Clinical Protocol #03-CC-0015: **Collection of Blood from Volunteers and Patients for Studies of Endothelial Function and Systemic Inflammation.**
6. Associate Investigator; NIH Clinical Protocol #00-H-0031: **Vascular Effects of Endothelium-Derived Versus Hemoglobin-Transported Nitric Oxide in Healthy Subjects.**
7. Principal Investigator; NIH Clinical Protocol #03-CC-0127**: Evaluation of Potential Synergy of Combining Hydroxyurea with Nitric Oxide Donors on Fetal Hemoglobin Synthesis in Patients with Sickle Cell Anemia.**
8. Principal Investigator; **DeNOVO Trial (Delivery of NO for Vaso-Occlusion): A Prospective, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of Nitric Oxide for Inhalation in the Acute Treatment of Sickle Cell Pain Episode.** Status: protocol in final stages of development.
9. Principal Investigator; **Atorvastatin Therapy to Improve Endothelial Function in Sickle Cell Disease.** Status: protocol in final stages of development.

- ***Implementation of these studies will make the intramural NIH one of the largest national centers for translational sickle cell disease research and the most active center developing phase II therapeutics.*** We propose to increase the scope and productivity of this project with the specific goals of 1) exploring novel therapeutic targets for adults with sickle cell anemia, and 2) initiating rapid and efficient, rationally designed phase II clinical trials of currently available FDA approved medications and new novel agents to bring such therapies to clinical practice in a timely manner. Based on the proven success of this program in terms of patient recruitment, publications (see below), national scientific impact, development of novel therapeutic targets and agents, and industry and supplemental support (CRADA, bench-to-bedside awards and three year funding from the Center for Research on Minority Health and Health Disparities total 476K per year), an increased and continued investment in personnel and financial support will produce even more significant results.

Selected Publications:

1999

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14. Zuzak KJ, Schaeberle MD, Gladwin MT, Cannon RO, 3rd, Levin IW. Noninvasive determination of spatially resolved and time-resolved tissue perfusion in humans during nitric oxide inhibition and inhalation by use of a visible-reflectance hyperspectral imaging technique. Circulation 2001;104:2905-2910.

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Von Willebrand Disease

The Hematology laboratory and clinical service within the Department of Laboratory Medicine, Clinical Center, has continued both clinical and laboratory work on von Willebrand factor, a hemostatic protein that is important in thrombosis and hemostasis. The laboratory's clinical efforts include the evaluation and suggested treatment of patients with a bleeding diathesis related to a deficiency or qualitative defect of von Willebrand factor. The laboratory staff also consults on patients with the syndrome of thrombotic thrombocytopenic purpura, a disease in which an enzyme

(ADAMTS 13) that normally cleaves large prothrombotic forms of von Willebrand factor is defective or inhibited, leading to diffuse thrombosis and serious clinical outcomes.

The Hematology laboratory has continued to utilize an assay developed in the laboratory to assess the activity of ADAMTS13 and recently participated in an international study comparing the utility of these assays. The clinical usefulness of these assays has been discussed in a peer-reviewed paper. In more basic studies, the laboratory has evaluated the ability of ADAMTS13 to cleave different size multimers of von Willebrand factor and have found that the reaction rate is more rapid for the more thrombotic high molecular weight multimers.

Voluntary activities have included chairing an Educational session at the American Society of Hematology National Meeting in December 2003, that included a talk and discussion on von Willebrand disease. Dr. Margaret Rick will speak on von Willebrand disease at a regional meeting arranged by the National Hemophilia Foundation in the spring of 2004.

OFFICE OF RESEARCH ON WOMEN'S HEALTH

Overview of Rare Disease Activities

The Office of Research on Women's Health (ORWH) serves as the focal point for women's health research for the Office of the Director, NIH, to ensure that research on women's health is appropriately addressed and supported across the NIH Institutes and Centers, to ensure that women are appropriately represented in biomedical and bio-behavioral research studies supported by the NIH, and to develop and support opportunities for biomedical careers for women or investigators interested in women's health research.

The report, *An Agenda for Research on Women's Health for the 21st Century,* provides the basis for ORWH to collaborate with the scientific and advocacy communities to address scientific initiatives about women's health and sex and gender factors in health and disease. Research priorities for women's health emphasize the importance of interdisciplinary collaboration. Many rare diseases are identified in this research agenda as areas of priority for which there are gaps in knowledge that need to be addressed. ORWH continues to successfully partner with institutes and centers to fund or co-fund new and innovative research, both basic and clinical, related to women's health or sex and gender factors. Because the ORWH does not have direct funding authority, ORWH support for research initiatives is always in conjunction with the primary institute or centers. Below are listed a number of areas of research focus for which ORWH has provided support during FY 2003.

Research Funded During FY 2003 by the Office of Research on Women's Health (ORWH)

During fiscal year 2003, the ORWH supported 39 grants that focused on disorders classified as “rare diseases” by the NIH. These disorders include chronic fatigue syndrome, fibromyalgia, rheumatoid arthritis, multiple sclerosis, scleroderma, Sjogren's syndrome, systemic lupus erythematosus, diabetes mellitus, TMJ/TMD, Fragile X mental retardation, and osteoarthritis. Because the ORWH does not have direct funding authority, these grants were funded through established collaborations with seven NIH institutes and centers (ICs). Specifically, ORWH co-funded these grants with NIAID, NIAMS, NIA, NEI, NICHD, NIDCR, and NINDS.

FY 2003 Scientific Activities in Rare Diseases Research:

Chronic Fatigue Syndrome

ORWH coordinates all of the NIH research activities on chronic fatigue syndrome through its chair of the Trans-NIH Working Group on Chronic Fatigue Syndrome and spearheaded program announcement PA-O2-34 through this group. In FY 2003, ORWH co-funded with the National Institute of Child and Human Development (NICHD) a five-year prospective, interdisciplinary study to explore the development of chronic fatigue syndrome following mononucleosis among adolescents at the University of Illinois at Chicago. This study will permit the development of a preliminary model of the etiology and natural course of the illness for adolescents with post-viral chronic fatigue syndrome.

Systemic Lupus Erythematosus (SLE)

ORWH has co-funded nine SLE grants with NIAID and NIAMS. Specifically, studies are exploring the correlation between SLE and previous infection with Epstein Barr virus (EBV), and the environmental factors associated with SLE, including EBV. A new research project grant focuses on a large clinical study related to thrombosis and pregnancy loss in SLE, particularly the presence of antiphospholipid antibodies. Several grants, all funded through a RFA based in NIAMS, are evaluating the neuro-psychiatric manifestations of SLE, including exploring the genetic aspects of SLE, gene-mapping and clinical therapy grants. In FY 2003, the Autoimmune Centers of Excellence grants were recompeted and co-funded by ORWH and NIAID. These grants support large translational studies that bridge basic science with clinical research. Within these large center grants, SLE-specific studies are being undertaken along with a variety of studies focused on other autoimmune disorders such as Rheumatoid Arthritis and Multiple Sclerosis.

Temporomandibular Joint Disorders (TMJ/TMD)

ORWH is co-funding six TMJ grants with NIDCR. Several focus on behavioral aspects, such as testing the efficacy of psychological interventions, pharmacological interventions, and a combination of the two to reduce pain and improve function in persons (both male and female) with TMJ. One specific grant seeks to elucidate the cellular mechanisms of paclitaxel-induced painful peripheral neuropathy in the rat. By improving our understanding of the cellular mechanisms of neuropathic pain, these studies can potentially provide important insights into the pathophysiology and treatment of orofacial neuropathies. Other studies focus on the genotyping of peripheral tissue to better understand the system response in humans with respect to disease characteristics of TMJ. Specifically, sensitivity to pain and inhibition of pain are traits of considerable variability, so the effect of genes on a person's response characteristics to experimentally induced jaw muscle pain will be studied. Another genetic project seeks to identify and characterize genes through which steroidal hormones affect the onset and/or the severity of human disease. The last grant focuses on establishing a TMJ implant registry and repository that will allow collection of clinical information and biological specimens in patients with TMJ implants across the United States.

Specialized Centers on Research (SCOR) Funding

ORWH developed and implemented the Specialized Centers on Research (SCORs) on Sex and Gender Factors Affecting Women's Health to expedite interdisciplinary development and application of new knowledge to human diseases, to learn more about the etiology of these diseases, and to foster improved approaches to treatment and/or prevention. ORWH is funding a SCOR that will elucidate the mechanisms associated with sex and gender differences in persistent and chronic pain. The focus is to explore the neural basis of TMJ and to also examine sex differences in pain perception.

Fibromyalgia

Research co-funded by ORWH and NIDCR focuses on elucidating the role of craniofacial primary afferent neurons in musculoskeletal disorders such as fibromyalgia (PM), using animal models. The primary aim of this study is to test the functional properties of muscle afferent neurons in part by evoking spontaneous activity and increasing their excitability. Because a sex/gender difference is reported for Fibromyalgia, the experiments will be tested in males, estrous females, and diestrous females.

Rheumatoid Arthritis (RA)

ORWH co-funded with NIAID and NIAMS four specific grants in this area: a translational study of the differences in neutrophil function in pregnant women, non-pregnant women, and men. Studying neutrophil biology during pregnancy will result in a mechanistic understanding of factors responsible for clinical improvement of certain autoimmune disorders during pregnancy, and will lead to the development of novel therapeutic approaches to control inflammation and autoimmunity. Another study is evaluating the relationship between cardiovascular disease and RA because this combination of disorders is increasing in frequency. A new study seeks to identify markers of autoimmunity, like RA, that would allow identification of individuals at high risk and the design of a prevention strategy. OR WH has also funded the lead research group that is establishing a multi-institutional longitudinal registry of African American women diagnosed with early RA in order to identify genetic and non-genetic prognostic factors of disease outcome to permit prospective analyses of factors predictive of the clinical phenotype and outcomes.

Multiple Sclerosis (MS)

OR WH is supporting with NIAID an Autoimmune Center of Excellence project that focuses on B- and T-cell function in relation to the pathogenesis and treatment of MS. A second NEI co-funded grant by ORWH focuses on defining the visual profile of multiple sclerosis in a large cohort of 400 patients and determining which measures best identify visual dysfunction in patients with MS. The investigators will then determine the relationship of visual function and disease-specific health related quality of life in patients with MS.

Sjögren's syndrome (SS)

In FY 2003, ORWH co-funded with NIDCR the first international research registry network for Sjögren's Syndrome (SS), a rheumatic autoimmune disease that initially affects the salivary and lacrimal glands but can affect the lungs, kidneys, central nervous system, and vasculature. The key elements of this registry include establishing standardized diagnostic criteria for recruiting patients and collecting, storing and analyzing clinical information for patients and families.

Osteoarthritis (OA)

Two grants were co-funded in FY 2003. The major activity is the public-private partnership called the Osteoarthritis Initiative (OAI), which is supported by ORWH, with NIAMS and NIA as the lead institutes, along with other institutes and pharmaceutical partners. This multi-institutional project is bringing together new resources to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5-7 years, the Osteoarthritis Initiative (OAI) is collecting information and defining disease standards on 5,000 people at high risk of having osteoarthritis and at high risk of progressing to severe osteoarthritis during the course of the study. Currently, new drug development for OA is hindered by the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. The OAI consortium includes public funding from the NIH and private funding from several pharmaceutical companies. The consortium is being facilitated by the Foundation for the National Institutes of Health, Inc. The OAI is supporting six clinical research centers that are establishing and maintaining a natural history database for osteoarthritis that will include clinical evaluation data and radiological images, and a bio-specimen repository. All data and images collected will be available to researchers worldwide to help quicken the pace of scientific studies and biomarker identification. The second OA grant, co-funded with NIAMS, focuses on ethnic differences in the management of OA, especially the utilization of elective total joint replacement.

Scleroderma

Two grants, both co-funded with NIAMS, address the important problem of the significance of autoantibodies in Scleroderma patients. This work will lead to the search for a pathogen in the environment that could lead to an immune response to the cross-reacting antigen. The possibility of tissue damage due to autoantibodies will also be investigated. The second project will utilize two mouse mutations that are models for Scleroderma. Both mutations display excessive accumulation of collagen and other extracellular matrix components in the skin, a hallmark of the human disease. The long-range objective of this research is to utilize the two mutations, combined with several lines of transgenic mice as experimental tools, to dissect molecular mechanisms of disease pathogenesis.

Graves Disease

ORWH and NEI co-funded an innovative research grant that is evaluating the relationship between ophthalmopathy and Graves disease. The overall goal of this project is to use this model to investigate critical issues of Graves disease to examine the role of CD40 for orbital fibroblasts/preadipocytes and to characterize certain effects in their relationship to Graves ophthalmopathy. The ophthalmopathy of Graves disease is a disfiguring, sight-threatening condition of unclear pathogenesis and no specific of definitive therapy. Often ophthalmopathy accompanies the hyperthyroidism. Rather than being considered two separate entities, hyperthyroidism and ophthalmopathy are different manifestations of the same underlying autoimmune process. No spontaneous animal model of Graves disease exists. Recently, an animal model has been developed in which a proportion of individuals manifest immunological and endocrinological features of Graves disease.

Myocarditis

ORWH and NIAID co-funded a research grant that is exploring the sex differences in myocarditis, an inflammatory disease of the myocardium. Approximately 65 percent of cases follow recent enterovirus infections and occur in males. As in humans, CVB3 infections cause severe myocarditis in male, but not virgin female mice. Androgens (progesterone and testosterone) increase virus receptor expression on cardiac myocytes while 17-beta-estradiol treatment does not. Since lymphocytes also express CVB3 receptors, the hormones might modulate lymphocyte expression of these molecules as well. Cytokine release differs between male and female lymphocytes with male cells producing interferon (IFN) gamma and female cells producing
interleukin (IL)-10. It is hypothesized that viruses, which have repetitive symmetry of the virus capsid, cross-link important cell surface molecules on lymphocytes and cause rapid nonantigen-specific lymphocyte activation. This project will determine virus receptor expression, activation potential, and cytokine production on male and female lymphoid cells to a noninfectious virus, and the effects of direct virus interaction and hormone signaling. These studies may provide new insights as to how viruses affect developing host defense responses and how hormones can modulate this initial response

Type 1 Diabetes Mellitus (IDDM)

Several of the Autoimmune Centers of Excellence grants, all funded jointly by NIAID and ORWH, focus on type 1 Diabetes Mellitus research. Some specific areas covered are using tetramers to analyze the peripheral antigen-specific T-cell profile in IDDM; how does blockage ofCD4O/CD4O1 prevent autoimmunity; pathogenesis and treatment, including clinical trials on IDDM.

Fragile X Syndrome

NICHD and ORWH have co-funded a grant focusing on Fragile X syndrome (FRX), a form of congenital mental retardation in humans, usually resulting from lack of expression of the Fragile X Mental Retardation Gene (FMR1). Unaffected carriers or so-called FRX permutation carriers show an increased prevalence of Premature Ovarian Failure (PO F), estimated to affect 1 % of women worldwide. The prevalence of POF in FRX premutation carriers has been reported to be 16%. The study will characterize the cell-specific FMR1 gene expression changes in normal human and mouse ovaries through their respective reproductive cycles and define the physiology of hypothalamic-pituitary-ovarian function in human female FRX premutation carriers. A repository will be established of genetic material and extensive phenotypic information about affected women that could eventually be used to test other candidate genes for POF.

Vulvodynia

ORWH co-funded two grants with NICHD to elucidate the pathophysiological mechanisms of vulvodynia in order to develop improved treatment strategies and to assess the differences in specific neuroimmunological characteristics between women with vulvodynia and asymptomatic

controls. Results from this study will lead to improved understanding of neuroimmunologic alterations in women with vulvodynia that will direct future therapeutic strategies for this disorder.

Rare Diseases-Specific Workshops and Symposia:

In FY 2003, ORWH sponsored a two-day scientific workshop, titled *Neuro-immune Mechanisms and Chronic Fatigue Syndrome: Will understanding central mechanisms enhance the causes, consequences and treatment of CFS?* Scientists of diverse disciplines from within the NIH intramural community as well as distinguished extramural experts were convened to explore the mechanisms by which hormones, cytokines, and other mediator's act as intermediaries between the brain and other body systems. These scientists also explored how new methodologies developed for the neurosciences could be used to understand CFS and similar conditions. The recommendations from this workshop will be used as the basis for an interdisciplinary RF A, prepared by the CFS Working Group, and other future CFS efforts.

FASEB Research Conference on Autoimmunity

The meeting, co-funded with NIAID, focused on the latest developments in the field of autoimmunity; especially how recent advances in basic immunology and cell biology have influenced the field of autoimmunity. The conference presented a comprehensive view of basic immunological mechanism related to autoimmunity, as well as mechanism involved in the autoimmune process, and immune intervention.

Vulvodynia- Toward Understanding a Pain Syndrome Workshop

Vulvodynia is a condition characterized by burning, stinging, irritation, or rawness of the female genital area when there is no apparent infection or skin disease that could cause these symptoms. Vulvodynia can have a profound impact on a woman's quality of life, hindering her ability to exercise and take part in social activities. A workshop was held from April 14-15, 2003, at the NIH. The aims of this workshop were to present an overview of the science and epidemiology of vulvodynia, to elucidate the fundamental mechanisms of vulvodynia and related pain syndromes, to stimulate innovative research approaches to vulvodynia, and to develop clinical strategies for the appropriate and evidence-based methods of alleviating vulvar pain.

Outcome Measures for Sjögren's Syndrome Workshop

The conference covered definitions and identification of Sjogren's syndrome, outcome measures, quality of life, clinical trials, serial biopsies and focus scores, additional outcome measures that have already been used in clinical trials, and an open forum to discuss individual outcome measures that have not already been proposed.

Rare Disease-Specific RFAs for FY03:

1. Pathobiology of Temporomandibular Joint Disorders-NIAMS/NIDCR/ORWH
2. Microcirculation and Target Organ Damage in Rheumatic and Skin Diseases--NIAMS/NEI/ORWH
3. Autoimmune Centers of Excellence-NIAID, NIDDK, ORWH

New/Planned Extramural Research Initiatives

ORWH coordinates all of the NIH research activities on Chronic Fatigue Syndrome. In FY 2004, the ORWH will sponsor a new intramural scientific interest group on scientific integrated medicine that resulted from this workshop. For FY 2005, efforts will concentrate on a new request for applications to stimulate and broaden the scope of CFS research. This RFA will be based on the recommendations from the June 2003 workshop on central mechanisms in CFS.

OFFICE OF RARE DISEASES (ORD), OFFICE OF THE DIRECTOR

Overview of Rare Diseases Research Activities

The Rare Diseases Act of 2002, Public Law 107-280, formally established the Office of Rare Diseases (ORD) at the National Institutes of Health (NIH). To foster the collaboration and coordination of rare diseases research across the NIH and other agencies, ORD works with NIH Institutes, Centers, and Offices and other rare diseases entities to support an extramural research program, an intramural research program, a scientific conferences program, an information center and other information dissemination mechanisms, and a number of other seminal rare diseases research activities.

Recent Scientific Advances in Rare Diseases Research

Rare Diseases Extramural Research Program

Rare Diseases Clinical Research Network

Through its Extramural Program, the ORD dedicated the majority of its FY 2003 appropriation to a Request for Applications (RFA) for a Rare Diseases Clinical Research Network together with the National Center for Research Resources (NCRR) and other NIH Institutes and Centers (ICs). The primary goal for the network is the systematic collection of clinical information to develop biomarkers and new approaches to diagnosis, treatment, and prevention of rare diseases, as well as to promote training of new clinical research investigators in rare diseases. The RFA resulted in the submission of 57 applications for research consortia and 12 applications for the Data and Technology Coordinating Center (DTCC) despite a very short response time for the applicants. The review of the applications resulted in a large number of excellent scores due to the extraordinary quality of the proposed science in these applications. Together with the ICs, ORD funded seven Rare Diseases Clinical Research Consortia and one Data and Technology Resources Coordinating Center, all of which form the Rare Diseases Clinical Research Network. Each component of the network consists of a consortium of investigators, institutions, and organizations across the U.S., including partnerships with patient support organizations. In addition to clinical research and research training, the network will provide a Web-based resource for researchers and the public.

ORD had sufficient support for four research consortia. With additional support from NCRR, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Child Health and Human Development (NICHD), National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), three additional research consortia were funded and the DTCC.

Table 1 lists the title of each component consortium, the Principal Investigator and primary institution.

Table 1: The Rare Diseases Clinical Research Network

Consortium Title	Principal Investigator	Primary Performance Site
1. Rare Diseases Clinical Research Center (CRC) - Urea Cycle Disorders	Batshaw, Mark L., M.D.	Children's National Medical Center, Children's Research Institute (CNMC), Washington, D.C.
2. Rare Diseases Clinical Research Center for New Therapies and Diagnosis [in inborn errors of metabolism.]	Beaudet, Arthur L., M.D.	Baylor College of Medicine, Houston, TX
3. Nervous System Channelopathies: Pathogenesis and Treatment	Griggs, Robert C., M.D.	University of Rochester School of Medicine, Rochester, NY
4. Bone Marrow Failure Clinical Research Center	Maciejewski, Jaroslav P., M.D., Ph.D.	Cleveland Clinic Foundation, Cleveland, OH
5. Vasculitis Clinical Research Network	Merkel, Peter A., M.D., Ph.D.	Boston University Medical Center, Boston, MA
6. The Natural History of Rare Genetic Steroid Disorders	New, Maria I., M.D.	Weill Medical College of Cornell University at the New York Presbyterian Hospital, New York, NY
7. Rare Lung Diseases Clinical Research Network	Trapnell, Bruce C., M.D.	Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, OH
8. Rare Diseases Data and Technology Coordinating Center	Krischer, Jeffrey P., Ph.D.	H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

I. Rare Diseases Clinical Research Center (CRC) - Urea Cycle Disorders

The Principal Investigator of this consortium is Mark Batshaw, M.D. The Principal Investigator will establish a Rare Diseases Clinical Research Center (RDCRC) at the Children's National Medical Center (CNMC) in Washington, DC. The unifying clinical theme of the RDCRC is the study of urea cycle disorders (UCD). This RDCRC will consist of a consortium of five academic institutions. The proposed RDCRC will comprise a multidisciplinary team of 10 investigators in the following specialties: Genetics, Metabolism, Developmental Pediatrics, Clinical Pharmacology, Neurology, Psychology, Biostatistics, and Neuroimaging. The primary goals of the RDCRC are to:

- Establish a registry and nationwide network of regional centers for the diagnosis, treatment, and clinical research in UCD;
- Conduct a longitudinal study to determine the natural history of UCD;
- Conduct a clinical trial of an investigational new drug (IND), N-carbamyI-L-glutamate, for treatment of these disorders;
- Conduct a demonstration/pilot project to develop a novel method for measuring *in vivo* urea genesis in UCD that will be important for diagnosis and classification of patients and for evaluation of treatment efficacy;
- Train graduate students, pediatric residents, clinical fellows, and junior faculty members in the field of inborn errors of metabolism; and
- Develop and maintain UCD website content that will include guidelines for health care providers regarding diagnosis and treatment; provide information to the lay public regarding consultation and treatment at major centers; and provide links to recent scientific literature for interested investigators.

The consortium includes the following performance sites:

- Children's National Medical Center, Children's Research Institute (CNMC), Washington, DC
- Georgetown University Medical Center (GUMC), Washington, DC
- Children's Hospital of Philadelphia (CHOP), Philadelphia, PA
- Vanderbilt University (VU), Nashville, TN
- Baylor College of Medicine, Houston, TX
- University of California at Los Angeles (UCLA), Los Angeles, CA

This initiative will be undertaken in close collaboration with the National Urea Cycle Disease Foundation (NUCDF), the leading public advocacy organization for this group of diseases.

II. Rare Diseases Clinical Research Center for New Therapies and Diagnosis [in Inborn Errors of Metabolism]

The Principal Investigator is Arthur L. Beaudet, M.D. His inter-institutional group of investigators with long-standing interest in Rett syndrome (RS), Angelman syndrome (AS), and Prader-Willi syndrome (PWS) will establish a Rare Diseases Clinical Research Center (RDCRC) that will be part of the proposed Rare Diseases Clinical Research Network (RDCRN). The Center will focus on these three disorders with the expectation that they may have near-term potential for meaningful therapy.

- The specific aims for Rett syndrome (RS) will be to establish a phenotype/genotype correlation over a broad spectrum of Rett phenotypes, to perform longitudinal studies on a broad sample of individuals with Rett syndrome, and to perform a survival study on a

broad spectrum of Rett syndrome individuals. Clinical trials may be developed based on results of studies of animal models.

- The specific aims for Angelman syndrome (AS) are to conduct a longitudinal assessment of patients with AS according to genotype, to complete the ongoing double-blind, placebo controlled trial of folic acid and betaine in AS, and to develop a follow-on clinical trial for activation of the paternal allele for UBE3A in AS patients.
- The specific aims for Prader-Willi syndrome (PWS) are to conduct longitudinal studies according to genotype, to develop parameters and tools for clinical trials, to test whether autistic features are more frequent in uniparental disomy (UPD) than in deletion cases, and other hypotheses from collaborators. The aim of a pilot project using comparative genomic hybridization (CGH) on microarrays would be to develop a cytogenetic test that would detect all sizable deletions and duplications of clinical relevance on a single analysis using CGH microarrays. This new methodology would also have the potential to identify new deletion and duplication syndromes.

Performance sites will be at:

- Baylor College of Medicine, Houston, TX
- Greenwood Genetic Center, Greenwood, SC
- University of Alabama at Birmingham, AL
- University of Florida, Gainesville, FL
- Children's Hospital, Boston, MA
- Children's Hospital, San Diego, CA
- University of California, Irvine (UCI) Medical Center, Orange, CA

It is anticipated that the RDCRC will expand to include other geographic sites for the three diseases to be studied initially, and it is expected that the Center can also expand to include other disorders, such as inborn errors of metabolism amenable to hepatocyte gene therapy, disorders treatable by enzyme replacement therapy, CHARGE association, incontinentia pigmenti, Smith-Magenis syndrome, Xp deletion syndromes, and other chromosomal deletion and duplication syndromes. The consortium will include an extensive program that will train new investigators in clinical research on rare diseases.

The Center will have active affiliation with the International Rett Syndrome Association (IRSA), the Angelman Syndrome Foundation (ASF), and the Prader-Willi Syndrome Association (PWSA).

III. Nervous System Channelopathies: Pathogenesis and Treatment

The Principal Investigator is Robert C. Griggs, M.D. The aim of this consortium is to investigate three rare neurological channelopathies: periodic paralysis, nondystrophic myotonic disorders, and episodic ataxia. The research will exploit the strengths of seven collaborating centers to link molecular scientists studying these disorders with clinical investigators with established expertise in the development of new treatments for neurological disease. The consortium will extend a prototype NIH training program in experimental therapeutics to train a cadre of patient-oriented researchers committed to rare disorders. A particular strength of the collaborating institutions is

an established nationwide infrastructure, including GCRCs and a biostatistician for the implementation of multicenter clinical trials that will facilitate investigation of the efficacy of putative new treatments for rare diseases. Currently funded studies of the pathophysiology of the three specific target diseases will provide resources for molecular characterization of subjects and make it possible to begin the characterization of the phenotype/natural history of each; devise outcome measures for treatment trials; and assess quality of life in preparation for pilot clinical trials of novel treatments.

The focus of investigation is on:

- Andersen's syndrome, a periodic paralysis with associated life-threatening cardiac arrythmias for which no treatment has been identified;
- The nondystrophic myotonias caused by sodium and chloride channel mutations for which there is no established treatment and there have been no well-designed clinical trials; and
- The episodic ataxias EA1 and EA2 for which treatment is not yet defined.

Both cellular model systems and animal models, funded separately, are/or soon will be available for each of these disorders and can provide preclinical data necessary for proposed phase one and two trials of novel treatments. The three disorders are prototypes for the development of treatment strategies for more than 50 other rare neurological channelopathies. They may also offer a window for understanding more common disorders likely to be caused by CNS channel mutations/dysfunction such as migraine and epilepsy.

The performance sites include:

- University of Rochester School of Medicine, Rochester, NY
- Brigham and Women's Hospital, Boston, MA
- National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD
- University of California, Los Angeles, CA
- University of California, San Francisco, CA
- University of Kansas Medical Center, Kansas City, KS
- University of Texas Southwestern Medical Center at Dallas, TX

Study investigators have strong links with the patient advocacy organizations focused on these rare disorders: The Periodic Paralysis Association, the National Ataxia Foundation, and the Muscular Dystrophy Association.

IV. Bone Marrow Failure Clinical Research Center

The Principal Investigator of this consortium is Jaroslav P. Maciejewski, M.D., Ph.D. Idiopathic bone marrow failure states and cytopenias (IBMFS&C) are rare disorders characterized by hematopoietic progenitor or stem cell failure resulting in deficient production of one, or all, blood cell lineages. Immune pathophysiology is a unifying factor in many cases of all these diseases. Prior collaborative trials have led to the improvement of effective medical therapy for aplastic anemia (AA), but ongoing multicenter studies are required to advance further the

outcome for AA and especially the other bone IBMFS for which few useful treatment options exist.

The IBMFS&C Rare Disease Clinical Research Center (RDCRC) at The Cleveland Clinic Foundation (CCF) Cancer Center will encompass a consortium of several specialized centers, the patient advocacy group, and collaboration with a data technology coordinating center (DTCC). The IBMFS&C RDCRC will focus on AA, paroxysmal nocturnal hemoglobinuria, single-lineage cytopenias, including large granular lymphocyte leukemia and pure red cell aplasia, and various myelodysplastic syndromes. This center presents a multi targeted approach to improving the medical therapy for IBMFS&C that includes:

- Implementing treatment algorithms for each IBMFS that define standards of care.
- Systematically evaluating novel laboratory assays that may improve the diagnostic accuracy or understanding of pathophysiologic mechanisms.
- Enrolling patients into a longitudinal follow-up study to correlate new and established diagnostic variables with outcome.
- Comparing medical and transplant approaches for each relevant disorder.
- Developing experimental treatment protocols for disease subsets currently without good treatment options or without a standard treatment approach.
- Training of postdoctoral fellows to develop clinical trials and translational research projects for the IBMFS&C.
- Educating community physicians in the diagnosis and management of the IBMFS&C.

A number of leading experts formed a consortium of medical centers that will be an integral part of the RDCRC. To support further its activities, additional infrastructure for this effort will include a formation of a rare diseases office in each of the centers of the consortium, specialized laboratory testing sites, oversight of clinical trials, data management by the DTCC, and patient referral and education by the AAMDSIF. The IBMFS&C RDCRC and the consortium have developed a plan for educating fellows and community physicians about IBMFS&C.

Performance sites will include:

- Cleveland Clinic Foundation, Cleveland, OH
- UCLA Department of Hematology and Oncology, Los Angeles, CA
- The Penn State Cancer Institute, Milton S. Hershey Medical Center, Hershey, PA
- H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

The research plan includes improving outreach, education, and referral resources for patients and physicians, in collaboration with the Aplastic Anemia & MDS International Foundation (AAMDSIF).

V. Vasculitis Clinical Research Network

The Principal Investigator of this consortium is Peter A. Merkel, M.D., Ph.D. The consortium has five overall goals:

1. Establish a multicenter Vasculitis Clinical Research Network (VCRN) to foster and facilitate clinical investigation in the inflammatory vasculitides. The four major U.S. vasculitis centers will combine their clinical and research expertise with the resources of the General Clinical Research Centers at each site to form the core of the consortium. Additionally, the combined strengths of several domestic and foreign secondary centers will be incorporated into the Network. The VCRN will serve as the focal point for vasculitis research in the United States and internationally for both clinical investigators and patients. To achieve this aim, the following activities are proposed:

- Develop a clinical data repository in collaboration with other Rare Diseases Clinical Research Networks and the Rare Diseases Data and Technology Coordinating Center.
- Build a vasculitis clinical specimen bank for storage of serum, plasma, DNA, and tissue samples linked to the clinical data repository.
- Enact a national recruitment program in cooperation with various vasculitis patient advocacy groups.
- Utilize the extensive resources of the General Clinical Research Centers at each Primary Network Site.

2. Conduct a series of related longitudinal studies of novel biomarkers of vasculitis disease activity. Utilizing the VCRN Clinical Data Repository and Clinical Specimen Bank and in coordination with biostatistical support from the Data and Technology Coordinating Center, the VCRN Biomarkers Project will use several promising techniques to develop new markers of disease activity including:

- Proteomics;
- Molecular Markers of Oxidative Stress and Inflammation; and
- Additionally, this program will be established in a fashion that would easily allow for testing of future novel biomarkers by investigators both within and beyond the Network.

3. Utilize the VCRN and patient base to conduct phase one and two clinical trials within the proposed grant period and create the infrastructure to greatly facilitate the design and performance of other future trials.

4. Establish the Vasculitis Clinical Investigator Fellowship as a core mission of the VCRN to provide a mechanism to support, train, and mentor fellows interested in establishing academic careers focused on vasculitis research. This aim will address the pressing need in academic medicine for the training and retaining of rare disease patient oriented clinical investigators.

5. Build and contribute to an electronic website resource with substantive content for clinicians, researchers, and patients.

Performance sites include:

- Boston University Medical Center, Boston, MA
- Cleveland Clinic Foundation, Cleveland, OH

- Johns Hopkins University, Baltimore, MD
- Mayo Clinic, Rochester, MN

Secondary sites include:

- National Cancer Institute, NCI/FDA Clinical Proteomics Program, Bethesda, MD
- University Health Network, Mount Sinai Hospital, Toronto University, ON, Canada
- Rheumaklinik Bad Bramstedt, Germany
- Assistance Hôpitaux Publique De Paris, Hôpital Avicenne, Paris, France
- University of Alabama at Birmingham, AL
- New York Bone & Joint Beth Israel Medical Center, New York, NY

Participating patient support groups include:

- Wegener's Granulomatosis Association
- Takayasu's Arteritis Association
- Takayasu's Arteritis Foundation International
- Takayasu's Arteritis Research Association
- Churg-Strauss Syndrome International

VI. The Natural History of Rare Genetic Steroid Disorders

The Principal Investigator is Maria I. New, M.D. A consortium of investigators, institutions, and patient support groups will focus on a diverse group of disorders characterized by defects in steroidogenesis. The consortium will study the longitudinal history of these rare disorders and determine the outcome of treatment on height, fertility, and gender. Long-standing informal collaboration between investigators at Weill Medical College, Rockefeller University, Columbia University, the University of Texas Southwestern Medical Center, the University of Quebec, Hospital Debrosses (Lyons), and the Hospital das Clinicas da FMUSP (Sao Paulo) will facilitate the creation of a productive cooperative research network that draws on the extensive experience of each investigator. Clinical Research Centers at Weill, Rockefeller, and the University of Texas Southwestern Medical Center will participate.

Each investigator in the consortium has followed a large group of patients with a specific genetic defect affecting steroid synthesis over many years, encompassing the natural history of these diseases from prenatal life to death. Creation of a storage and management database will constitute a scaffold for ongoing research, enabling the preservation and use of this large body of clinical data assembled by experts in each disorder. Moreover, design of templates for a standardized clinical description of these disorders will permit prospective studies which can offer open enrollment to affected individuals or individuals at risk. The research group includes the investigators who have identified the molecular genetic defect for each disorder (where known), and who maintain laboratories dedicated to the identification of new mutations.

The combination of clinical and molecular genetic information will raise the standard of medical care and may permit development of novel treatments based on detailed knowledge of the natural

history and molecular genetic basis of these disorders. Important elements of the research plan are to:

- Establish the clinical research network which pools data from all sites in cooperation with the DTCC and analyzes this data,
- Educate young investigators in the management and clinical research of steroid disorders, and
- Strengthen connections with patient support groups to enable individuals affected or at risk to have new kinds of input and access to optimal medical care.

Participating patient support groups include:

- Congenital Adrenal Hyperplasia Research, Education, and Support; and
- CARES Foundation, Inc.

VII. Rare Lung Diseases Clinical Research Network

The consortium seeks to facilitate clinical research in rare lung diseases by:

- Promoting collaboration among centers already focused to clinical research on rare lung diseases;
- Attracting and training highly qualified investigators;
- Collecting clinical data from geographically distributed patients into a large, centralized database; and
- Making the accumulated clinical data available to those affected (or possibly affected) by a rare lung disease, their clinicians, clinical and basic investigators, and the general public.

Disorders chosen for the initial focus of this network include: Alpha-1 Antitrypsin Deficiency (AATD), Lymphangioleiomyomatosis (LAM), pulmonary alveolar proteinosis (PAP), and hereditary idiopathic pulmonary fibrosis (HIPF). The network consists of clinical centers in Ohio (the coordinating center), Colorado, Florida, Maryland, Massachusetts, Oregon, South Carolina, and Texas, as well as in Japan and Australia. Centers are required to have and maintain an exemplary record of active clinical research and an adequate rare lung disease patient base.

Many of these centers already work together closely and the foundations are already closely integrated. For example, the scientific directors of all three participating foundations are active clinical investigators at clinical sites within the network. Furthermore, clinical sites were chosen from three currently active networks of collaborating clinical centers that include more than 50 sites in 24 states distributed throughout the United States. All participating domestic clinical sites are associated with an active, NIH-supported general clinical research center (GCRC). Each center provides components required of the consortium. The components include ongoing longitudinal clinical studies, an excellent clinical training program, and an active clinical research trials program designed to test novel therapies and develop diagnostic tests or evaluate outcome measures for rare lung diseases. Ongoing clinical, basic, and translational studies at the

centers chosen have already yielded critical insights into molecular mechanisms underlying lung function and defense in health and disease.

Each of the foundations provides education for patients, the lay public, and the medical community. Importantly, one consequence has been already the formation of the "Rare Lung Disease Foundation Consortium," which permits patient support groups with a greater infrastructure to "nurture" the growth of less well-developed groups. It also provides support for individuals affected by a rare lung disease for which there is currently no foundation.

Participating patient support groups include:

- the Alpha-1 Foundation, the LAM Foundation, and
- the Pulmonary Fibrosis Foundation.

VIII. Rare Diseases Data and Technology Coordinating Center

The Data and Technology Coordinating Center (DTCC) will play an active role in the development of the Rare Diseases Clinical Research Network. It will facilitate research in the design of clinical protocols and the data management and analysis necessary to support them. Working with the Rare Diseases Clinical Research Centers, the DTCC will make available a coordinated clinical data management system for the collection, storage, and analysis of data from multiple diseases and multiple clinical sites. The data management system will be a secure Web-based system that includes the capability to capture and integrate many different forms of data (clinical, imaging, genetics, pathology, etc.), and the scalability to thereby serve as a national clinical information coordinating center.

Among its features will be a user-friendly system for recruitment and referral, tools for cross-disease data mining, data sharing, and a public portal to relevant data resources. This center will apply novel approaches to and technologies for data management and training, including the use of Web-based video streaming. The Center also seeks to conduct research and development of new approaches to distributed computing, federated databases, and data mining.

Exploratory and Developmental Research Grants for Investigations in Rare Diseases

ORD co-sponsored with the National Heart, Lung, and Blood Institute (NHLBI) Exploratory and Developmental Research Grants (R21) for Investigations in Rare Diseases. The purpose of this program announcement is to define the scope of exploratory and developmental grant applications to the NHLBI for support of investigators with novel approaches to understanding, treating, and preventing rare diseases in the areas of heart, lung, and blood disease as well as sleep disorders. The ORD will co-fund applications in these rare diseases. Availability of the R21 awards is expected to allow investigators with novel ideas to obtain research support without the need for large amounts of preliminary data that often serves as a barrier to entry into the NIH grants system. It is anticipated that these efforts will ultimately result in an increased pipeline of therapeutic approaches to treatment and prevention of rare diseases.

Clinical Trial Planning Grant Program

The ORD co-sponsored with a number of NIH Institutes and NIH Offices a *Clinical Trial Planning Grant Program*. The purpose of the NIH Clinical Trial Planning Grant (R34) is to provide support for the development of a Phase three clinical trial, including the establishment of the research team, the development of tools for data management and oversight of the research, the definition of recruitment strategies, and the finalization of the protocol and other essential elements of the study included in a manual of operations/procedures.

An NIH-defined Phase three clinical trial is a broadly based prospective clinical investigation for the purpose of evaluating an experimental intervention in comparison to a standard or control intervention or comparing two or more existing treatments.

Rare Diseases Intramural Research Program

The ORD intramural program promotes fellowship training in the areas of clinical and basic research into rare diseases, fosters protocol-based initiatives into rare diseases not currently investigated in the intramural program, assists in the investigation of select, unique disorders of unknown etiology, and provides overall research support for diagnostics and therapeutics of rare disorders.

Biochemical Geneticists Training Program

In FY 2003, the ORD supported three fellows training in Clinical Biochemical Genetics, an important field of genetics that brings needed therapy to rare diseases patients. These fellowship opportunities provide for physicians exposure to rare diseases research early in their careers, reinforce their interest in and dedication to the field, and promote future research experts in rare diseases. Upon completion of the training program, the research fellows will also be eligible to sit for the examination in biochemical genetics offered by the American College of Medical Genetics (ACMG). The staff of the ORD intramural program, in collaboration with the National Human Genome Research Institute (NHGRI), now includes a gynecologist who provides consultations specifically for Clinical Center patients with rare disorders and a clinical geneticist who conducts a new study of patients with autosomal recessive polycystic kidney disease. The ORD intramural program has supported the care of approximately 150 Clinical Center inpatients in the past year, with certain specific rare diseases including cystinosis (a kidney disease of children that also affects other organs), Hermansky-Pudlak syndrome (HPS, a type of albinism), Gray platelet syndrome (GPS, a bleeding disorder), alkaptonuria (a joint disease of adults), Bartter syndrome (a kidney disease), and a variety of immunologic disorders. Clinical trials are being pursued using drugs targeted against the kidney disease of cystinosis, the fatal lung fibrosis of HPS, and the joint disease alkaptonuria.

Patient Travel to Research at the Clinical Center Hospital (Mercy Medical Airlift)

The intramural program of ORD and the NHGRI have initiated a demonstration project on a limited scale to provide free travel through Mercy Medical Airlift for patients participating in research projects at the ORD/NHGRI intramural research program and for one accompanying

family member Mercy Medical Airlift refers research participants to the most appropriate forms of charitable (free), long-distance medical air transportation available in the national charitable medical air transportation network. Expansion of these national services to the Clinical Center (CC) as a whole will be based on the outcome of an evaluation of the demonstration project.

Bench-to-Bedside Grant Awards

Intramural ORD/NHGRI staff also participates in and reviews those NIH Bench-to-Bedside grants that foster basic and clinical investigations into rare diseases. In addition, the ORD fully supported five Bench-to-Bedside grants. The two-year Bench-to-Bedside grants encourage intramural clinical, translational, and basic scientists at the NIH to enter into basic science-clinical collaboration with colleagues in other NIH laboratories, clinics, Institutes, or Centers. The grants focus on Williams syndrome, hereditary inclusion body myopathy (HIBM), acute lymphoblastic leukemia (ALL), pulmonary sarcoidosis, and leukemogenesis. In FY 2004, the ORD plans to increase to 10 the number of supported Bench-to-Bedside grants by collaborating with the NIH ICs in the cofunding of these grants. When fully implemented, ORD anticipates 20 active Bench-to-Bedside grant awards each year. The activities are coordinated with the IC Scientific Directors and the CC Director.

Undiagnosed Diseases

The ORD/NHGRI intramural program is now initiating a new program to bring to the NIH Clinical Center patients with unique and undiagnosed disorders. The full capacity of the Clinical Center (CC) will be brought to bear upon these disorders, eliciting both research into optimal diagnostic approaches and follow-on studies of therapy. Establishing the correct diagnosis will provide new insights into the biology of these diseases and offer hope to the broader community of individuals afflicted with rare and poorly understood genetic maladies. In addition, the program will provide educational opportunities for those in NIH training programs at the CC to learn more about rare diseases.

Scientific Conferences Program

In FY 2003, the ORD co-sponsored 57 scientific conferences on rare diseases as well as four additional science-related events. Diseases of interest included Niemann Pick Type C disease, cystic fibrosis, sickle cell disease, spina bifida, Hutchinson-Gilford progeria syndrome, osteopetrosis, Gaucher disease, Batten disease, Werner syndrome, and neurofibromatosis. In FY 2004, ORD expects to increase the number of co-sponsored scientific conferences to 70 or more.

The conferences have been shown to be excellent venues to establish a research agenda for specific rare diseases, take advantage of scientific opportunities, or eliminate barriers to advancing research.

Outcomes of the more than 450 scientific conferences that ORD has sponsored or co-sponsored since 1995 include:

- Establishing research priorities and agendas

- Establishing diagnostic and assessment criteria for clinical research
- Identifying needed disease models for future research
- Promoting research coordination and data sharing; patient and tissue registries
- Attracting new research investigators
- Developing research protocols and collaborative research arrangements (within clinical and between basic and clinical scientists)
- Planning clinical trials
- Developing NIH Program Announcements (PAs) and Requests for Applications (RFAs) and solicitations for research by patient support organizations.

Table 2 provides the scientific conferences that were co-funded in FY 2003 and Table 3 shows those that will be funded in FY 2004.

Table 2: ORD Cosponsored Scientific Conferences in FY 2003

Primary Cosponsor	Title
NCI	• Integrating Research on Spirituality and Health and Well-Being into Service Delivery: A Research Conference • International Conference on DNA Repair and Mutagenesis: From Molecular Structure to Biological Consequences • Inflammatory Breast Cancer Case-Control Study Collaborators' Meeting • Model Systems in Plasma Cell Neoplasia • India Health Study and Rare Cancers Meeting • Pathology Workshop on Borderline Ovarian Tumors (BOT) • Improving Outreach and Communication of Scientific Program with Ataxia-Telangiectasia (AT) Families • First International Symposium on Childhood and Adolescent Non-Hodgkin's Lymphoma • UICC International Conference on Familial Cancer
NHGRI	• 3rd International Anophthalmia/Microphthalmia (A/M) Conference • The 2003 International Conference on Niemann-Pick Type C (NPC) Disease
NHLBI	• Lymphangioleiomyomatosis • Vascular Anomalies 2003: Research Controversies • Macro-Molecular Interactions and Ion Transport in Cystic Fibrosis (CF) • Long-Term Follow-Up of Patients with Sickle Cell Anemia Who Receive Blood or Marrow Transplants
NIA	• International Skeletal Dysplasia Society Conference • Hutchinson-Gilford Progeria Syndrome (HGPS) Workshop • International Workshop on Werner Syndrome
NIAAA	• Ketone Bodies in the Treatment of Disease Including Duchenne Muscular Dystrophy

NIAID	• Humoral Rejection in Solid Organ Transplantation • Pediatric Transplantation Clinical Study Workshop • Conference on Calcific Cysticercosis • 3rd Biennial Symposium of the International Eosinophil Society • Fifth International Conference on Anthrax • Bacterial Genomics and Proteomics as Related to Biodefense • Post Transplant Lymphoproliferative Disorder (PTLD)
NIAMS	• Neonatal Onset Multisystem Inflammatory Disease (NOMID) • First International Symposium on Osteopetrosis: Biology and Therapy • Immunomodulatory Drugs in the Treatment of Skin Disease: What Can We Learn about Pathophysiology?
NICHD	• Vulvodynia: Towards Understanding a Pain Syndrome • Physical Disabilities through the Lifespan • Preventing Bilirubin-Induced Brain Injury in the Newborn (BIBIN) and Kernicterus: From Bench-to-Bedside • Pediatric Critical Care: Pulmonary Processes and Informatics Solutions
NIDCD	• 9th International Conference on Cochlear Implants in Children • Neurologic Motor Speech Disorders in Adults
NIDDK	• The Conduct of Clinical Trials in Crohn's Disease • 6th International Workshop on Resistance to Thyroid Hormone (RTH)
NIEHS	• Environmental Factors in Autoimmune Disease • Ion Channel Regulation • Metabolic Profiling: Application to Toxicology and Risk Reduction, an International Conference • Functional Alterations in Uncommon p53 Mutations: Characterization of Sporadic and Inherited p53 Defects and Relevance to Human Cancers
NIMH	• Research on Survivors of Suicide Workshop • Workshop on Gaucher Disease and Parkinsonism
NINDS	• 9th International Congress on Neuronal Ceroid Lipofuscinosis (NCL) (Batten Disease) • Workshop on Friedreich Ataxia (FRDA) • Gordon Conference on Calcium Signaling • The National Neurofibromatosis Foundation (NNFF) International Consortium for the Molecular Biology of NF1 and NF2 • International Conference on Human Retrovirology: Human T Cell Leukemia Virus (HTLV) and Related Viruses • Amyotrophic Lateral Sclerosis (ALS) Clinical Trials: The Challenge of the Next Century • Gordon Conference on CAG Triplet Repeat Disorders • Hereditary Inclusion Body Myopathy and Sialuria due to GNE Gene Mutations: Genetics, Biochemistry and Implications for Therapy
NINR	• Moving the Research Agenda forward for Children with Cancer
FDA/OOPD	• Regional ORD Workshop: Gaining Access to Research Resources

ACMG	• Workshop on Ultra-Orphan Genetic Disease Therapeutics, Surrogate Markers, and Related Issues
AHRQ	• Evidence-Based Practice in Spina Bifida: Developing a Research Agenda
EP-Foundation for Education	• Fourth Annual World Congress and Exposition on Disabilities
NDRI	• The Genetics of Rare Diseases: Window to Common Disorders

Table 3: ORD Cosponsored Scientific Conferences in FY 2004

Primary Cosponsor	Title
NCI	• International Workshop on Biliary Tract Cancers: Current Perspectives and Future Directions • Lymphangiogenesis and Cancer: Research Directions and Therapeutic Opportunities • Childhood Cancer Survivorship: Improving Care After Treatment • Sarcoma and Mesenchymal Stem Cell Biology Workshop • RNA Interference: Target Validation and Potential Therapeutic Applications for Childhood Cancers • Genetic Diseases Caused by ABC Transporters • Genetic Susceptibility and Second Primary Cancers • Bloom Syndrome: Molecular Basis of Genomic Instability • Natural History and Treatment of Peritoneal Mesothelioma • Collaborative Approaches to Discovering Genes in African Americans and Hispanics Utilizing Mapping by Admixture Linkage Disequilibrium (MALD) • 19th International Pigment Cell Conference "A Focus on Human Pigmentary Disorders" • Global Increases in Esophageal Adenocarcinoma: Current Epidemiologic Research and Future Directions • Linking Haplotypes and Genetic Variation with Cancer Risk Assessment, Prevention, Detection, and Treatment
NCRR	• Networks of Rare Disease Communities: Overcoming Barriers, Exploiting Opportunities
NEI	• Conference on Central Nervous System (CNS Including Brain and Ocular) Lymphoma
NHGRI	• Gene Therapy for Wiskott-Aldrich Syndrome (WAS): Current Status and Plans for the Future Clinical, Molecular, and Cell Biological Aspects of Cystinosis
NHLBI	• Working Group for the Development of a Sickle Cell Disease Physician Consultation Network • Pulmonary Hypertension Scientific Conference • Frontiers of Knowledge in Sleep and Sleep Disorders: Opportunities for Improving Health and Quality of Life • Needs and Opportunities to Study Hypersensitivity Pneumonitis Workshop • Working Group on Research in Adult Congenital Heart Disease

NIA	• Cockayne Syndrome and Related Disorders of DNA Repair and Transcription
NIAAA	• Alcohol and Upper Alimentary Tract Cancer (Squamous Cell Carcinoma)
NIAID	• FASEB Summer Research Conference: Transplantation Immunology • International Conference on Burkholderia Pathogenesis: Approaches and Opportunities for Research on Glanders and Melioidosis
NIAMS	• Pathogenic Mechanisms of Fibrosis: Search for Common Ground • Mild Osteogenesis Imperfecta (OI): Toward Better Understanding and Treatment • New Directions in Biology and Disease of Skeletal Muscle • Biology of Calpains in Health and Disease
NICHD	• Pineal Cell Biology • Signaling in Vertebrate Organogenesis • Rare Illnesses in Childhood: Emergency and Critical Care Presentation and Management to Maximize Outcomes • The World Congress on Chromosome Abnormalities • Collaborative Genetic Disease Research: Needs and Opportunities • Reproduction and the Fragile X Premutation • Fetal Therapy: Needs Assessment and Future Directions
NIDCD	• Towards Universal Characterization of Speech Production in Speakers with Cleft Palate
NIDCR	• Advancing Diagnostic Approaches for TMJ Diseases and Disorders
NIDDK	• Ninth International Workshop on Multiple Endocrine Neoplasia (MEN2004) • Workshop on Bioiron, Thalassemia, Sickle Cell Disease and Hemochromatosis Protein Misfolding and Misprocessing in Disease
NIEHS	• Environmental Neuroscience • Toxic Molds in the Indoor Environment: Exposures and Health Effects Workshop • Epigenetics: Mechanisms and Role in Environmentally-Induced Disease and Dysfunction • Assessing Human Germ Cell Mutagenesis in the Post-Genome Era
NIMH	• Research Workgroup on Culture and Suicide

NINDS	• The Glycoproteinoses: An International Workshop on Advances in Pathogenesis and Therapy • Pathogenesis of Rare Neuroimmunologic Disorders • Developing Therapies for the Neurofibromatoses • Frontotemporal Dementia and Pick's Disease Satellite Meeting at 9th World Alzheimer's Congress • Fourth International Scientific and Clinical Symposium on Tourette Syndrome • Annual Symposium WORLD Lysosomal Diseases Clinical Research Network • Glutamic Acid Decarboxylase Autoimmunity in Batten Disease/Juvenile Neuronal Ceroid Lipofuscinosis (JNCL) • Brain Uptake and Utilization of Fatty Acids, Lipids and Lipoproteins: Applications to Neurological Disorders • First International Conference on Ideomotor Apraxia
NINR	• Developing the Capacity for End of Life and Palliative Care Research • Increasing Opportunities in Biobehavioral Research Utilizing Allergic Bronchopulmonary Aspergillosis (ABPA) as a Framework • Improving Patient Health Through Improved Mental Functioning

Information Dissemination

Genetic and Rare Diseases (GARD) Information Center

The GARD information center disseminates reliable information on research and treatment to patients and their families, health care providers, patient support groups, and others. In the responses, the information specialists provide information in plain English on the disease in question and links to sites that have been evaluated as accurate, reliable, and up-to-date. In 2003, together with NHGRI, ORD expanded the contract for the Genetic and Rare Diseases Information Center to provide services not only in English but also in Spanish. ORD, NHGRI, and the contractor are developing an outreach program that will include input from the Latino health provider community. In 2003, the information center responded to 2,864 inquiries for 1,460 different specific genetic and/or rare diseases.

Frequently, the information center is the last resort when patients and/or family members are unable to locate information on their own or from other sources. The information center responses are stored without personal identifiers in a Web-based, secure system and are retrieved and updated to make sure that the response is fully up-to-date and responsive to the particular question(s) at hand.

The information center does not provide medical advice. However, ORD has a medical advisor with a broad understanding of NIH activities and researchers. Through his efforts it was possible in one case for a patient to be accepted into a clinical trial within four hours from the time of the original inquiry.

ORD Website

Development of the ORD Web site was a major step forward in the transfer of information to the rare diseases community. ORD completed the redesign of its Web site to increase its usability as

and content for a portal to national and international information on rare diseases. In 2003, the Web site increased its number of visits to more than 500,000. In addition to providing information about ORD's major programs, the ORD Web site serves as a gateway to information about rare diseases and research. The Web site is organized around the following topics:

- Research and Clinical Trials
- Rare Diseases Information
- Patient Support Organizations
- ORD Extramural Research Program
- ORD/NHGRI Intramural Research Program
- Scientific Conferences Program
- Research Resources
- Genetics Information
- Charitable Patient Travel and Lodging
- Contact information for the Genetic and Rare Diseases Information Center, and
- A listing of more than 6,000 distinct rare diseases terms.

Currently, ORD is in the process of linking each disease term to NIH databases and summary information.

Other Rare Diseases Activities

In addition, ORD supported a number of research and education related activities.

- ORD supported the Medical Genetics and Rare Disorders subfile of the Combined Health Information Database (CHID). The subfile provides information about and available from voluntary patient support groups. In 2002 and 2003, ORD reviewed, updated, and expanded the subfile through a contract with the National Organization for Rare Disorders. At this time, 1,350 organizations are included in the subfile as well as 6,876 indexed documents. In 2003, 4,419 searches were conducted specifically against the subfile, in addition to the approximately 750,000 searches across CHID as a whole (a total of 16 subfiles.)

- ORD also supported the National Coalition for Health Professional Education in Genetics (NCHPEG). Established in 1996 by the American Medical Association, the American Nurses Association, and the NHGRI, NCHPEG is a national effort to promote health professional education and access to information about advances in human genetics. NCHPEG members are an interdisciplinary group of leaders from approximately 120 diverse consumer and voluntary groups, medical societies, government agencies, private industry, managed care organizations, and genetics professional societies. By promoting frequent and open communication between stakeholders, NCHPEG seeks to capitalize on the collective expertise and experience of members and to reduce duplication of effort.

  As patients ask more questions about genetic tests and disease risk, more responsibility for the use and interpretation of genetic tests and information will fall to primary care physicians, nurses, physician assistants, advanced practice nurses, and other health

professionals who may not be formally trained in genetics. This is of importance to ORD since it is estimated that 80 percent of rare diseases have a genetic basis.

NCHPEG is currently coordinating "Genetic Resources on the Web (GROW)" a source of quality information about human genetics for health professionals and the public. ORD co-founded GROW with other NIH components and federal agencies. A first training module has been developed for dentists and dental hygienists. The next module to be completed with the American Academy of Family Physicians will be for physicians in family practice.

- ORD is funding a planning project and a needs assessment for an initiative in rare diseases research tissue procurement through the Human Tissues and Organs Resource (HTOR) Cooperative Agreement with NCRR. HTOR is a part of the National Disease Research Interchange (NDRI). By collaborating with various medical centers, hospitals, pathology services, eye banks, tissue banks, and organ procurement organizations, HTOR provides a wide variety of human tissues and organs--both diseased and normal--to researchers for a nominal fee.

- ORD conducted two regional workshops in New York and in San Francisco for more than 85 leaders of national patient support groups to assist the support groups in being an active participant in the rare diseases research enterprise by getting a better understanding of the structure and function of the NIH and the Food and Drug Administration (FDA). Program evaluations from the participants were overwhelmingly positive.

- ORD continued to support the annual meetings of the Genetic Alliance and the National Organizations for Rare Disorders (NORD). These two umbrella organizations represent collectively more than 600 rare diseases patient advocacy groups. ORD utilized these meetings to conduct focus groups to determine the needs of member organizations and to identify programs ORD should consider implementing. Also, NIH research scientists and ORD staff are active participants in all sessions of the annual meetings.

- ORD continued its co-sponsorship with the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) of the Biliary Atresia Research Consortium (BARC), which contains nine pediatric liver disease centers. Researchers at the consortium develop and test hypotheses on the cause of biliary atresia and are defining the best means of diagnosis and management of this disease.

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Acronyms

a-1	alpha-one
AA	aplastic anemia
AAMDSIF	Aplastic Anemia & MDS International Foundation
AAT	α1-antitrypsin,
AATD	α1-antitrypsin deficiency
ABPA	allergic bronchopulmonary aspergillosis
ACCESS	A Case Control Etiologic Study of Sarcoidosis (NHLBI)
ACMG	American College of Medical Genetics
ADCC	Autoimmune Diseases Coordinating Committee
ADHD	attention deficit hyperactivity disorder
AFSP	American Foundation for Suicide Prevention
AGS	Alagille syndrome
ALD	adrenoleukodystrophy (NLM)
ALL	(childhood) acute lymphoblastic leukemia
ALPS	autoimmune lymphoproliferative syndrome
ALS	amyotrophic lateral sclerosis
A/M	anophthalmia/microphthalmia
APS	antiphospholipid syndrome
ARDS	acute respiratory distress syndrome
ARND	alcohol-related neurodevelopmental disorder
ARVD	arrhythmogenic right ventricular dysplasia
AS	Angelman syndrome
ASCUS	atypical squamous cells of undetermined significance
ASF	Angelman Syndrome Foundation
ASPS	advanced sleep phase syndrome
AT	ataxia telangiectasia
BAA	broad agency announcement (NHLBI)
BBS	Bardet-Biedl syndrome
BDNF	brain-derived neurotrophic factor
BE	Barrett's esophagus
BH4	tetrahydrobiopterin
BIBIN	bilirubin-induced brain injury in the newborn

BLM	human gene encoding Bloom syndrome
BN	bulimia nervosa
BPD	bronchopulmonary dysplasia
BS	Bloom syndrome
BSE	bovine spongiform encephalopathy
CAG (triplet repeat)	nucleotides (CAG) consecutively repeated within a region of DNA
CAM	complementary and alternative medicine
CASG	Collaborative Antiviral Study Group
CASPAR	computerized affected sibling pair analyzer and reporter
CBV	coxsackievirus B
CC	Warren Grant Magnuson Clinical Center, NIH
CCHS	congenital central hypoventilation syndrome
CDC	Centers for Disease Control and Prevention
CDH	congenital diaphragmatic hernia
CDG	congenital disorders of glycosylation
CDH	congenital diaphragmatic hernia
CF	cystic fibrosis
CFS	chronic fatigue syndrome
CFTR	cystic fibrosis (CF) transmembrane conductance regulator
CGD	chronic granulomatous disease
CHD	coronary heart disease
CHID	Combined Health Information Database
CHOP	Children's Hospital of Philadelphia
CIN	cervical intraepithelial neoplasia
CJD	Creutzfeldt-Jakob disease
CLL	chronic lymphocytic leukemia
CL/P	cleft lip and cleft palate
CMV	congenital cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CRADA	cooperative research and development agreement
CRC	clinical research center
CRD	cannabis-related disorder
CRF	corticotropin-releasing factor
CS	Cockayne syndrome
CVB3	Cocksackie virus B3
CWD	chronic wasting disease
DCIPS	Developing Centers on Interventions for the Prevention of Suicide (NIMH)
DDG	Drug Development Group (NIH)
DeNOVO	delivery of NO for vaso-occlusion (clinical trial title)

DHHS	Department of Health and Human Services
DMAC	disseminated infection with mycobacterium avium complex
DNA	deoxyribonucleic acid
DOE	Department of Energy
DSRCT	desmoplastic small round-cell tumor
DTCC	Data and Technology Coordinating Center
EB	epidermolysis bullosa, severe blistering skin diseases
EBV	Epstein-Barr virus
ECMO	extracorporeal membrane oxygenation
EDS	Ehlers-Danlos syndrome
ES	Ewing's sarcoma
FA	Fanconi anemia
FAS	fetal alcohol syndrome
FASD	fetal alcohol spectrum disorders
FBN1	fibrillin 1
FDA	Food and Drug Administration
FENIB	familial encephalopathy with neuronal inclusion bodies
FGFR3	fibroblast growth factor receptor 3
FH	familial hypercholesterolemia
FHBL	familial hypobetalipoproteinemia
FMR1	fragile X mental retardation gene
FRDA	Friedreich ataxia
FRX	fragile X syndrome
FSHD	facio-scapulo-humeral dystrophy
GCPS	Greig cephalopolysyndactyly syndrome
GCRC	General Clinical Research Center (NCRR)
GHR	Genetics Home Reference (NLM)
GLP	good laboratory practice
GMP	good manufacturing practice
GPS	Gray platelet syndrome
HAART	highly active anti-retroviral therapy
HbF	fetal hemoglobin
HD	Huntington disease
HDL	high-density lipoprotein
HEV	hepatitis E virus
HGP	human genome project
HGPS	Hutchinson-Gilford progeria syndrome
Hh	hedgehog (signaling pathway)
HHT	hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)
HHV-8	human herpesvirus 8
HIBM	hereditary inclusion body myopathy
hIPF	hereditary idiopathic pulmonary fibrosis

HIV/AIDS	human immunodeficiency virus/acquired immune deficiency syndrome
HPP	health partnership program (NIAMS)
HPT-JT	hyperparathyroidism-jaw tumor (syndrome)
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HTLV	human T cell leukemia virus
IBMFS&C	idiopathic bone marrow failure states and cytopenias
IBS	irritable bowel syndrome
ICBG	International Cooperative Biodiversity Groups (NHLBI)
ICs	(NIH) institutes and centers
IDDM	insulin dependent diabetes mellitus
IFN	interferon
IGFs	insulin-like growth factors
IL	interleukin
IND	investigational new drug
IPF	idiopathic pulmonary fibrosis
IRSA	International Rett Syndrome Association
ISIS	Imaging Science and Information Systems Center (NLM)
JDRF	Juvenile Diabetes Research Foundation International
JRA	juvenile rheumatoid arthritis
KTWS	Klippel-Trenaunay-Weber syndrome
LAM	lymphangioleiomyomatosis
LDL	low-density lipoprotein
LMNA	lamin A (gene)
LQTS	long QT syndrome
LVAD	left ventricular assist device
mAB	monoclonal antibodies
MADGC	Multiple Autoimmune Diseases Genetics Consortium
MALD	mapping by admixture linkage disequilibrium
MATT	Methamphetamine Addiction Treatment Think Tank (NIDA)
MCA/MR	multiple congenital anomaly/mental retardation
MD-CARE	P.L. 107-84, Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001
MDCC	Muscular Dystrophy Coordinating Committee
MDS	myelodysplastic syndrome
MDA	Muscular Dystrophy Association
MDD	Medications Development Division (NIDA)
MDMA	Methylene-dioxy-meth-amphetamine (ecstasy)
MEN1	multiple endocrine neoplasia type 1
MHC	major histocompatibility complex
MKS	McKusick-Kaufman syndrome
MMP	matrix metalloproteinase

MOU	Memorandum of Understanding
MPD	myeloproliferative disease
MR4	Malaria Research and Reference Reagent Resource (Center)
MS	multiple sclerosis
MSC	mesenchymal stem cell
MSH	Multicenter Study of Hydroxyurea
MTA	material transfer agreement
NBLs	National Biocontainment Laboratories
NBN	National Biospecimen Network
NBTT	New Approaches to Brain Tumor Therapy Consortium (NCI)
NCBI	National Center for Biotechnology Information
NCCAM	National Center for Complementary and Alternative Medicine
NCI	National Cancer Institute
NCL	neuronal ceroid lipofuscinosis (Batten disease)
NCMHD	National Center on Minority Health and Health Disparities (Office of the Director, NIH)
NCRR	National Center for Research Resources
NCS	National Children's Study
NDA	new drug application
ND-BD	non-dementing brain disorders
NEI	National Eye Institute
NF1	neurofibromatosis type 1
NF-kappaB	nuclear factor kappaB
NGI	next generation Internet
NHGRI	National Human Genome Research Institute
NHL	non-Hodgkin lymphoma
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Disease
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute of Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine

NNFF	National Neurofibromatosis Foundation
NO	nitric oxide
NOMID	neonatal onset multisystem inflammatory disease
NPA	Niemann-Pick type A disease
NPB	Niemann-Pick type B disease
NPC	Niemann-Pick type C disease
NPD	Niemann-Pick type D disease
OA	osteoarthritis
OCRL	oculo-cerebro-renal syndrome (Lowe syndrome, LS)
ODS	Office of Dietary Supplements (Office of the Director, NIH)
OI	osteogenesis imperfecta
ORD	Office of Rare Diseases (Office of the Director, NIH)
ORWH	Office of Research on Women's Health (Office of the Director, NIH)
OTP	opiate treatment program (NIDA)
PA	program announcement
PACT-G	Pediatric AIDS Clinical Trial Group
PAP	pulmonary alveolar proteinosis
PCD	primary ciliary dyskinesia
PCP	phencyclidine
PCP	pneumocystis carinii pneumonia
PEGT	Programs of Excellence in Gene Therapy (NHLBI)
PGA	Programs for Genomic Applications (NHLBI)
PHS	Pallister-Hall syndrome
PKC	protein kinase C
PKU	phenylketonuria
PML	progressive multifocal leuceoencephalopathy
POF	premature ovarian failure
PPH	primary pulmonary hypertension
PPHN	persistent pulmonary hypertension of the newborn
PTLD	post-transplant lymphoproliferative disease
PTS	post-traumatic stress syndrome
PWS	Prader-Willi syndrome
PXE	pseudoxanthoma elasticum
RA	rheumatoid arthritis
RAID	Rapid Access to Intervention Development Program (NCI)
RBLs	regional biocontainment laboratories
RDCRC	Rare Disease Clinical Research Consortium
RDCRN	Rare Diseases Clinical Research Center Network
REM	rapid eye movement (characteristic of deep sleep)
RFA	request for applications
RFP	request for proposals
RLGS	restriction landmark genome scanning

RNA	ribonucleic acid
RS	Rett syndrome
RTH	resistance to thyroid hormone
RTOG	Radiation Therapy Oncology Group
RTS	Rothmund-Thompson syndrome
SADDAN	severe achondroplasia with developmental delay and acanthosis nigricans
SAMHSA	Substance Abuse and Mental Health Services Administration
SAGA	Sarcoidosis Genetic Analysis Consortium
SARS	severe acute respiratory syndrome
SBIR	small business innovative research
SCD	sickle cell disease
SCD	sudden cardiac death
SCID	severe combined immunodeficiency disorder
SCOR	specialized center of research
SGBS	Simpson Golabi Behmel syndrome
SIDS	sudden infant death syndrome
SLE	systemic lupus erythematosus
SLOS	Smith-Lemli-Opitz syndrome
SMA	spinal muscular atrophy
SPORE	Specialized Program of Research Excellence
SUD	substance use disorder
SS	sickle cell
SS	Sjögren syndrome
SVAS	supravalvular aortic stenosis
TB	tuberculosis
TCR	transcription-coupled repair
TIGR	The Institute for Genomic Research
TMAU	trimethylaminuria
TMD	temporo-mandibular disorders
TMJ	temporomandibular joint
TSC	tuberous sclerosis complex
TSEs	transmissible spongiform encephalopathies
TTP	thrombotic thrombocytopenic purpura
UCD	urea cycle disorder
UIP	usual interstitial pneumonitis
UPD	uniparental disomy
UV	ultraviolet
VA	(Department of)Veterans Affairs
vCFD	variant Creutzfeldt-Jakob disease
VCFS	velo-cardio-facial syndrome
VCRN	Vasculitis Clinical Research Network
VEG5Q	vascular endothelial gene on chromosome 5q

VEGF	vascular endothelial growth factor
VLBW	very low birth weight
VLDL	very low-density lipoprotein
VTUs	vaccine treatment and evaluation units
VWD	von Willebrand disease
VWF	von Willebrand factor
WAS	Wiscott-Aldrich syndrome
WNV	West Nile virus
WRN	defective gene for Werner syndrome
WS	Waardenburg Syndrome (NIDCD)
WS	Werner syndrome (NIA)
WS1	Wilm's tumor suppressor
XPD	a human DNA repair protein