National Institutes of Health

Report on Research on Rare Diseases in Children: FY 2000 to FY 2005

Contents

Research on Rare Diseases in Children Supported by the NIH: FY 2000 to FY 2005

Introduction

Public Law No. 106-310, The Children's Health Act, requires in Section 2801 that the Director of the National Institutes of Health (NIH) submit to the Congress a report on the activities that, during fiscal year (FY) 2000, were conducted and supported by NIH Institutes with respect to rare diseases in children, including Friedreich's ataxia and Hutchinson-Gilford progeria syndrome; and the activities that are planned to be conducted and supported by such Institutes with respect to such diseases during FY 2001 through FY 2005.

The rare diseases research programs sponsored by NIH Institutes and Centers (ICs) are well-established and well-recognized and include a high percentage of research on children. These basic, clinical, and research training programs continue to contribute to the development and dissemination of information on the prevention, etiology, diagnosis, and treatment of rare diseases in children as well as adults.

This report presents the contributions and research advances of the NIH research programs and the Office of Rare Diseases (ORD). Many advances presented in this report are the result of years of basic research sponsored by NIH. Children with rare diseases continue to benefit from the treatment applications realized from the diverse nature of and emphasis placed on both basic and translational research by NIH.

This report defines a rare disease as a disease, condition, or syndrome with a prevalence of fewer than 200,000 persons in the United States. Prevalence is the number of persons living with the rare disease.

Specific Conditions

As noted above, the Act specifically requests information on two rare diseases in children, **Friedreich's ataxia (FRDA)** and **Hutchinson-Gilford progeria syndrome**. Information on these diseases can be found in the following sections of this report:

Friedreich's Ataxia (FRDA)

Hutchinson-Gilford Progeria Syndrome

National Institute on Aging (NIA)

Overview of NIA Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NIA conducts and supports biomedical, social, and behavioral research, training, health information dissemination, and other programs with respect to the aging process. Although NIA does not focus on rare diseases per se, 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's syndrome, Bloom's syndrome, and Cockayne's syndrome that have implications for age-related diseases.

Recent Scientific Advances in Rare Diseases in Children Research

Friedreich's Ataxia (FRDA)

FRDA is a disorder that usually manifests before adolescence and is generally characterized by incoordination of limb movements, dysarthria, nystagmus, diminished or absent tendon reflexes, Babinski sign, impairment of position and vibratory senses, scoliosis, pes cavus, and hammer toe. The triad of 1) hypoactive knee and ankle jerks, 2) signs of progressive cerebellar dysfunction, and 3) preadolescent onset is commonly regarded as sufficient for diagnosis.

NIA grantee Dr. Grazia Isaya has been studying the function of frataxin, the protein that is defective in **FRDA**. Dr. Isaya has validated the use of the yeast *Saccharomyces cerevisiae* to study this disease by showing that the human frataxin gene can replace a defective frataxin homolog in yeast. Furthermore, Dr. Isaya has made the seminal observation that frataxin is an iron-binding protein. The project period for Dr. Isaya's research is 1997-2001.

Another NIA investigator, Dr. Gino Cortopassi, has demonstrated that fibroblasts from **FRDA** are sensitive to oxidative stress, and that this stress may be rescued by iron chelators. The project period for Dr. Cortopassi's ongoing research is 1993-2005. Dr. Cortopassi plans to characterize the type of damage that occurs to the mitochondria at a molecular level to evaluate the physiological endpoints and to attempt to rescue the damaged cells by inhibiting the damage-causing pathway.

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Overview of NIAAA Rare Diseases in Children Research Activities, FY 2000 - FY 2005

The mission of NIAAA is to conduct and support research activities on the causes, consequences, and treatment of alcoholism and alcohol abuse. Alcoholism results in widespread and damaging consequences to the health of children, both psychologically in child abuse and neglect and physically in mental retardation and birth defects associated with fetal alcohol syndrome (FAS). Please see "Ongoing, New, and Planned Research Initiatives" for more information. In terms of funding, many NIAAA FAS studies are funded through FY 2004. Funding for research on other diseases and conditions discussed in this report is assured, although specifics in terms of funding allocation are linked to progress and Principal Investigator evaluation of scientific merit.

Recent Scientific Advances in Rare Diseases Research Relevant to Children

Friedreich's Ataxia (FRDA)

FRDA is an autosomal recessive disease clinically characterized by progressive ataxia, hypertrophic cardiomyopathy, early onset of insulin-resistant diabetes, invalidism, and premature death. Current therapy for **FRDA** is palliative. **FRDA** is caused by a deficiency of frataxin, a 210 amino acid nuclear-encoded mitochondrial protein, resulting from the expansion of an intronic GAA repeat that leads to inhibition of transcription in the nucleus, leading to decreased message. In yeast, frataxin appears to be involved in iron export from mitochondria. In experiments, yeast cells with deleted frataxin accumulated mitochondrial iron, showed a high sensitivity to oxidation damage, and showed decreased mitochondrial respiration. In human cells, however, **FRDA** patients show a decrease in activity of the mitochondrial enzyme aconitase (EC 4.2.1.3), the enzyme responsible for conversion of citrate to isocitrate, the first step in the Krebs (also known as citric acid or TCA) cycle. Over-expression of frataxin in mammalian cells results in increases in the flux through the TCA cycle, in the electric potential between mitochondria and cytoplasm, and in the cellular adenosine triphosphate (ATP) content. These findings in mammalian cells indicate that deficiency of frataxin in human patients results primarily from defects in the TCA cycle and not from mitochondrial iron overload.

The clinical phenotype of **FRDA** patients is indistinguishable from the phenotype of patients with familial α-tocopherol (vitamin E) deficiency, and is different from patients with iron overload. Recent work shows that elevation of blood ketone bodies, a normal response to fasting, can increase mitochondrial citrate and isocitrate contents, thus overcoming the block in aconitase found in **FRDA**. In addition, ketone bodies increase the electric potential between mitochondria and cytoplasm, and with that, the energy contained in ATP. At the same time, ketone bodies oxidize coenzyme Q, thus decreasing the major source of mitochondrial free radicals. Ketone bodies also reduce the free $NADP^+$,which is the major source of the detoxification of free radicals. It is proposed that a diet containing ketone bodies might prove an effective therapy for this currently untreatable disease. Such dietary therapy could provide an earlier treatment for this group of patients than attempting to transfect the gene for frataxin into heart, muscle, and brain.

GLUT1-deficient Epilepsy

GLUT1 is the enzyme responsible for the transport of glucose from blood into the brain across the blood-brain barrier. The activity of this enzyme is not responsive to insulin. *GLUT1*-deficient epilepsy results from several types of mutation in the gene of *GLUT1*, located on the short arm of chromosome 1. The phenotypic expression of this mutation is infantile seizures (often refractory to anti-epileptic medication), delay of development, and acquired microcephaly with subsequent mental retardation. Under most conditions, the brain is entirely dependent upon blood glucose for all its energy needs; however, ketone bodies can provide a source of energy that can enter the cell on its own transporter, which differs from the glucose transporter. With the transport of glucose blocked as it is in these patients, ketone bodies provide the only physiologically normal alternative nutrient for the brain. Administering a diet rich in ketone bodies can provide a way to maintain normal brain growth and development and reduce or eliminate seizures. Feeding high-fat diets, the normal procedure for the treatment of drug-resistant epilepsy, can lead to elevation of blood cholesterol with consequently accelerated atherosclerosis. Therefore, a high-fat diet cannot be continued past age 17. A diet high in ketone bodies cannot lead to increased cholesterol synthesis, because ketone bodies are not utilized by the liver (the source of cholesterol synthesis). High-ketone diet therapy may therefore become a practical method for lifelong treatment of these patients.

Leprechaunism and Rabson-Mendenhall Syndrome

Leprechaunism and Rabson-Mendenhall syndrome are rare syndromes that result from mutations in the gene for the insulin receptor, which leave it incapable of binding insulin. These mutations produce the most extreme form of insulin resistance, leading to persistent hyperglycemia and attendant pathology and retardation of growth. The current treatment consists of administration of increasing doses of insulin (up to several thousand units per day). This treatment, if producing a result at all, yields only a very partial result due to the absence of insulin binding by its receptor. Treatment with insulin-like growth factor, while potentially effective, is unavailable to these children. Survival into the teens is rare. Ketone bodies in physiological amounts have been shown to mimic the effects of insulin's stimulation of the PDH multienzyme complex. Ketone bodies can increase the Krebs TCA cycle metabolite contents, increase the energy of ATP, and enhance metabolic efficiency. A ketone-rich, low-carbohydrate diet might prove an effective treatment of these conditions, which are currently without effective therapy.

Lafora Body Disease

Lafora body disease is an autosomal recessive form of progressive myoclonic epilepsy resulting from a mutation on chromosome 6 in a region encoding a calcium-activated protein phosphatase. Lafora body disease is pathologically characterized by the deposition of polyglucan inclusion bodies in the skin, liver, and brain. Patients present with progressive myoclonic epilepsy, mild liver disease, rapid intellectual deterioration, and insulin resistance, usually without frank diabetes; death results within 10 years of the onset of clinical symptoms. Currently, there is no treatment other than the administration of a high-fat, ketogenic diet. However, because the patients are often in their teens at presentation, the use of the ketogenic diet is not desirable due to its long-term atherogenic potential. A diet high in ketone bodies may prove an effective palliative step in the treatment of these patients.

Fetal Alcohol Syndrome (FAS)

FAS is a set of specific birth defects caused by maternal alcohol consumption during pregnancy. Unlike most other birth defects, FAS has the potential to be entirely preventable, because its direct cause, maternal drinking, is presumed to be a controllable behavior.

Scientists have shown that exposure to alcohol at critical times during brain development can induce excessive cell death during normal programmed death (apoptosis) or trigger apoptosis at inappropriate times. The result is smaller or abnormal brain structures with fewer connections between brain cells. This type of damage translates into developmental delays and permanent cognitive and behavioral disabilities. Because normal cell death is triggered by a highly regulated biochemical pathway inside the cells, researchers have examined alcohol's effects on various steps in the pathway in sensitive cells. Evidence from several models and different neuronal cell populations showed that alcohol reduces the availability or effectiveness of regulatory molecules (neurotrophic factors) that promote cell growth and survival by inhibiting the cell death pathway. When certain sensitive neuronal cells were removed from the brain and grown in culture in the presence of alcohol, their survival rate was diminished. The survival rate was restored to control levels by the addition of specific neurotrophic factors. Current research continues to elucidate the exact mechanisms by which alcohol interacts with these growth factors. Furthermore, scientists are now testing whether alcohol's deleterious effects can be prevented in the living animal by treatments that restore the effectiveness of these regulatory factors.

Recent advances in FAS research have been related to this general theme of potential in vivo treatments for amelioration of alcohol's effects on factors that support cell survival. For the first time, a mammalian model (mouse) has demonstrated that enhanced endogenous expression of a neurotrophic factor (nerve growth factor [NGF]) can protect against ethanol-induced cell death in a sensitive neuronal cell population of the cerebellum. The results provide strong in vivo evidence that the neurotoxic effects of ethanol on this cell population are mediated by interactions with a neurotrophic factor that is known to regulate apoptosis.

Another recent discovery is that performance on a learning discrimination task is normal in animals exposed to ethanol prenatally when their diet is supplemented with choline shortly after birth. Choline is a nutrient that has multiple actions on prenatal and early postnatal brain development, including elevation of NGF. As expected, ethanol-exposed animals with no choline treatment performed much more poorly than non-exposed animals. Importantly, ethanol-exposed animals who received the choline treatment performed at a level equal to that of the non-exposed animals, with or without choline. The mechanisms by which choline enhances learning are unknown. However, the importance of choline in development has led to a recent recommendation by the Institute of Medicine for a minimum amount of choline in the diets of pregnant and lactating women.

During brain development, the neurotransmitter serotonin stimulates the release of S100, which promotes serotonergic neuron differentiation and growth of connective projections. Scientists had previously shown that alcohol reduces the level of serotonin during a critical period of development. New findings suggest that during ethanol exposure, insufficient serotonin levels diminish the ability of the serotonin receptor to release S100, thus causing further loss of neurons and glia. Treatment of the mother with serotonin agonists enhances the ability of the remaining receptor-containing cells to mediate S100 release.

N-methyl-D-aspartate (NMDA) receptors are critical for growth, proliferation, differentiation, migration, and programmed death of neurons in the developing brain. Recent research has resulted in the first report that alcohol's well-documented deleterious actions on the NMDA receptor may be mediated through selective inhibition of neurosteroids. The findings may explain the previously reported diminished behavioral response of alcohol-exposed rat pups to maternal separation-induced stress after treatment with an exogenous neurosteroid.

In an advance related to genetic influences on apoptosis in FAS, a series of chick strains expressing differential sensitivity to ethanol has provided major insights into the relationship between alcohol-induced apoptotic events and variability in expression of craniofacial dysmorphology, one of the landmarks of FAS. After exposure to ethanol during early embryogenesis, changes in facial morphology were correlated with severity of ethanol-induced apoptosis. Ethanol treatment resulted in multiple facial alterations that varied from strain to strain; however, the responses to ethanol were consistent and reproducible within strains. Thus, the genetic background modulated the ethanol response. The study demonstrates the power of using genetically distinct strains of animals with differential sensitivity to ethanol as tools to tease out the complex relationships between ethanol-induced molecular insults and manifestations of the FAS phenotype.

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

Ketone-Based Diet

Attempts are now being made to encourage the production of sufficient quantities of palatable ketone body esters, which can be used in an artificial diet for use in FRDA, GLUT1-deficient epilepsy, leprechaunism, Rabson-Mendenhall syndrome, and lafora body disease. Because it is estimated that patients may require 100 to 200 g per day of these ketones, industrial collaboration will be required. Attempts to obtain this collaboration are now under way. Trials of this therapy in selected cases of this type are being planned for when collaboration is obtained and animal toxicity tests performed.

Fetal Alcohol Syndrome (FAS)

More than 110 projects now contribute to the NIAAA FAS portfolio, many of them with a particular focus on minority health and health disparity issues. In addition, an ongoing RFA on DNA microarrays has recently garnered a number of FAS proposals. Many of the NIAAA's FAS-related projects and initiatives are funded through FY 2004. Funding has not yet been allocated for FY 2005 research.

Rare Disease-Specific Workshops, Symposia, and Meetings

A workshop seeking to identify candidate biomarkers of maternal alcohol use and/or fetal ethanol exposure that can be used to identify women at high risk of giving birth to a child with FAS is scheduled for June 2001. Because early diagnosis and intervention have been shown to improve developmental outcomes for many birth defects, a prenatal or neonatal screen would be desirable for patient counseling and identifying high-risk infants before or at birth. Approaches to be discussed include identifying metabolites, hormones, or proteins altered by ethanol and using DNA arrays to identify altered gene expression patterns. In addition, developmental stages and/or processes that would be likely targets for in utero intervention will be identified and potential in utero intervention strategies discussed. A research agenda to help focus efforts to advance this area of research will be developed.

In either the presence or the absence of diagnosable FAS, other significant medical and behavioral problems may arise from prenatal alcohol exposure and the resulting damage to the developing brain, spinal cord, and central nervous system. A conference to address the possible link observed between sudden infant death syndrome (SIDS) and drinking during pregnancy is planned for 2001. The conference will cover the scope of these health problems in specific American Indian/Alaskan Native communities, which exhibit a very high prevalence of maternal drinking during pregnancy. Goals are to define the research questions applicable to addressing the prenatal alcohol use/SIDS connection to design a research study using a collaborative multidisciplinary approach.

National Institute of Allergy and Infectious Diseases (NIAID)

Overview of NIAID Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NIAID conducts and supports research that strives to understand, treat, and ultimately prevent the myriad of infectious and immunologic diseases that threaten millions of human lives. NIAID programs include a focus on special populations, including children. NIAID has a long history of research support for diseases that are classified as rare in children and has made considerable progress from basic discoveries in microbiology and immunology to the development of diagnostics, therapeutics, and preventive measures such as vaccines. Continued progress in this area of research will have considerable impact on the future health and quality of life for our Nation's children.

NIAID research activities on rare childhood diseases are grouped into the following broad areas: infectious diseases, primary immunodeficiency diseases, autoimmune diseases, and allergic diseases.

- Infectious diseases include diseases caused by bacteria, parasites, viruses, and fungi. Research on rare childhood infectious diseases is aimed at delineating mechanisms of pathogenesis and developing more effective diagnostic, treatment, and prevention strategies.

- 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. NIAID research is focused on the development of technology to make gene transfer an effective and curative therapy, and the identification of gene defects and immunologic abnormalities that lead to defective function.

- Autoimmune diseases are diseases in which the immune system mistakenly attacks and damages the body's own organs, tissues, and cells. NIAID research is focused on identifying the underlying immune mechanisms that cause or trigger disease onset and on developing interventions to treat autoimmune diseases.

- Allergies are inappropriate or exaggerated reactions of the immune system to substances that, in the majority of people, cause no symptoms. NIAID research is focused on the development of new approaches to the diagnosis, prevention, and treatment of a wide range of allergic diseases.

Recent Scientific Advances in Rare Childhood Diseases in Children Research

Rare Infectious Diseases

Congenital Cytomegalovirus (CMV)

Consequences of CMV in congenitally infected children can be devastating; most infected infants who survive suffer from profound progressive deafness and/or mental retardation. NIAID's Collaborative Antiviral Study Group (CASG), a multicenter activity supporting the conduct of clinical trials of therapies for viral infections other than HIV, has completed a phase III trial of ganciclovir for the treatment of symptomatic congenital CMV infections. Symptomatic babies treated with intravenous ganciclovir showed improvement in or maintenance of their hearing.

Haemophilus Influenzae Type B (Hib)

Hib was the leading cause of bacterial meningitis and other invasive bacterial disease (meningitis, epiglottitis, septic arthritis, osteomyelitis, and pericarditis) among children younger than five years of age before the introduction of effective vaccines. New *haemophilus* strains constantly emerge through the process of transformation; that is, strains mutate and acquire new genetic information. Studies have linked the presence of a 26-base-pair sequence to several other known transformation genes. A better understanding of the mechanism of acquisition of new genes by *H. influenzae* may aid in the development of better strategies for the suppression of antibiotic-resistant strains and the identification of novel cellular targets for the action of new antimicrobial agents.

Streptococcus (Group B)

Group B streptococci (GBS) cause serious illness in newborns, including sepsis, pneumonia, and meningitis. Neurologic sequelae include sight or hearing loss and mental retardation. Infant and maternal GBS infections may be preventable by maternal immunization. A GBS Type II capsular polysaccharide-tetanus toxoid (Type II-TT) vaccine in which GBS capsular polysaccharide was coupled to tetanus toxoid was recently compared to an uncoupled GBS Type II capsular polysaccharide vaccine. The immune response in the recipients of the coupled vaccine was significantly higher than in recipients of the uncoupled vaccine; immune responses to the coupled vaccine were dose-dependent and correlated in vitro with the enhanced uptake of organisms by white blood cells. This study supports the inclusion of capsular polysaccharide Type II coupled to tetanus toxoid in the formulation of a GBS vaccine.

Rare Primary Immunodeficiency Diseases

Autoimmune Lymphoproliferative Syndrome (ALPS)

ALPS is a disease in which a genetic defect in programmed cell death, or apoptosis, leads to the breakdown of lymphocyte regulation, causing a proliferation of lymphocytes. Recent studies have determined that the risk of becoming ill with ALPS is significantly greater in people who have an abnormality at a specific location of the *fas* gene (a gene that codes for a protein that triggers lymphocytes to die at the completion of their normal life cycle). Individuals with *fas* gene mutations are at greater risk for later development of B and T cell lymphomas. Researchers have also identified other mutations involved in ALPS.

Chronic Granulomatous Disease (CGD)

CGD is an inherited genetic disorder characterized by a failure of white blood cells called neutrophils to make oxygen compounds that kill bacteria and fungi. The disorder leaves individuals vulnerable to life-threatening infections and inflammatory growths, or granulomas, which can damage the lungs, liver, and other organs. Scientists recently reported a promising therapeutic approach for individuals with CGD. Patients with CGD underwent a preparative regimen that causes intense immunosuppression without destroying the bone marrow, followed by the transplant of immunologically matched sibling stem cells; this approach provided a cure for a subset of CGD patients with fully immunologically matched siblings. In another clinical trial, investigators demonstrated functional correction of the genetic defect for the X-linked form of CGD in three of five patients treated with multiple infusions of gene corrected cells.

Familial Hemophagocytic Lymphohistiocytosis (FHL)

FHL is a rare genetic disorder caused by mutations in at least three genes that results in uncontrolled activation of the immune system, leading to death in early infancy or childhood. Researchers demonstrated that a protein called perforin, part of the cell-destroying apparatus in killer T cells, is missing or inactive in FHL patients. These results may prove beneficial in the development of better diagnostic approaches and new therapies for this disease and new approaches to control undesired T cell responses in autoimmune diseases, transplantation, allergy, and asthma.

Job's Syndrome

Job's syndrome, also known as hyperimmunoglobulin E recurrent infection syndrome (HIE), is a rare inherited disease characterized by recurrent bacterial infections of the ears, sinuses, lungs, or skin and elevated levels of the antibody immunoglobulin E. Patients may also have scoliosis, weak bones and recurrent bone fractures, strokes or other brain disorders, severe itching, and skin inflammation. Scientists have linked a genetic defect in HIE patients to chromosome 4. Finding the gene or genes involved in HIE will be critical for the development of better strategies for HIE, especially gene therapy.

Severe Combined Immunodeficiency Disorder (SCID)

SCID is a rare congenital syndrome characterized by little if any immune response. Some children with SCID have lived for years in germ-free rooms and "bubbles" required by their unusual susceptibility to infectious agents that can be life-threatening.

A study that may prove critical to the development of a treatment for SCID involves improving the function of the thymus by stem cell transplantation. Scientists studied 83 SCID patients who had undergone bone marrow transplantation to receive stem cells over an 18-year period. T cells that developed in each patient were identified, characterized, and followed over time with molecular and cellular markers. The number of T cells reconstituted in the thymus peaked to near normal levels 1-2 years after transplantation, with continued thymic function for up to 14 years.

X-linked Hyper-IgM Syndrome (XHIM)

Individuals with XHIM lack, or have only trace amounts of, several functional classes of antibodies, or immunoglobulins (IgG, IgA, IgE), but have normal or elevated levels of the antibody IgM, causing them to be highly susceptible to recurrent infections. The majority of cases of this disease are caused by a defect in the T cell surface molecule, CD40 ligand, which binds to the B cell receptor CD40. Scientists are studying the treatment of patients with XHIM with a human-made CD40 ligand protein.

A second form of XHIM associated with ectodermal dysplasia (the abnormal development of specific tissues including, among other structures, the skin, hair, nails, sweat glands, and teeth) may be caused by a mutation in both CD40 and a cell-signaling pathway. Patients with this mutation do not produce IL-12 (which is important in eliciting an immune response to intracellular organisms) upon signaling via CD40.

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

FY 2000 and FY 2001 Research Activities

NIAID supports a wide range of research activities in rare childhood diseases, including clinical trials. Because many clinical trials are ongoing and dependent on accrual, the termination date of funding is not always well-defined.

Rare Infectious Diseases

- NIAID supports the Collaborative Antiviral Study Group (CASG), a multicenter activity supporting conduct of clinical trials of therapies for viral infections other than HIV. The CASG:

  - Conducts Phase III studies evaluating the use of oral acyclovir following the standard-of-care treatment with intravenous acyclovir to limit the recurrence of neonatal herpes virus infections limited to the skin, eye and mouth, or central nervous system. (FY 1997 to present)

  - Conducts a clinical evaluation of treatment of neonatal enteroviral sepsis with pleconaril (VP63843). (FY 1999 to present)

- NIAID is supporting phase I/II trials for three different candidate vaccines for CMV: a glycoprotein subunit, engineered live recombinant viruses, and a prime-boost strategy using a glycoprotein delivered both as a subunit and in an avian poxvirus vector. (FY 1999 to present)

- NIAID is the sponsor of a phase I safety and immunogenicity trial at Baylor College utilizing a GBS type III polysaccharide-tetanus toxoid conjugate vaccine in third-trimester pregnant women. As a part of the maternal immunization program, this vaccine had previously been shown to be safe and well-tolerated in clinical trials in postpartum women and women of childbearing age. A trial with pregnant women is in progress. (FY 1999 to present)

- NIAID continues to support research on the epidemiology of GBS disease, basic biology of GBS, GBS vaccine research, and clinical trials of GBS conjugate vaccines through a multidisciplinary contract awarded to Brigham and Women's Hospital. (FY 1997 through FY 2002)

- NIAID will be the investigational new drug (IND) sponsor for a safety and immunogenicity clinical trial to evaluate a GBS Type V capsular polysaccharide-tetanus toxoid conjugate vaccine in healthy women. The IND has been submitted to the U.S. Food and Drug Administration (FDA), and the clinical trial is expected to begin in 2001. (FY 2001 through undetermined time since research activity is a clinical trial)

- NIAID is supporting a study in three rural Alaskan villages to investigate the epidemiology of *Hib* carriage and transmission in Alaskan Native infants and to evaluate risk factors and immunologic parameters associated with carriage. An intervention study will be initiated in hopes of demonstrating the feasibility of at least one approach to Hib elimination in this high-risk population. (FY 2000 through FY 2002)

- NIAID participates with other national research agencies in support of The Global Alliance for Vaccines and Immunization (GAVI). GAVI was established in 1999 to replace the Children's Vaccine Initiative. The mission of GAVI is to protect health and save lives through the widespread use of safe vaccines, in the belief that every child, regardless of place of birth or socioeconomic status, should be protected against vaccine-preventable disease. (Activity is a consortium.)

Rare Primary Immunodeficiency Diseases

- NIAID, through a contract to the Immune Deficiency Foundation (IDF), established and maintains a registry of clinical information on U.S. residents affected by primary immunodeficiency diseases. For each disease, the registry collects information on incidence, clinical phenotypes and phenotype/genotype correlations, and natural course of the disease, including complications, effects of therapy, causes of death, and prognosis. (FY 1998 through FY 2002)

- NIAID, NCI, and NICHD co-funded a research project involving the use of a new screening device that specifically targets minority populations to determine if the occurrence of primary immunodeficiency diseases in large urban Hispanic and African American populations is under-diagnosed. (FY 2000 through FY 2002)

Rare Autoimmune Diseases

- NIAID chairs the Autoimmune Disease Coordinating Committee to increase collaboration and facilitate the development of coordinated research in autoimmune diseases among the many NIH Institutes, other Federal agencies, and private groups. (Funding years not applicable)

- Through the Clinical Trials Network for Stem Cell Transplantation for Autoimmune Diseases established in FY 2000, NIAID is sponsoring clinical trials to assess the safety and efficacy of hematopoietic stem cell transplantation for treating severe autoimmune diseases, along with integrated studies of underlying mechanisms. (FY 2000 through FY 2004)

- NIAID continues to support research projects awarded in FY 1999 in response to several new trans-NIH initiatives in autoimmunity, including: Environment/Infection/Gene Interaction in Autoimmunity (FY 1999 through FY 2001); Target Organ Damage in Autoimmune Diseases (FY 1999 through FY 2003); and Pilot Trials on Innovative Therapies for Rheumatic and Skin Diseases (FY 1999 through FY 2003).

- NIAID issued an RFA to establish the Cooperative Study Group for Autoimmune Disease Prevention, a collaborative network of investigators focused on the development of interventions to prevent autoimmune diseases. NIDDK, NICHD, NIDCR, NIAMS, ORWH, and the Juvenile Diabetes Research Foundation International are co-sponsoring this RFA. (FY 2001 through FY 2005. Funding after the first year will depend on progress in first year and availability of funds.)

Rare Allergic Diseases

- In FY 2001, NIAID will recompete its long-standing Asthma and Allergic Diseases Research Centers (AARDCs) program. With co-funding from NIEHS, this program will support basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases, with a major emphasis on human studies. (FY 2001 through FY 2005)

Broadly Relevant Rare Disease Activities

- Through the Immune Tolerance Network, an international consortium of more than 70 basic and clinical investigators from 40 institutions in 9 countries, NIAID supports clinical trials and assay development for promising tolerance induction strategies for the treatment of multiple immune-mediated disorders, including allergic and autoimmune diseases. (FY 1999 through FY 2005)

- In FY 2000, NIAID investigators entered into three Cooperative Research and Development Agreements (CRADAs) related to rare childhood diseases. CRADAs funded the production and evaluation of human anti-herpes simplex virus monoclonal antibody as a therapeutic agent for treatment of neonatal HSV (FY 1997 to FY 2002); a stem cell gene therapy system for CGD (FY 1993 to FY 2001); and the adoptive transfer of T cell clones for treatment of immunologically mediated and infectious disease (FY 1993 through FY 2001).

FY 2002 Planned Research Activities

In FY 2002, NIAID plans to fund the following initiatives:

- "Evaluation of Control Measures Against Diseases Other than AIDS," to address programmatic priorities in vaccine development, with a focus on candidate vaccines in general populations, including children. The evaluation of GBS vaccines is anticipated.

- "Prevention of Group B Streptococcal (GBS) Disease," to support preclinical and clinical studies of vaccine candidates for the prevention of GBS disease.

- "Partnerships for Novel Therapeutics and Vector Control Strategies in Infectious Diseases," to encourage private-sector involvement in research and development on novel treatments for human infectious diseases of high public health impact in areas that are currently not a high priority or that may be too financially risky.

- "Expanded Phase II and IV Vaccine Trials in Humans," for the clinical evaluation of new and improved vaccine candidates in various populations, including children.

- "Pathogen Functional Genomics Resource Center," to address the need for additional resources and facilities for functional analysis of pathogen genomes, including genomes of pathogens that cause rare childhood infectious diseases.

- Expansion of the primary immunodeficiency registry to include patients with additional genetically determined immunodeficiency diseases.

- Through NIAID's Vaccine and Treatment Evaluation Units, a study is planned to determine whether the unique immunologic effects of the *H. influenzae* Type B (*Hib*) polyribosylribitol phosphate *Neisseria meningitidis* outer membrane protein (PRP-OMP) conjugate vaccine causes a deficit in the immune response to *Hib* among very low birth-weight premature infants.

FY 2003 Through FY 2005 Research Plans

NIAID has an annual planning process to develop and select initiatives that solicit research applications in specific areas, including rare childhood diseases. Because planning for initiatives begins two years in advance of the award year, there are no currently approved initiatives for FY 2003 through FY 2005. However, projects are expected to be initiated as part of the regular structured planning process. NIAID will continue to stimulate and support research that may lead to more effective and accepted prophylactic and therapeutic approaches for the prevention and control of rare infectious and immunologic childhood diseases.

FY 2000 and FY 2001 Meetings Related to Rare Diseases in Children

- The NIAID-industry "Summit on Development of Infectious Disease Therapeutics" was held September 26-27, 2000. Issues of collaboration between NIAID and industry for the development of therapeutics for addressing public health priorities in infectious disease were discussed.

- In March 2000, NIAID, in collaboration with other NIH Institutes, the Jeffrey Modell Foundation, and the IDF, sponsored a symposium entitled, "Advances in the Diagnosis and Treatment of Primary Immunodeficiency Diseases: Risk of Cancer," focusing on advances in biomedical research that led to new insights into the diagnosis and treatment of primary immunodeficiency diseases and on the etiology of cancer in primary immunodeficient patients.

- At the 2001 American Academy of Asthma, Allergy, and Immunology Annual Meeting, NIAID sponsored a symposium entitled, "Re-thinking Immunotherapy for the Twenty-First Century: Bench to Bedside," focusing on immunotherapy for asthma and allergic diseases.

- NIAID, with the CDC National Program Office, organized a "Workshop on Cytomegalovirus (CMV) Vaccine Development," October 25-27, 2000.

Planned Meetings Related to Rare Diseases in Children

In an effort to stimulate research and research collaborations on rare diseases, including rare childhood diseases, NIAID and ORD will co-sponsor the following four meetings in FY 2001:

- "Gene Therapy: A Promising Treatment for Primary Immunodeficiency Disease," to explore the need for clinical trials and data collection strategies for primary immunodeficiency diseases and to assess the value of gene therapy for the treatment of primary immunodeficiency diseases.

- "Bare Lymphocyte Syndrome (BLS) and Gene Expression of Class II Major Histocompatability Complex (MHC)," to review and update the state of science, examine opportunities for

collaboration, and explore the implications of the regulation of MHC gene expression for BLS and other immunological diseases.

- "The Innate Immune System and Its Involvement in Autoimmune Diseases," to identify gaps in knowledge regarding the role of the innate immune system in etiology, pathology, and treatment of autoimmune diseases.

- "Animal Models of Autoimmune Disease: Current Models vs. Advanced Technology," to explore the strengths and weaknesses of each animal model, and determine if other models can and need to be developed to efficiently translate animal studies to humans.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Overview of NIAMS Rare Diseases in Children Research Activities, FY 2000 - FY 2005

The mission of NIAMS is to support basic and clinical research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases, the training of scientists to carry out this research, and the dissemination of information on research results in these diseases. Some of these diseases are rare and occur in children. Included in this group are rheumatic conditions such as juvenile rheumatoid arthritis and familial fever syndromes, muscle diseases such as Duchenne's muscular dystrophy and facioscapulohumeral dystrophy, musculoskeletal disorders such as osteogenesis imperfecta, and skin diseases such as epidermolysis bullosa, ichthyosis, and pseudoxanthoma elasticum. NIAMS-sponsored research has advanced understanding of these diseases, and several initiatives are under way. Other initiatives are being planned.

Recent Scientific Advances in Rare Diseases in Children Research

The conditions discussed below are under investigation by more than one investigator with support from NIAMS. All of these projects were funded in FY 2000. These conditions are in areas within the mission of NIAMS, and the Institute will be interested in funding future research in these areas.

Juvenile Rheumatoid Arthritis (JRA)

Etanercept has been shown to be a safe and effective drug in the treatment of children and teenagers with JRA, a type of arthritis that causes joint inflammation and stiffness for more than 6 weeks and begins when the child is 16 years of age or younger. In a clinical trial coordinated by the NIAMS Multipurpose Arthritis and Musculoskeletal Diseases Center at the Children's Hospital Medical Center of Cincinnati, investigators in the Pediatric Rheumatology Collaborative Study Group injected 69 children with etanercept twice a week. At the end of three months, all measures of arthritis impact (symptoms, joint abnormalities, ability to perform daily functions, and laboratory tests) were dramatically improved. Furthermore, the drug was well-tolerated.

The success of this clinical trial marks the culmination of many years of basic research supported by NIAMS and other NIH components. Etanercept belongs to a new class of drug treatments called biologic agents, which are designed to interfere with the specific biological process of a disease. The drug acts as a sponge to absorb a tumor necrosis factor, which is a naturally occurring protein that causes inflammation.

Duchenne's Muscular Dystrophy (DMD)

DMD is a genetic muscle-wasting disease caused by mutations in the gene for the protein dystrophin. NIAMS-funded scientists recently reported a number of exciting advances in mouse models of DMD. These include the successful application of the common antibiotic gentamicin to restore the function of the dystrophin protein, and the successful use of gene replacement to restore the missing protein and thereby reduce muscle disease. Such animal studies hold promise for potential future therapies for human patients affected by DMD.

Osteoporosis and Children

Osteoporosis, a bone-thinning disease that can lead to fractures, may actually start in childhood. Research studies on young girls have revealed that minor variations in a gene for the bone protein collagen can lead to lower bone density. In one investigation, more than 100 prepubertal girls were measured for bone mineral density. Also assessed were the bone size and genetic makeup of the collagen gene in each girl. The researchers found that girls with a particular type of collagen gene variant had almost 50% lower bone mineral density than girls with a different collagen gene variant. Identifying and understanding genetic susceptibility to osteoporosis early in life may facilitate the targeting of interventions to those who will most profit from them.

Pseudoxanthoma Elasticum (PXE)

PXE is an inherited disorder characterized by progressive calcification of elastic fibers in the skin, eye, and cardiovascular system. Scientists studying PXE have identified the gene that causes this disease. The researchers took a population genetics approach to narrow the location of the gene to a portion of human chromosome 16, and one gene in this region (*MRP6*) was later determined to be the gene associated with the disease. Work is continuing to determine the function of the gene and how mutations in it result in clinical disease. This could lead to the design of therapeutic interventions to treat PXE.

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

This Institute's report notes several RFAs issued in 2001. The results and advances these RFAs may produce is yet to be determined. At this point, NIAMS has no commitments for FY 2002 - FY 2005 on rare diseases and conditions in children.

Opening of NIH Pediatric Rheumatology Clinic

The NIAMS Intramural Research Program launched an initiative in the fall of 2000 at the NIH research hospital, the new NIH Pediatric Rheumatology Clinic. The Clinic offers diagnosis, evaluation, and treatments for children with rheumatic diseases. In addition to JRA and familial fever syndromes, pediatric rheumatic diseases include lupus, scleroderma, and dermatomyositis. The Clinic is providing children with a place where they can be diagnosed and treated in a state-of-the-art facility, and researchers can learn more about rare rheumatic diseases in children.

In February 2001, NIAMS convened a roundtable meeting to consider current and future research needs and opportunities in pediatric rheumatology. NIAMS staff will be developing initiatives based on the recommendations of the medical experts who attended the meeting.

New Research Centers for Juvenile Rheumatic Diseases

In FY 2001, a Rheumatic Diseases Core Center was established at the Children's Hospital Medical Center in Cincinnati. The Center will concentrate on understanding the causes of and finding novel approaches to treating pediatric rheumatic diseases. The Center will comprise five cores:

- A repository to make tissues available to researchers.
- Magnetic resonance imaging (MRI) to monitor disease progression.

- Identification of cells involved in rheumatic diseases.
- Data processing and bioinformatics.
- Administrative support to coordinate projects.

Two pilot studies will be undertaken by the Center. The first will examine the relationship between a protein produced in response to inflammation and activation of the inner cells of blood vessels in the synovium (a lubricating tissue surrounding movable joints) of children with JRA. The second will study the effect of certain enzyme inhibitors on the production of antibodies against a child's own tissues in lupus nephritis, a kidney disease.

The Children's Hospital in Cincinnati is also the site of a Multidisciplinary Clinical Research Center, which was established in FY 2001. Projects to be conducted by this new Center include research on childhood-onset dermatomyositis (a rare, sometimes fatal disease in which the muscles and skin become inflamed), juvenile fibromyalgia (a chronic disorder characterized by widespread musculoskeletal pain and fatigue), quantitative MRI to assess JRA, and the relationship between genetic factors and responses to drugs.

Osteogenesis Imperfecta (OI)

NIAMS has a long-standing interest in OI, a genetic disorder characterized by bones that break easily, often for little or no apparent cause. NIAMS recently funded five new grants in OI supporting research activities ranging from cutting-edge gene and cell therapies to testing drug treatments in mouse models. Furthermore, along with several other Institutes, NIAMS is sponsoring an RFA entitled, "New Research Strategies in OI," which was issued in December 2000. NIAMS is also participating in an RFA on "Clinical Trial Planning Grants for Pediatric Rehabilitation." This RFA was issued in November 2000 and focuses on pediatric musculoskeletal conditions, burn wounds, and genetic skin disorders.

Hereditary Multiple Exostoses

Hereditary multiple exostoses is a skeletal disorder that primarily affects bone growth in children. Patients with this disease present with benign cartilage-capped exostoses (growths projected outward from the surface of a bone), usually originating in the growth plate, and typically have short stature and curved bones. A significant proportion of the patients will develop malignant chondrosarcoma, a cancer originating from cartilage cells. Even in the absence of malignancy, the disease can be debilitating when the exostoses compress soft tissues such as surrounding muscles or nerves. The only known treatment is surgical removal of the exostoses, which often grow back at the original site. NIAMS is planning to support a two-day meeting on multiple hereditary exostoses at the University of Arizona in Tucson in November 2001.

Duchenne's Muscular Dystrophy (DMD)

In May 2000, NIAMS partnered with the National Institute of Neurological Disorders and Stroke (NINDS) and the Office of Rare Diseases (ORD) to sponsor a scientific workshop on Therapeutic Approaches for DMD. The meeting provided an opportunity for DMD investigators to share new findings, identify gaps in current research, and recommend future directions for promising studies of this disease. The insights from this conference are being used to develop new NIH research solicitations in DMD and other muscular dystrophies. These initiatives will build on projects funded through the

currently active FY 1999 program announcement on "Pathogenesis and Therapy of the Muscular Dystrophies."

Facioscapulohumeral Muscular Dystrophy (FSHD)

NIAMS has a number of initiatives under way in the area of FSHD, a genetic disease of the skeletal muscle that leads to progressive weakening of the muscles of the face, shoulders, and upper arms. Several projects with potential implications for FSHD have been funded as a result of the above-mentioned FY 1999 Program Announcement (PA) on pathogenesis and therapy, including grants focused on developing safe and effective methods to perform gene therapy on skeletal muscle.

Last spring, together with NINDS, ORD, the FSH Society, Inc., and the Muscular Dystrophy Association of America, NIAMS co-sponsored a scientific conference on the "Cause and Treatment of FSHD." Researchers from the United States, Canada, Europe, South America, and Asia met to share their latest findings and identify directions for future investigations. The recommendations that emerged from the conference include efforts to enhance understanding of the molecular processes and tissue changes associated with FSHD, ways to explore possible therapies to treat the disorder, strategies to promote the establishment of population-based studies of the disease, and development of research resources. Implementation of these recommendations has begun with the issuance of a November 2000 RFA entitled, "Exploratory Research on Facioscapulohumeral Dystrophy."

To develop research resources for FSHD, NIAMS has joined with NINDS to fund a registry on FSHD and another form of muscular dystrophy known as myotonic dystrophy (DM). The long-term goal of the registry is to facilitate research in FSHD and DM by serving as a liaison between families affected by these diseases who are eager to participate in specific research projects and investigators interested in studying these disorders. The registry will recruit and classify patients, and store medical and family history data for individuals with clinically diagnosed FSHD and DM. Scientists will be provided with statistical analyses of the registry data, as well as access to registry members who have agreed to assist with particular research studies.

Muscular Dystrophy (all forms)

To stimulate further research on all forms of muscular dystrophy (inherited disorders in which there is progressive degeneration of muscle fibers), NIAMS issued a program announcement with set-aside funds, "Therapeutic and Pathogenic Approaches for the Muscular Dystrophies," in January 200l. Responses to the announcement may include studies in appropriate animal models or preclinical or clinical studies in patients with DMD, Becker muscular dystrophy, FSHD, limb-girdle muscular dystrophy, DM, congenital muscular dystrophy, Emery-Dreifuss muscular dystrophy, or other forms of muscular dystrophy.

National Cancer Institute (NCI)

Overview of NCI Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NCI conducts and supports research in cancer biology, models, causes, prevention, control, early detection, diagnosis, treatment, and care.

While childhood cancer is relatively uncommon, with an annual incidence of 150 new cases per 1 million children in the United States, it accounts for 10% of childhood deaths and is second only to accidents as a cause of death in U.S. children. Although the overall cure rate for pediatric cancer exceeds 70%, it remains the leading cause of death by disease in children and adolescents in North America.

In general, childhood cancers are more aggressive than adult cancers and derive from more primitive cell types. The ability of a cancer cell to metastasize represents the major challenge in the treatment of pediatric cancers, with prognosis for children with metastatic cancer remaining quite poor.

NCI efforts are focused on rare cancers in children to improve our understanding of the biology of specific cancers and to translate this improved understanding to novel and better interventions for preventing, detecting, and treating cancer in children. NCI's section of this report discusses selected major research advances and current research initiatives conducted by the NCI intramural and extramural programs.

Recent Scientific Advances in Rare Diseases in Children Research

Biology

Dietary Bioflavonoid-Induced Breaks in the *MLL* Gene and Infant Leukemia

Approximately 80% of infants with acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL) have chromosome translocations involving the *MLL* gene at 11q23. Also, some cancer patients treated with chemotherapeutic agents such as etoposide or doxorubicin develop therapy-related leukemia involving *MLL*. These agents are known inhibitors of eukaryotic topoisomerase II (topo II), an enzyme that alters the deoxyribonucleic acid (DNA) topology pivotal for various cell functions by catalyzing double-strand breakage and rejoining of DNA. In one NCI/Division of Cancer Biology (DCB)-supported study, the researcher identified bioflavonoids (natural substances in food as well as in dietary supplements) that caused site-specific DNA cleavage in the *MLL* breakpoint cluster region in vivo; this site co-localized with the *MLL* breakpoint cluster region cleavage site induced by etoposide or doxorubicin. Topo II was identified as the target in both cases. Based on a test of 20 bioflavonoids, a common structure essential for topo II-induced DNA cleavage was identified. The results obtained in this study suggest that maternal ingestion of bioflavonoids induces *MLL* breaks and translocations in utero, leading to infant and early childhood leukemia. This study supports conclusions from a preliminary epidemiological study in which it was demonstrated that maternal consumption of topo II inhibitor-containing foods (including bioflavonoids) led to an approximately 10-fold higher risk of infant AML. Although the increased consumption of flavonoid-containing foods is associated with a decreased risk of adult malignancies in most epidemiologic studies to date, the results from this study may lead to

altered chemoprevention strategies in order to avoid leukemia induction in infants. (FY 1985 through FY 2002)

Mechanisms in Perinatal Carcinogenesis

Perinatal exposures may lead to increased risk of both childhood cancers and those occurring later in life. Carcinogenic nitrosamine (N-nitrosodimethylamine), which is present in tobacco smoke and other environmental sources, was examined in animal models to increase the understanding of cellular and molecular mechanisms of carcinogenesis. After administration to lactating rat mothers, N-nitrosodimethylamine caused, in tissues of suckling infants, formation of a DNA adduct known to be associated with tumor initiation. Furthermore, if the mother received ethanol simultaneously, there was a 10-fold increase in these adducts in some tissues. These results indicate that exposures to carcinogens via breast milk require further study. (Funding started FY 1983, duration is indefinite)

Mechanisms in Trans-generational Perinatal Carcinogenesis

Exposure of male mice to chromium(III), a chemical widely encountered in work settings, before mating leads to increased incidence of several types of neoplasms in the offspring. Preliminary results of tests to identify the mechanics of carcinogenesis indicate that paternal exposure is associated with changes in serum hormones in the offspring and altered expression of a number of hepatic genes, including insulin-like growth factor binding protein 1. (Funding started FY 1983, duration is indefinite)

Molecular Basis of Metastases in Osteosarcoma

Osteosarcoma is the most common bone cancer in children and young adults. The major cause of mortality in this tumor is metastatic spread, predominantly to the lungs. A mouse model of osteosarcoma that grows in a manner similar to the human tumor and metastasizes to the lung following amputation in a manner very similar to humans was developed. This model was used to apply gene expression profiling experiments to identify a limited group of genes that appear to play a major role in metastatic behavior. One such gene, called *ezrin*, has now been shown to be associated with metastatic behavior and poor outcome in osteosarcoma in dogs. Its expression and correlation with outcome in human osteosarcoma is currently being evaluated. Continued examination of the biology of *ezrin* in the mouse model found that it enhances cell motility and alters cell shape--features associated with metastatic behavior. Once the association of specific genetic changes with metastatic behavior in osteosarcoma is clearly established, drugs that inhibit activity can be identified, and genetic changes associated with metastatic behavior in other pediatric sarcomas can be identified and studied. (FY 1997 through FY 2003)

Etiology

Childhood Leukemia

A large case-control study conducted in conjunction with the Children's Cancer Group (an NCI-funded clinical trials cooperative group) evaluated the role of exposures to extremely low frequency magnetic fields (50 or 60 Hertz) from power lines and electrical appliances in the risk of childhood leukemia. Neither high, directly measured residential magnetic field levels nor high wire code levels (a proxy measure for close distance of residence to power lines) were found to be associated with significantly

increased risks of childhood ALL. A separate study showed no association of residential radon levels with childhood leukemia. Further analyses are being completed on other potential risk factors for childhood leukemia, including vaccinations and medical x-rays. (FY 1989 through FY 2001)

Pesticide Exposure in Children with Non-Hodgkin's Lymphoma (NHL)

The Children's Cancer Group conducted a study of children who developed NHL or leukemia and found a significant association between risk of NHL and increased frequency of reported pesticide use in the home, professional exterminations within the home, and postnatal exposure to pesticide. The results of the study provide further evidence linking pesticide exposure to the risk of NHL but do not implicate any specific agent. (FY 1996 though FY 2000)

Allergic Disorders & the Risk of Childhood Acute Lymphoblastic Leukemia (ALL)

Investigators compared the histories of selected allergic disorders (asthma, hay fever, food or drug allergies, eczema, and hives) in 1,842 cases of ALL. The results from this study, in agreement with most previous studies on adult cancer, suggested that allergic disorders are associated with a reduced risk of childhood ALL. Data from this study also suggested that genetic and/or environmental factors that cause allergic disorders may also be protective against ALL. (FY 1996 though FY 2002)

Treatment

Development of Immunotherapy Treatment in Pediatric Sarcomas

Preclinical models demonstrated that small protein fragments (peptides) derived from chromosomal alterations could be specifically recognized by cytotoxic T lymphocytes (CTL), and in some cases the tumor could be eliminated from mice by these CTL. These findings led to the development of a clinical study in children with refractory or recurrent Ewing's rhabdomyosarcoma. Patients were given specific peptide vaccinations in an attempt to generate anti-tumor CTL. The preliminary findings provide some evidence that CTL can be generated using a targeted approach. Follow-up studies are needed to explore this new modality of treatment to further understand immune-mediated anti-tumor effects. (FY 1997 through FY 2003)

Cancer Control, Survivorship, and Outcomes

Studies of Families at High Risk of Cancer: Beckwith-Wiedemann Syndrome

Investigations of families and individuals at high risk of cancer often lead to etiologic clues that may be important in the general population. Families with multiple members who have an unusual pattern or number of cancers are evaluated clinically, and risk factor information is obtained. Current studies include research on Beckwith-Wiedemann syndrome, an overgrowth disorder that occurs approximately once in every 15,000 births. Children with this syndrome can be mildly to greatly affected and are at risk for developing hypoglycemia and various types of tumors. NCI recently published a brochure entitled "Living with Beckwith-Wiedemann Syndrome" that provides a brief overview of the disorder, explains the specialized care that these children may need, and outlines the resources available to help affected families. (FY 1994 through FY 2002)

Follow-Up of Childhood Cancer Survivors

To study the long-term impact of treatment for childhood cancer, children participating in clinical trials sponsored by the NCI-funded Children's Cancer Group were identified, and interviews were conducted with long-term survivors and their siblings. In this large cohort, younger female patients who received 1,800 cGy cranial radiation and those who received 2,400 cGy below the diaphragm experienced early or delayed menarche. Patients treated with 2,400 cGy cranial radiation experienced educational difficulties. Other long-term effects studied in this cohort include loss of fertility, birth defects, psychosocial outcomes, and general health problems. (Funding started FY 1990, duration is indefinite)

Heritable Retinoblastoma and Susceptibility to Radiation-Induced Bone Sarcoma

Bone sarcoma incidence data from patients treated for bilateral retinoblastoma by x-ray during early childhood are being analyzed and compared to that from patients treated by injection of 224Ra for tuberculosis and other benign diseases. Preliminary analyses suggest that heritable retinoblastoma patients, whose baseline risk of bone sarcoma is already high, are unusually susceptible to radiation-related bone sarcoma. (FY 1989 through FY 2002)

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

Biology

Biology of Pediatric Hematopoietic Malignancies

Leukemias and lymphomas are among the most common pediatric malignancies. Although cure rates are excellent for a number of subtypes (e.g., ALL, Hodgkin's disease, Burkitt's lymphoma), long-term prognosis is poor for those who relapse or have disease that is refractory to standard therapy. A new collaborative analysis of gene expression patterns in pediatric leukemias was recently initiated to improve the understanding of the pathobiology of childhood leukemias. This effort could result in a better classification and risk stratification and will ultimately assist in the identification of novel therapeutic targets.

Pediatric Division of the Cooperative Human Tissue Network (CHTN)

Pediatric tumor specimens that have been carefully annotated with histopathologic and clinical data are critical to further research progress. The Pediatric Division of the CHTN collects tissue specimens and associated data from pediatric patients enrolled in trials nationwide, including trials involving rare pediatric tumors, and distributes them to qualified researchers throughout North America. Research made possible by the availability of these specimens includes:

- The identification of p53 alterations as a molecular marker for anaplastic Wilms' tumor, a form of Wilms' disease with a very poor prognosis.
- Studies to define novel genes and mechanisms associated with familial predisposition to Wilms' tumor.
- Investigation of the diagnostic utility of cytogenetic abnormalities in primitive neuroectodermal tumors of the central nervous system.

- Studies of the expression of the bcl-2 family of genes in neuroblastoma and their role in inhibiting chemotherapy-induced apoptosis.
- Work to identify the molecular and prognostic significance of genetic translocations in rhabdomyosarcomas.

(FY 1988 through FY 2006)

Gene Expression Analysis in Sarcoma

NCI is supporting a comprehensive, population-based study of gene expression in high-risk bone and soft tissue sarcomas of children and adolescents, with the goal of constructing a "mesoderm-sarcoma" microchip array with genes relevant to diagnosis and treatment. This research is expected to define comprehensive molecular "signatures" associated with critical clinical questions in any cancer. (FY 2000 through FY 2005)

Molecular Classification of Leukemias

Research efforts are being conducted to identify cDNA microarray technology, multivariate clustering methods, and links to clinical databases to perform molecular classification of AML and acute lymphoid leukemia. Molecular signatures of therapeutic response or resistance, minimal residual disease, or the influence of specific genotypes or cytogenetic abnormalities will be sought. The Pediatric CHTN's partnership with the newly unified Children's Oncology Group (COG) should further facilitate pediatric cancer research by providing access to specimens from 94% of pediatric cancers in North America and up to two-thirds of all patients joining clinical protocols. (FY 2000 through FY 2005)

Oncogenes and Tumor Suppressor Genes in Childhood Malignancies

A chromosomal translocation, t(2;13), that creates the fusion protein PAX3-FKHR has been identified as an early event in the childhood cancer alveolar rhabdomyosarcoma. Activities are under way to determine how PAX3-FKHR functions as an oncogene and to identify the secondary genetic alterations that are required to induce a full tumor phenotype.

A novel germline p53 mutation (p53R337H) has been identified in a cluster of pediatric patients in southern Brazil who have adrenal cortical carcinoma (ACC). These patients lack features of the Li-Fraumeni syndrome, suggesting that p53R337H is functionally inactive only under the intracellular conditions found in the adrenal cortical cells, thus specifically predisposing patients to ACC. Planned studies will test this hypothesis by direct examination of the biochemical and biophysical properties of this mutant p53 protein. Transgenic mice that carry this mutation in the germline will be developed. (FY 1996 through FY 2006)

Etiology

Swedish Childhood Cancer Study

Record-linkage of the Swedish Birth Registry and the Swedish Cancer Registry yielded 10,000 cases of childhood cancer (years 1973-1995). Nearly 2,000 cases of rare childhood cancers (500 lymphoma, 400 bone and connective tissue cancer, 300 Wilms' tumor, 250 neuroblastoma, 200 retinoblastoma, 130 germ cell tumors, and 50 hepatoblastoma) were matched to 10,000 controls with the same year of birth and

same gender as their matched case. Analysis of perinatal variables will focus on conditions and characteristics of the mother (including cigarette use), conditions and characteristics of the newborn baby, and medical procedures in labor, delivery, and care of the newborn. (FY 1993 through FY 2003)

Fanconi Anemia (FA) and Other Hereditary Pediatric Bone Marrow Failure Syndromes as Models for Study of Carcinogenesis in Humans

A number of hereditary pediatric disorders predispose to bone marrow failure, acute leukemia, and unusual solid tumors (notably head/neck cancers and gynecological carcinomas) in adult survivors. This atypical pattern of second malignancies suggests that there may be important, but as yet uncharacterized, gene-environmental interactions in their pathogenesis. A new project will identify cancer-prone families before the appearance of cancer, by virtue of underlying genetic hematologic diseases. The prototype disorder will be FA, but other bone marrow failure syndromes such as Diamond-Blackfan anemia, Shwachman-Diamond syndrome, and dyskeratosis congenita will also be studied. These disorders will be used as models of mechanisms of carcinogenesis in humans, and for investigation of the pathogenesis of neoplastic complications in these conditions. This project represents the first systematic, comprehensive, etiologically oriented, and epidemiologically grounded study of the cancers that complicate the hereditary bone marrow failure disorders of childhood. (FY 2001 through FY 2006)

The Pattern and Reproducibility of Recall for Past Exposures and Behavior for Two Different Intervals Between Childhood Cancer Diagnosis and Maternal Interview

Little is known about the etiology of most cancers occurring in children. In the past couple of decades, several environmental, occupational, and proxy factors for infections or immunological diseases have been linked with modest increases in risk of specific childhood cancers, but it is unclear whether these associations are etiologic or due in whole or part to recall bias or other forms of bias. The objective of this study is to establish the presence or absence of differential misclassification resulting from rumination bias by assessing the pattern of maternal responses to questions about prenatal and early infant diet, pre- and post-natal exposure to electrical appliances, maternal reproductive history, and other birth-related characteristics in relation to the timing of the maternal interview. A second objective is to assess the reproducibility of maternal responses to the topics listed above between two interviews of the mother approximately 6 months apart. The study will enroll 400 mothers of children newly diagnosed with leukemia, lymphoma, or brain tumors and randomize them into two groups: one to be interviewed within 14 days of diagnosis (“early”) and the second to be interviewed 6 months after diagnosis (“late,” as is currently done). Each group will also be interviewed using the same questionnaire six months after the initial interview. (FY 2002 through FY 2004)

Malignant Germ Cell Tumors (GCTs) in Children

The etiology of GCTs is poorly understood. Studies conducted among adult populations have suggested that certain prenatal exposures and parental occupational exposures may be associated with an increased risk of GCT. A proposed study will investigate risk factors for three types of GCT (testicular, ovarian, and non-gonadal) by utilizing resources available through the Children’s Cancer Group. This study represents the first large epidemiologic investigation to study risk factors of childhood GCT and examines the interaction between genetic and environmental factors in the development of GCT. (FY 1996 through FY 2002)

Case-Control Study of Risk Factors for Wilms' Tumor

Wilms' tumor is the most common kidney tumor of childhood. Epidemiologic studies have suggested but not proven an environmental influence. A major aim of this study is to evaluate the role of specific paternal occupations and related exposures reported in previous studies as risk factors for Wilms' tumor. The most consistent associations have involved paternal employment as welders, mechanics, and machinists. Related exposures found in these and other occupations include metals and solvents. The study will evaluate maternal employment and related exposures to dyes, electromagnetic fields, solvents, and metals. (FY 1998 through FY 2003)

Epidemiology of Down Syndrome (DS) - Leukemia and DS

The environmental etiology of DS is largely unknown. DS children are run a nearly 20-fold increased risk of developing leukemia compared to children in the general population. Because only 1% of DS children ever develop leukemia, subsequent environmental exposures could be responsible for leukemia in this population. In the first case-control study (DS with leukemia compared to DS without leukemia), investigators will determine whether children with DS and leukemia share similar risk factors reported to be associated with childhood ALL and/or AML. In the second case-control study (DS compared to normal population), investigators will examine the potential risk factors for DS, including parental occupations, exposures, smoking, and alcohol use, among other factors. (FY 1997 through FY 2002)

Treatment

Experimental Therapeutics of Pediatric Hematopoietic Malignancies

In an effort to develop new treatment strategies for pediatric hematopoietic malignancies, a number of clinical trials for patients with relapsed leukemias and lymphomas recently opened. These include phase I trials of arsenic trioxide and the farnesyl transferase inhibitor R115777, a phase II trial of intrathecal topotecan, and a pilot trial of non-myeloablative allogeneic stem cell transplantation. In addition, a trial is planned using a newly developed immunotoxin that targets CD22, a specific antigen found on the surface of approximately two-thirds of malignant cells in patients with ALL and NHL. These efforts promise to lead to the development of new, specific therapies for hematopoietic malignancies of childhood and adolescence. (Funding is indefinite)

Children's Oncology Group (COG) and Other Consortia

Nearly 90% of children with cancer in North America now have access to the state-of-the-art care provided by COG physician-researchers. Member institutions are located in almost every state, at more than 235 medical centers. These groups are currently achieving a cure rate of approximately 70% for children with cancer. The success of the pediatric cooperative group program can be measured by the continuing decline in childhood cancer mortality and by the continuing improvements in survival rates for many types of childhood cancer. Between 1989 and 1998, overall childhood cancer mortality declined by approximately 25%, with an approximately 30% decline in leukemia-related mortality and an approximately 50% decline in lymphoma-related mortality.

The primary objective of COG is to conduct clinical trials of new therapies for childhood cancer. Examples of research protocols under COG include: 1) a phase II randomized trial of standard versus

dose-intensified chemotherapy for children younger than 3 years with central nervous system (CNS) malignancy, 2) development of intervention strategies to increase enrollments, 3) evaluation of topotecan given with cyclophosphamide to improve outcomes for children with rhabdomyosarcoma, and 4) evaluation of the duration of intensive chemotherapy required after remission is achieved in order to obtain a cure for ALL.

NCI also supports consortia of institutions conducting pediatric clinical trials to evaluate new agents in children with cancer. Of special note is the phase I evaluation of the Bcr-Abl tyrosine kinase inhibitor ST1571 for children with Philadelphia chromosome-positive leukemias. This group of leukemias has a particularly poor prognosis, and studies of ST1571 in adults have shown high levels of anti-leukemia activity at doses producing minimal toxicity. Several studies in this area are ongoing and others are planned. Examples include an upcoming pilot study that will combine ST1571 with conventional chemotherapy agents and a study that will evaluate the use of ST1571 combined with radiation therapy for children with high-grade gliomas.

Another very active consortium is the Pediatric Brain Tumor Clinical Trials Consortium. In 2000, this consortium's clinical trials included a phase I study of a molecularly targeted anti-angiogenic agent in children with recurrent brain tumors and a pilot study evaluating the use of intrathecal therapy given in combination with intensive chemotherapy as an alternative to radiation for infants. Future studies will focus on agents that target the molecular characteristics of cancer cells as well as neurosurgical approaches. (Funding started FY 1991, duration is indefinite)

Cancer Control, Survivorship and Outcomes

Genetic Epidemiology of Medulloblastoma

A study of patients with medulloblastoma was recently initiated in collaboration with researchers from NIH and the Children's National Medical Center, Washington, D.C. The study is clinically evaluating patients with this type of brain cancer, assessing risks for all types of cancer among family members; examining tumors for mutations in the *PTCH*, *APC,* or other candidate genes; and evaluating the relationship between molecular genetic alterations, tumor characteristics, response to chemotherapy and radiation treatment, and survival in the cohort. (FY 1997 through FY 2002)

National Institute of Child Health and Human Development (NICHD)

Overview of NICHD Rare Diseases in Children Research, FY 2000 - FY 2005

The mission of NICHD is to ensure that babies are born healthy and develop, through childhood and adolescence, into productive adults. NICHD works to achieve this mission in part by conducting and supporting a broad range of innovative research activities that address the issue of rare diseases in children. Some of NICHD's activities have recently resulted in significant stories of discovery and scientific advances. In addition, to spur further discoveries and advances, NICHD is leading and supporting a variety of initiatives and workshops related to rare diseases or conditions in children. This report highlights some of the many NICHD activities related to rare diseases or conditions in children.

NICHD will continue to support research into FYs 2002 to 2005 that improves the lives of children, including research that ameliorates the symptoms or reduces the incidence of rare diseases in children. NICHD recently developed and published six strategic plans and research agendas to guide the direction of the Institute's research over the next five years. Three of these strategic plans address issues that are particularly related to rare diseases and conditions: 1) "Developmental Biology: Understanding Normal and Abnormal Development" helps to clarify the underlying mechanisms of normal and abnormal developmental processes needed to provide the bases for understanding how birth defects form; 2) "Genetics and Fetal Antecedents of Disease Susceptibility" targets understanding the early genetic pathways and processes that may lead to various diseases and conditions over the life span; and 3) "Sudden Infant Death Syndrome: New Directions" outlines a research agenda on SIDS for the next five years.

For each of the extramural activities listed below, the funding years since FY 2000 and the project period of the research project are indicated. The intramural projects are ongoing; therefore, the funding years and project period for all of these projects are listed as FY 2000-FY 2005.

Recent Scientific Advances in Rare Diseases in Children Research

Rett Syndrome

Rett syndrome is a neurodevelopmental disorder reported only in girls. The girls develop normally for the first 6 to 18 months of age, then begin to regress in speech development and develop repetitive hand motions, such as hand wringing or hand "washing." Although they may survive to adulthood, most affected girls never regain the ability to walk or even learn to feed themselves. While the disorder currently has no cure, scientists have found a faulty gene that fails to switch off other genes that are related to Rett syndrome. Previous findings suggested that the disorder was passed through the mother's X chromosome. After searching through the X chromosome, NICHD scientists found the disorder results from the mutation of the gene that makes methyl cytosine-binding protein 2 (MECP2). MECP2 is the lynchpin in one of the elaborate networks of proteins needed to switch off a group of genes. The discovery of a gene for the disorder holds the promise of a test that may lead to an earlier and more accurate diagnosis of Rett syndrome. In addition, new studies on the faulty gene itself may lead to effective treatments for the disorder. Furthermore, this discovery may also explain why only females are affected by the syndrome. Because they have only one X chromosome, males with the Rett syndrome gene possess only the mutant version of MECP2. Presumably, because they do not have a "backup"

copy of the normal gene, males with the gene for Rett syndrome die before birth. (FY 2000 through FY 2001; project period 1998-2001)

Osteogenesis Imperfecta (OI)

"Brittle bone disease" is a genetic defect of collagen, the connective tissue scaffolding upon which bones are built. Technically known as OI, this hereditary disorder ranges from mild to severe. Mild cases may go undiscovered, but individuals with the most severe form break so many bones during birth that they do not survive. Currently, there is no cure for OI, and treatment is usually directed toward preventing bone fractures and caring for fractures that have occurred. NICHD scientists, who sought to prevent the abnormal collagen from being made in patients with more severe cases of OI, examined a comparatively new gene technology that involves a plant virus. The RNA of the tobacco mosaic virus, which scientists have dubbed the "hammerhead ribozyme," can be tailor-made to bind to particular kinds of RNA. Taking advantage of that fact, the scientists engineered ribozymes that break apart the RNA that codes for the defective Type I collagen RNA, inserted the ribozymes into laboratory cultures of skin cells from patients with OI, and succeeded in stopping the skin cells from producing the abnormal collagen. Building on this achievement, the scientists are exploring ways to introduce the ribozymes into the bone marrow stem cells that manufacture bone. Using mouse models, the scientists are now attempting to insert the ribozyme into the cells of the mice in hopes of providing a treatment for this disorder. (FY 2000 through FY 2005; project period 2000-2005 [intramural])

Immune Mechanisms to Suppress Leukemia

Throughout life, white blood cells, a critical component of the immune system, begin developing from immature precursor cells in the bone marrow and complete their development in the thymus gland. Scientists have recently studied the biological effects of one of the many gene products involved in this process, interferon consensus-binding protein (ICSBP), on the cellular immune system. The researchers discovered that ICSBP is essential to the development of macrophages, a type of white blood cell that devours foreign organisms and constitutes one of the body's most powerful weapons against disease-causing microbes. By creating transgenic mice lacking ICSBP, these scientists also learned that this regulatory protein prevents the uncontrolled cell growth of another type of white blood cell that typically causes a condition similar to chronic myelogenous leukemia in humans. These insights into the function of ICSBP shed light on normal and abnormal immune system development, on the biochemical mechanisms involved in fighting infections, and on pathological processes leading to leukemia. (FY 2000 through FY 2005; project period: 2000-2005 [intramural])

<u>Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children</u>

Wiskott-Aldrich Syndrome (WAS)

NICHD scientists are focusing on factors that characterize the molecular mechanisms and clarify the signal transduction pathways that result in the primary immunodeficiency WAS. Scientists have found that a WAS protein plays a major role in forming the cytoskeleton and influencing cell signaling and development, as well as the programmed death of platelets and hematopoietic cells in WAS patients. These findings may lead to the development of a prenatal genetic test for WAS mutations. (FY 2000 through FY 2002; project period 1995-2004)

Sudden Infant Death Syndrome (SIDS)

Recent research has led to new insights into the neurological basis of SIDS. Building on earlier findings of brain abnormalities in babies who died of SIDS, scientists have now discovered that many babies have flaws in a neural network that likely plays a role in controlling breathing, heartbeat, temperature, and waking during sleep. Defects in this network could interfere with a baby's ability to awaken itself when he or she has trouble breathing or becomes overheated while asleep. Further research in this area could lead to a better way to screen newborns for the defective network. (FY 2000 through FY 2001; project period 1992-2005)

Beckwith-Wiedemann Syndrome (BWS)

NICHD scientists are studying the genomic imprinting of a gene cluster on chromosome 7 in mice, which is similar to chromosome 11 in humans. Disruptions in the genomic imprinting at chromosome 11 are associated with BWS, a developmental disorder in children characterized by a spectrum of symptoms such as excessive size and height, enlarged abdominal organs, and enlargement of cells related around the adrenal glands. Furthermore, BWS patients are also more susceptible to developing childhood tumors. Continued research using genomic imprinting in mice may result in methods to prevent or treat BWS. (FY 2000 through FY 2005; project period 2000-2005 [intramural])

Carney Complex (CNC)

NICHD scientists are investigating how genetic and molecular mechanisms of rare disorders, especially those that are hereditary and associated with multiple tumors and abnormalities in other endocrine glands, affect the adrenal cortex. Studies of families with CNC, a combination of myxomas, spotty skin pigmentation, endocrine hyperactivity and schwannomas, and other related syndromes, have revealed that chromosomes 2 and 17 harbor genes for CNC. Genetic and physical mapping of chromosome 2 was conducted to clone the CNC-causing gene. In addition, studies of chromosome 17 show that a novel tumor suppressor gene, abbreviated *PRKAR1A*, is responsible for many CNC cases.

In future studies, scientists will examine the functional consequences of *PRKAR1A* mutations and how these mutant genes affect development in mouse models. (FY 2000 through FY 2001; project period 2000-2005 [intramural])

Xeroderma Pigmentosum

To better understand the development of xeroderma pigmentosum, NICHD scientists are examining proteins to determine which mechanisms facilitate errors in DNA repair and synthesis. Xeroderma pigmentosum is a rare condition that makes patients very sensitive to sunlight. As a result, patients with this disease often suffer multiple sunlight-induced cancers, and many die before reaching adulthood. In addition, these scientists are planning to apply the methods they developed in DNA synthesis and repair to the study of **Hutchinson-Gilford progeria syndrome**. (FY 2000 through FY 2005; project period 2000-2005 [intramural])

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

Strategic Plans

NICHD recently developed and published five strategic plans designed to guide the direction of the Institute's research over the next five years. Two of these strategic plans address issues that are particularly related to rare diseases and conditions: 1) the "Developmental Biology: Understanding Normal and Abnormal Development" strategic plan helps to clarify the underlying mechanisms of normal and abnormal developmental processes needed to provide the bases for understanding how birth defects form; and 2) the "Genetics and Fetal Antecedents of Disease Susceptibility" plan serves to gain insight into how diseases form by defining early genetic pathways and processes that may lead to disease over the lifespan, and by identifying the role of "modifiers" such as gene-gene interactions or environmental influences that may influence the disease process. Another plan, "Sudden Infant Death Syndrome: New Directions," outlines a research agenda on SIDS for the next five years and should be completed during Summer 2001.

Initiatives

In FY 2000, NICHD led several initiatives to stimulate research related to rare diseases and conditions in children. For instance, NICHD is helping to lead the trans-NIH initiative, "Mutagenesis Screens/Phenotyping Tools for Zebrafish," which encourages scientists to use mutagenesis screening in the zebrafish model to detect and characterize genes, pathways, and phenotypes of interest in processes related to early development, behavior, organ formation, and disease progression. In addition, NICHD is leading an initiative, "Neurobiology and Genetics of Fragile X Syndrome," to stimulate research in areas such as developmental neurobiology, pathophysiology, genetics, proteomics, epidemiology, structure-function correlation, and clinical studies that have a direct link to fragile X syndrome.

In FY 2001, NICHD is participating in a trans-NIH initiative entitled, "Developing the Potential of *Xenopus tropicalis* as a Genetic Model," to stimulate research that examines the feasibility of using *X. tropicalis* for standard genetic manipulations such as mutagenesis, phenotyping, and gene cloning. The research will help identify and characterize genes that regulate cellular and developmental processes. In addition, NICHD is participating in autism initiatives aimed at stimulating research that clarifies the diagnosis, epidemiology, etiology, and genetics of (and develops innovative treatments for) autism and autism spectrum disorders.

Conferences

Workshop on Laboratory and Clinical Research Strategies in OI

Together with ORD and NIAMS, NICHD conducted a workshop in March 2001 where researchers discussed the many exciting developments in the field of OI. Discussion covered new drug treatments and their testing in mouse models and humans, the development of new mouse models, bone cell biology, mesenchymal cell transplantation, bone cell biology, and new genetic therapy approaches. The outcomes from this workshop will influence and guide future OI research and collaborations with scientists in related fields.

Workshop on Research on Chromosome 18

A workshop, co-sponsored with ORD, will be convened in July 2001 to bring together basic and clinical scientists who are familiar with syndromes associated with Chromosome 18, and scientists who have expertise in related areas of research. The meeting should lead to a consensus concerning the state of research in the study of disorders associated with chromosome 18 and identify critical areas for future research.

Conference on Endocrine Hypertension

Hypertension is a major risk factor for cerebrovascular and cardiovascular diseases. Togther with ORD, NICHD will conduct a conference in Fall 2001 where researchers will discuss several recent genetic, biochemical, and radiological discoveries, as well as new approaches and surgical procedures that have influenced the management of endocrine hypertension. Researchers will also discuss how endocrine hypertension relates to Cushing's syndrome and endocrine tumors in children.

Pain in Children with Developmental Disabilities

In November 2001, a conference is planned to examine the basic and clinical aspects of pain in children with significant physical and neurological impairments (brain or spinal cord injury and other relatively rare neurodevelopmental disorders) and how these aspects may differ significantly from those identified in able-bodied adults. This conference will bring together scientists to discuss the neurological basis of pain, therapeutic strategies for pain management, psychosocial aspects of coping with pain, and how best to apply this research to children. This conference will have specific relevance for children with spina bifida or cerebral palsy and will help build the pediatric rehabilitation program at the National Center of Medical Rehabilitation Research.

Warren Grant Magnuson Clinical Center (CC)

Overview of CC Rare Diseases in Children Research Activities, FY 2000 - FY 2005

Clinical Research Support for Pediatric Patients - Warren Grant Magnuson Clinical Center, NIH

The CC, which opened in 1953, is the clinical research facility that provides the venue for translating the basic science discoveries and scientific advances made at the benches and laboratories of NIH Institutes into clinical medicine. The CC is a hospital entirely dedicated to clinical research. The mission of the CC, as a national resource, is to provide the protocol-specific patient care, services, training, and environment needed to initiate and support the clinical research sponsored by individual NIH Institutes. Of the 19 NIH Institutes, 15 have clinical programs that involve clinical research activities in the CC. The scope of care provided in the approximately 1,000 active clinical protocols ranges from acute, intensive medical care to studies of patients who have bipolar disorder, schizophrenia, depression, or other behavioral illnesses. General areas in which ongoing studies are active include: medical, surgical, and pediatric oncology, medical genetics, endocrinology, rheumatology, nephrology, infectious diseases, hematology, cardiology, ophthalmology, otolaryngology, immunology, allergy, gastroenterology, neurology, neurosurgery, dentistry and oral surgery, alcohol dependence, gerontology, pulmonology, psychiatry and psychology, rehabilitation medicine, and imaging sciences.

The CC, in collaboration with Institute investigators and staff, provides comprehensive support for pediatric patients admitted to participate in clinical research protocols. The centerpiece of this support is the CC Pediatric Service. This program provides house-wide inpatient and outpatient pediatric consultative support for patients. The CC's inpatient and outpatient pediatric programs provide family-centered care (See Table 1). Children and families are provided with age-appropriate education, health promotion, and physical and emotional support. Nurses experienced in the care of children and their families staff both units. Recreational therapy, art therapy, social work assessment, dietary evaluation and nutritional support, spiritual ministry, and a schoolteacher all contribute to making the hospitalization of a child as comfortable as possible for the child and the family. The delivery of comprehensive pediatric clinical care is provided by the departments of Rehabilitation Medicine, Critical Care Medicine, Nursing, Social Work, Transfusion Medicine, Laboratory Medicine, Pain and Palliative Care, Imaging Sciences, Spiritual Ministry, and Nutrition. In addition to the clinical support provided, many of these departments provide extensive research support for Institute investigators.

Pediatric patients and, in particular, children with rare diseases and/or children requiring extended hospitalizations, have unique care requirements. To ensure that these needs are adequately addressed, the CC, partnering with the NIH community and the private sector, has implemented a variety of services and programs designed to meet the complex social, emotional, and educational needs of our pediatric patient-volunteers.

The Rehabilitation Medicine Department provides recreational therapy to all CC patients. Art therapy, arts and crafts programs, library services, recreational field trips, and pet therapy are available to all of our pediatric patients, as appropriate.

In June 1990, The Children's Inn at NIH opened its doors to receive pediatric patients and their families. The Inn, set on two acres of wooded land on the NIH campus, was funded by a generous gift from Merck

& Co., Inc. The Inn offers the comforts of a friendly, home-like environment that facilitates the family unity necessary to support sick children. During the past 10 years, more than 4,000 seriously ill children and their families have made 23,265 visits to the Inn. Amenities of the Children's Inn include private guest rooms (including facilities for families with assistance animals), a children's library, communal kitchen and dining facilities, family entertainment areas, a computer room, quiet rooms, and an outdoor playground and walking paths. This facility offers the patients and their families a place to retreat from the rigors of treatment and therapy.

Through the Starbright Foundation, the CC's youngest patients now have new worlds to explore. Starbright World is a private interactive computer network designed for hospitalized children and teenagers. Steven Spielberg envisioned this escape for kids, hoping to create a haven and tool to help children cope with illness. The Foundation provided four computer units for the Clinical Center. Programming includes games, videoconferencing, specialized chat rooms, and interactive multimedia programs that help explain common medical procedures.

To ensure that a child's education is not interrupted during participation in a clinical research study, the CC, through an arrangement with the Montgomery County, Maryland school district, provides in-hospital instruction to all pediatric patients, as appropriate. Instructors from the school district's Home and Hospital Instruction Service staff this program. The school's goal is to maintain the continuity of education between the student's home school and the NIH children's school.

Providing exceptional care and services to patients enrolled in clinical research studies is the CC's mission. Providing this care to pediatric patients requires the development and implementation of programs to meet the special and complex needs of ill children. The CC, working with Institute colleagues, patients, and public and private partners, continually strives to meet the needs and expectations of our pediatric patients and their families.

Table 1. Selected Pediatric Diseases Studied at the Clinical Center

Institute	Diagnosis
NCI	HIV infection
	Acute lymphoblastic leukemia
	Diffuse non-Hodgkin’s lymphoma
	Metastatic brain tumors
	Sarcomas
	Xeroderma pigmentosum
	Cockayne syndrome
	Trichothiodystrophy
NEI	Nystagmus
	Strabismus
	Uveitis associated with juvenile rheumatoid arthritis

NHGRI	X-linked severe combined immunodeficiency (XSCID) Primary immunodeficiency diseases Attention deficit hyperactivity disorder (ADHD)
NHLBI	Obstructive hypertrophic cardiomyopathy (HCM) Severe aplastic anemia
NIAID	Autoimmune lymphoproliferative syndrome (ALPS) Invasive mycoses X-linked hyper IgM syndrome Chronic granulomatous disease Hyper IgE-recurrent infection (Job's) syndrome Leukocyte adhesion deficiency Interferon-gamma receptor deficiency
NICHD	Childhood idiopathic inflammatory myopathies Osteogenesis imperfecta (OI) Congenital adrenal hyperplasia Obesity Turner syndrome Chediak-Higashi syndrome Short stature Familial isosexual precocious puberty LHRH analog-resistant precocious puberty Idiopathic juvenile osteoporosis Smith-Lemli-Opitz (SLO) syndrome Infantile neuronal ceroid lipofuscinosis
NIDCR	McCune-Albright syndrome (MAS)
NIMH	Autoimmune neuropsychiatric disorders associated with streptococcal infections Atypical neuroleptics Attention-deficit/hyperactivity disorder (ADHD) Sydenham chorea Bipolar disorder Schizophrenia
NINDS	Leukodystrophies of unknown cause Porencephaly and stroke Epilepsy Menkes disease Lafora disease Neuronopathic Gaucher disease

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children - Department of Rehabilitation Medicine

Juvenile Osteoporosis

The diagnosis of osteoporosis in children is rare. Juvenile osteoporosis can develop after long-time steroid use or idiopathically, and can result in back pain and overall decreased endurance. Data collection is ongoing for children diagnosed with osteoporosis and referred to the Department of Rehabilitation Medicine. Clinical evaluations include the back range of motion to determine if back pain is related to decreased motion, manual muscle strength testing, and the 9/12-minute walk test to determine level of endurance to ambulation.

Juvenile Dermatomyositis

Children with juvenile dermatomyositis present with generalized muscle weakness and decreased joint motion due to lack of strength needed to move through the entire range. Data collection for this population has been completed and analyzed for manuscript preparation. Clinical evaluations included the manual muscle test, range of motion, and a functional ability test, the Pediatric Evaluation of Disability Inventory (PEDI). Decreased aerobic capacity and swallowing dysfunction have also been identified in this population.

Juvenile Rheumatoid Arthritis (JRA)

Children with JRA are referred to the Department of Rehabilitation Medicine Department for evaluation on two protocols:

- Children with JRA/uveitis (an eye condition affecting many children with JRA) are referred to physical therapy for evaluation of their functional abilities on the PEDI, gait parameters using the stride analyzer, and hand function using the Jebsen hand test.

- Children with JRA are referred to physical therapy for evaluation of their functional abilities using the PEDI, gait parameters using the stride analyzer, and walking endurance using the nine-minute walk-run test.

Osteogenesis Imperfecta (OI)

OI is a heritable type I collagen disorder associated with brittle bones, muscle weakness, and short stature. Infants and children with OI types III and IV are referred to the Department of Rehabilitation Medicine for assessment of their gross motor performance level using the Brief Assessment of Motor Function (BAMF) and the Peabody Developmental Motor Scales (PDMS); level of independence using the Childhood Health Assessment Questionnaire (CHAQ); daily activity using the Pediatric Activity Record (PAR); and self-perceived competence using the Harter scales. A study of children's temperament in relation to motor performance has been completed. A study of resilience as a potential influence on performance is under consideration.

Smith-Magenis Syndrome (SMS)

SMS is a deletion of the 17p11.2 chromosomal disorder characterized by dysmorphic facial features, brachydactyly, short stature, hypotonia, self-hugging behaviors, speech delays with and without hearing loss, ranging degrees of cognitive deficits, peripheral neuropathy, scoliosis, sleep disturbances, and self-injurious behaviors. Sensorimotor and functional evaluations administered by the Department of Rehabilitation Medicine would provide information related to the physical/sensorimotor and behavioral characteristics seen in children with SMS. This protocol is scheduled to begin in June 2001.

A comprehensive battery of evaluations such as the PEDI, the Sensory Profile, the PDMS-2, and the BAMF will enhance the natural history protocol and provide additional information for descriptive research in the areas of sensorimotor skills and functional abilities in children with SMS. This will provide more comprehensive data to delineate and characterize the physical, cognitive, and neurobehavioral abnormalities currently being studied in children with SMS.

Ongoing Research Protocols - Speech-Language Pathology Section, Department of Rehabilitation Medicine

Smith-Lemli-Opitz (SLO) Syndrome

The Speech-Language Pathology Section is actively involved in this protocol designed to assess oral sensory motor development, feeding and swallowing abilities, and speech characteristics. Assessments are conducted on each patient visit to the Clinical Center and consist of:

- Speech pathology pediatric swallowing questionnaire.
- Oral-sensory motor evaluation.
- Clinical feeding assessments.
- Videofluoroscopic study of swallowing function.
- Evaluation of speech-language development.

SMS

This protocol was recently approved by the Internal Review Board, and patient accrual was anticipated beginning in April 2001. Past experience with this patient population includes the study of 12 children documenting oral sensory motor, swallowing, and speech and voice characteristics. Findings included observance of laryngeal pathology in approximately 90% of the population studied, along with several oral sensory motor findings such as open mouth posturing, decreased lingual range of motion and strength, oral hypersensitivity, and clinical feeding and swallowing difficulties.

The procedures for the upcoming protocol will include the following:

- Feeding and swallowing questionnaire completed by parent (21-item questionnaire assessed with 4-point rating scale).
- Clinical feeding and swallowing evaluations (4-point rating scale of oral pharyngeal swallowing behaviors).
- Oral sensory motor examination (clinical evaluation oral sensory motor function by cranial nerve. Assessed on a 4-point rating scale [1=normal, 2=mild, 3=moderate, 4=severe]).

- Digital audio tape recording of child's voice, articulation, and speech patterns.
- Computer speech laboratory analysis of voice fundamental frequency, intensity, and parameters.
- Speech parameters scale (assessed with a 4-point rating scale of speech and voice parameters).
- Assessments of resonance and laryngeal function with flexible nasoendoscopy and videostroboscopy.

Cystinosis

Assessments include:

- Oral sensory motor evaluation.
- Swallowing questionnaires.
- Oropharyngeal ultrasound of swallowing.
- Videofluoroscopic evaluation of swallowing functions.

Stickler's Syndrome

This is a research study assessing oral sensory motor, speech/voice, and swallowing functions of family members diagnosed with Stickler's syndrome.

The testing battery consists of:

- 21-item swallowing questionnaire.
- Oral sensory motor evaluation by cranial nerve function.
- Oropharyngeal ultrasound.
- Digital audio tape recordings and vocal analysis.
- Endoscopic evaluation of the velopharyngeal port.
- Videostroboscopic evaluation of laryngeal function.
- Speech parameters ratings.

Gaucher Disease

Patients are seen clinically in this protocol for assessment of oral sensory motor and swallowing abilities.

Mucolipidosis type IV

Patients are seen in this protocol to document the natural history of oral sensory motor, speech, and swallowing functions of children with mucolipidosis type IV.

Leukodystrophy

Patients are seen clinically in this protocol for assessment of oral sensory motor and swallowing abilities.

Sydenham's Chorea

Patients are seen for evaluation of oral sensory motor abilities, swallowing function, and documentation of speech characteristics. Assessments also include videofluoroscopic evaluation of swallowing.

Carbohydrate Glycoprotein Deficiency Syndrome

Evaluations include:

- Assessment of oral sensory motor abilities.
- Clinical feeding and swallowing function.
- Speech-language development and communication abilities.

Fibrous Dysplasias

Clinical assessments of speech and swallowing function are conducted, assessing the impairment level of speech, language, and swallowing function to facilitate therapeutic interventions and education planning in these children.

Additional Funding Information

The CC is able to project funding for the current and immediately upcoming programs and initiatives in which it participates. Projected funding for future activities depends upon the funding mechanisms and plans of the NIH Institutes and Centers (ICs) with which the CC collaborates on research initiatives and programs.

National Center for Complementary and Alternative Medicine (NCCAM)

Overview of NCCAM Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NCCAM is dedicated to exploring complementary and alterative medicine (CAM) healing practices in the context of rigorous science. To achieve this goal, NCCAM:

- Identifies and evaluates CAM treatment, diagnostic, and prevention modalities in each of the broad domains of CAM.
- Conducts or supports clinical trials, basic science research, epidemiological studies, health services research, and other appropriate research and investigational activities.
- Studies CAM treatment, diagnostic, and prevention systems, modalities, disciplines, and their potential for integration into the health care delivery system.

All diseases or conditions for which CAM is used are of concern to NCCAM. NCCAM therefore supports research in the prevention, diagnosis, evaluation, and treatment of several rare diseases and disorders.

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

Spastic Cerebral Palsy

NCCAM currently supports a phase II clinical trial (FY 1998-FY 2003) at the University of Arizona to evaluate two alternative or complementary medical modalities (osteopathic manipulation and acupuncture) that have been used in children to reduce complications associated with cerebral palsy versus a control group (therapeutic play). Of particular interest will be evaluations of the incorporation of and compliance with the two modalities in the participating groups already providing clinical services.

National Institute on Deafness and Other Communication Disorders (NIDCD)

Overview of NIDCD Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NIDCD conducts and supports research and research training on normal mechanisms as well as on diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. Many of these disorders occur in children. NIDCD achieves its mission 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. NIDCD 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 communication impairments or disorders and supports efforts to create devices that substitute for lost and impaired sensory and communication functions.

Recent Scientific Advances in Rare Diseases in Children 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 act to replicate the mitochondria 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 investigators have identified several specific mitochondrial mutations that predispose an individual to hearing damage from aminoglycoside ototoxicity. Most recently, these investigators have identified a genetic locus, in the nucleus of the cell, which acts to modify the effects of the mitochondrial mutations. These findings could be used to develop genetic tests to determine whether an individual has an increased risk for minoglycoside-induced hearing damage. (FY 2000 through FY 2002)

Usher's Syndrome

Usher's syndrome is characterized by hearing loss, retinitis pigmentosa, and/or vestibular areflexia. The frequency of this syndrome has been estimated at 5% of the deaf population, with more than half of the deaf and blind individuals (>10,000) in the United States afflicted with this disease. The severity of the hearing loss and the presence of vestibular dysfunction distinguishes two clinical subtypes of Usher's syndrome, types I and II. A third form of Usher's syndrome (type III), which has a late onset, has recently been described. These three phenotypes are genetically distinct. The NIDCD Intramural Research Program is continuing to support the Hereditary Hearing Impairment Consortium, the members of which are working to identify and characterize all the genes responsible for Usher's syndrome. A major advance in this area of research was the finding that the gene for Usher's type Ib codes for an unconventional myosin protein, information that led to the realization that a known animal model of deafness was a homolog for this type of Usher's syndrome.

Recently, several NIDCD-supported scientists reported the cloning of the gene for Usher's syndrome type IIa. The *USH2A* gene encodes a protein ("Usherin") that has structures similar to other proteins

involved in assembling cells and tissues into functional organs. In addition, within the last six months NIDCD-supported scientists have identified the genes responsible for Usher type Ic and Usher type Id. The cloning of these genes and analysis of the proteins they produce are critical steps towards developing strategies to treat this devastating disease. (FY 2000 through FY 2005)

Waardenburg's Syndrome (WS)

WS is an autosomal dominant disorder characterized by pigmentary disturbances and cochlear deafness in some individuals. There are at least three distinct forms of this syndrome (types I, II, and III). A transcription factor gene, microphthalmia-associated transcription factor (*MITF*), was cloned by NIDCD intramural scientists and was assigned to chromosome 3p14.1-p12.3. This gene is a human homolog of the mouse mi gene. Phenotypes of mice with mutations at mi alleles are closely related to those of WS type II (WS2), and mutations of *MITF* have been found in some WS type II families. Mutation of a second gene, *PAX3*, also encoding a transcription factor, causes WS type I as well as WS type III. Current evidence suggests that variable disease expression depends on the genetic background provided by both parents. Importantly, recent characterization of the *PAX3* regulation by NIDCD intramural scientists will enable a comprehensive mutation screen for individuals with WS. (FY 2000 through FY 2002)

Stickler's Syndrome

Stickler's syndrome is a rare autosomal dominant disorder causing progressive sensorineural hearing loss, myopia, retinal detachments, arthropathy, and craniofacial abnormalities in affected individuals. It may be caused by mutations in any of the genes encoding the three polypeptide subunits of type XI collagen: *COL2A1*, *COL11A1*, and *COL11A2*. In conjunction with scientists from NHGRI, NIDCD intramural scientists are characterizing the otolaryngologic and auditory phenotypes of individuals affected by Stickler's syndrome. (FY 2000 through FY 2001)

Auditory Neuropathy

A small but substantial number of patients with bilateral hearing loss that was assumed to be sensory in etiology, have, in fact, normal cochlear function. These patients have severely abnormal neural function as evidenced by poor or absent auditory brainstem responses. Standard remediation strategies for bilateral hearing loss, such as hearing aids, are of little use to these patients. When this disorder strikes young children or infants, it can cause severe disruption of normal language and speech development. The most likely etiology is a neuropathy 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. (FY 2000 through FY 2001)

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

Studies are being conducted in the intramural division of NIDCD on a group of individuals affected by VHL disease and tumors of the inner ear. These endolymphatic sac tumors (ELST) have been found to develop in approximately 10% of individuals carrying mutations of the VHL gene. Symptoms of hearing loss, balance disturbances, and tinnitus represent the primary clinical manifestations. 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. Preliminary results from a clinical trial of hearing preservation surgery in individuals with early-stage ELST suggest that these tumors can be safely resected 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 auditory and vestibular dysfunction. (FY 2000 through FY 2002)

Large Vestibular Aqueduct Syndrome (LVAS)

LVAS 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*). NIDCD intramural scientists are working to identify the genetic basis of LVAS, including several cases where it is clearly not caused by mutations in *PDS*. Whether congenital cytomegalovirus infection is involved in this form of hearing loss is currently being investigated. (FY 2000 through FY 2005)

Hereditary Cerebellar Ataxia Syndrome of Early Onset

Several abnormal genes that are associated with inherited cerebellar syndromes of imbalance and incoordination have been identified. Relatively little is known about how different mutations lead to specific phenotypes, however. There is typically great heterogeneity in the clinical signs and symptoms within families with the same mutation and across families with mutations in the same gene. An NIDCD-funded group of investigators at the University of California, Los Angeles, has demonstrated linkage to chromosome 19p in four families with episodic vertigo and ataxia. This research group has 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 extremities, and speech.

More recent work has identified a number of related ataxias associated with different mutations in the same calcium channel gene. In addition, mutations in other calcium channel genes have been found to be associated with inherited ataxias. Thus, calcium channelopathies have emerged as important model systems to study the role of calcium channels in neuronal function. (FY 2000 through FY 2003)

Kallmann's Syndrome

Kallmann's syndrome is a rare genetic disorder with an absence of the sense of smell and a failure of the gonads to mature as primary symptoms. There is a 5- to 7-fold preponderance of affected males compared 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 neuronal migration, which links the two major disease symptoms. A unique family of proteins and their receptors that regulate neuronal migration and direction during development are under investigation by NIDCD-funded scientists. Additional research is focused on the isolation and cloning of an X-linked gene responsible for Kallmann's syndrome. (FY 2000 through FY 2003)

Papilloma and Carcinoma of the Vocal Tract

Papillomas and carcinomas are the most important neoplasms affecting the human vocal and speech tract. Carcinomas of the upper airway and vocal tract have affected the lives of more than 320,000 Americans and lead to more than 12,000 deaths annually in the United States. A major cause of these recurrent tumors is human papillomaviruses that infect the whole airway in these patients. NIDCD intramural scientists and an extramural team of molecular biologists/virologists and clinicians funded by NIDCD are addressing the molecular basis for the disease and possible new treatments. A recent finding is that these tumors show an accentuated response to growth factors when compared to other cells. The specific intracellular signaling molecules that mediate this effect have been identified. It has also been shown that 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 factors may provide a new approach for prevention and therapy of these cancers.

The multiple recurrences of these respiratory papillomas and the importance of immune function in controlling viral infection has led to studies demonstrating that patients have a normal immune response to most infections but a suppressed immune response to papillomaviruses. NIDCD-supported investigators recently identified the mechanism by which papillomaviruses evade the immune system and subsequently developed a strategy to block this immune evasion. In parallel preclinical studies, NIDCD intramural scientists are testing the possibility of interleukin therapy to enhance the cytotoxic T cell response to these papillomas. Additional approaches being tested include photodynamic therapy with Foscan as an adjunct to surgery. These exciting findings, which have stimulated multiple new therapeutic approaches, could ultimately result in nonsurgical treatment of laryngeal papillomas. (FY 2000 through FY 2004)

Velocardiofacial Syndrome (VCFS)

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 have a missing chromosomal segment at 22q11. VCFS is inherited in only about 10% to 15% of cases. In most instances, neither parent has the syndrome nor carries the defective gene, and the cause of the deletion in the affected child is unknown. A team of NIDCD-supported researchers has 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 a palatal defect, strongly suggesting that modifier genes may interact with the genes of the deletion region. Due to the heterogeneity of chromosomal deletions it has been difficult to identify a single gene responsible for any of the observed phenotypes; however, recent work now suggests that the Clathrin heavy chain-like gene is a strong candidate gene for VCFS. (FY 2000 through FY 2004)

Williams Syndrome (WMS)

WMS is a rare (estimated incidence: 1 in 25,000 live births) genetic disorder in children, characterized by a constellation of distinctive facial features, cardiac and dental anomalies, hypercalcemia, mental retardation, and a unique behavioral profile (linguistic abilities selectively preserved in the face of severe

general cognitive deficits). NIDCD-supported studies of young children with WMS have documented extreme retardation early on in all developmental milestones, including language. Results suggest that different cognitive domains in WMS (language, spatial cognition, affect) have different starting points and different trajectories, unlike patterns discerned in normal controls, and that some aspects of brain organization (e.g., cerebellar abnormalities) are present from a very early age.
(FY 2000 through FY 2001)

Autism

NIDCD-supported researchers are investigating the communication difficulties/differences of children with autism. Research is being conducted to assess brain imaging as a means to study the neurodevelopmental origins and functional brain abnormalities thought to underlie autism in children. Progress is also being made in the development of effective language intervention techniques and the characterization of early communication behaviors in this population. (FY 2000 through FY 2005)

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

Rare Diseases Research Initiatives and Program Activities in FY 2000

On September 12, 2000, NICHD and ORD supported an NIH Workshop entitled, "The Olfactory Model System and Rett and Kallmann Syndromes: Sniffing Out Insights into Brain Development." Several of the less common neurologic developmental disorders, such as Rett's and Kallmann's syndromes, are associated with severe anomalies of the olfactory sensory system. There has been recent progress in characterizing the impact of these developmental disorders on the olfactory system and in characterizing molecular and genetic defects associated with these syndromes. The workshop focused on recent findings in these syndromes and explored the feasibility of using the olfactory system as an accessible sensorineural model for exploring primary molecular genetic defects at the level of the developing central nervous system.

Ongoing and Planned Rare Diseases Research Initiatives and Program Activities

NIDCD is participating with other members of the NIH Autism Coordinating Committee in the following initiatives:

- A PA on autism and autism spectrum disorders has just been released and will be active from FY 2001 through FY 2004.
- An RFA on innovative treatments for autism was published in FY 2001. Research awarded through this RFA will be active from FY 2001 through FY 2004.
- An RFA for planning activities for autism centers will soon be released. Awards are planned to start in FY 2002.

National Institute of Dental and Craniofacial Research (NIDCR)

Overview of NIDCR Rare Diseases in Children Research Activities, FY 2000 - FY 2005

The mission of NIDCR is to improve and promote dental, oral, and craniofacial health through research and research training. NIDCR's programs encompass basic and clinical studies of a broad range of rare diseases, disorders, and syndromes involving the oral cavity and craniofacial structures of children (younger than age 21); related developmental biology studies; applied research on biologically compatible and biomimetic materials and methods to re-engineer damaged or dysfunctional tissues; and behavioral and epidemiological studies to better assess the scope of the problem, identify risk factors for and biomarkers of disease, understand health disparities, and provide the knowledge base for improved preventive and health care.

Most craniofacial anomalies are associated with abnormal developmental events and are apparent in pediatric populations. Rare diseases and syndromes affecting children compose a significant portion of NIDCR's program activities and include clefting syndromes; craniosynostosis syndromes; hemifacial microsomia and other congenital craniofacial anomalies; early-onset periodontitis; storage diseases; ectodermal dysplasias; chondrodysplasias; disorders of tooth and bone formation such as osteogenesis, amelogenesis, and dentinogenesis imperfecta; and noma.

Recent Scientific Advances in Rare Diseases in Children Research

Papillon-Lefevre Syndrome (PLS)

NIDCR-supported researchers identified mutations in the *cathepsin C* gene as the primary cause of PLS. PLS is a rare and devastating condition that affects the skin and teeth, causing an early-onset periodontitis that is unresponsive to traditional treatment. Affected individuals lose their primary teeth during their pre-school years and all their permanent teeth by the time they are young adults. The periodontitis infection results in severe destruction of bone tissue in the jaws that support the teeth. Twenty-five different mutations in *cathepsin C* have been identified, all of which render the enzyme non-functional as a lysosomal protease. Discovery of the gene for PLS may provide the means for early diagnosis and future therapies to prevent or slow the associated tooth loss. (FY 2000 through FY 2002)

Cleft Lip and Palate Syndrome

While clefts of the lip with or without cleft palate (CL/P) are one of the most common birth defects, there are different syndromes that include oral clefting and wide variations in types of oral clefts that are individually rare. Most cases of CL/P are non-syndromic; however, in approximately 30% of cases, CL/P occurs as part of a single-gene syndrome. Scientists recently announced the discovery of the gene responsible for autosomal recessive CL/P-ectodermal dysplasia syndrome type 1 (CLPED1). This syndrome is characterized by cleft lip/palate, hidrotic ectodermal dysplasia, and developmental defects of the hands. CLPED1 is generally a rare syndrome, but it occurs with a high frequency of 1 per 2,000 among the population of Margarita Island. The gene responsible, *PVRL1* on chromosome 11, encodes the protein nectin-1, an immunoglobulin-related cell-cell adhesion molecule that plays a role in the development of the palate, teeth, and skin. The mutations identified in *PVRL1* produce truncated proteins that are thought to interfere with cell-cell adhesion. (FY 2000 through FY 2003)

Ectodermal Dysplasia

Hypohidrotic ectodermal dysplasia results in abnormal development of the teeth, hair, and eccrine sweat glands. Affected children are hyperthermic and have sparse hair, misshapen or absent teeth, and dry skin. Scientists recently identified the gene responsible for the autosomal form of hypohidrotic ectodermal dysplasia. The discovery of the gene, *DL*, located on chromosome 2, was accelerated by the identification of a mutation in a mouse gene ("downless") that resulted in animals with sparse hair and other features that mimic the human disorder. The protein encoded by this gene acts as a receptor and, in fact, may be serving as the receptor for *ED1*, the gene previously identified for X-linked hypohidrotic ectodermal dysplasia. (FY 2000 through FY 2003)

Tooth Agenesis

Congenital anomalies involving missing teeth range in severity from mild hypodontia, to oligodontia (six or more missing teeth), to anodontia (the absence of teeth). The incidence of tooth agenesis disorders varies with each class of tooth, with third molars being the most commonly affected. Oligodontia involving the first and second molars is extremely rare. A recent study has identified a frameshift mutation in the *PAX9* gene that results in an autosomal dominant form of oligodontia. Affected family members have normal primary dentition but lack most permanent molars. Some individuals also lack premolars as well as incisors. *PAX9* is a member of a transcription factor family of genes involved in the formation of the eyes, teeth, palate, and thyroid gland. *PAX9* is now the second developmental gene to be linked to the patterning of dentition. Previously, the homeobox gene *MSX1* was linked to agenesis of the second premolars and third molars. (FY 2000 through FY 2003)

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

Global Network for Women's and Children's Health Research

An RFA was published in March 2000, jointly sponsored by NIDCR and six other NIH Institutes, inviting applications to establish a flexible research network focused on critical global health problems of women and children. International, multidisciplinary teams of investigators will work collaboratively on research questions that are aimed at improving health and preventing premature disease and death among women and children in developing countries. In FY 2001, NIDCR plans to cosponsor one project focused on evaluating treatment interventions to reduce the prevalence of oral clefts in the Philippines.

Mouse Mutagenesis and Phenotyping: Developmental Defects

NIDCR is a participant in this multi-Institute-sponsored RFA that has established a facility in FY 2000 for large-scale mutagenesis and phenotyping of developmental defects in the laboratory mouse. The mouse models produced in this facility are expected to elucidate cellular, molecular, and genetic mechanisms that direct embryonic and post-embryonic growth and function and advance understanding of the mechanisms of human disease, including many rare diseases affecting children.

Center for Inherited Disease Research (CIDR)

NIDCR participation in the CIDR began in February 2000. CIDR is a centralized facility that provides genotyping and statistical genetics services for investigators seeking to identify genes that contribute to

human disease. It is a joint effort supported by several NIH Institutes and the Johns Hopkins University. NIDCR-funded investigators seeking to identify gene mutations that contribute to inherited diseases, including many rare diseases that affect children, can now apply for use of the CIDR genotyping facility.

World Health Organization (WHO) Conference on International Collaborative Research on Craniofacial Anomalies

NIDCR supported an international consensus conference on craniofacial anomalies that was organized by the WHO and held in Geneva, Switzerland in November 2000. This three-day meeting brought together clinicians, epidemiologists, statisticians, and molecular and developmental biologists from around the world. Sessions focused on clinical treatment, genetics, gene/environment interactions, epidemiology, and bioethical issues in medical genetics. Experts described the state of the science and addressed guidelines for standardizing criteria, protocols, and methodologies that are needed to facilitate future global collaborative research efforts in the prevention and treatment of craniofacial anomalies.

Workshop on Strategies for Tooth Structure Regeneration

On May 12, 2000, NIDCR and ORD co-sponsored a workshop on "Strategies for Tooth Structure Regeneration." A variety of rare disorders that affect children are characterized by tooth abnormalities such as missing dentition, early tooth loss, and deformities in tooth structure. These disorders include the ectodermal dysplasias, Van der Woude syndrome, Williams syndrome (WMS), osteogenesis imperfecta (OI) type I, osteopetrosis, and many others. The specific purpose of the workshop was to provide a critical assessment of the state of knowledge in molecular genetics and bioengineering approaches that are essential for developing therapeutic strategies for tooth regeneration. The workshop provided a forum for biomedical researchers, clinicians, and engineers to discuss their vision for solving current obstacles to developing therapeutic strategies.

Workgroup on Genetics and Craniofacial and Dental Anomalies

In Novermber 1999, NIDCR held a workshop to assess the current status of dental, oral, and craniofacial genetics research. A committee of 60 scientists met to identify opportunities and obstacles for genetics research in the NIDCR research portfolio. The workgroup identified 47 heritable disease categories involving craniofacial, oral, and dental manifestations, the majority of which are rare disorders affecting children. The workgroup developed a set of prioritized recommendations for genetic and genomic research activities and resources to be developed during the next five years that will accelerate discoveries of causal gene products and facilitate prenatal diagnoses of these disorders.

Office of International Health Activities on Noma

NIDCR is a Collaborating Center of the International Action Network Against Noma that was launched by WHO in 1994. Noma is a devastating infection of severely protein-malnourished children in which extensive amounts of facial tissues are destroyed. The mortality rate exceeds 80%. The etiology and pathogenesis of the disease remains unknown. To enhance awareness of the disease and discuss research directions, NIDCR sponsored a seminar on international collaborative research on noma in June 1999. NIDCR is funding research on noma at the Forsyth Institute in Boston involving the use of new techniques to identify bacteria in the lesions that currently cannot be cultured. Through a supplement to a Fogarty International Training and Research in Emerging Infections grant to the University of

Maryland, NIDCR is supporting clinical studies to characterize the earliest lesions in noma patients. The results will help identify ways to manage the infection while addressing the nutritional deprivation.

FY 2001 WHO Conference on the Prevention of Craniofacial Anomalies

NIDCR is supporting a consensus conference organized by the WHO entitled, "International Collaborative Studies on the Prevention of Craniofacial Anomalies," which will be held in Utah in May 2001. This WHO meeting will develop recommendations for global activities directed towards the prevention of craniofacial anomalies. The conference will focus on recent evidence that specific maternal vitamin deficiencies are associated with an increased risk of cleft lip and palate and will develop recommendations for the design of intervention trials to determine whether maternal vitamin supplementation will reduce the birth prevalence of clefts. The impact of environmental exposures during pregnancy such as maternal tobacco and alcohol use on the risk of craniofacial birth defects will also be discussed.

Activities with Voluntary Rare Diseases Organizations to Stimulate Research

Skeletal Disorders and Diseases

NIDCR is a participant in an NIH consortium that provides support for the NIH Osteoporosis and Related Bone Diseases National Resource Center. The Center is mandated to increase awareness and knowledge about osteoporosis and related bone diseases and is a partnership between the leading national nonprofit organizations in the field (the National Osteoporosis Foundation, the Paget Foundation, and the Osteogenesis Imperfecta Foundation) and NIH. Adolescent females represent a major at-risk population for future osteoporosis, and they are a key target of several of the Center's programs. Tasks of the Center include expanding the acquisition of research information; promoting the Center to physician and public audiences through exhibits and public service announcements; and disseminating information via electronic methods and print publications to medical and managed care organizations and at-risk populations. The Center also develops partnerships to evaluate model education programs to enhance bone health and reduce future risk of osteoporosis among at-risk populations. (FY 2000 through FY 2003)

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Overview of NIDDK Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NIDDK supports research on many diseases affecting children. Although diseases such as type 1 diabetes, which primarily affects children, and type 2 diabetes, which has become more prevalent in children, are not rare, there are rare single-gene defects that cause diabetes such as maturity-onset diabetes of the young (MODY) and lipodystrophy. Many of the genes causing these disorders have recently been identified.

NIDDK also supports research on kidney and liver diseases in children. Approximately 5,000 children are being treated with dialysis or have a transplanted kidney because of end-stage renal disease (ESRD) and kidney failure; about 60% are 12 years old or younger. Every year, 20,000 babies are born with kidney problems, 2,000 of whom will die, and 1,000 of whom will begin treatment for renal failure. The most common childhood renal problems are genetic renal diseases, kidney and urinary tract malformations, focal segmental glomerulosclerosis, and primary glomerulonephritis.

NIDDK also supports research on genetic metabolic and hematologic diseases such as cystic fibrosis, lysosomal storage diseases, peroxisomal biogenesis disorders, Cooley's anemia, and sickle cell disease. Many of these diseases are rare diseases primarily affecting children.

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

Activities Supported in FY 2000

Lipodystrophy

Lipodystrophy refers to a group of conditions caused by abnormal lipid metabolism and resulting in the reduction or absence of adipose (fatty) tissue. The lipodystrophies may be acquired or inherited, and both the anatomic location and degree of fat loss vary among the different disorders. These conditions are often accompanied by insulin resistance and/or diabetes, elevated levels of blood lipids, and vascular disease. There is a congenital form of the disorder in which the patients have no subcutaneous fat. This year, the gene for this form of lipodystrophy has been localized to 9q.

At puberty, patients with Dunnigan variety familial partial lipodystrophy (FPLD) lose subcutaneous fat from the extremities, trunk, and gluteal regions of the body, while excess fat becomes deposited in the face, neck, and back. In 2000, investigators found that mutations in the lamin *A/C* gene, which was known to cause a form of muscular dystrophy, also caused FPLD. The lamin *A/C* protein is a component of the cell's nuclear envelope. NIDDK-supported researchers detected 4 independent mutations in this gene in members of 14 families. All of the alterations resulting in FPLD occur within a particular region of the lamin *A/C* protein. Mice with a targeted deletion of this gene not only develop a form of muscular dystrophy, but also lack distinguishable white fat, which serves as a valuable source of energy. Collectively, these data imply that mutations within this region of the lamin *A/C* protein are involved in one or more activities required by fat cells in specific tissue beds. It has been hypothesized that in FPLD, loss of fat cells affects insulin sensitivity through reduced levels of "adipocyte-derived circulating factors" such as leptin, a hormone produced by fat cells that regulates food intake and energy

metabolism. A clinical trial has been initiated to determine if the symptoms of lipoatrophy improve with leptin treatment. The clinical trial is planned to continue until 2003.

Polycystic Kidney Disease (PKD)

PKD is a genetic disorder characterized by the progressive development and subsequent growth of numerous cysts in the kidneys. It can be inherited as autosomal dominant (ADPKD) or as autosomal recessive (ARPKD) types. In humans, ADPKD has a later onset and slower development than ARPKD, which usually affects newborns and young children. Most children who survive the neonatal period die from renal insufficiency associated with ARPKD. NIDDK supports a comprehensive research portfolio on PKD, which includes investigator-initiated research programs, more complex program project grants, specialized centers of research in PKD, and a new research program (the CRISP Study), which includes a consortium established to develop and test new or improved radio-imaging techniques to ascertain renal diseases progression in PKD patients. (FY 2000 through FY 2004)

Alport Syndrome

Alport syndrome is an inherited renal disorder characterized by familial occurrence in successive generations of progressive hematuric nephritis, changes in the glomerular basement membrane, and hearing loss. Ocular defects are also commonly associated with Alport syndrome. Male patients have a more severe course. In the autosomal recessive form, the nephritis progresses to early-onset ESRD. In the autosomal dominant type, renal prognosis is better than in the X-linked form, with median renal survival of 51 versus 25 years. Four research programs currently supported under the Pediatric Nephrology Program are looking into the molecular genetic aspects of renal disease progression and the urogenital development of Alport syndrome. (FY 2000 though FY 2005)

IgA Nephropathy

IgA nephropathy is one of the most common primary forms of glomerulonephritis in children worldwide. It was initially considered a benign condition, but in the light of more recent studies and extended follow-up of patients, the overall prognosis remains unclear. Most adult patients continue to have hematuria and 20% to 30% have been found to progress to end-stage renal failure one or two decades after the initial diagnosis. Four research projects currently receive support, the focus being on determinants of the autoimmune process and studies of mechanisms of fibrosis leading to progression to ESRD. An ongoing clinical trial comparing different treatment approaches to halt progression in children and young adults affected with IgA nephropathy should reach completion within the next 12-18 months. (FY 2000 through FY 2004)

Focal Segmental Glomerulosclerosis (FSGS)

FSGS is a common, irreversible glomerular process, with steroid-resistant nephritic syndrome. Complications such as frequently relapsing nephrotic syndrome, generalized edema, cardiovascular problems, thromboembolisms, and progression to ESRD are commonly found and make management difficult, especially in pediatric patients. The risk of disease progression is even greater in African American children. FSGS is one of the most common recurrent renal diseases in children, resulting in new injury to the transplanted kidneys in 20% to 30% of cases and in graft loss in 40% to 50% of the

transplanted children. Three projects are currently supported under the Pediatric Nephrology program, studying the molecular genetic mechanisms of nephritic syndrome in FSGS. (FY 2000 through FY 2005)

Cystic Fibrosis (CF)

CF is the most common fatal genetic disease in Caucasians, affecting approximately 1 in 2,500 newborns. Patients are diagnosed in early childhood, often due to symptoms such as failure to thrive. With management of nutritional problems and infections, the life expectancy for CF has been increased to 30 years. 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. NIDDK supports a research portfolio directed at further defining the molecular mechanisms underlying CF and translating information about the molecular basis of the disease into new treatments. NIDDK also supports several clinical studies investigating ways to improve treatment for CF patients. Two of these studies investigate whether behavioral interventions such as improving eating in children with CF leads to increased weight gain and an improved clinical prognosis.

A pilot newborn screening program was initiated in Wisconsin to identify infants with CF and intervene before the appearance of symptoms. This study is in its 13th year of following these patients. Patients who received treated from birth had increased weight, height, and head circumferences. This study is continuing to follow these patients to determine if early intervention results in improved lung function. Another clinical trial is under way to test whether the prophylactic use of inhaled tobramycin to prevent infections in infants with CF will improve long-term lung function. (FY 2000 through FY 2005)

Lysosomal Storage Diseases (LSDs)

LSDs are a group of disorders that are caused by a missing enzyme, resulting in the accumulation of undegraded material in the lysosome. These disorders are relatively rare but as a group have been estimated to occur in 1 in 5,000 newborns. This group of disorders includes the mucopolysaccharidoses, Batten disease, Krabbe disease, Tay-Sachs disease, and Niemann-Pick disease, all of which are fatal in childhood. NIDDK supports research into several methods of treating these largely untreatable disorders. These methods include:

- Enzyme replacement therapy.
- Substrate deprivation.
- Bone marrow transplantation.
- Gene therapy to replace the defective gene.

Enzyme replacement therapy has effectively treated the adult form of Gaucher disease, which does not involve the brain. The juvenile form of Gaucher disease, like many of the LSDs, however, involves storage of material in the brain that is not corrected because the enzyme cannot penetrate the blood-brain barrier.

Niemann-Pick disease type C (NPC), a lysosomal storage disease, is an autosomal recessive lipid storage disorder characterized by progressive deterioration of the central nervous system, resulting in death in early childhood. Biochemical characterization of cells from NPC patients reveals that patients accumulate large amounts of unesterified cholesterol, resulting in downstream effects on cholesterol homeostasis. The frequency of the disease is estimated at approximately 1 in 105 live births. Defects in

the gene for NPC1 account for approximately 95% of the cases of NPC disease, while defects in the gene for NPC2 account for the remaining cases. Researchers funded by NIDDK have made two important findings in the past year. First, they established that NPC1 can function to transport fatty acids (but not cholesterol) out of endosomes and lysosomes. Second, they found that the protein defective in NPC2 is a widely expressed lysosomal protein that binds cholesterol. These results provide new avenues for investigating the functions of NPC1 and NPC2 in cholesterol transport and homeostasis, which are greatly impaired in children with NPC. (FY 2000 through FY 2005)

Peroxisomal Biogenesis Disorders (PBDs)

Peroxisomes are organelles present in almost all eukaryotic cells that participate in important metabolic processes. In humans, these processes include beta-oxidation of fatty acids; synthesis of bile acids, cholesterol, and plasmalogens; and catalysis of a variety of hydrogen peroxide-producing oxidation reactions. The enzymes responsible for these functions are synthesized in the cytoplasm and are post-translationally imported into the peroxisome where they function. PBDs are a genetically heterogeneous group of rare human diseases caused by an inability to import peroxisomal proteins. The PBDs include Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum disease, and rhizomelic chondrodysplasia punctata. These diseases often result in neurological, hepatic, and renal abnormalities; mental retardation; and death in childhood. Since the peroxisomal import process has been conserved from yeast to humans, investigators have used genetic screens and selection in yeast to identify more than 16 proteins required for peroxisome biogenesis and normal peroxisome import. NIDDK investigators are actively trying to elucidate how these proteins are involved in recognition, targeting, and translocation of proteins into peroxisomes, with the ultimate goal of creating therapeutics to alter the progression of the disease processes in PBDs. (FY 2000 through FY 2005)

Cooley's Anemia

Patients with beta-thalassemia (Cooley's anemia) continue to suffer from the sequelae of transfusion-induced iron overload due to the inadequacies of current iron-chelation therapy. Most of the patients are children and young adults. Compliance with the use of subcutaneous desferrioxamine continues to be a major problem, despite convincing evidence that it markedly reduces morbidity and prolongs life. The full potential of iron-chelation therapy will not be realized until a more effective and more easily administered drug is available. NIDDK is supporting two new clinical studies: one examining tissue damage potentially arising from free iron appearing in the blood immediately after chelator treatment, and a second assessing oral and subcutaneous iron chelation in combination, which is proving to be a more effective therapy than use of individual chelating drugs alone.

On the basis of recommendations from the 1998 NIDDK workshop, "Iron: From Current Biochemistry to New Chelator Development Strategies," a Request for Grant Applications was issued to improve the control of iron transport and metabolism, develop a better understanding of the biological consequences of iron overload, and improve therapy. As a result, several new projects were funded that will increase our understanding of how chelating drugs act and how to use them more effectively. NIDDK is currently conducting preclinical testing of a new iron-chelating drug that will go into clinical studies late in 2001, sponsored by a pharmaceutical company. (FY 2000 through FY 2005)

Hereditary Liver Disease

Research is under way to identify and characterize the molecular bases for two forms of inherited liver disease: cholestasis-lymphedema syndrome (CLS) and familial hyperbileacidemia (FHB). The study will contribute to an overall understanding of the genes and proteins critical for normal liver function. It is also possible that these genes contribute to prevalent adult diseases involving the biliary system such as gallstones. Another study investigates a different inherited form of liver disease, alpha-1-antitrypsin deficiency. In this disease, an abnormal alpha-1-antitrypsin molecule (alpha-1-ATZ) is produced and, as a result of its accumulation in hepatocytes, creates liver damage, leading to cirrhosis and in some cases, cancer. These studies will ultimately allow the investigators to predict susceptibility among alpha-1-antitrypsin-deficient patients and target susceptible hosts for specific pharmacologic interventions. (FY 2000 through FY 2005)

Alagille Syndrome (AGS)

AGS (syndromic bile duct paucity) is a dominant genetic disorder affecting the liver, heart, eyes, vertebrae, and facial structures. Expressivity is highly variable and penetrance is incomplete, making accurate diagnosis and genetic counseling difficult. A number of projects support research in the etiology, pathogenesis, diagnosis, and treatment of this condition, including the study of growth and nutrition in children with this syndrome. (FY 2000 through FY 2005)

Biliary Atresia (BA)

BA is a neonatal liver disorder. NIDDK supports a clinical study seeking to determine the basis of poor growth for children with BA and to ascertain if these patients are likely to benefit from the anabolic and growth-promoting effects of supplemental growth hormone (GH)and/or supplemental nutrition. Although surgical approaches have attempted to correct the anatomic problem, these children typically fail to grow adequately. Ultimately, 70% of these children require liver transplantation, and the most common indication for transplantation is poor growth. Patients have a disturbance of the growth hormone insulin-like growth factor (GH-IGF) axis, along with increased insulin, increased GH, increased IGFBP-1, depressed IGF-I, and depressed IGFBP-3. This pattern of disturbance can be seen with either malnutrition or GH resistance. An interventional study will determine if treatment of children with BA with either recombinant human growth hormone or supplemental nutrition early in the course of the liver disease will correct the alterations of the GH-IGF axis and improve outcomes. (FY 2000 through FY 2004)

Activities Planned for FY 2001 - FY 2005

Conferences

Congenital Disorders of Glycosylation - November 2000
Lipoatrophic Diabetes and Other Syndromes of Lipodystrophy - March 2001
Workshop on Noninvasive Measurements of Iron for Cooley's Anemia - April 2001
Strategies for Therapy of MPS and Related Diseases - June 2001
Society for Inherited Metabolic Diseases - March 2001
Workshop on PKD - 2002

Research Initiatives

Genetic Modifiers of Single-Gene Defect Diseases

NIDDK has joined NHLBI in this initiative to fund studies to identify and characterize the modifier genes responsible for variation in clinical progression and outcome of heart, lung, and blood disease due to single-gene defects. It is anticipated that 18 applications will be funded in FY 2001. NIDDK may reissue this initiative in 2002 and expand it to cover diabetes and metabolic, liver, and kidney diseases.

Polycystic Kidney Disease (PKD) Pilot Clinical Projects

An RFA was recently issued to initiate pilot clinical projects followed with a full-scale clinical trial to improve the management and outcome of disease progression in PKD patients.

Cystic Fibrosis (CF) Specialized Center of Research

This initiative will recompete funding for one CF SCOR. NIDDK plans to fund the successful Center in 2002 through 2007.

Clinical Centers in Focal Segmental Glomerulosclerosis (FSGS)

The goal of this initiative is to establish a consortium of clinical centers and a data coordinating center, in order to participate with NIH in developing and testing treatment interventions to prevent progression of renal disease in FSGS in children and young adults. (Planned for FY 2002 through FY 2007)

Pediatric Clinical Research Centers in Biliary Atresia (BA) and Neonatal Hepatitis

This initiative aims to establish a database of clinical information and serum/tissue samples to expand research into the pathogenesis of these disorders. (Planned for FY 2002)

Database and Registry for Genetic Renal and Genitourinary Patients

The goal of this initiative is to create a registry of well-characterized pediatric urology and nephrology patients with single-gene disorders for basic and clinical studies. (Planned for FY 2002)

National Institute of Environmental Health Sciences (NIEHS)

Overview of NIEHS Rare Diseases in Children Research Activities, FY 2000 - FY 2005

Children are not small adults, but rather young, developing individuals whose physiologic makeup makes them potentially more vulnerable than adults to adverse environmental effects. Chemical exposures that have negligible effects in adults may have devastating effects in infants or children. This enhanced vulnerability of children is due to three factors:

- Organ systems in children are still developing and thus are more susceptible to disruption and damage caused by environmental agents.

- Body mass in children is much smaller than in adults. Compared to an adult, a child consumes more food and water and breathes more air in proportion to his or her body mass. This means children generally receive a proportionally larger dose of toxic agents in contaminated food, water, or air than do adults.

- Common early childhood behaviors such as crawling, putting objects into the mouth, and ingesting dirt put infants and very young children in closer contact than adults with some toxic agents in the environment.

The consequences of childhood effects of environmental toxins can last a lifetime, which makes it imperative to focus on reduction of childhood exposures as a critical component of environmental public policy. NIEHS has traditionally played a pivotal role in shaping public policy in ways that protect the health of children, and the Institute continues to define how environmental exposures affect risks of diseases and disorders such as birth defects, neurological damage, cancers, and asthma. This information will inform policy-makers of changes in safety standards designed to ensure the safety of children.

Recent Scientific Advances in Rare Diseases in Children Research

Tristetraprolin and Related Proteins in Inflammatory Diseases

One major area of study in the laboratory began with the cloning of a gene that was rapidly induced by insulin. The protein encoded by this gene, known as tristetraprolin, is the prototype of a novel class of CCCH zinc finger proteins. Tristetraprolin is rapidly induced, translocated from the nucleus to the cytosol, and phosphorylated on serine residues by insulin and by many other mitogens and growth factors. Mice deficient in this protein develop a complex syndrome consisting of arthritis, wasting, dermatitis, and early death.

During the past year, NIEHS scientists demonstrated that tristetraprolin deficiency in mice also led to increased stability of the mRNA-encoding granulocyte-macrophage colony stimulating factor (GM-CSF), a cytokine important for maintenance of the normal white blood cell count. Studies in cell-free systems and in cultured cells are under way to identify inhibitors of this interaction, which might be useful therapies for neutropenic states. Concerning the mechanism of action of tristetraprolin and its relatives, NIEHS reported that these proteins can destabilize certain mRNAs, even when those mRNAs do not contain polyA tails, indicating that initial deadenylation is not required for subsequent mRNA

degradation. "Rules" that govern the binding of this novel class of RNA-binding proteins to its target sequences were established. Finally, researchers identified a number of protein-coding polymorphisms and one non-expressing mutation in the human gene-encoding members of this family of proteins. Studies are under way to determine the biochemical and clinical significance of some of these variants. (FY 2000 through FY 2005)

Effect of Diet on Occurrence of Chronic Disease

Diet may affect the risk of several chronic human diseases. This research project has two main foci: 1) the study of diet-cancer relations and 2) the study of diet in relation to risk of amyotrophic lateral sclerosis (ALS).

Defects in antioxidant defenses (e.g., superoxide dismutase 1 [SOD1]) are a cause of ALS, and thus it is reasonable to suspect that antioxidant intake may also affect the incidence or progression of this disease. One research focus on diet and ALS has been an analysis of dietary data from a case-control study of ALS. NIEHS examined the dietary intake of calcium, magnesium, and antioxidants among 107 ALS cases and 262 community controls. Overall, these dietary factors were not related to risk of ALS, though modestly protective associations were suggested for magnesium and lycopene.

A second study of the same relationship is an add-on to a large cohort study under way at NCI. The cohort consists of members of the American Association of Retired Persons (AARP) who have completed a dietary questionnaire (approximately 600,000 people). Researchers expect approximately 150 cases of ALS to develop in this cohort by 2002. (FY 2000 through FY 2005)

Systemic Lupus Erythematosus (SLE)

SLE is a severe, disabling autoimmune disease. Approximately 90% of lupus patients are women. Although few studies provide detailed data pertaining to the prevalence of this disease, conservative estimates indicate that 100,000 women in the United States are living with SLE. Researchers recently finished data collection in the Carolina Lupus Study, the largest population-based case-control study of hormonal and environmental risk factors for the development of SLE conducted to date. Four specific analyses based on these data were presented at the annual meeting of the American College of Rheumatology in 1999 and 2000. These analyses include hormonal and reproductive risk factors, medical history risk factors (i.e., allergies, infections), occupational silica dust exposure, and demographic differences in the clinical and immunologic presentation of the disease. Manuscripts for these and other analyses have been submitted for publication. (FY 2000 through FY 2005)

Friedreich's Ataxia (FRDA)

FRDA is the most common cause of recessive ataxia and occurs at an incidence of 1 in 30,000 Caucasians. The yeast homologue of the **FRDA** gene, *YFH1*, which codes for the protein frataxin, is responsible for regulating the amount of iron in the mitochondria. The absence of frataxin leads to iron accumulation and the production of radicals. NIEHS scientists have established that frataxin limitation leads to nuclear as well as mitochondrial DNA damage. This novel finding has implications for the pathological symptoms associated with the disease and potential treatment strategies. It also has many implications for possible origins of aging and cancer. (FY 2000 through FY 2005)

Lung Hemorrhage in Cleveland, Ohio Infants

Over the past five years a relatively rare disorder, acute pulmonary hemosiderosis, or hemorrhage, has been found in a large number of infants in inner-city Cleveland. There have been 37 cases in a limited area of Cleveland resulting in 12 deaths, including 7 deaths originally thought to be due to sudden infant death syndrome (SIDS). The environmental mold *Stachybotrus chartarum* has been identified as the causative agent, with the young child's developing lung being particularly vulnerable. NIEHS is supporting a pilot study that will allow a local physician to further define the environmental components for a condition that has a 30% mortality rate and is disproportionately affecting inner-city children. The researchers have identified environmental tobacco smoke as a possible trigger for the acute bleeding. Additionally, the research has led to the development of a home remediation program that completely eliminates the mold spores from contaminated homes. (FY 2000 through FY 2005)

Diethylstilbestrol (DES)

Once used by pregnant women to prevent miscarriage, the potent synthetic estrogen DES was shown to cause health problems in women exposed to DES in utero ("DES daughters"). These women were at risk of developing clear cell adenocarcinoma, a rare vaginal cancer, as well as having reproductive abnormalities. To date, "DES sons" have shown increased reproductive tract abnormalities but not an increased cancer risk, although this is a possibility as the population ages. A recent NIEHS study shows the unexpected, that the environmental exposures of one's parents and grandparents can have adverse effects on our own health, even if we have never been directly exposed to a particular compound.

Although this multi-generational effect has only been demonstrated with DES, it suggests new avenues of investigation for assessing the many "environmental estrogens" that have been developed. Although these compounds have a far weaker estrogenic effect than DES, the possibility exists that subtle adverse effects could show up in our sons, daughters, grandsons, and granddaughters. More immediately, this research proves that the sons of "DES daughters" need to be closely monitored by their physicians. (FY 2000 through FY 2005)

Incontinentia Pigmenti (IP)

IP is a genetic disorder characterized by unusual patterns of discolored skin. Males with this disorder usually die before birth, so females are the major patient group. In rare cases, IP can cause developmental abnormalities such as dwarfism and club foot. NIEHS studies have definitively linked IP with deficiency of IKKγ/NEMO expression. This connection provides additional evidence for the importance of the IKK complex and NFκB for prevention of programmed cell death in mice and in humans. IKKγ/NEMO-deficient mice can be used as a model for studying IP, which will help women with IP to make more informed reproductive decisions. (FY 2000 through FY 2005)

<u>Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children</u>

Refsum's Disease

NIEHS scientists are studying phytol metabolites, which are activators for the nuclear receptor RXR. Patients with Refsum's disease accumulate the metabolite phytanic acid to levels that are approximately

100 times normal values. Since it is alleged that phytanic acid has its sole origins from the diet, NIEHS is examining the effects of its removal from the diets of rodents. (Through FY 2001)

SGD Syndrome

Lactoferrin is an antibacterial and antiviral protein. It is the major protein in the specific granules of the neutrophils. The only genetic disease linked to lactoferrin is SGD syndrome, in which patients lack the specific granules in neutrophils. SGD is characterized by lactoferrin deficiency with recurrent infections. Defects in lactoferrin gene expression and function in children due to either genetic or regulatory means could cause recurrent infections, as shown in SGD syndrome. (At least through FY 2005)

Friedreich's Ataxia (FRDA)

FRDA is an autosomal recessive neurological disease that affects mitochondrial iron homeostasis. Deletion of the yeast homolog of this gene causes mitochondrial iron accumulation and a petite phenotype. Experiments have indicated nuclear DNA damage in yeast by reactive oxygen species. These experiments therefore have implications in the treatment of this disease and establish a novel paradigm of mitochondrial proteins having a nuclear-protective role. (At least through FY 2005)

Ataxia Telangiectasia Cancer

This research effort investigates the molecular mechanisms involved in cell cycle checkpoint responses to exposures to ionizing radiation (IR) and other environmental agents in both normal human fibroblasts and fibroblasts that lack normal function of the ataxia telangiectasia cancer susceptibility gene products. Researchers are interested in the role of the ataxia telangiectasia mutated (ATM) gene product in cell cycle checkpoint responses to exposures to environmental carcinogens and the signaling pathways that are generated from broken DNA to the inactivation of cyclin/CDK protein kinase complexes. In addition to aiding the understanding of the process of carcinogenesis, these studies hold great potential for providing insight into the mechanism of action of non-genotoxic environmental carcinogens. By understanding the underlying pathways impacted by the lack of ATM function in ataxia telangiectasia syndrome, it may be possible to design therapeutic approaches that will be able to prevent or minimize the devastating accompanying pathologies, such as the death of Purkinje cells and immune defects, in affected individuals. (At least through FY 2005)

Nijmegen Breakage Syndrome (NBS)

NBS is a rare autosomal recessive disorder characterized by increased sensitivity to IR, defective cell cycle checkpoint responses, and elevated cancer incidence. Both NBS and a related ataxia telangiectasia-like disorder are caused by mutations in the chromosomal DNA repair genes *hNBS1* and *hMRE11*, respectively. Functional homologs of the human genes, referred to as *XRS2* and *MRE11*, are present in the genetically tractable budding yeast *Saccharomyces cerevisiae*. NIEHS scientists and others have demonstrated that these genes perform similar functions in both yeast and human cells, leading to the view that the *MRE11* and *XRS2* proteins are components of a complex with DNA ex- and endonuclease activities. The nuclease function has been found to be critical for repair of broken chromosomal DNA by homologous recombination, but not for recombination-independent mechanisms of repair performed by the complex. In addition, these proteins may be important in dealing with categories of double-strand

breaks that differ from those induced by IR. This information will be useful in understanding consequences of the genetic defect. (At least through FY 2005)

DNA Triplet-Repeat-Based Diseases

There are more than 14 rare neurological and neuromuscular diseases (including Haw River syndrome, affecting a small group of African American families in North Carolina) that result from the expansion of triplet-repeat DNA sequences. NIEHS scientists are investigating the underlying systems responsible for triplet-repeat expansion and have proposed a molecular model in which triplet expansion is due to a deficiency of 5'-flap cleavage during DNA replication. In particular, the interaction of the human enzyme responsible for 5'-flap cleavage (*FEN1*) with other components of DNA metabolism (such as proliferating cell nuclear antigen [PCNA] and DNA polymerases delta and epsilon) is being addressed genetically.

Researchers have now established that the nuclease function of the replication protein DNA polymerase delta may also play an important role in processing replication intermediates. During lagging strand synthesis, a replication intermediate is created that must be processed by either DNA polymerase delta or the *FEN1* nuclease. The lack of processing is proposed to lead to a double-strand break that may be instrumental in triplet-repeat expansion. This research will provide further understanding of how the disease might arise and the possible consequences of variations in the relevant DNA metabolic proteins. (At least through FY 2005)

National Eye Institute (NEI)

Overview of NEI Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NEI was created on August 16, 1968 by Public Law No. 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. Children are our nation's greatest resource, and protecting their visual health and preventing eye diseases that afflict them with permanent visual impairment will help maintain our nation's prosperity and security in the future. Over the years, vision researchers supported by NEI have conducted many pioneering studies that have greatly advanced our understanding of eye diseases, including those classified as rare, and have provided eye-care professionals with new tools and methods to prevent or cure many sight-threatening conditions.

Recent Scientific Advances in Rare Diseases in Children Research

Leber's Congenital Amaurosis (LCA)

In 1869, Theodor Leber described an early-onset recessive retinal degeneration that caused incurable blindness in children. This disease became known as Leber's congenital amaurosis (LCA). For many childhood genetic diseases like LCA, no treatment is currently available; the necessary gene is either missing or defective. With recent advances in our understanding of the basis for genetic diseases, scientists have been able to identify defective genes that are associated with specific diseases. Once the gene is identified, however, the patient is still faced with the prospect of no immediate cure. Such was the case for LCA, when in 1997 the disease-causing mutations in a gene known as *RPE-65* were linked to an estimated 10% of LCA cases. Recently, NEI scientists have produced mice lacking the *RPE-65* gene. The absence of the *RPE-65* gene produces a defect in the visual cycle, a series of biochemical events in the light-sensing retina that initiate vision. The defect eventually results in impairment of photoreceptor cell function and retinal degeneration. In order to better understand the function of *RPE-65*, scientists studied the individual components of the visual cycle pathway and found that *RPE-65* is involved in a biochemical reaction called an isomerization. Thus, the analysis of mice lacking *RPE-65* allowed scientists to focus on the possible function of this molecule. Next, a way was found to bypass the defect in the visual cycle. For this, *RPE-65*-deficient mice were fed a form of vitamin A called 9-cis-retinal. This chemical is not normally found in photoreceptor cells, but it forms part of the functional visual pigment isorhodopsin. The resulting improved photoreceptor physiology and function were dramatic.

Administration of compounds like 9-cis-retinal for LCA is an example of a pharmacological intervention that could restore vision and relieve the suffering and burden caused by some blinding diseases. Animal studies with 9-cis-retinal have opened the door to studies in humans that may contribute to the development of improved treatments for retinal degenerative diseases such as LCA.

Dramatic progress toward finding a cure for LCA was recently reported by NEI-supported scientists. These scientists conducted experiments in which they successfully restored vision in a naturally occurring large animal model (dog) of LCA that suffers from visual impairment typical of that seen in children with LCA. The researchers inserted a wild-type *RPE-65* gene into the retina of a dog using recombinant adeno-associated virus (AAV) as a vector. While this research shows great promise, there is still much work to be done before gene therapy can be used to treat human patients with LCA.

NEI has funded research on LCA from the Institute's inception and will continue to fund research on this disorder through FY 2005.

Retinopathy of Prematurity (ROP)

Many premature infants need supplemental oxygen soon after birth because their lungs are not sufficiently mature to efficiently bring oxygen into their bodies. Researchers have long known that supplemental oxygen, while helping infants survive, might increase cases of retinopathy of prematurity (ROP). ROP develops in very premature infants when abnormal blood vessels grow and spread throughout the retina. The scarring and bleeding caused by the excess growth of these blood vessels can lead to retinal detachment, resulting in vision loss. ROP develops in 14,000-16,000 infants each year who weigh less than 2¾ pounds (1,250 grams) at birth. In most cases (80%), the disease improves and leaves no permanent damage. However, 1,100-1,500 infants annually develop ROP that is severe enough to require surgical treatment, which usually will stop the growth of abnormal blood vessels and prevents retinal detachment. Even with these therapies, about 400-600 infants with ROP become legally blind each year.

Recent research had suggested that controlled amounts of supplemental oxygen keeps ROP from progressing from moderate to severe. If controlled amounts of supplemental oxygen could help prevent the progression of ROP, then infants could avoid this threat to their sight and consequently the invasive surgery for severe ROP, with its possible long-term side effects. In order to test the safety and efficacy of providing infants supplemental oxygen, NEI supported the Supplemental Therapeutic Oxygen for Pre-threshold ROP (STOP-ROP) study. Researchers found that while modest supplemental oxygen given to premature infants with moderate cases of ROP may not improve ROP outcomes, it definitely does not worsen outcomes. Although the relative risk/benefit of supplemental oxygen for each infant must be individually considered, clinicians need no longer be concerned that supplemental oxygen, as used in this study, will worsen pre-threshold ROP.

NEI has funded research on ROP from the Institute's inception and will continue to fund research on this disorder through FY 2005.

Aniridia

Early eye development of the vertebrate lens is controlled by specific genes that operate in a hierarchy of expression. The first of these genes to be identified was *Pax-6*. Mutations in *Pax-6* are responsible for causing aniridia, a congenital malformation of the eye in which the iris is not completely formed, resulting in cataract formation and congenital glaucoma. Subsequent to this discovery, *Pax-6* expression was found in other embryonic tissue, including the tissues destined to form the nose, suggesting its more general involvement in craniofacial development. The significance of *Pax-6* as a key developmental regulator has been substantiated in a number of experimental systems, most notably mouse and *Drosophila*, and its protein product is now characterized at the structural and functional levels. Researchers now view *Pax-6* as a "master gene" controlling the expression of downstream genes during development. Recent studies have described a number of genes downstream of *Pax-6* that may play a significant role in eye formation. As these genes and their products are characterized, the developmental hierarchy controlling ocular and more generally craniofacial development will be pieced together to form a picture of the developmental process and enhance our understanding of the molecular basis of early eye developmental defects such as aniridia.

NEI has funded research on aniridia from the Institute's inception and will continue to fund research on this disorder through FY 2005.

X-linked Juvenile Retinoschisis

Juvenile retinoschisis is a degenerative X-linked recessive retinal disorder that gradually robs the patient of useful vision. The disease is characterized by the formation of a cystlike structures on the retina. Though not usually diagnosed until children start school, visual acuity is often reduced to 20/200 by the time the child reaches puberty. The disease symptoms are similar to those of macular degeneration, and in fact, most cases of juvenile macular degeneration are caused by retinoschisis. Peripheral vision is also affected by retinoschisis. Other complications associated with juvenile retinoschisis are strabismus, nystagmus, retinal detachment, and massive vitreous hemorrhages.

Researchers funded by NEI have localized the molecular defect of retinoschisis to the *XLRS1* gene. These scientists have reported finding 23 different *XLRS1* gene mutations in 28 patients affected by this disorder. Additionally, these researchers have demonstrated that molecular screening for retinoschisis is an effective diagnostic tool in at-risk males.

NEI has funded research on X-linked juvenile retinoschisis from the Institute's inception and will continue to fund research on this disorder through FY 2005.

Retinoblastoma (RB)

RB is mainly a disease of childhood and is now one of the best understood of all solid tumors. Ninety percent of individuals who inherit specific mutations in the RB gene will develop the tumor. Each year, 300 to 400 new cases of RB are diagnosed in the United States. Unfortunately, the most prevalent treatment for RB at this time is surgical removal of the affected eye. Scientists supported by NEI have recently published results of experiments that were undertaken to determine the toxicity and dose-response of vitamin D3 for the treatment of retinoblastoma. An analogue of vitamin D3 has been shown to inhibit growth of RB tumors in transgenic mice. The results of this research showed that in transgenic mice, it was possible to achieve an effective dose of the vitamin D3 analog that had no systemic toxicity.

NEI has funded research on RB from the Institute's inception and will continue to fund research on this disease through FY 2005.

<u>Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children</u>

NEI will continue to fund high-quality investigator-initiated research on the prevention, etiology, pathology, and clinical intervention of rare childhood diseases that cause visual impairment and disability.

Rare Diseases-Related Program Activities, FY 2003 - FY 2005

For more than 20 years, NEI and the National Advisory Eye Council (NAEC), through the Vision Research Program Planning Subcommittee, have attempted to meet their stewardship responsibilities through a comprehensive planning process. The process has resulted in the development and publication of a series of strategic plans addressing the most pressing visual health needs of the nation. To this end,

the vision research community, the medical scientific research community at large, and NEI will pursue the highest-quality research to attempt to achieve the established goals of this plan, including better prevention, early diagnosis, and safe, effective treatments of rare diseases and disorders in children. NEI will continue, with the advice and guidance of the NAEC, to invest in the very best investigator-initiated research through FY 2005 and well beyond to protect our nation's children from the consequences of blinding rare diseases.

The NAEC and NEI have established the following goals for rare disease research in *Vision Research: A National Plan 1999 - 2003:*

- Identify novel causes of inherited retinal degenerations; further examine the cellular and molecular mechanisms whereby identified gene defects cause retinal degenerations.
- Further develop and critically evaluate therapies involving gene delivery, growth factors, and transplantation for the treatment of retinal disease.

National Institute of General Medical Sciences (NIGMS)

Overview of NIGMS Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NIGMS supports broad-based fundamental research that is not targeted to any specific organ system or disease. In general, support of investigations related to specific diseases, unless of wide applicability across disease or organ system lines, is not the responsibility of NIGMS, but rather would be assigned to one of the categorical Institutes.

NIGMS does not provide support specifically for rare diseases in children but does provide funding for the Human Genetic Cell Repository, which provides a valuable resource for investigators studying genetic disorders, many of which affect children. The Repository, located at the Coriell Institute for Medical Research in Camden, New Jersey collects, characterizes, maintains, and distributes cell lines from patients and families with a wide variety of genetic disorders and from normal persons whose tissues serve as controls. More than 6,600 cell lines representing more than 500 different diseases 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 are not otherwise readily available. Among the cell lines requested most frequently in the last year are those that affect children, such as ataxia telangiectasia, xeroderma pigmentosum, cystic fibrosis (CF), Bloom syndrome, fragile X-linked mental retardation, Nijmegen breakage syndrome (NBS), Cockayne syndrome, and glycogen storage disease.

Recent acquisitions for the collection include samples from patients with the following rare disorders: ceroid lipofuscinosis, Rett syndrome, **Friedreich's ataxia (FRDA)**, glutaric acidemia, atransferrinemia, factor X deficiency, and immuno-osseous dysplasia. 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 samples with characterized trinucleotide expansions from patients with fragile X and characterized mutations in Bloom syndrome, hemochromatosis, and CF.

The Institute has no specific plans at this time to support additional research directly relevant to rare disease in children as NIGMS primarily supports investigator-initiated research, which will largely determine the research portfolio.

Recent Scientific Advances in Rare Diseases in Children Research

Carbohydrate-Deficient Glycoprotein Syndromes (CDGS)

CDGS are a collection of human metabolic disorders that involve the absence or inappropriate addition of sugar residues to proteins, as they are made in the cell. The majority of these disorders result in neurological impairment with mental and psychomotor retardation. NIGMS provided approximately $850,000 in support of CDGS research in FY 2000. One CDGS project is currently funded through FY 2002, and one project is soon to receive funding for a competitive renewal through FY 2005.

Two NIGMS-supported investigators have been instrumental in identifying defects in the metabolism of the sugars that result in CDGS. One researcher has demonstrated that the sugar mannose, rather than

glucose, is imported into the body's cells from the bloodstream and is used as the primary source of sugar in human glycosylation. Additionally, this researcher has discovered the specific membrane protein that transports mannose into the cell. Initial results of a clinical trial suggest that one form of CDGS can be reversed by daily oral administration of mannose to increase the blood serum levels of this sugar and improve the import of this sugar into the cell for use in glycosylation of proteins.

Another NIGMS-supported researcher is examining a second form of CDGS. Leukocyte adhesion deficiency II (LADII) syndrome, a member of the CDGS group of disorders, is a syndrome in which reduced amounts of the sugar L-fucose are incorporated into glycoconjugates. The syndrome results in severe growth and mental retardation, unusual facial appearance, and recurrent infection. Initial evidence suggested LADII is caused either by a defect(s) in fucose biosynthesis, the conversion of GDP-mannose to GDP-fucose in the cell, or a defect in the transport of fucose into the lumen of the Golgi apparatus for use in glycosylation of proteins. The researcher has identified, purified, and characterized a protein that transports fucose into the Golgi of the cell and is attempting to clone the gene for this transporter to facilitate its further study.

National Heart, Lung, and Blood Institute (NHLBI)

Overview of NLBI Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NHLBI provides leadership for a national program in the causes, diagnosis, treatment, and prevention of diseases of the heart, blood vessels, lungs, and blood, and in the uses of blood, and the management of blood resources. NHLBI's mission also includes investigation and treatment of sleep disorders. While the major part of the research supported by 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.

Recent Scientific Advances in Rare Diseases in Children Research

NHLBI activities related to rare disease research in children in FY 2000 are described below.

Heart and Vascular Diseases Program

Abetalipoproteinemia

Abetalipoproteinemia is a rare congenital disorder that prevents the body from producing low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and chylomicrons. Individuals with this condition are unable to digest fats properly. In FY 2000, NHLBI-supported studies directed at understanding abnormal synthesis of apolipoprotein B (apoB), the major protein in LDL, found that the amount of microsomal triglyceride transfer protein (MTP) may determine apoB levels.

Antiphospholipid Syndrome (APS)

Patients with APS have circulating autoantibodies to certain phospholipids (lipids containing phosphorus), chiefly cardiolipin, as well as the lupus anticoagulant. Recent findings provide strong support for the involvement of antiphospholipid antibodies in atherogenesis. Autoreactive antibodies were found to form against phospholipid components of dead or dying (apoptotic) cells and then were found to cross-react with normal vascular constituents that are produced in response to environmental stimuli, including bacteria. In other studies, small differences in a common lipid carrier protein appeared to be genetically linked to APS as well as to atherosclerosis.

Arrhythmogenic Right Ventricular Dysplasia (ARVD)

ARVD is a family of rare cardiomyopathies that result in sudden cardiac death and malignant heart rhythm disturbances, including fibrillation. NHLBI investigators have reported on the localization of a mutation to chromosome 10p12-14 in one family with a common congenital form of ARVD.

Bartter's Syndrome

Bartter's syndrome, a rare autosomal recessive disease, typically manifests itself through salt imbalance and low blood pressure. A NHLBI-supported investigator has found that the disease is genetically heterogeneous. In addition to the mutation on the Na-K-Cl co-transporter, mutations on potassium and

chloride channels have been discovered, and there are indications that additional Bartter's genes remain to be found. The hypotensive state of Bartter's syndrome suggests that these mutated genes protect against the development of high blood pressure.

ß-sitosterolemia

ß-sitosterolemia is a rare genetic disease characterized by increased absorption of dietary cholesterol and plant and shellfish sterols that entails an increased risk of premature cardiovascular disease. In FY 2000, NHLBI intramural scientists established the genetic defect in ß-sitosterolemia as a defect in either the ABCG5 or ABCG8 transporters present in the enterocyte and liver.

Brugada's Syndrome

Brugada's syndrome is a rare inherited disorder characterized by cardiac electrophysiological abnormalities, specifically right bundle branch block and ST elevation in the precordial leads, and is associated with a high occurrence of sudden cardiac death. One group of NHLBI-supported investigators has identified a second site on chromosome 3 associated with Brugada's syndrome and has extensively characterized cardiac electrical abnormalities in families with this mutation.

Congenital Heart Disease

Congenital heart disease affects approximately 8 in 1,000 live-born infants, or approximatley 32,000 per year in the United States, making it the most common birth defect and an important cause of infant mortality, pediatric and adult morbidity, and shortened adult life expectancy. In 2001, two NHLBI-supported researchers reported discovery of a genetic abnormality associated with congenital heart defects in mice. Other researchers have been able to develop high-resolution ultrasound imaging for the characterization of hemodynamic function in the developing mouse embryo and have shown that mutations in a single human gene, *Nkx2.5*, are responsible for a variety of structural congenital cardiovascular malformations, some of which are also associated with arrhythmias.

DiGeorge Syndrome

DiGeorge syndrome is characterized by many abnormalities, including cardiac outflow tract anomalies, hypoplasia of the thymus and parathyroid glands, cleft palate, and facial dysmorphogenesis. Recent studies in mice implicate the transcription factor *Tbx1* as a key candidate gene for the cardiac outflow tract defects seen in DiGeorge syndrome.

Doxorubicin Cardiomyopathy

Doxorubicin cardiomyopathy is a serious side effect of using the potent, broad-spectrum antitumor agent doxorubicin (brand name: Adriamycin) in treating a variety of cancers, including solid tumors and leukemia. NHLBI-supported investigators have demonstrated that doxorubicin selectively deregulates the expression of cardiac-specific or cardiac-restricted genes by depleting the levels of tissue-specific transcription factors and co-factors, resulting in disruption of normal cardiomyocyte function. Another investigator found that mitochondrial changes seem to contribute to the progressive inability of cardiac tissue to tolerate metabolic stress, particularly when associated with induction of the membrane permeability transition pore by doxorubicin.

Dysbetalipoproteinemia

Dysbetalipoproteinemia is a rare disorder with a strong heritable component characterized by the presence of beta-migrating VLDL. The disorder leads to formation of characteristic yellow skin plaque (xanthomas) and predisposes to early ischemic heart disease and peripheral vascular disease. A mutant form of the protein apoprotein E (apoE2) has been identified as the primary molecular defect. In FY 2000, NHLBI-supported investigators demonstrated that apoE2 has a significantly higher half-life (an indicator of the time the protein spends in the cell) than apoE3 and apoE4.

Familial Hypertrophic Cardiomyopathy (FHC)

FHC is associated with myofibrillar disarray in the heart muscle, which leads to hypertrophy (enlargement of the heart). Using a genetically engineered animal model for FHC, one NHLBI-supported investigator has decreased hypertrophy and fibrous tissue by using Losartan, an angiotensin II blocker. The same investigator has successfully used Doppler myocardial tissue imaging on the transgenic rabbit model of human hypertrophic cardiomyopathy (HCM) to detect those afflicted with FHC before hypertrophy develops. A second investigator has produced two genetically engineered mouse models of FHC. Each model has a single-site mutation comparable to mutations observed in humans with FHC.

Familial Hypobetalipoproteinemia (FHBL)

FHBL is an apparently autosomal dominant disorder of lipid metabolism characterized by very low levels of apoprotein B-containing lipoprotein cholesterol. A newly identified genetic susceptibility for FHBL has been identified on chromosome 3 (p21.1-22), which has been narrowed down to an area containing three potential candidate genes.

Infectious Myocarditis

Infectious myocarditis, which affects both children and adults, is an inflammation of the heart muscle that sometimes leads to progressive heart failure and the need for heart transplantation. Using a primate model infected with simian immunodeficiency virus (SIV), a virus similar to HIV, a NHLBI-supported investigator has made a critical discovery regarding the pathogenesis of AIDS-related cardiac dysfunction, namely that cardiac myocytes are not the target for SIV. Instead, the virus may be infecting cardiac dendritic cells or monocytes, both of which bear the CD4 receptor required for viral infection. Another investigator studying the effects of a soluble viral regulatory factor called Tat has found that Tat-mediated changes may create a pro-inflammatory stimulus, thereby increasing the morbidity of HIV infections.

Liddle's Syndrome

Liddle's syndrome is a rare autosomal dominant disorder of severe hypertension. A diagnostic test for Liddle's syndrome has been developed by one of the NHLBI Specialized Center of Research (SCOR) programs on Molecular Genetics of Hypertension. In order to study the responsible mechanism, the same SCOR has developed a mouse model that develops high blood pressure, metabolic alkalosis, and hypokalemia accompanied by cardiac and renal hypertrophy, very similar to a human form of 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, and thus represents the first potential digenic (reproduced in alternate generations) model for hypertension.

Long QT Syndrome (LQTS)

LQTS is characterized clinically by a prolonged QT segment on the cardiac electrocardiograph that is associated with syncope, ventricular arrhythmias, and, frequently, sudden cardiac death. This family of conditions is thought to be caused by alterations in the cardiac cell action potential induced by mutations in at least six cardiac ion channel genes. NHLBI investigators recently summarized the functional and clinical consequences of the various ion channel deficiencies that have been discovered. Their report includes suggestions that mutations in calcium, sodium, and potassium channels may all cause similar cardiac electrical abnormalities, and that sodium channel inhibitors may be useful in treating patients with one form of the disease. Studies of clinical symptoms and their respective mutations are producing data that may be useful in identifying and treating patients with different forms of the disease. Pharmacogenetic studies on mutations involved in acquired LQTS have also provided information important in identifying, and removing from the U.S. drug market, a number of prescription and over-the-counter drugs that increase susceptibility to sudden death by these same mechanisms.

Niemann-Pick Type C (NPC) Disease

NPC disease is an autosomal recessive lipid-storage disorder usually characterized by hepatosplenomegaly (enlargement of the liver and spleen) and severe progressive neurological dysfunction. In 2001, a putative cholesterol sensor in the plasma membrane that affects cholesterol trafficking into and out of cells was further characterized.

Smith-Lemli-Opitz (SLO) Syndrome

SLO syndrome is an inherited disorder caused by a defect in the enzyme involved in cholesterol biosynthesis. NHLBI-supported investigators this year improved the commonly used diagnostic and screening tests for SLO by improving the separation of accumulated unsynthesized cholesterol and thus achieved a more accurate determination of its concentrations in blood and other biological fluids such as amniotic fluid.

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. Recently, efforts by an NHLBI-supported investigator to understand the role of the ABCA1 transporter protein in intracellular cholesterol trafficking led to the finding that its cellular location was in areas distinct from the lipid-rich plasma membrane domains called rafts. Furthermore, the cholesterol transported out of the cell by ABCA1 does not appear to be from these lipid-rich rafts.

Williams Syndrome (WMS)

WMS is a rare genetic disorder characterized by a constellation of features, including mental retardation, aberrant cranial shape, unusually gregarious personality, premature wrinkling of the skin, dysmorphic facial features, and supravalvular aortic stenosis (SVAS; a congenital narrowing of the ascending aorta).

A NHLBI-supported study has established the elastin gene (*ELN*) as the locus for SVAS in both inherited and sporadic cases.

Lung Diseases Program

Advance Sleep Phase Syndrome (ASPS)

ASPS is a genetically based sleep disorder characterized by early evening onset of sleep and spontaneous early awakening with normal sleep duration. ASPS was linked to a variant of the biological clock gene, hPer2 (HL59596) using linkage analysis of a single family in which many related individuals exhibited a large 4-hour advance of sleep, temperature, and melatonin rhythms. Genetic studies identified a single base mutation that alters the ability of hPer2 to interact with other components of the biological clock. The hPer2 mutation linked to ASPS is hypothesized to advance the biological clock by accelerating the accumulation of other gene products composing the biological clock.

Bronchopulmonary Dysplasia (BPD)

BPD is a chronic lung disease characterized by disordered lung growth, with changes in cell size and shape and a reduction in the number of alveolar structures available for gas exchange. Recent progress by the NHLBI Collaborative Program for Research in BPD includes identification of a new marker (bombesin peptide) that is predictive for the development of BPD and will enable infants at particular risk for the disorder to be identified. Other results indicate that early delivery of a recombinant antioxidant enzyme to human infants at high risk for BPD may reduce lung injury. Delivery of a synthetic antioxidant has also been found to be prophylactic against the development of BPD.

Cystic Fibrosis (CF)

CF is a multi-system disease characterized by defective transport of chloride and sodium across the cell membrane. *Pseudomonas aeruginosa* is the main cause of chronic lung infection leading to lung failure in individuals with CF. NHLBI-supported studies are providing insight into how *Pseudomonas* endures for long periods in the lung and how it can be controlled. The bacteria were recently shown to form, through a process called quorum-sensing, a protective outer layer, or biofilm, on the lungs of CF patients, serving to protect the bacteria from conventional antibiotics and the body's natural immune responses. The biofilm allows the bacteria to remain in the CF lungs, causing life-long *Pseudomonas* infections. Recently, NHLBI-supported research found that xylitol, a non-ionic osmolyte that lowers salt concentrations without providing an energy source for bacteria, may provide an important new therapeutic to prevent or slow the onset of bacterial infection in CF.

Lymphangioleiomyomatosis (LAM)

LAM is a rare lung disease that affects girls and women from puberty through menopause. Symptoms develop as the result of proliferation of atypical, non-malignant smooth muscle cells in the lungs. A prospective study within the NHLBI Intramural Program discovered that mutations in the tuberous sclerosis complex gene *TSC2* can cause pulmonary LAM. In another scientific advance, an immunohistochemical analysis suggests that the production of proteins that inhibit cell death in LAM cells may be controlled by estrogen and progesterone. NHLBI ORWH support a national LAM Patient Registry that by the end of FY 2000 had enrolled more than 200 LAM patients.

Persistent Pulmonary Hypertension of the Newborn (PPHN)

In PPHN, inappropriate muscularization of fetal pulmonary vessels prevents the lung arteries of affected newborns from dilating after birth and thus interferes with normal blood flow to the lung. A NHLBI SCOR on the Pathobiology of Lung Development has demonstrated that treatment of neonatal rats with the synthetic adrenocortical steroid dexamethasone causes lung hypoplasia, decreases alveolization, and results in an increase in the development of subsequent pulmonary hypertension. The results demonstrate the importance of temporospatial relationships in the coordination of vascularization and cardiopulmonary development and the limits of our understanding of those relationships.

Primary Ciliary Dyskinesia (PCD)

PCD, also known as Kartegener's syndrome or immobile ciliary syndrome, is an inherited disease characterized by defects in the cilia lining the respiratory tract. A NHLBI-supported study characterizing HFH-4, a regulatory protein expressed specifically in ciliated epithelial cells, suggests that the protein has a role in the regulation of the early development of cilia (ciliogenesis) and that cilia function may be critical in left-right body axis symmetry.

Primary Pulmonary Hypertension (PPH)

PPH is a rare, progressive lung disorder characterized by a sustained elevation of the pulmonary artery pressure. Recently, two research groups independently identified germ line mutations in the bone morphogenetic protein receptor II (BMPR2) gene in patients with the disease. Another recent study reported that endothelial cells (ECs) from the lung tissue of sporadic PPH patients acquire somatic mutations from other genes involved in EC growth and apoptosis.

Sarcoidosis

Sarcoidosis is a chronic multi-system disease of unknown cause in which affected organs, especially the lungs, are invaded by different types of inflammatory cells that become organized into clusters of cells called granulomas. In recent studies, histologic and clinical similarities between tuberculosis and sarcoidosis have suggested a shared underlying pathophysiology related to the NRAMP1 human protein. Contrary to previous findings in tuberculosis patients, the less common gene variations were found more often in control subjects than in sarcoidosis patients, and one variation was actually found to have a protective effect.

Blood Diseases and Resources Programs

Acute Graft versus Host Disease (GvHD)

Acute GvHD is a condition that typically occurs within three months after allogeneic hematopoietic stem cell transplantation when donor T cells react against "foreign" tissue antigens in the recipient. Combining data from their respective registries, the International Bone Marrow Transplant Registry and the Eurocord-Cord Blood Transplant Group compared results of sibling umbilical cord blood (UCB) and bone marrow (BM) transplantation for a group of patients younger than 15 years. Their study found that although engraftment (the time for new white blood cells and platelets to grow in the recipient) was longer in the UCB recipients, the incidence of GvHD was lower, and the overall survival was the same.

The results suggest that unrelated umbilical cord blood transplants might compare favorably with unrelated donor marrow transplants.

Aplastic Anemia (AA) and Paroxysmal Nocturnal Hemoglobinuria (PNH)

AA is a form of bone marrow failure in which hematopoietic cells are replaced by fat, resulting in low blood counts. In PNH, a clone derived from a single hematopoietic stem cell expands, leading to marrow failure, red blood cell destruction, and venous thrombosis. Using sensitive flow cytometry, NHLBI intramural scientists have established that an expanded PNH clone is present in a large proportion of patients with aplastic anemia. In a randomized trial to compare conventional antithymocyte globulin immunosuppression to high-dose cyclophosphamide, the researchers established that the latter treatment is excessively toxic and leads to a high rate of severe fungal infections and increased mortality.

Cooley's Anemia

Cooley's anemia (also called beta-thalassemia, thalassemia major, or Mediterranean anemia) is a genetic blood disease that results in an inadequate production of hemoglobin. In FY 2000, NHLBI grantees used a beta-globin gene/beta-locus control region retroviral vector to optimize gene transfer and expression in a mouse transplant model. New methods of transfusion therapy were developed; less toxic methods of stem cell transplantation that provide potential utility for patients with thalassemia were developed; new iron chelators were evaluated; a new clinical research network designed protocols that will provide clinically useful information in the areas of hepatitis and osteoporosis management as well as insights into the potential utility of fetal hemoglobin (hemoglobin F) induction as a function of genotype; and several compounds that increase hemoglobin F values were described.

Fanconi Anemia (FA)

FA is an autosomal recessive bone marrow failure syndrome characterized by a decrease in blood cells and platelets (pancytopenia), developmental defects, and cancer susceptibility. A number of studies over the past year have further defined the FA complex of proteins and provided insight into their potential function. Developments include cellular localization of the functional complex and determination of the role of the complex in DNA repair and prevention of mutagenesis. Recent transplantation protocols using Fludarabine have provided new hope that stem cell transplantation may become a therapeutic option for patients with FA.

Hemophilia

Hemophilia is a hereditary bleeding disorder that results from a deficiency in either blood coagulation factor VIII or factor IX. Gene therapy studies by NHLBI-supported scientists have shown sustained expression of factor IX in mice and hemophilic dogs after muscle injection or intraportal administration of AAV vector containing factor IX. Preliminary results of the first phase I clinical study for AAV-mediated muscle directed gene transfer of factor IX indicate that the procedure is well-tolerated and show evidence of protein expression. On the basis of pre-clinical safety and efficacy data, a clinical study for intrahepatic delivery of AAV vector-expressing factor IX has been proposed.

Hereditary Hemorrhagic Telangiectasia (HHT)

HHT, or Osler-Weber-Rendu disease, is a bleeding disorder that is due to weakness of the vascular support structure. Progress has been made in determining the underlying molecular basis of HHT, which appears to be a mutation in the genes of two TGF beta receptor family members on the endothelial cell. Eight mutations in endoglin leading to HHT have been identified, and a database on genetic mutations related to HHT has been established.

Immune Thrombocytopenic Purpura (ITP)

ITP is an autoimmune disease resulting in rapid clearance or destruction of the platelets (thrombocytopenia) and clinically significant bleeding. In FY 2000, it was shown that the transcription factor GATA-1 is necessary for megakaryocyte maturation and platelet production. Subtractive hybridization experiments between megakaryocytes lacking GATA-1 and controls show that the 4-Ptase I enzyme is essential for this process. A transgenic mouse model has been developed.

Sickle Cell Disease (SCD)

SCD occurs when an infant inherits the gene for sickle hemoglobin from both parents (sickle cell anemia) or the gene for sickle hemoglobin from one parent and the gene for another abnormal hemoglobin from the other parent (sickle cell disease types Hb SC, Hb S-Beta thalassemia, etc.). Research published in the past year confirmed that adhesive interactions between individual blood components and between blood components and cells that line blood vessels (endothelium) are likely to be important initiators of sickle cell vaso-occlusive crises. In addition, investigators have been able to induce inflammatory responses in sickle mice but not normal mice by removing and then providing oxygen. This observation was correlated in the sickle mice with oxidant production by vascular endothelial cells and was found to be completely prevented by prior infusion into mice of an antibody directed toward the P-selectin molecule expressed on vascular endothelium.

Systemic Lupus Erythematosus (SLE or Lupus)

SLE is an autoimmune disorder in which the body produces antibodies that harm its own cells and tissues. Recent NHLBI-supported studies have found that some lupus antibodies have catalytic properties and can specifically convert prothrombin to thrombin, thereby creating a hypercoagulable condition that may explain the high incidence of thrombosis in patients with SLE.

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

NHLBI-initiated programs in rare diseases in children totaled $119.7 million in FY 2000 and are estimated to increase by approximately 10 percent per year over the next five fiscal years.

Ongoing Initiatives

- Clinical Research on Cooley's Anemia (FY 1998-FY 2002)
- Comprehensive Sickle Cell Centers (FY 1998-FY 2002)
- Immunogenetics of Inhibitor Formation in Hemophilia (FY 1998-FY 2001)
- Mitochondrial DNA Mutations in Heart, Lung, and Blood Diseases (FY 1997-FY 2000)

- Specialized Centers of Research (SCOR) in Neurobiology of Sleep and Sleep Apnea, Airway Biology and Pathogenesis of Cystic Fibrosis, and Acute Lung Injury (FY 1997-FY 2001)
- Specialized Centers of Research (SCORs) in Pathobiology of Fibrotic Lung Disease, Pathobiology of Lung Development, and Cellular and Molecular Mechanisms of Asthma (FY 1997-FY 2001)
- Stem Cell Transplantation to Establish Allochimerism (FY 1999-FY 2002)
- Strategies to Augment Alveolization (FY 1999-FY 2002)
- T Cell Depletion of Marrow for Unrelated Bone Marrow Transplantation: Clinical Trial to Ascertain Risk-Benefit Ratio (FY 1994-FY 2001)
- Thrombocytopenia: Pathogenesis and Treatment (FY 1998-FY 2002)

Initiatives Begun in FY 2000

- Cellular and Molecular Mechanisms of Primary Pulmonary Hypertension (PPH) (FY 2000-FY 2002)
- Programs of Excellence in Gene Therapy (PEGT) (FY 2000-FY 2004)
- Specialized Centers of Research (SCOR) in Hematopoietic Stem Cell Biology (FY 2000-FY 2004)

Initiatives Planned for the Future

- Blood and Marrow Transplant Clinical Research Network (FY 2001-FY 2005)
- Genetic Modifiers of Single Gene Defect Diseases (FY 2001-FY 2005)
- Pathogenesis and Treatment of Lymphedema (FY 2001-FY 2004)
- Pediatric Heart Disease Clinical Research Network (FY 2001-FY 2005)
- Comprehensive Sickle Cell Centers (FY 2003-FY 2007)

Rare Diseases in Children-Related Program Activities

- A "Workshop on Bronchopulmonary Dysplasia" was organized by NICHD, NHLBI, and ORD, to review the definition of BPD and lung injury in very pre-term infants, to identify gaps in knowledge of lung development, to select the best indicators of outcome for infants with BPD, and to prioritize areas for future research.

- A "Working Group on Stem Cell Plasticity" met in March 2000 and developed RFA-HL-01-007, *Hematopoietic Stem Cell Plasticity*, issued in November 2000.

- The NHLBI Hematology Branch participated in the "Symposium on Fanconi Anemia" at the Annual Scientific Meeting of the International Society for Experimental Hematology in Tampa Florida, and in the Annual International Fanconi Anemia Scientific Symposium, held in Amsterdam, The Netherlands.

- A "Forum on Allogeneic Unrelated Cord Blood Banking and Transplantation," co-sponsored by FDA, met in August 2000. Leaders in cord blood banking and transplantation from around the world discussed requirements for collecting, processing, storing, and transplanting unrelated allogeneic umbilical cord blood. The recommended practices included infectious disease screening and testing, determining the number of viable cells post-processing, collecting donor

family histories, and maintaining a sample attached to the frozen cord blood unit for follow-up testing.

- NHLBI and the LAM Foundation co-sponsored the "International LAM Symposium" held at Columbia University in November 1999.

- A May 2000 meeting on "Conquering Lymphatic Disease: Setting the Research Agenda," co-sponsored with the Lymphatic Research Foundation, ORD, and four other NIH Institutes resulted in a Program Announcement, PA-01-035, *Pathogenesis and Treatment of Lymphedema*, released in December 2000.

- NHLBI and the Pulmonary Hypertension Association (PHA) have agreed to joint sponsorship of a program to train clinicians to perform biomedical research related to pulmonary hypertension. The training will be supported by the Mentored Clinical Scientist Development Award (K08) mechanism.

- At a "Workshop on Nitric Oxide as a Potential Therapeutic Agent for Sickle Cell Disease and Other Vascular Diseases" in September 2000, a discussion was held on the promise of nitric oxide (NO) as a possible therapy for sickle cell disease associated acute chest syndrome, respiratory distress in premature infants, and other severe vascular problems.

- A "Workshop on Central Nervous System Disease in Children with Sickle Cell Disease" was held in September 2000 at NHLBI to discuss current understanding of the effects of SCD on the central nervous system (CNS), contemporary methods of evaluation of the CNS, prophylactic and therapeutic interventions that may alleviate brain damage, and future directions for research.

- After 20 years and more than 40 publications, the Cooperative Study of Sickle Cell Disease has ended. In September 2000, the investigators met to discuss manuscripts still to be written based on the database and the stored genetic and sera samples.

- At the STOP Trial Steering Committee Meeting in September 2000, the STOP investigators met to discuss the STOP II Trial protocol to be submitted for review by the Data and Safety Monitoring Board. The STOP II Trial will attempt to ascertain if it is safe to stop transfusing children for stroke prevention after 30 months.

- At the "MSH Patients' Follow-up Steering Committee Meeting" in September 2000, the investigators met to discuss follow-up of the study cohort for the next five years. A paper summarizing survival over the past eight years is planned. Data from the study suggest that survival is improved if fetal hemoglobin levels are elevated by continuing hydroxyurea therapy.

- At the first "BABY HUG Steering Committee Meeting" in September 2000, investigators discussed plans for protocol development and recruitment. The objective of the clinical trial is to determine if hydroxyurea therapy is effective in preventing chronic end-organ damage in young pediatric patients with sickle cell anemia.

- At a "Workshop on von Willebrand Factor and Thrombotic Thrombocytopenic Purpura" held in July 2000, investigators in the area of TTP gained a clearer understanding of worldwide efforts to address the disorder and laid the groundwork to develop new collaborations.

Problem Areas Related to Rare Diseases in Children

Aplastic Anemia (AA) and Paroxysmal Nocturnal Hemoglobinuria (PNH)

The viral agent in post-hepatitis aplastic anemia, which is probably the same agent that is responsible for seronegative acute hepatitis and fulminant hepatitis of childhood, needs to be identified using samples of blood, liver, and stool from patients with acute hepatitis. Better immunosuppressive treatment of aplastic anemia requires large clinical trials, and patients must be recruited to specified research centers rather than treated haphazardly in private practice. To elucidate the relationship between an autoimmune disease (AA) and clonal expansion of mutated cells (PNH), large numbers of patients must be available for study.

Arrhythmogenic Right Ventricular Dysplasia (ARVD)

A concerted multi-laboratory program, combining basic, clinical, and genetic approaches, is needed to identify the causes of this highly lethal form of cardiomyopathy so that a rational search for therapies can begin. Additional clinical centers, and perhaps a national registry, would be useful to investigators who are already studying its origins and potential treatments.

Creutzfeldt-Jakob Disease (CJD)

Standardized reference materials to validate assay systems to detect transmissible spongiform encephalopathies (TSE) such as CJD are urgently needed. In April 1999, the World Health Organization (WHO) recommended the establishment of international reference materials for TSE diagnosis. Standards proposed would include human brain tissue, human blood, animal tissues, and animal blood. These materials would be used to calibrate the in-house reference materials of individual laboratories to the same single, international standard. The need for blind panel validation of all assays, (i.e., the validation of the sensitivity, reproducibility, and predictive abilities of any given candidate assay) is emphasized. Without standardized reference materials, it is not possible to evaluate the relative merits of any assay developed, or even to know for sure whether or not they are more sensitive than existing Western blots or ELISAs.

Fanconi Anemia (FA)

The eight distinct complementation groups represent a high degree of locus heterogeneity, which complicates molecular diagnosis of FA and may make screening cumbersome. However, certain complementation groups prevail in specific populations (FA-C in Ashkenazi Jews, FA-A in Afrikaans-speaking people and Italians), which helps to set priorities for mutation screens. The FA-A and FA-C proteins have no sequence homologs in the current databases, although structural homologs may exist. Thus, resolution of difficulties in FA protein purification and pursuit of the X-ray crystallographic structure of FA proteins is considered a high priority.

Graft Versus Host Disease (GvHD)

The nature of the responding cells in GvHD and reliable methods to predict and ameliorate the problem remain elusive. A challenge remains in fostering graft versus leukemia or graft versus tumor effect while avoiding GvHD. In addition, the basic immunology, biology, and tissue specificities of the response require further definition.

Infectious Myocarditis

A non-invasive test for infectious myocarditis having appropriate sensitivity and specificity is needed. At present, the endomyocardial biopsy, which is invasive and has limited specificity and sensitivity, is the gold standard for diagnosis.

Lymphangioleiomyomatosis (LAM)

Scarcity of data and LAM tissue has hindered learning about the etiology and pathogenesis of LAM. The small number of patients makes it difficult to learn about important aspects of the disease such as its prevalence, prognosis, and clinical course, or the effects of various treatments. A lack of animal models makes it necessary to obtain human cells or tissue to do LAM research. The LAM Foundation continues to facilitate collection of LAM tissue at the time of lung transplantation. Progress in LAM research has increased demand for this scarce resource. A NHLBI LAM Tissue committee is establishing procedures and guidelines for LAM tissue collection and distribution.

Long QT Syndrome (LQTS)

Access and identification of sufficient numbers of new patients for studies remain a constant problem. Identification of mutant gene carriers would be greatly facilitated by accurate means of screening individuals in afflicted families for specific founder mutations. Improved means of identifying new mutations in the various genes involved would also be helpful.

National Human Genome Research Institute (NHGRI)

Overview of NHGRI Rare Diseases in Children Research Activities, FY 2000 - FY 2005

The mission of NHGRI is to understand the structure and function of the human genome and the role it plays in human health and disease. To that end, NHGRI supports the Human Genome Project (HGP), an international research effort to sequence the human genome and determine the function of the genes contained within the genome. The publication of the initial sequence and analysis of the human genome in February 2001 was an historic scientific achievement. The sequence information from the HGP has been continuously, immediately, and freely released to the world, with no restrictions on its use or redistribution.

This information is a major resource for all the areas of basic and applied biomedical and behavioral research in the 21st century. The HGP is producing research tools and information that are leading to improved detection and diagnosis of genetic disorders by intramural scientists and scientists in the broader biomedical research community.

Using the information and tools produced by the HGP, scientists in NHGRI's intramural research program are developing techniques to study the fundamental mechanisms of genetic disorders and genetic factors involved in common and rare diseases. These cutting-edge approaches are yielding new knowledge about human genetic diseases and their diagnosis, prevention, and treatment.

Recent Scientific Advances in Rare Diseases in Children Research

NHGRI's FY 2000 activities related to rare diseases and conditions research in children are described below.

Tools for Gene Discovery

Human DNA Sequencing

In March 1999, the HGP international consortium launched the full-scale effort to sequence the estimated 3 billion base pairs that make up the human genetic instruction book. In the following months, production of human genome sequence skyrocketed and the HGP produced 1,000 bases per second of raw sequence 7 days a week, 24 hours a day. June 26, 2000, marked an historic milestone when leaders of the public HGP and Celera Genomics Corporation announced that both had successfully completed the production of a "working draft" of the human genome.

In March 2001, public and private research teams published their data, including an initial analysis of the main features of the sequence. The intense phase of analyzing the sequence for gene content and a host of other biological features is now under way. A list of links to a number of important Web sites that contain information about the human genome sequence, other genome sequences, and other relevant genomic information can be found at: http://www.nhgri.nih.gov/genome_hub.html.

"DNA Chip" Microarrays

The newfound abundance of genomic information is propelling scientists out of the pattern of studying genes individually. Scientists are now able to monitor thousands of genes at a time. For such large-scale analyses, miniaturized "DNA chip" technologies, also called microarrays, can be rapid, efficient, and economical. Microarrays are being used to compare gene activity in people with or without a disorder. This technology will benefit rare disease research because it can identify altered patterns of gene expression.

"Tissue Chip" Microarrays

In order to determine the importance of any gene in a more physiological setting, a second kind of array, called the tissue microarray, can confirm the importance of each gene that emerges as a candidate. NHGRI researchers have developed a way of arranging some 1,000 tiny cylindrical tissue biopsies in a small paraffin block. Tissue arrays permit researchers to examine the molecular details of many different healthy tissue types or in different stages of disease. NHGRI researchers combined cDNA and tissue microarray technologies to make rapid diagnoses of rare disorders and to better predict how a given patient will respond to available treatments and medications.

Genetics of Human Disease

Severe Combined Immunodeficiency (SCID)

SCID, also known as Bubble Boy Disease, is a rare but devastating complete lack of T cell and B cell immunity. 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, can 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. 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 National Institute of Allergy and Infectious Diseases (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 three loci in the human genome that may be associated with hyper-IgE syndrome. Scientists are currently investigating the genetic regions and hope to identify disease genes for this condition.

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 the severity of the case of ALPS 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.

Hirschsprung Disease

Animals heterozygous for dominant megacolon (Dom/+) exhibit multiple defects in neural crest development, including reduced numbers of melanocytes in the skin and an absence of myenteric ganglion in the colon. A human congenital disorder, Hirschsprung disease also exhibits rectocolic aganglionosis and can be associated with hypopigmentation. Thus, Dom/+ mice, as well as the piebald and lethal spotting mutants, serve as mouse models for this disease. Investigation of the involvement of Dom in Hirschsprung disease will be explored.

Congenital Disorders of Glycosylation (CDGs)

CDGs are 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. CDGs result 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.

Smith-Magenis Syndrome (SMS)

SMS, due to deletion on the short arm of chromosome 17, is associated with a distinct phenotype of physical features, developmental delay, speech delay with or without associated hearing loss, clinical signs of peripheral neuropathy, and neurobehavioral problems including sleep disturbance, outbursts, and self-injurious behaviors. More than 200 individuals representing a diversity of ethnic backgrounds have been identified with the syndrome worldwide. Utilizing existing physical maps and comprehensive clinical analysis of the physical, cognitive, and neurobehavioral aspects of SMS, the SMS Research Team seeks to define the natural history and pathophysiology of SMS across the life span and identify genes in the chromosome 17p11.2 region that contribute to physiologic and functional aspects of human cognition, speech/language development, and behavior.

Holoprosencephaly (HPE)

NHGRI researchers are studying HPE, the most common structural disorder of the developing human forebrain. HPE is associated with varying degrees of developmental disability and mental retardation. Scientists have located four genes that cause HPE in humans. These findings suggest that the following genes play an important role in the brain's separating into left and right hemispheres: Sonic Hedgehog (*SHH*), *ZIC2*, *SIX3*, and TG-interacting factor (*TGIF*). Maternal diabetes, low maternal cholesterol, and other environmental factors have been associated with abnormal brain development. Analysis of regulation, interaction, and physiological role of these genes and factors will help our understanding of normal and abnormal formation of the central nervous system.

Batten Disease

Juvenile neuronal ceroid lipofuscinosis (NCL type III), known as Batten disease, is a degenerative neurological disease resulting from a lysosomal storage disorder. The Batten gene, *CLN3*, encodes a protein with an as yet incompletely understood function. Scientists at NHGRI have created a mouse carrying a deletion of the *CLN3* gene that encodes a transmembrane lysosomal protein of unknown function. The mouse has the same biochemical abnormalities seen in human patients with Batten disease. Work in yeast performed at the University of Rochester has revealed that the yeast ortholog of *CLN3* is a vacuolar protein which, when deficient, abnormally lowers the vacuolar pH. NHGRI scientists hypothesized that humans (and mice) deficient in *CLN3* might store lipofuscin in their lysosomes because of abnormal depression of lysosomal pH that interferes with degradative enzyme function. Scientists have started a treatment protocol of mice with chloroquine, an alkaline base that accumulates in the lysosome, to see if they can correct the biochemical abnormalities seen in Batten disease with this widely used and characterized drug.

Lowe Syndrome

Lowe syndrome is a rare X-linked 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.

Idiopathic Scoliosis (IS)

IS is a structural lateral curvature of the spine present in the late juvenile or adolescent period in otherwise normal individuals. Previous studies from a number of populations have suggested autosomal dominant, X-linked, and/or multifactorial modes of inheritance. As part of a large collaborative study of familial IS, 200 families (1,200 individuals) with at least 2 individuals with scoliosis have been ascertained and clinically characterized. A genome-wide screen for 1,200 individuals was performed at the Center for Inherited Disease Research (CIDR). Preliminary analysis for linkage has been completed for all 1,200 individuals. Several candidate regions have been identified, and flanking markers are being typed to corroborate the findings from the genomic screen.

Camptodactyly-arthropay-coxa vara-pericarditis (CACP) Syndrome

Scientists have identified mutations in a gene previously known as megakaryocyte growth and stimulating factor, which causes CACP syndrome. This is an autosomal recessive disease with synovial hyperplasia as the basic underlying defect, which leads to several clinical phenotypes (mainly loss of proper joint growth and function). Scientists have made a mouse knockout construct and are currently studying these animals to see whether they can replicate the human phenotype in mice. This will allow better understanding of joint development and the identification of the basic molecular components responsible for CACP.

Achondroplasia and Other Fibroblast Growth Factor Receptor 3 (FGFR3) Disorders

The achondroplasia family of skeletal dysplasias includes three previously recognized diagnoses and one that has been defined under this project. The three well-established conditions are achondroplasia, hypochondroplasia, and thanatophoric dysplasia (TD). Work published over the last year has described a new syndrome, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN). All four disorders in this family of conditions are caused by mutations in the gene encoding fibroblast growth factor receptor 3 (FGFR3). Work during FY 2000 has focused on the creation and characterization of two mouse models for FGFR3 disorders.

Marfan Syndrome and Related Conditions

NHGRI scientists are studying patients with Marfan syndrome and related conditions (Ehlers-Danlos syndrome [EDS] and Stickler's syndrome). Studies have documented newly recognized gastrointestinal complications of these disorders and shown that chronic musculoskeletal pain is a significant complication of both EDS and Stickler's syndrome. Studies have also documented an increased risk of femoral head failure in children with Stickler's syndrome. Scientists have proposed diagnostic criteria for Stickler's syndrome based on clinical and molecular studies in this population, and have identified a previously undescribed connective tissue disorder with features resembling Marfan syndrome, Stickler's syndrome, and EDS. Chronic musculoskeletal pain is a serious complication of many of the hereditary disorders of connective tissue. During FY 2000, scientists performed a pilot study of the Mindfulness-Based Stress Reduction Program to examine its efficacy in the relief of chronic pain in this population.

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 the liver, heart, eyes, 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 three homologous genes termed Jagged 1, 2, and 3 from zebrafish. Expression of dominant negative forms of the Jaggeds and blocking their expression with antisense oligonucleotides are being carried out to evaluate the function of the Jagged proteins.

Cleft Lip and Palate

NHGRI collaborates on a study of the genetics of oral clefts (cleft lip, cleft palate, or both) with investigators in Syria. Several hundred persons have been studied in Syria, and genotyping and linkage

analysis of the first set of families has been completed for a genome-wide set of markers. Regions with suggestive evidence of linkage are currently being studied with fine-mapping techniques in the original set of families and in a new set of recently collected families. These analyses and the collaborative data collection in Syria will continue into FY 2001.

Pallister-Hall Syndrome, Greig Cephalo Polysyndactyly Syndrome (GCPS), Polydactyly

This research study encompasses a range of phenotypes that include Pallister-Hall syndrome, the allelic disorder Greig cephalo polysyndactyly syndrome (GCPS), and disorders with overlapping phenotypic manifestations. These overlapping disorders include the McKusick-Kaufman syndrome, Bardet-Biedl syndrome, the oral-facial-digital syndromes, and the short-rib-polydactyly syndromes. The clinical 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. Scientists are using positional cloning strategies, biochemical approaches, and cell biologic studies to understand the genomic alterations, predict consequences to the proteins, and integrate these at the cellular or embryologic level. These data are then used to develop additional hypotheses that can be investigated at the clinical or molecular level.

McKusick-Kaufman Syndrome (MKS) and Bardet-Biedl Syndrome (BBS)

Scientists at NHGRI have identified an altered gene responsible for a rare developmental syndrome found predominantly among the Old Order Amish population. MKS is the first human disorder to be attributed to a mutation in a gene affecting a type of molecule called a chaperonin. Chaperonins, sometimes called "protein cages," protect cells by capturing and refolding misshapen proteins that could otherwise interfere with normal cellular functions. Females with MKS are affected by hydrometrocolpos (accumulation of fluids in the uterus and vagina). Both males and females have a form of polydactyly (the presence of extra fingers or toes) and congenital heart disease. The disorder is most serious in female infants in whom the hydrometrocolpos can cause death due to lung compression complications. Further research has shown that this gene is also mutated in some persons with BBS, an inherited form of blindness, mental retardation, and obesity. These results suggest that therapies directed at chaperonin function may ameliorate these symptoms.

Amish Nemaline Myopathy

Amish nemaline myopathy is a progressive muscle disease that has so far only been identified in the Old Order Amish of Pennsylvania. It causes muscle wasting that results in death before five years of age. NHGRI scientists isolated the disease-causing mutation in this disorder in FY 2000. This alteration is in the Troponin T1 gene, known to play a role in the muscle, but not previously known to cause any human disease. A collaborative group of scientists and physicians are working to translate these results into a potential treatment for this disease.

Lenz Microphthalmia Syndrome

Lenz microphthalmia syndrome causes small or absent eyes, mental retardation, and other anomalies. Its rarity is matched by its variability, and there is a significant confusion and controversy about the range of the phenotype and its overlap with other disorders that cause microphthalmia. NHGRI scientists, in collaboration with doctors at Children's National Medical Center, have teamed up to analyze a large

family with multiple members affected with this disorder. The results of this research should allow development of accurate diagnostic tests.

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; 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 CIDR on 21 DNA samples, and efforts to fine-map the gene are currently under way.

Rieger Syndrome

A continuing area of interest of this group involves the homeodomain family of proteins, which play a fundamental role in the specification of body plan, pattern formation, and the determination of cell fate. Recent work has focused on two genetic disorders caused by defects in *Pitx2*, which codes for a homeodomain protein. Mutations in the human *Pitx2* gene in 4q25-q26 lead to two eye-related disorders, Rieger syndrome and iridogoniodysgenesis. Sequelae include iris hypoplasia and the eventual development of glaucoma. In the past, biochemical observations explaining these diseases were documented simply as "loss-of-function"; this is the first time that a concrete, structural underpinning for the development of these disorders has been proposed. Continuing work in this area involves another homeodomain protein called FOXC1 that has also been implicated in Rieger syndrome and iridogoniodysgenesis.

Left-Right (L-R) Axis Malformations

A study of the complex genetics of L-R axis malformations has been undertaken with an emphasis on those 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. It is the aim of these investigations 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. NHGRI scientists have recently identified the human *CFC1* gene as causing laterality defects and are studying this and other genes in individuals with cardiac anomalies.

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

Planned FY 2001 Scientific Meetings and Workshops

Congenital Disorders of Glycosylation (CDGs) -Type 1A

NHGRI is planning a workshop entitled, "Exploration of Therapeutic Interventions for Congenital Disorders of Glycosylation-Type 1A," for summer 2001. CDGs are a group of rare metabolic disorders with a multisystemic clinical presentation. CDG-Type 1A is the most common of the CDG types, with

approximately 200 cases worldwide. The clinical presentation includes severe developmental delay, coagulopathy, cerebellar hypoplasia, failure to thrive, seizures, liver disease, and stroke-like episodes. The metabolic basis of CDG-type 1A is a deficiency of phosphomannomutase with mutations defined in its gene, *PMM2*. This reflects defective synthesis of N-linked oligosaccharides, with clinical manifestations a direct result of the role of N-linked glycans in human embryogenesis and physiology.

It was reported in 1996 that in vitro addition of mannose to fibroblasts of patients with CDG-Type 1A corrected the N-linked synthetic defect in these cells. Brief therapeutic trials were performed with oral and intravenous mannose on six children with CDG-Type 1A in Europe in 1998. While these trials showed some changes in laboratory tests, no major clinical changes were seen in these children. A satellite meeting, "Congenital Disorders of Glycosylation," was held in conjunction with the Society of Glycobiology meetings in Boston in November 2000. At this meeting, a brief report was presented about two children with CDG-Type 1A on oral mannose for two years who are making significant clinical improvement. This report renewed interest in the issue among the clinical experts in this disorder of the need for a randomized therapeutic trial for children with CDG-type 1A. Several investigators also expressed interest in alternative chemical forms of mannose as therapeutic options.

Affected children have significant morbidity related to their failure to thrive, skeletal deterioration, coagulopathy, and stroke-like episodes. If there is any therapeutic intervention worthy of trial, it should be evaluated on children with this devastating disorder.

Genetic And Rare Diseases Information Center

NHGRI and ORD, in order to respond to the public's need for information on genetic and rare disorders, are establishing the NHGRI/ORD Genetic and Rare Diseases Information Center. The Information Center will focus 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:

- Serve as a central, national repository of information materials and resources on genetic and rare diseases, conditions, and disorders.
- Collect, produce, update, and disseminate information on the diagnosis, treatment, and prevention of genetic and rare disorders.
- Coordinate with organizations and associations interested in genetic and rare disorders to explore networking capabilities, avoid duplication of effort, and identify information gaps.

Planned Research Initiatives, FY 2001 Through FY 2005

As the human genome is further defined, this information will be used by scientists to better understand the genetics of the rare diseases affecting children. Ongoing research activities over the next five years will continue in the areas discussed above.

National Institute of Mental Health (NIMH)

Overview of NIMH Rare Diseases in Children Research Activities, FY 2000 - FY 2005

The mission of NIMH is to reduce the burden of mental illness and behavioral disorders through research on mind, brain, and behavior. As documented in the landmark Global Burden of Disease study, conducted by Harvard University, the World Health Organization (WHO), and the World Bank, the challenges before NIMH are immense, with common and prevalent mental disorders accounting for 4 of the 10 leading causes of disability in the United States.

The massive public health burden notwithstanding, NIMH directs substantial attention to less common disorders and conditions that occur across the life span and meet the criteria for "rare diseases," that is, including a prevalence of fewer than 200,000 affected individuals in the United States. In the arena of childhood disorders, such conditions may be subtypes of common adult disorders; prepubertal bipolar disorder and child-onset schizophrenia are two examples. In other instances (autism, for example), rare disorders appear to be pathophysiologic and clinical entities unto themselves. As understanding of the genetic, neurobiological, and behavioral bases of mental disorders expands, insights into a number of rare diseases of the brain and central nervous systems are accumulating. Conversely, research into relatively rare, early-onset subtypes of disorder has value-added benefit for the light it often sheds on the more prevalent adult forms of the disorder. An example is seen in imaging studies of brain volume in child-onset schizophrenia, which has helped to pinpoint when critical changes in apparently healthy brain structure and function occur that, when seen in adult subjects, appear to be unexplained concomitants of the illness.

Recent Scientific Advances in Rare Diseases in Children Research

Autism

Autism is a biologically based developmental disorder characterized by qualitative impairments in social interaction and both verbal and nonverbal communication and behaviors, resulting in a markedly restricted repertoire of activities. The origins of autism are not known. In FY 2000, a NIMH-funded research team working in collaboration with four others published results from genome scans in autism. Regions on chromosomes 1, 2, 4, 5, 6, 7, 10, 13, 15, 16, 17, 18, 19, X, and 22 were identified as putative locations for disease vulnerability genes. Pooling and meta-analyses of these small data sets will be a useful next scientific step. Examination of linkage signals across studies to date shows that one region (7q) has been identified in all studies; however, none of the studies has reported evidence that is conclusive. In another set of subsequent analyses, NIMH-funded teams re-examined a genomic region on chromosome 15q and two specific genes, *HOXA1* (chromosome 7p) and *HOXB1* (chromosome 17q), which had been implicated in previous studies. Evidence was not found for involvement of this genomic region or for these two genes in vulnerability to autism, suggesting that their roles are at best minimal in the majority of individuals with autism.

In FY 2000, a NIMH-funded network of research units on pediatric psychopharmacology (RUPPs) completed enrollment of the first multi-site controlled trial of the antipsychotic medication risperidone in children with autism, with results scheduled to become available in 2001.

In FY 2000, NIMH and NICHD co-sponsored an RFA entitled, "Neurobiology and Genetics of Fragile X Syndrome," which solicited innovative research applications that address the epidemiology, genetics, and neurobiology of fragile X syndrome. (FY 2000 through FY 2005)

NIMH and NICHD organized a conference in April 2000 entitled, "Fragile X Mental Retardation Gene Protein (FMRP): What Does it Do?" on the genetic and neurobiological basis of fragile X syndrome. The conference allowed the development of efficient research strategies by which the genetic dissection of other mental disorders might occur.

Schizophrenia Subtypes: Childhood-onset Schizophrenia

Schizophrenia usually manifests in late adolescence and early adulthood. Childhood-onset schizophrenia (onset before age 12) is a rare form of the disease, occurring at about 1/300 the rate of adult-onset cases. Brain imaging of adult schizophrenia patients has usually found slightly decreased total brain volume, enlarged ventricular volume, and smaller medial temporal lobe structures such as the hippocampus. Earlier studies in child-onset schizophrenia also showed these decreases in brain volume, but these changes seemed progressive, which does not appear to be the case in adult-onset schizophrenia. New data from a larger cohort of patients, including adolescents, have reconciled these findings. The new findings show that reductions in brain volume seen in child-onset schizophrenia slow and stabilize during adolescence. This suggests a common causal mechanism for both the adult- and child-onset disorder. Adolescence offers a unique window of opportunity to study late brain changes in child-onset schizophrenia. These findings also have implications for better drug treatment of child-onset schizophrenia because drug dosing can be matched to brain changes that appear to correlate with symptoms. (Ongoing NIMH intramural research)

Childhood Bipolar Disorder

Early-onset bipolar disorder has only recently been recognized in adolescents. NIMH-supported research, based on a community sample that has been followed since adolescence, reported a prevalence of 1% during adolescence and found that less than 1% of adolescents with major depression switch to bipolar disorder by age 24. An ongoing study of prepubertal and early adolescent bipolar disorder (PEA-BP) is examining the course of early-onset bipolar disorder in children who also have a diagnosis of attention deficit hyperactivity disorder (ADHD). Ninety-three children (ages 8-13) with a current diagnosis of severe mania or hypomania with elated mood and/or grandiosity were compared to children with ADHD and no manic symptoms as well as normal controls. Compared to both groups, the PEA-BP children had significantly greater impairment on items that assessed maternal-child warmth, maternal-child and paternal-child tension, and peer relationships. At 6-month follow-up, 86% of the PEA-BP children still met full criteria and severity level for mania or hypomania, with elated mood and grandiosity highly stable. These findings suggest that PEA-BP may be a stable, valid, and previously under-recognized condition. (FY 1995 through FY 2001)

To advance research on the identification of prepubertal bipolar disorder, NIMH held a workshop in FY 2000 that focused on research methods to detect bipolar disorder in children. In the same year, NIMH funded the first multi-site controlled study of lithium and valproate as treatment of children with acute mania. The study is being conducted at 3 sites and will enroll about 150 children. (FY 2000 through FY 2004)

In FY 2000, NIMH awarded funds for a 3-site collaborative study of the course and outcome of 12- to 17-year-old adolescents with bipolar illness. It is the first large-scale comprehensive naturalistic evaluation of the long-term course of bipolar disorder in this age group. It will track the naturalistic course of episode recovery and relapse, predictors of course, psychosocial outcomes, and naturalistic treatment effects.

Youth Suicide

Suicide is a rare behavior that, in an estimated 90% of instances, occurs in the context of a mental and/or substance abuse disorder. In 2000, NIMH-funded research on youth suicide included family genetic studies, long-term follow-up of depressed youth, and a co-funded (multiple NIH institutes, Centers for Disease Control and Prevention [CDC], Substance Abuse and Mental Health Services Administration [SAMHSA]) conference grant focused, in its first year, on youth suicide. Annual conferences are planned for 2000 through 2004.

Other research studies are focused on youth who attempt suicide. A number of studies are following adolescent suicide attempters over time, but few researchers are willing to test treatments for adolescent attempters due to liability concerns; the need to develop research eligibility criteria for suicidal individuals of all ages is being addressed by NIMH and the larger research community. A workshop om this topic funded by ORD is scheduled for summer 2001.

Pediatric HIV Infection

In the United States, due to medication advances during prenatal care for HIV-infected mothers, the incidence of HIV infection among children has slowed considerably. However, it is estimated that there are still between 500 and 1,000 new cases of infection per year of children younger than age 13. Moreover, many of the much larger cohort of children born with HIV before the routine use of antiretroviral therapy (ART) during pregnancy have now survived into pre-adolescence. These children with pediatric AIDS, their families, and their treatment providers are dealing with a host of sequelae from HIV disease.

Neuropsychological deficits and developmental delays continue to be a significant cause of morbidity in HIV-infected children. In the 1990s, NIMH-sponsored research demonstrated that these deficits may be related to elevated concentrations of the neurotoxin quinolinate in the cerebrospinal fluid (CSF). Notably, there was also a correlation between the levels of CSF quinolinate and the degree of brain atrophy as assessed by magnetic resonance imaging (MRI). More recent efforts in NIMH's extramural program indicate that the biological and psychosocial effects of HIV disease include neuropsychological deficits, emergence of behavioral/social disorders and school-related problems (oppositional behavior, learning disabilities, ADHD), treatment adherence difficulties, and other co-morbid mental health issues. Clinicians are also observing abnormalities that may be attributable to the toxicities of long-term use of medications for HIV (i.e., antiretroviral therapies). There is a pressing need for more systematic understanding of these problems, their interaction, and how best to provide integrated treatment. A workshop on this topic, funded by ORD, will be held in September 2001. An RFA with funding for FY 2002 through FY 2003, followed by meetings in 2004 and 2005 that encourage collaboration with international researchers working on similar problems in developing countries, is planned.

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

Rare Childhood Mental Disorder Research Initiatives - FY 2001 Through FY 2005

Autism and Related Conditions

NIMH plans a joint initiative with NIA and the National Institute of Neurological Disorders and Stroke (NINDS) to promote the identification of genes that cause or contribute to human neurological and neurobehavioral diseases. Autism and fragile X projects will be solicited to encourage applications for genetics research projects. Because of the interdisciplinary nature of such projects, collaborative studies are encouraged. Another initiative will fund high-throughput projects, including those focusing on autism, that target the whole genome to identify in patients with mental disorders the genetic basis of therapeutic response to one of several compounds (e.g., anxiolytic, antidepressant, antipsychotic, and antimanic drugs). Also planned are proteomics projects in mammalian species that will develop novel technologies or apply existing state-of-the-art approaches to the analysis of the complete repertoire of proteins in the nervous system.

In March 2001, NIMH funded a conference grant to hold a series of five annual interdisciplinary conferences on basic and clinical research relevant to fragile X syndrome, intended to bring together a broad range of scientists, including those working on fragile X syndrome and others in allied relevant fields.

NIMH will convene a workshop in FY 2002 to examine co-morbid symptomatology between fragile X and other mental disorders such as anxiety and mood disorders. The workshop will explore approaches to accelerate neurobiologic research to identify underlying circuits and pathways common to fragile X and other mental disorders. This may help point the way to understand common pathophysiological mechanisms and to identify new targets useful for therapeutic drug discovery.

Highlights of autism-related research activities begun in FY 2001 include a NIMH-funded study that will use MRI and magnetic resonance spectroscopy (MRS) to investigate the structural anatomy and biochemistry of the brain in developmental language disorder (DLD) and autistic groups of children. These structural anatomical and biochemical measures would then be examined in relation to quantifiable aspects of social communication using measures of formal thought disorder and discourse. The proposed study has the potential to contribute to our knowledge of the neuroanatomical and neurochemical abnormalities associated with the social communication deficits seen in autistic and developmental language disorders in children. In a separate project, an investigator proposes to assess the relation between brain morphology and autism through structural neuroimaging of siblings discordant for autism.

The results of these studies have the potential to allow investigators greater experimental control of those genetic and environmental factors that influence normal and abnormal brain development and may clarify biologically based subtypes of autism. Another study will use structural and functional MRI (fMRI) to assess how the abnormal structure and function of the neural systems in persons with autism may affect the processing of emotional information, particularly emotional information conveyed through faces and facial expressions.

Human focal cortical dysplasia (FCD) is a developmental brain malformation characterized histologically by disorganized cerebral cortical cytoarchitecture and lamination. FCD is associated with several mental disorders, including mental retardation and autism. A newly funded project will test the hypothesis that FCD is the result of abnormal neuronal migration occurring because of a failure to develop appropriate and necessary genes for migration. Anatomical and molecular experiments will assess the presence of immature or other abnormal genes in individual abnormal cells in cortical dysplasia.

In 2001, a RUPP network will launch a new protocol to test the efficacy and safety of treatments of inattention and hyperactivity in children with autism. An expansion of the network is planned for FY 2002 through FY 2003.

In December 2000, NIMH held a workshop entitled, "Genetics in the New Millennium: Modeling Autism." This meeting was an initial step to foster development of new models in the area of autism and the translation of research to the clinical treatment of this devastating disease. One of the main questions raised had to do with whether the assembled group could help define phenotypes that could be defined genetically in the mouse. Several possible approaches were outlined: 1) identify associated genetic markers, 2) map the disease vulnerability gene(s), 3) re-synthesize the disease in mice, or 4) survey inbred strains for important phenotypes and perform further quantitative trait loci mapping.

Childhood Schizophrenia

In 2001, NIMH plans to fund the first multi-site trial of the efficacy and safety of different antipsychotics for the treatment of childhood schizophrenia. This will be a four-site randomized controlled study with extended treatment and follow-up.

Childhood Bipolar Disorder

Responding to the need to understand how prepubertal bipolar disorder develops and what treatments are effective, the NIMH intramural program established (in FY 2001) a research unit to study the etiology and pathophysiology of childhood bipolar disorder. The Unit, which will complement ongoing extramural activities, will collaborate with the newly created Intramural Program in Mood and Anxiety Disorders to understand the major differences between childhood and adult forms of the disorder. The Unit will address questions regarding the phenomenology of the illness, probe the neural circuitry of emotion in patients with bipolar disorder compared to psychiatrically normal adolescents, develop and test innovative therapies for childhood bipolar disorder, and capitalize on the unique opportunities that early-onset probands provide to understanding the genetic basis of bipolar disorder.

In 2001, NIMH plans to fund a controlled study of antipsychotic medications for children with bipolar disorder who have psychosis and/or aggression.

In FY 2001, NIMH will award supplements to grants involved in the three-site collaborative study of course and outcome of child/adolescent bipolar disorder to extend the age range downward to include 7- to 11-year-old children. NIMH will also fund a study to evaluate 7- to 18-year-old children of bipolar parents and follow prospectively only those who do not have bipolar disorder at intake. At intake and annual follow-up, children will be assessed for differential incidence of psychopathology, behavior and emotion regulation, psychosocial functioning, pubertal status, and family psychiatric history. The study

is expected to provide information on early manifestations of childhood-onset bipolar disorder and on the boundary between bipolar and disruptive disorders, seeking to identify prodromal symptoms and factors that may promote or prevent the onset of bipolar disorder in children.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS)

Following up on an FY 2000 research workshop to discuss new investigations on tic disorders associated with streptococcal infections (PANDAS), NIMH has received new applications for research in this area and plans to fund new studies in 2001 and 2002. Public awareness of the potential link between common childhood infections and neuropsychiatric disorders has outpaced the scientific knowledge base, with particular need for studies of basic cellular and immune mechanisms underlying PANDAS.

Youth Suicide

ORD is co-funding an NIMH-sponsored workshop on the safety and ethics of clinical trials in June 2001, where approaches to research for individuals at risk for suicidal behavior, including youth, will be considered.

Pediatric HIV Infection

NIMH has expanded its program focus on coping with pediatric AIDS, both in the United States and internationally, where the implications of this research may affect millions of infected children. NIMH will convene a workshop on September 10-11, 2001, to summarize what is known about the effects of AIDS and its treatment on the development of children. The meeting will include representatives from government (e.g., the Office of AIDS Research [OAR], NIMH), academia, clinicians/treatment providers, and basic scientists, all with interest and expertise in pediatric HIV/AIDS treatment and prevention. The outcome will be a road map for immediate, short-term, and long-term goals for research in this area.

Rare Diseases-Related Program Activities in Children - FY 2001 Through FY 2005

Autism

In collaboration with the other Institutes represented on the NIH Autism Coordinating Committee, NIMH has initiated a planning process for activities that would implement the provisions of the recently enacted Children's Health Act of 2000 (Public Law No. 106-310). A major component of these activities will be a collaborative effort to support broadly based Centers of Excellence in Autism. This effort will provide additional infrastructure, organization, and focus to autism research efforts by establishing nodes of activity with a critical mass of expertise and resources.

NIMH plans an FY 2001 workshop to bring together outstanding human statistical and molecular geneticists and neuroscientists to identify strategies to accelerate the discovery of vulnerability genes for mental disorders (including autism).

In FY 2002, NIMH plans to bring together diverse groups of genetics researchers and develop strategies by which all available data sets may be assembled. Such efforts will enhance the power to detect vulnerability genes and elucidate their functions.

In December 2000, the NIH Autism Coordinating Committee, supported by NIMH, NICHD, NINDS, and NIDCD, issued an RFA for innovative methods and feasibility studies in the area of treatments for autism. The definition of its focus and scope grew out of a workshop hosted by these Institutes.

National Institute of Neurological Disorders and Stroke (NINDS)

Overview of NINDS Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NINDS conducts and supports research on the causes, diagnosis, treatment, and prevention of hundreds of disorders that affect the nervous system. Many of these disorders are caused by rare genetic mutations that produce symptoms appearing very early in life. As a result, thousands of children are impaired by motor dysfunction, cognitive problems, seizures, and other serious effects of their neurological conditions. Without effective treatment, a great number of these children will not survive into adulthood, and those who do will continue to experience debilitating symptoms of the disorder throughout their lives.

As many of the diseases studied by NINDS are rare disorders, and many of these conditions affect children, the following highlights represent only a snapshot of the involvement of NINDS in this area of research.

Recent Scientific Advances in Rare Diseases in Children Research

Duchenne's Muscular Dystrophy (DMD)

DMD is the most common form of childhood muscular dystrophy, affecting 1 in 3,500 boys, with a prevalence in the United States of 10,000. In DMD, a mutation in the gene that codes for dystrophin (a large muscle protein) leads to progressive degeneration of muscle beginning within the first few years of life. No treatment has been identified that can stop the muscle degeneration, and affected children typically die of respiratory or cardiac failure by their teens or early twenties. In approximately 15% of individuals with DMD, the mutation is a premature stop codon, an incorrect "code word" in the gene that causes the protein-synthesizing machinery of the cell to halt, resulting in the absence of dystrophin.

For several years scientists have known that specific antibiotics cause misreading of the genetic code and can sometimes suppress premature stop codons by causing the protein synthesizing machinery to misread the stop, insert another amino acid protein building block, and continue. In 1999, a team of scientists supported by NIAMS and NINDS developed an antibiotic treatment approach for DMD, first evaluating the therapy in cultured muscle cells and then in live mice with a mutation similar to that which causes DMD in humans. Following treatment with gentamicin, skeletal muscle cells of these mice expressed dystrophin at about 10% to 20% of normal levels, and tests showed that these levels restored muscle strength to that present in normal mice and protected muscle cells against degeneration.

The treatment approach has recently been evaluated in clinical trials to evaluate its effectiveness in improving the function of the 15% of boys with DMD whose genetic defect is a premature stop codon. Unfortunately, the results from the initial trial did not show increased dystrophin levels after two weeks of gentamicin treatment. Indicators of muscle breakdown were reduced in the subjects, however, making these antibiotics an important line of investigation to continue. The results of the gentamicin clinical trial (February through September 2000) were published in April 2001 in the *Annals of Neurology*.

Batten Disease

Batten disease, the juvenile form of a group of disorders called neuronal ceroid lipofuscinoses (NCLs), is a fatal, inherited disease of the nervous system that begins in childhood. Early symptoms usually appear between the ages of 5 and 10, when a previously normal child begins to develop vision problems or seizures. Over time, affected children suffer mental impairment, worsening seizures, and progressive loss of sight and motor skills. Eventually, children with Batten disease become blind, bedridden, and demented, and the disease is often fatal by the late teens or twenties. Batten is caused by mutations in enzymes that are necessary for the normal breakdown of fats, sugars, and proteins inside the cell. As a result, these materials accumulate in the brain and elsewhere in the body, which leads to the characteristic effects on cognition and behavior.

NINDS currently funds several projects relevant to Batten disease and late infantile NCL, a closely related disorder. These studies are examining issues such as the molecular basis for the neuronal degeneration that occurs in Batten and related diseases, and the potential use of therapeutic agents to reduce the cell death that occurs in both the brain and the retina in association with the disease. Several of these studies are funded through FY 2003 and FY 2004.

Fabry Disease

Fabry disease is the second most common type of inherited metabolic storage disease. The disorder typically first appears during childhood or adolescence with recurrent episodes of severe pain in the extremities, characteristic skin lesions, and effects on the cornea. Several years ago researchers determined that the disease is caused by insufficient activity of the enzyme a-galactosidase A that normally degrades a lipid (fatty substance) called globotriaosylceramide. Without adequate enzyme activity, this lipid accumulates throughout the body, damaging the kidneys, heart, and blood vessels of the brain, causing death by the fourth or fifth decade. In the past, NINDS intramural scientists successfully isolated the critical enzyme from placental tissue, and showed that administration of the enzyme to individuals with Fabry disease reduced the levels of globotriaosylceramide in the blood. Lack of sufficient enzyme quantities hampered further tests. To overcome this limitation, scientists developed a procedure to prepare the enzyme using DNA technology and human cells in culture. With adequate supplies of enzyme in hand, researchers at NINDS conducted a phase I safety and dose-escalation clinical trial showing that enzyme therapy was safe and that it reduced globotriaosylceramide in the liver, blood, and urine. Moreover, several of the patients were able to permanently discontinue the medications they were taking for the pains in their hands and feet. This trial provided the basis for a double-blind placebo-controlled phase II clinical efficacy trial of enzyme replacement therapy in Fabry disease that recently confirmed the reduction of pain in the hands and feet in subjects, as well as improvements in kidney and heart function. Results of this trial (conducted FY 1999 through FY 2000) were reported in the *Journal of the American Medical Association* (*JAMA*) in June 2001.

Canavan Disease

Canavan disease is a rare, inherited neurological disorder characterized by spongy degeneration of the brain (in which the white matter is replaced by microscopic fluid-filled spaces). Symptoms of Canavan disease, which appear in early infancy and progress rapidly, may include mental retardation, loss of previously acquired motor skills, feeding difficulties, abnormal muscle tone (i.e., floppiness or stiffness), poor head control, and megalocephaly (abnormally enlarged head). Paralysis, blindness, or hearing loss

may also occur. The disease is not currently treatable, and death usually occurs by age four. Canavan disease is one of a group of genetic disorders called the leukodystrophies that affect growth of the myelin sheath of nerve fibers in the brain. The fatty myelin covering normally acts as an electrical insulator and is essential for proper nerve cell function.

Canavan disease is caused by inherited defects in the enzyme aspartoacylase (ASPA) encoded by the gene *ASPA*, which was discovered in 1993. An important focus for Canavan disease research has been the effort to develop a mouse model that carries this genetic mutation. A NINDS-supported scientist recently succeeded in creating a genetically engineered mouse model of Canavan disease, and results were published in early 2000. Funding for this project has been approved through FY 2002, and it is anticipated that this model will enable researchers to study how the gene defects harm the brain. The model will also be crucial for developing enzyme and gene therapy.

Friedreich's Ataxia (FRDA)

FRDA, the most common hereditary ataxia (disorder characterized by a loss of coordinated movement), is a progressive disease that impacts the nervous system, the heart, and the pancreas. The disease affects about 1 in 50,000 persons, or several thousand individuals in the United States. Loss of coordination, an unsteady gait, slurred speech, and other symptoms usually appear between the ages of 5 and 15 years. Eventually, most affected children experience an enlargement of the heart and progressive loss of muscle control, leading to motor incapacitation and wheelchair confinement. Most young people with this disease die in early adulthood.

The defective gene causing **FRDA**, identified in 1996, codes for a previously unknown protein called frataxin. This is the first triplet-repeat expansion implicated in an autosomal recessive disorder. The repeat, GAA in a non-coding region, causes too little frataxin to be made. A mitochondrial frataxin-like protein in yeast regulates iron metabolism, and following that lead, iron metabolism has been implicated in the human disorder.

At a recent international scientific workshop on **FRDA** co-hosted by NINDS, French investigators reported promising preliminary research results from a study of the drug compound idebenone. Idebenone was developed as a neuroprotective antioxidant for treatment of stroke and dementia but did not show efficacy in these uses. The French study was based on the hypothesis that the drug acts on iron metabolism pathways in **FRDA**, a subclass of oxidative metabolism for which an effect of idebenone might be achieved. The research results were sufficiently encouraging in reducing cardiomyopathy in **FRDA** that NINDS plans to initiate a study to determine the effectiveness of idebenone in the treatment of the disease. Sufficient supplies of the drug have been secured, and an Investigational New Drug (IND) application for a phase I dose-escalation trial is currently being prepared for submission to the FDA.

NINDS is also supporting research targeted to understanding the normal cellular function of frataxin, the molecular effects of GAA repeats on gene expression, and how mutations in frataxin lead to the pathological changes associated with the disease. Other studies also involve the development of an animal model of **FRDA** by disrupting expression of the frataxin gene. These studies are currently funded through FY 2002/FY 2003.

Ataxia Telangiectasia

Ataxia telangiectasia is an inherited disorder that causes progressive movement problems beginning usually between one and two years of age. In addition to loss of certain brain cells, children with this disease often suffer immune deficiency, increased likelihood of cancer, and abnormally high sensitivity to radiation. Most children are severely disabled by age 10, and many develop cancer. The disease is fatal, typically resulting in death in the second or third decade. Each year about 500 people inherit damaged copies of the relevant gene from both parents, and thus the disease ataxia telangiectasia. In 1995, scientists identified the previously unknown *ATM* gene which, when defective, causes ataxia telangiectasia. Subsequent study has revealed that the normal *ATM* gene helps prevent a cell from becoming cancerous when its DNA is damaged.

One study currently funded by NINDS through FY 2003 is exploring the mechanism underlying the increased sensitivity of individuals with ataxia telangiectasia to DNA-damaging agents, such as ultraviolet and infrared radiation. It is anticipated that this information will assist in understanding the affected individuals' susceptibility to cancer and in developing treatments for the disorder. Another project, funded through FY 2002, involves the large-scale analysis of DNA defects in ataxia telangiectasia patients, in order to better understand how specific mutations in the *ATM* gene lead to individual disease symptoms. It is also hoped that this knowledge will assist in the design of effective therapies.

Rett Syndrome

Rett syndrome is a severely disabling neurodevelopmental disorder that affects 1 in 10,000 to 15,000 females. Development is apparently normal until age 6-18 months. Diagnostic criteria include impaired expressive and receptive language, loss of acquired purposeful hand skills, and repetitive hand movements. Rett syndrome is often misdiagnosed as autism or cerebral palsy.

The genetic abnormality responsible for Rett syndrome interferes with the operation of one of the many biochemical switches that regulate how genes are expressed. Specifically, the disorder results from the mutation of the gene that makes methyl cytosine binding protein 2 (MECP2). MECP2 is the lynchpin in one of the elaborate networks of proteins needed to switch off a group of genes. In the absence of this genetic switch, certain genes fail to shut down, and excessive amounts of otherwise beneficial proteins are made. The molecular events leading to the children’s decline in their second year of life can be explained by the over-expression of specific genes that govern the development of the nervous system.

NINDS is currently supporting research on this syndrome that involves the use of cultured olfactory neurons biopsied from Rett patients as a model for understanding the molecular and cellular changes that lead to the degeneration of these neurons (funded through FY 2005).

Another NINDS-funded study involves extending previously conducted gene mapping studies as a step toward characterization of both the gene and the protein that are responsible for this disorder (funded through FY 2002).

Hutchinson-Gilford Progeria Syndrome

Hutchinson-Gilford progeria syndrome is an exceedingly rare disease that causes premature aging in children. A number of NIH Institutes are committed to enhancing research in this area. To this end, staff from NINDS, along with NHLBI, NICHD, NIAMS, ORD, and NIA, are working together to organize a scientific workshop on this form of progeria, planned for fall 2001. It is expected that this meeting will assist individual Institutes in identifying promising lines of investigation in this field and in stimulating research on this disorder.

Other Rare Diseases in Children

In addition to the disorders listed above, NINDS is extremely interested in many other rare diseases that affect children. This list includes (but is not limited to): fragile X syndrome, a disease similar to **FRDA** in that it is caused by expanded repeats of nucleotide sequences; Sturge-Weber syndrome, a congenital, non-familial disorder of vascular development that can affect the nervous system; disorders caused by mutations in Chromosome 18; and holoprosencephaly, a severe neurological birth defect caused by the failure of the cerebral hemispheres to separate into distinct left and right sides during development.

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

Program Actions on Rare Diseases in Children

Solicitations

"Rett Syndrome: Genetics, Pathophysiology, and Biomarkers" (PAS-99-037, revised as NOT-HD-00-001, jointly with NICHD, released 1/18/2000).

"Exploratory Grant in Pediatric Brain Disorders: Integrating the Science" (PAS-99-080, revised as NOT-NS-00-009, jointly with NICHD, NIMH, released 7/14/2000) includes **FRDA**, ataxia telangiectasia, Batten disease, DMD, fragile X syndrome, Sturge-Weber syndrome, holoprosencephaly, and many others.

"Development of Innovative Treatment Approaches to Autism" (RFA-MH-01-010, jointly with NIMH, NICHD, and NIDCD, released 11/29/2000) includes Rett syndrome.

"Research on Autism and Autism Spectrum Disorders" (PA-01-051, jointly with NIDCD, NIMH, NICHD, NIEHS, released 2/13/01) includes Rett syndrome.

Workshops and Meetings

The workshops/meetings sponsored by NINDS on rare diseases in children are often joint ventures with other NIH Institutes and frequently involve the participation of outside disease advocacy organizations. The following list provides information about the topics of workshops held in FY 2000 and those planned for the upcoming year.

Past Workshops

"Brain Fatty Acid Uptake, Utilization and Relevance to PB," held March 2-4, 2000; jointly sponsored by NINDS, NIDDK, NICHD, and ORD.

"Symposium on Hereditary Spastic Paraplegia," held March 16-18, 2000; jointly sponsored by NINDS, NICHD, and ORD.

"Conference on Cause and Treatment of FSH Dystrophy," held May 8-9, 2000; jointly sponsored by NINDS, NIAMS, and ORD.

"Workshop on Therapeutic Approaches for Duchenne's Muscular Dystrophy," held May 15-16, 2000; jointly sponsored by NINDS, NIAMS, and ORD.

"First Scientific Workshop of Hallervorden-Spatz Syndrome," held May 19-20, 2001; jointly sponsored by NINDS, NICHD, and ORD.

"Cerebral Blood Flow and Development Metabolism," held June 8-11, 2000; sponsored by NINDS.

"The Olfactory Model System and Rett and Kallmann Syndromes: Sniffing Out Insights into Brain Development," held September 12, 2000; jointly sponsored by NINDS, ORD, NIDCD, NIMH, and NICHD.

"International Conference on the Neuronal-Lipofuscinosis," held September 20-24, 2000; jointly sponsored by NINDS, NIDDK, and NICHD.

"Gene Therapy for Neurological Disorders," held October 23-24, 2000; jointly sponsored by NINDS and ORD. [Gene therapy for metabolic storage disorders, such as Batten and Fabry disease, were a focus of the meeting]

"From Gene to Function in Dystonia," held January 19-21, 2001; sponsored by NINDS.

Upcoming Workshops

"Hypertonic Movement Disorders Workshop," to be held April 22-24, 2001; jointly sponsored by NINDS and ORD. [Relevant to disorders in children that cause increased muscle tone, leading to rigidity, spasticity, and dystonia]

"Strategies for Therapy of MPS and Related Diseases," to be held June 21-24, 2001; jointly sponsored by NINDS, NIDDK, and NICHD.

"2001 CAG Triplet Repeat Disorders," a Gordon Conference, to be held July 15-19, 2001; jointly sponsored by NINDS and NIA.

"Mucolipin, TRPs and Human Disease," September 8-10, 2001; jointly sponsored by NINDS, NIDDK, NICHD, NIMH, and ORD.

"Fourth International Dystonia Symposium," to be held September 20-23, 2001; jointly sponsored by NINDS, NIA, NIAMS, and ORD.

"Neurobiology of Disease in Children Conferences," to be held October 17, 2001; jointly sponsored by NINDS, NIAMS, NICHD, and NIMH.

In addition to these meetings, a workshop on pediatric neurotransmitter diseases is planned for 2002.

National Institute of Nursing Research (NINR)

Overview of NINR Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NINR supports and conducts research and research training on the biological and behavioral processes that underlie the promotion of health, amelioration of illness and its sequelae, and effective delivery of care. NINR's rare diseases research in children portfolio describes and develops strategies to control, manage, and prevent biobehavioral complications of conditions such as autism, childhood cancers, epilepsy, and cystic fibrosis (CF).

Recent Scientific Advances in Rare Diseases in Children Research

The research projects discussed below were funded in FY 2000 and will be funded through FY 2001.

Childhood Leukemia

Standard therapy for children diagnosed with acute lymphoblastic leukemia (ALL) is intrathecal and systemic chemotherapy. NINR-supported research is investigating how long-term chemotherapeutic toxicities to the central nervous system (CNS) can be ameliorated. A study reported in the *Journal of Pediatric Psychology* (Moore, et al., 2001) determined whether prophylactic CNS chemotherapy for childhood ALL was associated with declines in neuropsychological abilities. Growth curve analysis was used to examine neuropsychological outcome and treatment-related change in children who were treated at two childhood cancer centers. A comprehensive test battery was administered at baseline (eight months) and at two, three, and four years post-diagnosis. Results indicated modest declines in arithmetic, visual motor integration, and verbal fluency. Intrathecal and systemic treatment was related to poorer visual motor integration at four years post-diagnosis and a faster rate of decline in visual motor integration skills than intrathecal treatment alone. Arithmetic proficiency at four years post-diagnosis was related to maternal education, but the rate of decline was not. Verbal fluency was unrelated to demographic or treatment variables. These findings suggest that neuropsychological outcome and declines are related to both demographic and treatment characteristics, depending on the cognitive domain examined. The investigator is currently addressing the cognitive and academic sequelae associated with CNS treatment in the first randomized intervention trial designed to prevent or minimize math deficits in children receiving treatment for ALL.

Another NINR-funded investigator is determining ways to lessen the adverse effects of adding dexamethasone to ALL therapy. Mounting evidence indicates that adding dexamethasone to the therapy for children and adolescents with ALL contributes to more positive long-term outcomes, such as lower rates of meningeal leukemia. However, the benefits are accompanied by adverse effects such as aberrant sleep and fatigue. The investigator is testing whether individualized dosing schedules based on patient sensitivity are effective in minimizing adverse effects while maintaining antileukemic effects. The goal of this study is to explicate the relationship between sleep efficiency and fatigue, and between sleep, fatigue, and systemic exposure to dexamethasone.

Epilepsy

NINR researchers are identifying factors that predict child adaptation to epilepsy. Research published in *The Journal of Neuroscience Nursing* (Sawin, et al., 2001) reports findings on campers with epilepsy who were 8-16 years of age. The purpose of the study was to examine the effect of a camp experience on their attitudes toward epilepsy. Most health care providers report anecdotally that a camping experience helps children and adolescents with chronic health conditions to develop more positive attitudes toward their condition, although children's and adolescents' perceptions have rarely been studied systematically. Attitudes, measured by the 13-item Child Attitude Toward Illness Scale (CATIS), were assessed before and after the camp experience. No pretest or posttest difference in attitude toward epilepsy was found in the total group. When attitudes were examined by seizure frequency, however, there was a trend for those with more frequent seizures to report a more positive attitude after the camp experience. The conclusion of this pilot study was that families might consider a camp experience for a child challenged with seizures.

Cystic Fibrosis (CF)

Advances in biomedical sciences and technology have made longer life spans possible for children with CF. This new generation of adolescents and young adults with CF present new management challenges for health care providers. NINR researchers are testing the effectiveness of an intervention to improve the quality of life of children with CF (8-12 years) by teaching them life skills for managing the psychosocial demands of chronic illness that impact their ability to understand and manage the physiologic and functional demands of CF. A recent publication in the *Journal of Pediatric Nursing* (Christian et al., 2000) reported that knowledge of the progression of CF and increasing social interactions with peers with CF during hospitalization helped children with CF learn that the disease is lifelong with relentless demands. The research is continuing with interventions focusing on strategies to promote peer support, a positive attitude, and the hope to create a sense of belonging, social competence, and well-being.

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

Ongoing Extramural Research

Autism

Autistic children and their families must cope with a chronic condition that is characterized by severe communication difficulties, social deficits, and aberrant behaviors. Interventions are needed to teach family members methods for promoting social interactions in these children. NINR is funding research that is specifically targeting fathers as the caretaker of autistic children. The objectives of the study are to describe the father-child reciprocity in the clinic and home setting, to compare and contrast father-child turn-taking with data obtained from mother-child turn-taking, and to evaluate the effect of an in-home training program on the acquisition of skills by fathers and the pre-communication skills by the children.

Family Experience of Genetic Testing

Current understanding of issues related to a genetic testing experience is based primarily on narrative accounts and clinical observations reflecting the perspective of health care professionals. Few studies have examined how individuals undergoing testing define and manage ethical issues during genetic testing. NINR is funding research to develop and test family-centered interventions for families who undergo genetic testing. Ethical issues that emerge during triple marker screening for Down syndrome and carrier testing for CF are being examined and are relevant to rare diseases research in children.

Workshops Related to Rare Diseases in Children

NINR received support from ORD to conduct a rare disease in children workshop for FY 2001 entitled, "Increasing the Number of Nurse Scientists in Cystic Fibrosis Research." The purpose of this workshop is to discuss ways to increase the pool of nurse scientists in this important area of rare disease research. Invited participants have expertise in numerous scientific disciplines such as nursing, medicine, immunology, exercise physiology, psychology, and nutrition. Topics to be addressed by the workgroup include identifying areas of interest to nurse researchers/clinicians in the field of CF, such as bio-behavioral symptom management of a chronic disease, self-esteem issues of teens and adolescents, novel dietary and exercise programs to ease progression of the disease, educational interventions for pharmacogenetic therapy, and caregiver issues. Research opportunities in the home care needs of CF patients and caregivers will also be discussed. This workshop will add to the body of knowledge for NINR in areas of management of symptoms for chronic disease, health disparities among at-risk populations, genetics, and respiratory care.

National Center for Research Resources (NCRR)

Overview of NCRR Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NCRR develops and supports critical research technologies that underpin health-related research to maintain and improve the health of our nation's citizens. NCRR supports shared resources, sophisticated instrumentation and technology, animal models for study of human disease, clinical research, and research capacity building for under-represented groups. Its mission is achieved through support of a series of grant mechanisms, including large infrastructure grants supporting animal resources, biotechnology, minority research programs, and clinical research. The term of these awards is usually three to five years. The way NCRR centers are configured, the entire Center is funded for a given time, but each individual subproject has a time table of its own (determined by the local governing body) that may even span grant cycles. Consequently, it is difficult to determine the duration of a given project hosted at our NCRR-supported sites.

Through its support of multidisciplinary research, NCRR is uniquely positioned either to provide primary research support or 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 in children. Expansion of NCRR's present efforts in new biotechnologies and instrumentation, development of animal models, and clinical research will foster interdisciplinary collaborations and advance NIH's efforts to study rare diseases of children.

Ongoing, New, and Planned Research Initiatives in Rare Diseases in Children

Animal Models

Kallmann's Syndrome

Kallmann's syndrome is a neurogenetic disease that affects an estimated 1 in 10,000 males. Patients with this disease suffer from anosmia (inability to smell) and retarded sexual development. These conditions arise because both olfactory nerve axons (and the luteinizing hormone-releasing hormone [LHRH] neurons that migrate with them) fail to make contact with the brain. Loss-of-function mutations in a gene located on the X (female) chromosome *KAL1* cause Kallmann's syndrome.

No useful mouse model for this disease is available. A monkey model is currently being developed by NCRR-supported investigators at the University of Nebraska Medical Center in collaboration with the Oregon Regional Primate Research Center. The researchers have obtained the sequence of the complete coding region of the monkey *KAL1* gene. Monkey *KAL1* protein is 97.4% similar to human *KAL1,* and analysis of *KAL1* expression in the developing rhesus macaque brain is under way. The researchers propose to obtain the basic information and to establish the necessary methodology to develop a functional model of Kallmann's syndrome in the rhesus macaque. The production of such animals would provide: 1) proof that this methodology could be used for the development of primate models of human diseases, 2) the first in vivo model of Kallmann's syndrome, and 3) a primate model to study the role of LHRH neurons in reproductive function.

Niemann-Pick Disease Type C (NPC)

A storage disorder, NPC is characterized by abnormal accumulation of fatty substances in small bodies within the cells known as lysosomes. This human disease presents with a variety of clinical features, including enlarged organs, jaundice, seizures, delayed mental and motor development, and premature death. Onset of NPC can occur over a wide age spectrum, resulting in its classification as infantile, juvenile, or adult (although the adult form is quite rare). Progression is usually slower in patients with later onset. In the United States, approximately 1,000 children are affected. The primary defect is associated with processing intracellular cholesterol. NCRR-supported investigators at Colorado State University have identified and characterized the gene responsible for the most common type of human NPC (*NPC1*) and a corresponding gene in cats. The researchers have further demonstrated that these genes are similar in 91% of their components. These findings will enable the investigators to characterize the cat NPC model on a molecular, biological, and physiological level and to evaluate various treatment modalities for this human disease. The most promising avenue of further research will be an evaluation of the efficacy of a ganglioside synthesis inhibitor as potential NPC therapy.

Biomedical Engineering and Instrumentation

Sickle Cell Anemia (SCA)

SCA is the most common inherited blood disorder in the United States, affecting about 72,000 predominantly African American (1 in 500) individuals in this country. SCA is characterized by episodes of pain, chronic anemia, and severe infections, usually beginning in early childhood. SCA is caused by an error in the gene that tells the body how to make hemoglobin (the oxygen-carrying component of the blood). This mutation results in the production of structurally abnormal hemoglobin chains, which instead of remaining separate in the cell, clump together into large, inflexible complexes. This abnormal aggregation deforms the red blood cells into curved ("sickle") shapes, causing them to block and rupture tiny blood vessels, depriving organs and tissues of oxygen and causing severe damage.

NCRR-supported investigators at the Rockefeller University have developed a method for producing structurally authentic recombinant hemoglobin molecules in yeast to assist in the study of interactions between hemoglobin chains. The use of recombinant hemoglobin has provided the ability to ask very specific questions about how changes in protein sequence affect protein interactions. The yeast system produces a recombinant sickle hemoglobin that is identical by approximately a dozen biochemical and physiological criteria with the natural sickle hemoglobin purified from the red cells of sickle cell anemia patients. More important, the gelling concentration of this recombinant sickle hemoglobin is the same as that of the sickle hemoglobin purified from human sickle red cells. Fundamental studies are being conducted into the interactions of normal and fetal hemoglobin in order to better understand the correlation between amino acid sequence changes and hemoglobin function. Results obtained thus far show that this system will be very helpful in defining the interactions in normal and sickle hemoglobin chains. This new model system will allow significantly more complex studies of protein interactions in normal and sickle hemoglobin. The more sophisticated understanding of basic biophysical processes at work in SCA may lead to more effective treatments.

Osteogenesis Imperfecta (OI)

OI is a disease that is caused by mutation in the alpha-1 or alpha-2 genes of type I collagen, a structural protein important in bone formation. Mutations can occur in many different positions, and there is currently no known correlation between position of mutation and severity of the disease. An understanding of the nature of the factors that promote stability in the collagen triple helix will give insight into the pathology of the disease. Mutations in the collagen protein chain change its structure and therefore its interaction with other chains to form these important larger structures. NCRR-supported investigators at the University of California at San Francisco have developed computer modeling that has contributed to an understanding of how normal collagen molecules interact to form larger, more stable structures in order to determine the factors that contribute to a loss of stability in that interaction when mutations occur. Molecular dynamics simulations of collagen-like peptides show average structures and internal coordinates similar to x-ray crystallographic structures. These results demonstrate that molecular dynamics can be used to reproduce the experimental structures of fibril proteins by adaptation of software originally designed to model more conventional globular proteins. New information on protein interactions and structure have been reported.

Although fundamental in nature and in its infancy, this work extends the use of computational techniques to the realm of fibril proteins and has provided insight into the way collagen chains interact. Ultimately, an understanding of what factors are responsible for variations in the severity of OI may lead to effective treatments.

Clinical Research Applications

Peroxisomal Disorders

NCRR-supported investigators at the Johns Hopkins University have described an assay useful in testing for the presence of very long chain fatty acids, a blood abnormality observed in the so-called peroxisomal disorders such as Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum syndrome. These investigators extended the test to amniocytes and the outermost cells of the membrane surrounding the fetus, thus providing a prenatal test to predict the likelihood of the fetus being affected by these diseases. The investigators report results of 255 prenatal assays identifying 63 affected males. Five families elected to continue the pregnancies, and the abnormality has been confirmed in all these offspring. Among the fetuses that were aborted, the diagnosis was confirmed on autopsy in all. Among those determined by the assay to be unaffected, Zellweger syndrome has been ruled out in all. After 10 years of follow-up, no case of adrenoleukodystrophy has been manifested. Due to the heterogenous presentation of adrenoleukodystrophy, however, these findings are promising but not definitive. Thus, a sensitive and discriminating assay appears to be available for prenatal diagnosis of these serious rare diseases of childhood.

Cystic Fibrosis (CF)

CF is an inherited disease affecting transport of secretions. Thick lung secretions make children with CF particularly vulnerable to lung infections. *Pseudomonas aeruginosa* infections are particularly problematic in this population. NCRR-supported investigators at the University of Washington reported the results of two multicenter, double-blind, placebo-controlled trials of intermittent administration of

tobramycin (an inhaled antibiotic). A total of 520 patients with CF and pulmonary infection with *P. aeruginosa* infection were randomly assigned to receive either 300 mg of inhaled tobramycin or placebo twice daily for 4 weeks, followed by 4 weeks with no study drug. Patients received treatment or placebo in 3 off-on cycles for a total of 24 weeks. The patients treated with inhaled tobramycin experienced improved lung function (a 10% increase in FEV1, a measure of airway compliance), while patients receiving placebo had a statistically significant 2% decline in this measure. In the tobramycin group, the density of *Pseudomonas* in the sputum decreased by an average of 0.8 log colony-forming units, compared with an increase of 0.3 log units in the placebo group. These differences were statistically significant. The patients in the tobramycin group were 26% less likely to be hospitalized for antibiotic treatment of *Pseudomonas* infection than those in the placebo group. Inhaled tobramycin was not associated with detectable toxicity of the ear or kidney or with accumulation of the drug in serum. In summary, inhaled tobramycin was well-tolerated, had no serious side effects, and improved pulmonary function, decreased the density of *Pseudomonas* in sputum, and decreased the risk of hospitalization.

Severe Combined Immunodeficiency (SCID)

NCRR-supported investigators at Duke University summarized their experience with 89 consecutive patients treated for inborn errors of the immune system classified as SCID. Patients were treated with bone marrow transplantations and were surveyed between 3 months to 16.5 years post-transplantation. Of particular interest were the relative outcomes of patients receiving genetically matched (HLA-identical) versus genetically half-matched (HLA-haploidentical) donations of marrow. While some patients have a sibling with the identical histocompatibility genes, others do not and must rely on a donation from a parent, who is only half- or haploidentical. The exactness of the match is important because although the patient (having no immune system) cannot reject the donated marrow, the marrow, once reconstituting the immune system, can recognize the recipient's body as foreign and cause a serious condition known as graft versus-host disease (GvHD).

The hope is to maximize the chance for rebuilding the immune system while minimizing the chance of rejection. It was theorized that if the donor bone marrow was first depleted of T cells (those cells associated with GvHD) before transplantation, that both conditions would be satisfied. In reviewing the data, these investigators reported an overall 81% survival rate. Those 12 having had transplantations with immunologically identical donors were all alive. Sixty of 77 (78%) of those who received half-identical donations were alive. The latter group included two of three who, in addition to the bone marrow, received placental blood as a source of stem cells. Other factors favoring survival were gender, ethnicity, and age at transplant. All the transplanted girls survived, whites had a better survival than blacks or Hispanics, and 95% versus 76% of children transplanted before the age of 3.5 months survived. There were no deaths attributed to GvHD, although one recipient (of a half-matched donation plus placental blood) is being treated with continuous cyclosporine for chronic GvHD.

Future Plans for Research Activities

NCRR does not plan to issue any specific requests for applications, requests for proposals, program announcements, or workshops in the area of rare diseases in children during FY 2001- FY 2005. Through its support of unique resources, NCRR contributes a significant portion of its budget to rare diseases in general and to rare disease in children in particular. The demand for NCRR-supported

resources determines scientific and funding shifts. Therefore, future increases in rare diseases research in children supported by other components of NIH will result in corresponding NCRR increases.

Of note is that NCRR cosponsors a network of National Gene Vector Laboratories. These facilities are composed of an interactive group of academic laboratories functioning through a cooperative agreement and charged with providing vectors for clinical trials to eligible investigators in the gene therapy field. Through a request for applications in FY 2001, NCRR and its co-sponsors are seeking submission of competing grant applications for this resource, which has been and will continue to be instrumental in advancing the study of genetic diseases, including rare diseases in children. Successful applicants may be approved for funding through FY 2006.

National Library of Medicine (NLM)

Overview of NLM Rare Diseases in Children Research Activities, FY 2000 - FY 2005

NLM provides information resources useful to rare disease research and to those seeking information about conditions affecting themselves or their families.

In addition to providing informational support for all rare diseases (including those in children) through the NLM collection, PubMed, MEDLINEplus, ClinicalTrials.gov, and numerous other products and services, several ongoing NLM activities are specifically related to rare diseases in children, including:

- Online Multiple Congenital Anomaly/Mental Retardation Syndromes (see 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.

- A special bibliography on "Phenylketonuria (PKU): Screening and Management" (see http://www.nlm.nih.gov/pubs/cbm/pku.html) in the NLM's popular *Current Bibliographies in Medicine* series. (Published in 2000)

National Center for Biotechnology Information (NCBI)

The NCBI, a division of 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.

Online Mendelian Inheritance in Man (OMIM)

The OMIM database 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 World Wide Web by NLM.

Malaria

Malaria is estimated to cause more than one million deaths each year worldwide. The vast majority of deaths occur among young children in Africa. NLM chairs the Communications Working Group of the Multilateral Initiative on Malaria, which began in 1997. The objective is to support African scientists and the ability of malaria researchers to connect with each other 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 (see http://www.mimcom.net).

Additionally, NLM, in collaboration with 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.

Office of Dietary Supplements (ODS), Office of Disease Prevention, Office of the Director, NIH

Overview of ODS Rare Diseases in Children Research Activities, FY 2000 - FY 2005

The mission of ODS is to coordinate research at NIH on dietary supplements and to provide the public, practitioners, and other stakeholders with reliable information about these ingredients. Dietary supplements (which include vitamins, minerals, herbals, botanicals, metabolic intermediates, amino acids, and a number of other ingredients) are regulated by the FDA under the terms of the Dietary Supplement Health and Education Act (DSHEA) of 1994. DSHEA stipulates that products in this category may not be marketed for the treatment, prevention, mitigation, or cure of any disease. The DSHEA stipulation makes it appear that these ingredients should not be relevant to the management of children with rare diseases. In reality, there are two issues that make us reconsider the relevance of dietary supplement ingredients to rare diseases in children:

- Some of the ingredients marketed in the dietary supplement category are also available as orphan drugs or as over-the-counter preparations.

- Parents of children with a number of rare diseases (examples include, but are not limited to, Zellweger syndrome and related peroxisomal disorders, mitochondrial abnormalities, and some forms of attention deficit hyperactivity disorders [ADHDs]) look for answers to their children's care in unconventional places, including the use of ingredients, or combinations of ingredients, that are available as dietary supplements.

ODS, in collaboration with NICHD and other Institutes, organized a workshop on "Dietary Supplement Use in Children" held at NIH in February 2001. Ms. Abby Meyers, President of the National Organization of Rare Disorders, spoke about "Valid Medical Uses for Supplements" and emphasized that products marketed as orphan drugs for rare disease treatment (such as carnitine for a number of metabolic conditions) can often be obtained as dietary supplements, off the shelf, in food stores, pharmacies, and nutrition stores, but that these products are not in any way controlled for quality in the manner that the orphan drug version is. Sadly, some parents cannot afford the "orphan drug" version and settle, incautiously, for the dietary supplement version. ODS will continue to encourage research into the efficacy and safety of ingredients sold as dietary supplements, recognizing that these products should not be considered substitutes for orphan drugs.

Although dietary supplements cannot be marketed for disease treatment, this fact does not prevent consumers from using them in this manner when they are desperate for solutions to their children's intractable disease. Because of the rapid dissemination of information (through parent support groups and via the Internet) about unconventional treatments, all too often the use of these treatments far outstrips the scientific studies to support that use. ODS will continue to support research that is aimed at demonstrating efficacy and safety, in collaboration with other NIH Institutes and other Federal agencies.

While ODS does not have a specific research agenda in mind for the study of dietary supplement ingredients that are relevant to rare diseases in childhood, there is a general strategy that ODS will use to support research in this area:

- Establish the base of scientific studies in the area. This often requires an evidence-based review of the existing literature in order to identify gaps in knowledge about ingredients used in particular clinical situations. The ODS evidence-based review program for dietary supplements is guided by a Federal working group (including NIH, FDA, Agency for Healthcare Research and Quality [AHRQ], as well as other Department of Health and Human Services [DHHS] and non-DHHS members) that assists ODS in setting priorities and providing guidance to AHRQ's Evidence-Based Practice Centers, which conduct the reviews.

- Work with NIH Institutes, other Federal agencies, and private-sector organizations to support research activities that might include basic biological studies, clinical studies, epidemiologic surveys, and outcomes research.

Office of Medical Applications of Research (OMAR), Office of Disease Prevention, Office of the Director, NIH

Overview of OMAR Rare Diseases in Children Research Activities, FY 2000 - FY 2005

FY 2000

No pertinent activities**.**

FY 2001

Consensus Development Conference: Phenylketonuria (PKU): Screening and Management, October 16-18, 2000.

Classical PKU is a rare metabolic disorder (and orphan disease) affecting approximately one of every 15,000 infants in the United States. PKU usually results from a deficiency of a liver enzyme known as phenylalanine hydroxylase. This enzyme deficiency leads to elevated
levels of the amino acid phenylalanine in the blood and other tissues. The untreated state is characterized by mental retardation, microcephaly, delayed speech, seizures, eczema, behavior abnormalities, and other symptoms.

In October 2000, NIH held a consensus development conference on "Phenylketonuria (PKU): Screening and Management." NIH Consensus Statements are prepared by a non-advocate, non-Federal panel of experts, based on: 1) presentations by investigators working in areas relevant to the consensus questions during a two-day public session, 2) questions and statements from conference attendees during open discussion periods that are part of the public session, and 3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government. The report is available online at http://consensus.nih.gov.

FY 2002 - FY 2005

No activities planned yet.

Office of Rare Diseases (ORD),
Office of Disease Prevention, Office of the Director, NIH

Overview of ORD Rare Diseases in Children Research Activities, FY 2000 - FY 2005

ORD was developed to stimulate and coordinate research in rare diseases, which are defined as affecting fewer than 200,000 patients in the United States. ORD uses several approaches to leverage its resources to improve the understanding of the approximately 6,000 conditions that are considered "rare," many of which affect children.

Databases on Clinical Trials

ORD developed and maintained the Rare Diseases Clinical Research Database (RDCRD) and incorporated it into the ORD Web site. In FY 2001, ORD worked with the National Library of Medicine (NLM) to mesh RDCRD with the new ClinicalTrials.gov database. This database describes research protocols and provides contact information for principal investigators, thereby facilitating public access to clinical trials and studies.

Scientific Workshops

ORD collaborates with the Institutes and Centers at NIH to stimulate research by sponsoring scientific workshops. The outcomes of these workshops include the establishment of research priorities, development of collaborative research protocols, and agreements and criteria for diagnosing and monitoring rare diseases. Workshops have consistently supported the exchange of ideas among investigators, voluntary patient support groups, and NIH and have resulted in stimulating new research. Workshops that had a specific focus on rare diseases in children have been listed in this report by the respective Institutes and Centers.

Information Center

ORD is currently providing information on rare diseases through its Web site or in response to telephone or written inquiries. Since the number of direct requests has been ever-increasing despite the information sources available through the ORD Web site, ORD and the National Human Genome Research Institute (NHGRI) are in the process of establishing an Information Center to respond to inquiries about rare and genetic disorders. The Information Center will be operational late in FY 2001 and will provide access to existing information and develop new materials to be included in an interactive Web site. Information for health care providers and the public will include: 1) information about the disease or condition; 2) locations of genetic counseling centers available for consultation; 3) summaries and locations of current and planned research related to rare diseases and genetic disorders; 4) names, locations, and types of printed or audiovisual materials provided by voluntary patient support groups; and 5) disease-specific fact sheets. In addition to the Web site, the Information Center will operate a toll-free telephone information service to respond to inquiries about rare diseases and genetic disorders for those without access to the Internet or e-mail.

Medical Genetics and Rare Diseases Database in the Combined Health Information Database

In 1998, ORD and NHGRI developed the Medical Genetics and Rare Diseases Database in the Combined Health Information Database (CHID). Information available from nearly 1,500 voluntary patient support groups is now readily accessible from the CHID Web site.

Initiatives in FY 2002 and Beyond

Rare Diseases Research Centers of Excellence

With additional funding, ORD is planning to respond to the critical needs of patients with rare, life-threatening conditions, including children, by implementing at least one intramural Center of Excellence for patients in whom a diagnosis has been elusive despite extensive efforts to determine the exact nature of the problem. This pilot Center of Excellence is to be followed by four or more regional research centers across the United States.

Scientific Workshop Program

In addition, ORD expects to expand its program of cosponsoring scientific workshops with the NIH ICs. Currently, ORD is funding approximately 50 workshops a year. These workshops on rare diseases research are funded either if a particular scientific opportunity exists or if very little if any research is currently under way. Preliminary findings from an evaluation of the workshops show that the workshops are an effective means of generating research ideas and grant applications in rare disease areas that otherwise might not attract much attention.

Acronyms

AA	aplastic anemia
AARDCs	Asthma and Allergic Diseases Research Centers
AARP	American Association of Retired Persons
AAV	adeno-associated virus
ACC	adrenal cortical carcinoma
ADHD	attention deficit hyperactivity disorder
ADKPD	autosomal dominant polycystic kidney disease
AGS	Alagille syndrome
ALL	acute lymphoblastic leukemia
ALPS	autoimmune lymphoproliferative syndrome
ALS	amyotrophic lateral sclerosis
AML	acute myelogenous leukemia
APS	antiphospholipid syndrome
ARHQ	Agency for Healthcare Research and Quality
ARPKD	autosomal recessive polycystic kidney disease
ART	antiretroviral therapy
ARVD	arrhythmogenic right ventricular dysplasia
ASPS	advance sleep phase syndrome
AT	ataxia telangiectasia
ATM	ataxia telangiectasia mutated
ATP	adenosine triphosphate
BA	biliary atresia
BAMF	Brief Assessment of Motor Function
BBS	Bardet-Biedl syndrome
BLS	bare lymphocyte syndrome
BM	bone marrow
BMPR2	bone morphogenetic protein receptor II
BPD	bronchopulmonary dysplasia
BWS	Beckwith-Wiedemann syndrome
CACP	camptodactyly-arthropay-coxa vara-pericarditis
CASG	Collaborative Antiviral Study Group
CATIS	Child Attitude Toward Illness Scale
CC	Warren Grant Magnuson Clinical Center, NIH
CDC	Centers for Disease Control and Prevention
CDG	congenital disorders of glycosylation
CDGS	carbohydrate-deficient glycoprotein syndrome
CDH	congenital diaphragmatic hernia
CF	cystic fibrosis
CFTR	CF transmembrane conductance regulator
CGD	chronic granulomatous disease
CHAQ	Childhood Health Assessment Questionnaire
CHID	Combined Health Information Database
CHTN	Cooperative Human Tissue Network

CIDR	Center for Inherited Disease Research
CJD	Creutzfeldt-Jakob disease
CL/P	clefts of the lip with or without cleft palate
CLPED1	CL/P-ectodermal dysplasia syndrome type 1
CLS	cholestasis-lymphedema syndrome
CMV	congenital cytomegalovirus
CNC	Carney complex
CNS	central nervous system
COG	Children's Oncology Group
CRADA	Cooperative Research and Development Agreement
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocytes
DCB	Division of Cancer Biology
DCGR	DiGeorge chromosomal region
DES	diethylstilbestrol
DHHS	U.S. Department of Health and Human Services
DIR	Division of Intermural Research
DLD	developmental language disorder
DM	myotonic dystrophy
DMD	Duchenne's muscular dystrophy
DSHEA	Dietary Supplement Health and Education Act of 1994
EDS	Ehlers-Danlos syndrome
ELST	Endolymphatic sac tumor
ESRD	end-stage renal disease
FA	Fanconi anemia
FAS	fetal alcohol syndrome
FCD	focal cortical dysplasia
FDA	U.S. Food and Drug Administration
FGFR3	fibroblast growth factor receptor 3
FHB	familial hyperbileacidemia
FHBL	familial hypobetalipoproteinemia
FHC	familial hypertrophic cardiomyopathy
FHH	familial homozygous hypercholesterolemia
FHL	familial hemophagocytic lymphohistiocytosis
fMRI	functional magnetic resonance imaging
FMRP	fragile X mental retardation protein
FPLD	familial partial lipodystrophy
FPPH	familial primary pulmonary hypertension
FRDA	Friedreich's ataxia
FSGS	focal segmental glomerulosclerosis
FSHD	facioscapulohumeral muscular dystrophy
FY	fiscal year
GAVI	Global Alliance for Vaccines and Immunization
GBS	group B streptococci
GCPS	Greig cephalo polysyndactyly syndrome
GH	growth hormone

GHIGF	growth hormone-insulin-like growth factor
GP I	glycoprotein complex I
GRA	glucocorticoid remediable aldosteronism
GvHD	graft versus host disease
HCM	human hypertrophic cardiomyopathy
HDL	high-density lipoprotein
HGP	Human Genome Project
HHT	hereditary hemorrhagic telangiectasia
Hib	*Haemophilus influenzae* type B
HIE	hyperimmunoglobulin E recurrent infection (syndrome)
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPE	holoprosencephaly
HSV	*herpes simplex* virus
ICSBP	interferon consensus binding protein
IDF	Immune Deficiency Foundation
IND	Investigational New Drug
IP	incontinentia pigmenti
IR	ionizing radiation
IS	idiopathic scoliosis
ITP	immune thrombocytopenic purpura
JRA	juvenile rheumatoid arthritis
LADII	leukocyte adhesion deficiency II (syndrome)
LAM	lymphangioleiomyomatosis
LDL	low-density lipoprotein
LHRH	luteinizing hormone-releasing hormone
LQTS	long QT syndrome
LSD	lysosomal storage disease
LVAS	large vestibular aqueduct syndrome
MECP2	methyl cytosine binding protein 2
MHC	major histocompatability complex
MKS	McKusick-Kaufman syndrome
MODY	maturity onset diabetes of the young
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MSH	Multicenter Study of Hydroxyurea
NAEC	National Advisory Eye Council
NBS	Nijmegen breakage syndrome
NCBI	National Center for Biotechnology Information
NCCAM	National Center for Complementary and Alternative Medicine
NCI	National Cancer Institute
NCL	neuronal ceroid lipofuscinosis
NCRR	National Center for Research Resources
NEI	National Eye Institute
NGF	nerve growth factor
NHGRI	National Human Genome Research Institute

NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on 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
NIGMS	National Institute of General Medical 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
NISP	National Infant Sleep Position (study)
NLM	National Library of Medicine
NMDA	N-methyl-D-aspartate
NO	nitric oxide
NOS	nitric oxide synthase
NPC	Niemann-Pick type C
OAR	Office of AIDS Research (Office of the Director, NIH)
OD	Office of the Director, NIH
ODS	Office of Dietary Supplements (Office of the Director, NIH)
OI	osteogenesis imperfecta
OMIM	Online Mendelian Inheritance in Man
ORD	Office of Rare Diseases (Office of the Director, NIH)
ORWH	Office of Research on Women's Health (Office of the Director, NIH)
PA	program announcement
PANDAS	pediatric autoimmune neuropsychiatric disorders associated with streptococcus
PAP	pulmonary alveolar proteinosis
PAR	Pediatric Activity Record
PBD	peroxisomal biogenesis disorder
PCD	primary ciliary dyskinesia
PCNA	proliferating cell nuclear antigen
PDMS	Peabody Developmental Motor Scales
PDMS2	Peabody Developmental Motor Scales, 2nd Edition
PEA-BP	prepubertal and early adolescent bipolar disorder
PEDI	Pediatric Evaluation of Durability Inventory
PEGT	Programs of Excellence in Gene Therapy
PHA	Pulmonary Hypertension Association
PKD	polycystic kidney disease
PKU	phenylketonuria
PLS	Papillon-Lefevre syndrome
PNH	paroxysmal nocturnal hemoglobinuria
PPH	primary pulmonary hypertension
PPHN	persistent pulmonary hypertension of the newborn

PXE	pseudoxanthoma elasticum
RB	retinoblastoma
RDCRD	Rare Diseases Clinical Research Database
RFA	request for application(s)
RNA	ribonucleic acid
ROP	retinopathy of prematurity
RUPP	Research Unit of Pediatric Psychopharmacology
SADDAN	severe achondroplasia with developmental delay and acanthosis nigricans
SAMHSA	Substance Abuse and Mental Health Services Administration
SCA	sickle cell anemia
SCD	sickle cell disease
SCID	severe combined immunodeficiency
SCOR	Specialized Center(s) of Research
SHH	*Sonic hedgehog* (gene)
SIDS	sudden infant death syndrome
SIV	simian immunodeficiency virus
SLE	systemic lupus erythematosus
SLO	Smith-Lemli-Opitz (syndrome)
STOP-ROP	Supplemental Therapeutic Oxygen for Pre-threshold Retinopathy of Prematurity (study)
SVAS	supravalvular aortic stenosis
TD	thanatophoric dysplasia
TGIF	TG-interacting factor
TSC	tuberous sclerosis complex
TSE	transmissible spongiform encephalopathies
TTP	thrombotic thrombocytopenic purpura
UCB	umbilical cord blood
VCFS	velocardiofacial syndrome
VHL	von Hippel-Lindau (disease)
VLBW	very low-birthweight
VLDL	very low-density lipoprotein
vWF	von Willebrand factor
WAS	Wiskott-Aldrich syndrome
WBS	Williams-Beuren syndrome
WHO	World Health Organization
WS	Waardenburg's syndrome
WMS	Williams syndrome
XHIM	x-linked hyper-IgM syndrome
XSCID	x-linked severe combined immunodeficiency

Index

National Institutes of Health

Office of Rare Diseases

31 Center Drive, MSC 2084, Building 31, Room 1B19
Bethesda, Maryland 20892–2084
Telephone: 301–402–4336
Fax: 301–480–9655
E-mail: hh70f@nih.gov
Web site: http://rarediseases.info.nih.gov/ord

Staff

Henrietta D. Hyatt-Knorr
Acting Director

Mary Demory
Program Analyst

John H. Ferguson, M.D.
Medical Advisor

Michael Evnin
Information Specialist

Stephen C. Groft, Pharm.D.
Director (currently away on detail)