DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Report to Congress on Implementation of the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001

February 2005

TABLE OF CONTENTS

Introduction

In December 2001, President George W. Bush signed into law the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (the MD-CARE Act, Public Law 107-84). According to the major provisions of the Act:

- The Director of the National Institutes of Health (NIH), working with the Directors of the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Child Health and Human Development (NICHD), shall *expand and intensify research* on the muscular dystrophies.
- The NIH shall *establish centers of excellence* for research on muscular dystrophy.
- The NIH shall *facilitate sharing of tissue and genetic samples* for muscular dystrophy research.
- The Secretary of Health and Human Services (HHS) shall *establish the Muscular Dystrophy Coordinating Committee* (MDCC) with two-thirds Government and one-third public members.
- The *Coordinating Committee shall develop a plan* for conducting and supporting research and education on muscular dystrophy through the national research institutes.
- The Secretary, acting through the Director of the Centers for Disease Control and Prevention (CDC), may award grants and provide technical assistance for collection, analysis, and reporting of data on muscular dystrophy and for the purpose of carrying out *epidemiological activities* regarding muscular dystrophy.
- The Secretary shall establish a program to *provide information and education* on muscular dystrophy to health professionals and the general public.
- The Secretary shall enter into a *contract with the Institute of Medicine to study and make recommendations regarding centers of excellence at the NIH.*
- The Secretary shall annually *report to Congress on the implementation* of the Act.

This report is presented as an annual report to Congress on the implementation of the Act. This is the third annual report.

Background

The muscular dystrophies are a group of diseases that cause weakness and progressive degeneration of skeletal muscles. There are many different forms of muscular dystrophy (MD), which differ in their age of onset, severity, and pattern of muscles affected. Most types of MD are, in fact, multisystem disorders with manifestations in body systems including the heart, gastrointestinal system, endocrine glands, skin, eyes, and other organs. Mode of inheritance, severity, and the pattern of muscles affected vary among the many forms of MD.

Types of Muscular Dystrophy: Duchenne muscular dystrophy (DMD) is the most common childhood form of muscular dystrophy. DMD usually becomes clinically evident at walking.

Patients typically require a wheelchair by age 10 to 12 and die in their late teens or early 20s. More than 15 years ago, researchers supported by the NIH and the Muscular Dystrophy Association identified the gene for the protein dystrophin which, when absent, causes DMD. The dystrophin gene is the largest known gene in humans. Since the gene is on the X-chromosome, this disorder affects primarily males. Females who are carriers have milder symptoms. Sporadic mutations in this gene occur frequently, accounting for a third of cases. The remaining two-thirds of cases are inherited in a recessive pattern. Becker muscular dystrophy (BMD) is a less severe variant of the disease and is caused by the production of a truncated, but partially functional form of dystrophin. Dystrophin is part of a complex structure involving several other protein components. The "dystrophin-glycoprotein complex" helps anchor the structural scaffold within the muscle cells, through the outer membrane of each cell, to the tissue scaffold that surrounds each cell. Due to defects in this assembly, contraction of the muscle leads to disruption of the outer membrane of the muscle cells and eventual weakening and wasting of the muscle.

Myotonic dystrophy is the most common adult form of muscular dystrophy. It is marked by myotonia (an inability to relax muscles following contraction) as well as muscle wasting and weakness. Myotonic dystrophy varies in severity and manifestations and affects many body systems in addition to skeletal muscles, including the heart, endocrine organs, eyes, and gastrointestinal tract. Myotonic dystrophy follows an autosomal dominant pattern of inheritance. This means that the disorder can occur in either sex when a person inherits a single defective gene from either parent. Myotonic dystrophy results from the expansion of a short repeat in the DNA sequence (CTG in one gene or CCTG in another gene). More simply put, the inherited gene defect is an abnormally long repetition of a three- or four-letter "word" in the genetic code – normally, this "word" is repeated a number of times, but in people with myotonic dystrophy, it is repeated many more times. This molecular change may remove proteins that interact with this repeat and, in doing so, interfere with the production of other important muscle proteins.

Facioscapulohumeral muscular dystrophy (FSHD) initially affects muscles of the face (facio), shoulders (scapulo), and upper arms (humeral) with progressive weakness. Symptoms usually develop in the teenage years. Life expectancy is normal, but some affected individuals become severely disabled. The pattern of inheritance is, like myotonic dystrophy, autosomal dominant, but the underlying genetic defect is poorly understood. Most cases are associated with a deletion near the end of chromosome 4.

The limb-girdle muscular dystrophies (LGMDs) all show a similar distribution of muscle weakness, affecting both upper arms and legs. Many forms of LGMD have been identified, showing different patterns of inheritance (autosomal recessive vs. autosomal dominant). In an autosomal recessive pattern of inheritance, an individual receives two copies of the defective gene, one from each parent. The recessive LGMDs are more frequent than the dominant forms, and usually have childhood or teenage onset. The dominant LGMDs usually show adult onset. Some of the recessive forms have been associated with defects in proteins that make up the sarcoglycan complex, which, along with dystrophin, helps anchor muscle cells to the surrounding

tissue scaffold. Mutations in the gene for one form of sarcoglycan can cause severe childhood autosomal recessive muscular dystrophy. Mutations in other genes are implicated in other forms of LGMD, and the relation of these genes to the sarcoglycan complex is not clear.

The congenital muscular dystrophies, another class of muscular dystrophies, also include several disorders with a range of symptoms. Muscle degeneration may be mild or severe. Problems may be restricted to skeletal muscle, or muscle degeneration may be paired with effects on the brain and many other organ systems. Defects in the proteins merosin and integrin alpha-7 are responsible for many of the cases in the United States. Other cases are due to novel defects in a closely related protein, integrin. Mutations in the genes for proteins called fukutin and fukutin-related protein cause the most common forms of congenital muscular dystrophy found in Japan. All of these proteins are thought to have some relationship to the dystrophin-glycoprotein complex and to the connections between muscle cells and their surrounding scaffold.

Several other forms of MD also occur. Emery-Dreifuss MD is an X-linked inherited form. Defects in a previously unknown protein, called emerin, are responsible. Another form, oculopharyngeal MD, has been attributed to a short triplet repeat expansion in the poly-A binding protein 2 gene, a gene involved in translating the genetic code into functional proteins.

Available Treatments: Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Symptomatic treatment, though not able to stop disease progression, may improve the quality of life for some individuals. Options include physical therapy, appliances used for support, corrective orthopedic surgery, and drugs. Steroids can slow the progression of DMD, but there are side effects. However, several therapeutic approaches have shown promise in animal models and some early trials in humans have begun. Gene therapy is one promising area of research. In addition, a current clinical trial is exploring the use of the antibiotic gentamicin in DMD and LGMD patients. Other therapeutic approaches are also showing promise in culture and animal models, including cell-based therapies, functional compensation for dystrophin by upregulation of certain proteins, and increasing muscle mass via inhibition of other proteins that negatively regulate muscle growth.

Overview of NIH Programs

The National Institute of Neurological Disorders and Stroke, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Institute of Child Health and Human Development are the three main Institutes at NIH involved in the implementation of the MD-CARE Act. Other Institutes and Centers at NIH support activities relevant to MD as well.

National Institute of Neurological Disorders and Stroke (NINDS): The NINDS supports intramural and extramural research on many forms of the muscular dystrophies ranging from basic studies of normal protein function through projects on gene, stem cell, and drug therapies at levels from the development of experimental therapeutics through clinical trials. The NINDS also continues to support a very active portfolio of basic research on the neuromuscular junction,

the terminal between a nerve cell and muscle fiber. Much of this basic research is critical to advancing our understanding of the mechanisms underlying the muscular dystrophies. Since the Muscular Dystrophy Association and the NINDS supported the discovery in 1987 that dystrophin mutations cause DMD and BMD, NINDS has supported much subsequent work on understanding the role and function of the dystrophin-glycoprotein complex both in normal muscle and in MD-affected muscle tissue. The NINDS funds research relevant to understanding the molecular and genetic basis of FSHD, as well as research relevant to myotonic dystrophy, LGMD, and other forms of MD and neuromuscular disorders. Another area of focus is the improved diagnosis of the muscular dystrophies.

The NINDS also funds clinical research on MD and is currently funding a clinical trial to test the potential of the compound gentamicin as a therapy for DMD and LGMD. Gentamicin is one member of the class of compounds known as aminoglycosides, which are a type of antibiotics widely used to treat bacterial infections. The NINDS also funds translational research projects focused on the identification and preclinical testing of new therapeutics, including a project through the Institute's translational research program to design, test, and produce a viral vector for potential use in a gene therapy trial for DMD patients.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS): The NIAMS funds considerable research to advance the understanding of the cellular and molecular mechanisms of muscle degeneration associated with the muscular dystrophies and to develop potential strategies for the treatment of these and other muscle disorders. The Institute supports basic research projects to study normal muscle development and pathophysiology of muscle disorders using animal models and cells from human subjects. Other basic studies investigating the capacity of healthy muscle tissue to regenerate after injury have led to the identification and characterization of muscle stem cells and other cell types that can serve as precursors for muscle. These efforts have increased our understanding of the changes that occur during development, in the course of disease, and in response to injury. Discoveries from these basic projects have led to promising strategies for the treatment of degenerative muscle diseases including gene- and cell-therapies. The NIAMS supports several projects aimed at developing and testing recombinant viruses engineered to be vehicles for the delivery of therapeutic genes that may block or reverse muscle degeneration. NIAMS-supported investigators continue to advance the understanding of the inflammatory components in several forms of muscular dystrophy and the role of the immune system in disease progression. Additionally, the institute supports research in other areas of muscle biology, which may point to targeted interventions for the treatment of muscular dystrophies and other disorders.

National Institute of Child Health and Human Development (NICHD): The NICHD sponsors a portfolio of extramural research projects related to the muscular dystrophies and other neuromuscular disorders. Research topics related to MD are focused in two of the Institute's centers: the National Center for Medical Rehabilitation Research (NCMRR) and the Center for Developmental Biology and Perinatal Medicine (CDBPM). Several projects related to MD are being supported through the NCMRR. Current research topics include contractures (loss of

mobility in joints) and molecular remodeling of muscle, canine muscular dystrophy response to stress, microsensors for intramuscular pressure measurement, motor control in muscle diseases, and the role of strength, body fat, and energy cost for child mobility. Within the newly established CDBPM, the Mental Retardation and Developmental Disabilities Branch has supported research into cognitive disabilities in DMD and accepts applications for research on the nonskeletal manifestations of many of the muscular dystrophies. In addition, NICHD has been addressing issues related to newborn screening, which may have relevance to the muscular dystrophies. Finally, NICHD also sponsors several networks that are available to support MD research and research training. These include the Pediatric Pharmacology Research Network, available for the conduct of trials of new pharmacotherapeutic agents, and the Pediatric Scientist Training Program, which can contribute to the training of new young investigators as soon as candidates are identified. Both of these programs are managed through the Center for Research for Mothers and Children, another component of the NICHD.

Muscular Dystrophy Coordinating Committee / Development of the Muscular Dystrophy Research and Education Plan

The Secretary of HHS delegated authority to the NIH Director to establish the Muscular Dystrophy Coordinating Committee (MDCC) but reserved the authority to appoint the members of the Committee, including the Chair. The NIH drafted the Committee charter, solicited nominations, and developed a slate of recommended candidates, and the Secretary appointed the 15 members of the MDCC. In accordance with the MD-CARE Act, the Committee is composed of ten members from Government agencies and five members from the public. Government agencies with an interest in MD research and education, including components of the Department of HHS and the Department of Education, are represented. The Department of Defense (DOD) is also represented since it received an appropriation for MD research in its FY 2003 Appropriations Act. Dr. Stephen Katz, NIAMS Director, chairs the MDCC. A roster of the MDCC is included as part of the appendix to this report, which contains the Muscular Dystrophy Research and Education Plan for NIH.

The first meeting of the MDCC took place on July 1, 2003. Committee members presented an overview of their organizations' programs or their personal interests in MD. The members also discussed how to develop a research and education plan for NIH. The Committee recommended that a working group of the MDCC, consisting of prominent scientists in the field of MD research should draft a plan to be submitted to the MDCC. The minutes from the July 1, 2003, MDCC meeting are included as part of the appendix.

Based on the recommendations of the MDCC, a scientific working group was formed to begin to develop the research and education plan for MD. Patient advocacy groups were asked to recommend scientists to be included in the working group who they felt best represented their interests. The working group members included representatives from the MDCC (NIH, CDC, and DOD members or their designees) and leading scientists in the field, including NIH MD

Research Task Force participants (see page 10 of this report for information on the NIH MD Research Task Force). A roster of the working group is included as part of the appendix.

The working group met at NIH on October 8-9, 2003. Scientists present at the meeting discussed the state-of-the-science for topic areas including etiology, diagnosis and screening, pathogenesis and sequelae, and interventions for the muscular dystrophies. The participants identified key challenges and opportunities in these areas, as they relate to many forms of MD including DMD, BMD, congenital MD, LGMD, Emery-Dreifuss MD, FSHD, and myotonic dystrophy. A list of research priorities and goals was developed based on the discussions at the working group meeting, and a draft plan was distributed to the full MDCC prior to its second meeting on March 22, 2004.

At the second meeting of the MDCC on March 22, 2004, the working group presented research goals it developed, and the MDCC reviewed and discussed the draft plan. The minutes of the March meeting are included as part of the appendix. Comments from MDCC members were compiled, reviewed, and used to add to or modify the goals. A revised document was sent to the Committee, which approved the Muscular Dystrophy Research and Education Plan for the NIH. The Department of HHS sent the Plan to Congress in August 2004. The Plan is included in the appendix to this report and is also available online through the MDCC Web site at http://www.ninds.nih.gov/find_people/groups/mdcc/MD_Plan_submitted.pdf.

The next meeting of the MDCC was held on December 1, 2004. The purpose of the meeting was to learn about activities and recent initiatives at various Federal agencies and within the muscular dystrophy scientific community. The Committee also discussed strategies to implement the Muscular Dystrophy Research and Education Plan for the NIH and its future directions. Links to the agenda and minutes for the meeting are posted on the MDCC Web site (http://www.ninds.nih.gov/find_people/groups/mdcc/index.htm).

Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

The MD-CARE Act authorized NIH to establish centers of excellence for MD research. The May 2002 NIH MD Research Task Force meeting (see page 10 of this report) helped NIH to determine the goals and capabilities for centers of excellence for muscular dystrophy research. In September 2002, NIH issued a request for applications (RFA) to establish "Muscular Dystrophy Cooperative Research Centers" (RFA AR-03-001). Subsequent to this announcement, the FY 2004 Omnibus Appropriations bill included a provision to designate the NIH Muscular Dystrophy Cooperative Research Centers as the "Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers," in honor of late Senator Paul D. Wellstone.

In October 2003, following peer review of the submitted applications, NIH announced awards to establish three Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (referred to here as Wellstone Research Centers). The NINDS, NIAMS, and NICHD each currently funds one center at up to $1 million in direct costs per center per year for five years.

Each center brings together expertise, infrastructure, and resources focused on major questions about muscular dystrophy. The Wellstone Research Centers promote side-by-side basic, translational, and clinical research and provide resources that can be used by the national muscle biology and neuromuscular research communities. They provide training and advice about muscle diseases for researchers and physicians who provide initial diagnosis and treatment, including rehabilitation, care for cognitive and behavioral concerns, and therapy for other system complications. Taken together, the Wellstone Research Centers constitute a cohesive program operating under guidelines for NIH cooperative agreements. The three centers funded to date are as follows: The University of Pittsburgh (funded by NIAMS), the University of Washington, Seattle (funded by NICHD), and the University of Rochester, New York (funded by NINDS). Projects at the University of Pittsburgh and the University of Washington focus on DMD, including research to advance muscle stem cells and gene delivery as potential therapies for DMD. Projects at the University of Rochester focus on myotonic dystrophy and FSHD; researchers are studying these disorders at the cellular and molecular levels to examine which factors might contribute to these forms of MD.

Muscular Dystrophy Association Partnership: The Muscular Dystrophy Association agreed to commit up to $1.5 million to enhance research activities at each of these three centers funded by NIH. The NINDS, NIAMS, and NICHD signed a Memorandum of Understanding with the Muscular Dystrophy Association in May 2003 to formalize this partnership. The Muscular Dystrophy Association agreed to provide up to $500,000 per center per year for three years for additional projects and has awarded supplements to each of the three centers.

Steering Committee: As part of the cooperative agreement, a Steering Committee ensures overall coordination of the Wellstone Research Centers program. The membership includes a bioethicist and a public member in addition to the directors of each center and scientific program officers from NINDS, NIAMS, and NICHD. As part of its charge, the Steering Committee shares information, identifies new research opportunities, and develops and implements collaborative activities that will accelerate the translation of preclinical findings into clinical applications. Dr. Jeffrey Chamberlain (University of Washington) chairs the Steering Committee, and Dr. Richard Moxley (University of Rochester) is the cochair. The Steering Committee held its first meeting on February 25, 2004. Subsequent meetings have been held via telephone conferences to discuss proposed collaborative projects among the Centers.

Plans for Additional Centers: In March 2004, NIH reissued the RFA for Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (RFA AR-04-008). The NIH will fund up to three additional meritorious centers in FY 2005, based on the outcome of the peer review of applications that were received in August 2004. Although the financial plans of NINDS, NIAMS, and NICHD provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

Recent Efforts at NIH to Enhance Muscular Dystrophy Research / Implementation of the Muscular Dystrophy Research and Education Plan

Solicitations

Initiatives to Increase the Number of Investigators in MD Research: One of the goals of the Muscular Dystrophy Research and Education Plan developed by the MDCC is to increase the number of researchers to help understand the disease process and pathophysiology of MD and to develop new therapies for all forms of MD. As part of the implementation of the Plan, NIH will issue three initiatives related to training and career development in the area of muscle disease in recognition of the urgent need for highly skilled, interactive investigators who are able to integrate various disciplines and levels of expertise to successfully address the increasing challenges in the current research environment of muscle diseases. The three initiatives are as follows: (1) NIH Administrative Supplements for Senator Paul D. Wellstone Muscular Dystrophy Research Fellowships at Wellstone Muscular Dystrophy Cooperative Research Centers: a program for administrative supplements to support senior postdoctoral fellows or nontenure-track investigators affiliated with the Wellstone Research Centers and to encourage these candidates to develop new, one- to two-year, independent, collaborative, exploratory projects focusing on MD research; (2) Muscle Disease Research Training Fellowships: a program announcement to support individual fellowships for predoctoral, postdoctoral, and senior fellows in the areas of MD and other muscle diseases; and (3) Muscle Disease Research Career Development and Mentoring Awards: a program announcement for applications for mentored career development awards for research or clinical scientists engaged in laboratory, patient-oriented, or quantitative research, midcareer investigators in patient-oriented research, and newly independent scientists interested in expanding their programs in muscle disease research.

Muscular Dystrophy: Pathogenesis and Therapies: The NIH plans to issue a program announcement (PA) entitled, "Muscular Dystrophy: Pathogenesis and Therapies" to encourage investigator-initiated research grant applications for projects studying pathogenesis and therapies for the muscular dystrophies. Responses to this announcement may include basic, translational, or patient-oriented studies of DMD, BMD, FSHD, myotonic dystrophy, or other forms of muscular dystrophy. A principal goal of this initiative is to promote research that will lead to better treatment for all muscular dystrophies. Important research priorities include studies on gene, stem cell, or pharmacological therapies and clarification of the role of inflammatory mechanisms. Topics for research projects may include screening and/or diagnosis, understanding disease mechanisms, treatment strategies, and improving quality of life and may be studies in appropriate animal models or preclinical or clinical studies. It is the aim of this PA to promote research identified as priorities in the Muscular Dystrophy Research and Education Plan, and it therefore contributes to the implementation of the Plan. This PA replaces a previous solicitation entitled "Therapeutic and Pathogenic Approaches for the Muscular Dystrophies," which was released in January 2001 and contains recommendations from recent workshops and meetings.

Precursor Cells in Skeletal Muscle Repair and Hypertrophy: In July 2002, NIAMS, NINDS, NIA, and NICHD cosponsored a PA entitled "Precursor Cells in Skeletal Muscle Repair and Hypertrophy" (PA-02-136). The purpose of the PA is to solicit investigator-initiated research grant applications to characterize cells involved in the repair of skeletal muscle. The initiative encourages research to characterize muscle precursor cells and determine how these cells can be used in therapies for human disease and repair of muscle injury/tissue.

Exploratory Research on Facioscapulohumeral Dystrophy: In November 2000, the NIAMS and the NINDS jointly issued an RFA for exploratory research on FSHD (RFA AR-01-002). This solicitation was designed to encourage research proposals using creative, novel, potentially high risk/high payoff approaches that could produce innovative advances in this field and capitalized on recommendations from a May 2000 conference on the causes and treatment of FSHD. NIH funded six new projects from this solicitation, including both basic and clinical research studies. These ongoing projects include work to compare clinically affected versus unaffected muscles to help determine the primary cause of FSHD; studies of muscle-specific animal antibodies to better understand FSHD pathophysiology in tissues and cell cultures from patients and controls; and efforts to determine the abnormal intracellular processes in FSHD muscle cells.

Workshops and Meetings

Workshop on Burden of Muscle Diseases: The NIAMS and other NIH institutes, along with members of the MD patient and scientific communities, are planning a workshop to be held on January 26-27, 2005, on the burden of muscle diseases. One purpose of the workshop is to assess methods and data that give qualitative descriptions of the effect of muscle diseases and quantitative measures, such as costs, that can be compared with other conditions. Topics to be discussed at the workshop include the numerical scope of muscle disease, the general concepts of economic and psychosocial burden, traditional measures of burden of disease including health impact and economic impact, the impact (economic and psychosocial) on caregivers, quality of life measures, and societal impact measures. An assessment of currently available data sets will be discussed and strengths and gaps in these data sets will be evaluated at the workshop.

New Directions in Biology and Disease of Skeletal Muscle: Participants at the May 2002 meeting of the NIH MD Research Task Force (see below) noted that it is necessary to further the self-identification of a community of researchers involved with muscular dystrophy. They suggested organizing a conference to bring together researchers who focus on different aspects of muscular dystrophy. There had been no national meeting with a focus on the functions and disorders of skeletal muscle, and the lack of a centrally focused meeting had become an impediment in understanding and treating important muscle diseases. Several NIH MD Research Task Force participants, joined by other leading muscle researchers, organized a conference entitled "New Directions in Biology and Disease of Skeletal Muscle," which was held January 25-28, 2004, in San Diego. The meeting focused on mechanisms and treatments of muscle diseases, with an emphasis on muscular dystrophy. With support from NIH, MDA, and other groups, the conference attracted clinical and basic researchers and provided an excellent forum for them to interact and share ideas and advance the field of MD research.

NIH Muscular Dystrophy Research Task Force

The NIH formed the MD Research Task Force to help guide efforts to intensify research on muscular dystrophy and to help NIH add new capabilities to the national effort to understand and treat muscular dystrophies. At its first meeting in May 2002, the group discussed resource needs to further MD research and programs to support training and helped NIH set goals for developing centers of excellence for MD research. A report of the meeting is available at http://www.niams.nih.gov/ne/reports/sci_wrk/2002/mdmeet.htm. At the second meeting of the Task Force, in January 2003, treatment targets, outcome measures, data collection standards, and the Wellstone Research Centers RFA were discussed. A summary of the second meeting is available at http://www.niams.nih.gov/ne/reports/sci_wrk/index.htm. Many of the scientists who previously participated in the MD Research Task Force were part of the MDCC Working Group that met in October 2003 to help develop the Muscular Dystrophy Research and Education Plan for the NIH.

National Registry of Myotonic Dystrophy and Facioscapulohumeral Dystrophy Patients and Family Members

Since September 2000, the NIAMS and NINDS have supported the National Registry of Myotonic Dystrophy and Facioscapulohumeral Dystrophy Patients and Family Members, a resource for the collection and characterization of information from patients and their families to accelerate the advance of clinical research on these diseases. The long-term goal of the registry is to facilitate research in FSHD and myotonic dystrophy 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, based at the University of Rochester, recruits and classifies patients and stores medical and family history data for individuals with clinically diagnosed FSHD and myotonic dystrophy. Scientists can 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. The national registry serves as a resource for scientists seeking a cure for these diseases, in addition to enhancing research to understand what changes occur in muscular dystrophy. To date this registry is the base of eight active projects.

NIH Muscular Dystrophy Research Funding

The NIH has devoted significant financial resources to MD research, and these commitments have increased substantially in the past few years. From FY 2000 to FY 2003, funding for MD research more than tripled, growing from $12.6 million in FY 2000 to $39.1 million in FY 2003. The estimated funding for FY 2004 is $40.2 million, and estimated funding for FY 2005 is $41.0 million. As with other areas of research, funding for MD research in future years will depend on the nature and quality of grant applications received in this area and the outcome of the peer review process.

Centers for Disease Control and Prevention Activities

In order to provide people with DMD and BMD and their families with better services, public health departments and health care providers need better information about these disorders. Using traditional public health research approaches, the CDC is working with partners in State health departments and universities to answer questions about DMD and BMD including:
- How common are these disorders and are they equally common in different racial and ethnic groups?
- What are the early signs and symptoms of DMD and BMD?
- Does the type of care received affect the severity or course of DMD and BMD?
- Does the type of gene changes affect the severity or course of DMD and BMD?
- What medical and social services are families receiving?
- Do different groups of people receive different care?

Some of the CDC projects that address these and other questions are described below.

Muscular Dystrophy Surveillance Tracking and Research Network: As part of the Muscular Dystrophy Surveillance Tracking and Research Network, or MD STARnet, the CDC is working with researchers in Arizona, Colorado, Iowa, and western New York State to set up surveillance systems for DMD and BMD. The goal of the project is to find all DMD and BMD patients in these areas by using information from different sources, such as clinic medical records and hospital records. Information about each child's treatments and how he is doing medically will be collected from his medical records. Because many DMD and BMD patients are seen in Muscular Dystrophy Association clinics, the researchers are working closely with the Muscular Dystrophy Association clinics in their States. In addition, the researchers will be searching for DMD and BMD patients through other neuromuscular clinics, emergency rooms, pathology laboratories, orthopedists, and other muscular dystrophy associations to ensure that all patients with DMD and BMD are included in the project. The States have worked together to come up with a common system that can be used to find patients and collect information. Families who are identified in these areas will be asked to take part in interviews with public health workers to provide information related to DMD and BMD that might not be found in the medical records.

The types of information that will be collected include basic demographic information (such as race and ethnicity), the treatments that have been received, the clinics that the care was received in, and any medical problems associated with DMD and BMD. Information will be collected from medical records and interviews on a regular basis.

In April 2004, researchers began collecting information from medical records. The group has now developed and begun using a computer system for saving and combining the information collected and is also now developing the interview questionnaire. FY 2004 funds will be used to add another State (Georgia, in collaboration with CDC intramural researchers) to the system, add an independent quality assurance and control system, and pilot DNA analysis activities for the project.

Family Needs Assessments: The CDC is sponsoring two projects to identify the service needs of families with DMD and BMD. The results of these projects will help health departments and health care providers understand the needs of families with DMD and BMD so that needed resources can be identified.

National Initiative for Families with Duchenne: The CDC is working with researchers at the Children's National Medical Center in Washington, D.C., on a survey of parents of children with DMD and BMD in the United States and Puerto Rico. The survey will include a large number of families from many backgrounds, and the results will help State health departments improve services for families with DMD and BMD. The researchers on this project plan to ask parents of children with DMD and BMD how they have dealt with having a child with DMD and BMD, what services they have available, what services they need, what problems they have in getting needed services, and their feelings about newborn screening for DMD and BMD. In addition, because some of the families in this survey were first diagnosed through pilot newborn screening projects, the researchers will find out whether newborn screening had an impact on the family in terms of using available services and on their quality of life. The survey has now been developed and approved by appropriate Institutional Review Boards, and survey mailing began in September 2004.

Needs of Families and Patients with Muscular Dystrophy: The CDC is working with researchers at the University of Iowa on a project to identify the needs of families with DMD and childhood-onset BMD. The researchers are talking with families in Iowa who have a member with DMD and BMD, specifically young men with DMD or childhood-onset BMD who are older than 14 years of age and their parents, brothers, and sisters. The goals of the project are to (1) identify and rank the needs of patients and families with DMD and childhood-onset BMD at different stages in their lives; (2) identify things that can affect whether families can get services and resources; (3) find out how being told about DMD and childhood-onset BMD affects the patient and his immediate family; and (4) find out how the family feels about newborn screening. Interview protocols are currently being developed and interviews should begin in winter 2004.

Palliative Care and Hospice Needs of Families with Children who have DMD: Palliative care, which may also include end-of-life hospice care, is comprehensive care offered to a person with a progressive illness and his or her family, with the goals of improving quality of life and the easing of symptoms. Unofficial reports indicate that males with DMD and their families are less likely to use palliative care and hospice services than families with children with other conditions that result in premature death. Because many males with DMD live to be older than 21 years of age, one factor could be the differences in services that are available to pediatric and adult patients. Other factors are also likely to be involved, such as the idea that palliative care is only end-of-life care and a giving up of hope. The two main goals of this project are (1) to identify the palliative care and hospice needs of males with DMD and their families and (2) to identify the barriers that individuals and their families face in considering, seeking, or obtaining palliative and hospice care. The CDC awarded a cooperative agreement for this project in September 2004.

Health Care Issues for Hispanic Families with DMD: Hispanic families of children with special health care needs face specific barriers to services and care. The goal of this project is to begin to identify the needs and some of the problems for Hispanic families specific to DMD. A focus group to collect qualitative information was conducted August 2004 in Spanish. The information gathered from this initial project will be used to help develop future projects on this topic. A report on this issue is expected in December 2004.

Cardiac Health in Female Carriers of DMD: Females who are DMD carriers sometimes have heart problems that leave them short of breath or unable to do moderate exercise later in adult life. The chance that a female carrier will develop heart problems is not known. However, such heart problems can be serious and life threatening. While there is no cure, there are a number of medications that might help reduce the effects of these heart problems. This project will use a large-scale, mailed, self-completed survey to collect information about what female DMD carriers know or believe about cardiac health care and how they act based on this information. The objectives of the project are (1) to find out what things affect the use of preventive cardiac health care by female carriers of DMD and (2) to develop new and workable plans that will increase preventive cardiac health care in this population. While there are currently no official recommendations for female carriers of DMD regarding cardiac testing and treatments, one of goals of this project is to find ways to let women know about recommendations once they are available. It is likely that the results of this study can also be used to improve health messages to carriers of other X-linked conditions. Interviews and focus groups with carrier females and health care providers began in November 2004. The information from these interviews and focus groups will then be used to develop the survey instrument.

Newborn Screening for DMD:

Newborn Screening for DMD Workgroup: On March 12, 2004, the CDC sponsored a one-day meeting in Atlanta, Georgia, with experts from around the world to look at newborn screening for DMD. At the meeting, past and present DMD newborn screening programs were discussed, as well as known and potential risks and benefits of such programs. A report from this meeting was released in September 2004 (http://www.cdc.gov/ncbddd/duchenne/NBS_Lay_Report.pdf).

Early Screening and Diagnosis of Duchenne Muscular Dystrophy: To further research on the issues identified by the Newborn Screening for Duchenne Muscular Dystrophy Workgroup, the National Center on Birth Defects and Developmental Disabilities (NCBDDD) at CDC recently announced funding under a cooperative agreement for research in both infant and newborn screening for DMD (*Federal Register*: June 24, 2004 (Volume 69, Number 121)). NCBDDD plans to fund two programs. One program will conduct a trial of newborn screening of DMD and see if the informed consent process works well in the birth hospital. The other program will conduct a trial of screening during infancy through pediatricians' offices and look at the possibility that everyone will have equal access to the screening test. Both programs will look at the number of false-positive and false-negative screening results, how well the informed consent process works, what problems false-positive screening results can cause, how families go through the screening process, and how pediatricians and other clinicians feel about the screening

program. Two research groups were awarded cooperative agreements in September 2004. The Children's Research Institute in Ohio, in collaboration with the Ohio Department of Health, will pilot newborn screening for DMD and BMD and evaluate the informed consent process in the birth hospital. Emory University, in collaboration with local pediatric practices, will pilot infant screening for DMD and BMD and evaluate equity to screening.

Education and Training

The MD-CARE Act states that "The Secretary of Health and Human Services...shall establish and implement a program to provide information and education on muscular dystrophy to health professionals and the general public, including information and education on advances in the diagnosis and treatment of muscular dystrophy and training and continuing education through programs for scientists, physicians, medical students, and other health professionals who provide care for patients with muscular dystrophy." (Section 5(a))

The Department of HHS is committed to improving information and educational resources concerned with muscular dystrophy for health professionals, patients, and for the general public. The MDCC has a publicly available Web site (http://www.ninds.nih.gov/research/muscular_dystrophy/coordinating_committee), which contains a Committee roster, the Committee charter, short biosketches of Committee members, agendas and minutes from Committee meetings, and the Muscular Dystrophy Research and Education Plan for NIH. In addition, to help inform professionals, patients, and the public, NIH publishes summaries of MD workshops, descriptions of funding opportunities, and publications on the muscular dystrophies specifically developed for the public on its Web sites, including links to information provided by voluntary health organizations. The National Library of Medicine, a component of NIH, provides the MEDLINEplus.gov Web site. MEDLINEplus has many health-related information resources for professionals and the public, including the capability to search the extensive databases of the medical and scientific literature, in some cases with links to the full text of articles. The MEDLINEplus muscular dystrophy page at http://www.nlm.nih.gov/medlineplus/musculardystrophy.html provides links to sources of recent news, overviews, frequently asked questions, clinical trials, specific conditions, and other aspects of the muscular dystrophies from government agencies and private groups. The ClinicalTrials.gov Web site (http://clinicaltrials.gov) posts information about HHS-supported clinical trials as they become available for MD, as for other disorders.

Education and training are also goals of the Wellstone Research Centers program. In addition, one of the research goals of the Muscular Dystrophy Research and Education Plan is to increase the number of investigators in MD research. As mentioned above (see page 8), NIH is planning to issue a number of initiatives to enhance multidisciplinary and interdisciplinary research training of basic and clinical investigators in the area of MD. It is important to ensure an adequate number of highly skilled researchers and promote multidisciplinary approaches to advance our understanding and treatment of MD.

Institute of Medicine Study of Centers of Excellence

The MD-CARE Act directed the Secretary of HHS to contract with the Institute of Medicine to study and make recommendations regarding the use of Centers of Excellence at NIH in general. Among the several issues raised were the impact of centers, whether the centers are under- or over-used, their cost-effectiveness, the criteria for determining when centers are appropriate, and alternative research models. The Institute of Medicine report, "NIH Extramural Center Programs: Criteria for Initiation and Evaluation," was released February 2, 2004, and is available online at http://www.nap.edu/books/0309091527/html/.

Recent Scientific Advances

Given the time required to initiate new research projects and get results, it would not be appropriate to attribute recent scientific findings in muscular dystrophy research to implementation of the Act. However, a few recent highlights from ongoing NIH research activities are worth noting briefly in this report to give some indication of current scientific activity.

Towards gene therapy for Duchenne muscular dystrophy: NIH-funded researchers have developed a method to deliver therapeutic genes to all of the skeletal muscles throughout the body of a mouse model for MD (the mdx mouse). The investigators used a modified version of a specific type of virus, called adeno-associated virus (AAV), which is able to enter muscle cells and not trigger an immune response, to carry the corrective gene. The research team engineered these AAV vectors to carry a mini-dystrophin gene and injected the vectors into the bloodstream. Importantly, the investigators also co-injected a blood vessel regulatory molecule called vascular endothelial growth factor that temporarily renders the blood vessels permeable so that the vector can efficiently pass through. The mini-dystrophin gene was widely expressed throughout the skeletal muscles of the mice and resulted in an improvement of some of the measures of disease severity. Additional studies in animals are warranted in order to determine if this therapy should be tested in people. If successful, the strategy might be adapted to carry different genes for treating other muscle diseases, including the several forms of MD, and also to deliver therapeutic genes to heart muscle cells (Gregorevic P, et al., 2003, *Nature Medicine* 10: 828-34).

Delivery of microdystrophin to mdx mouse muscle by muscle progenitor cells: Previous studies identified a population of muscle cells called side population (SP) cells from mouse skeletal muscle and showed that these cells are capable of regenerating muscle. A recent study funded by NIH showed that it may be possible to use these SP cells to deliver dystrophin to muscle. The researchers introduced a portion of the human dystrophin gene using a viral vector (a micro-dystrophin construct) into SP cells and then transplanted these cells into mdx mice via a tail vein. They found that the transplanted cells were able to move through the mouse's circulation and take up residence within the host muscles. Moreover, human dystrophin expression was detected in muscle fibers of all transplanted mice, demonstrating that delivery of the dystrophin construct to muscle fibers had occurred. These results show that transplantation of SP cells expressing

microdystrophin represents a feasible way to systemically deliver human dystrophin to muscle. They also suggest that disease-damaged muscle is able to attract and recruit these cells to muscle from the circulation. These results have substantial implications for cell therapy in the treatment of human MD (Bachrach et al., 2004, *PNAS* 101: 3581-3586).

The protein LARGE overcomes defects in some forms of MD: In some forms of MD–including several forms of congenital MD and one form of LGMD–the attachment of sugar molecules to the membrane protein alpha-dystroglycan (a process known as glycosylation) does not occur correctly. Without the attached sugars, the ability of alpha-dystroglycan to provide structural support to the muscle membrane and protect it from the stresses of normal muscle use, is disrupted. Investigators, funded in part by NIH, have now shown that the protein LARGE may be able to correct this molecular defect. Researchers studied mice with a defect in the LARGE gene (and a resulting lack of LARGE protein); these mice have a type of MD similar to that seen in some patients. The investigators found that expressing the LARGE gene in these mice using a viral delivery system restored the glycosylation of alpha-dystroglycan to its normal levels. The treated mice also showed less muscle damage in response to exercise. The researchers then studied cells from patients with certain forms of MD and found that when these cells were treated with the virus carrying the LARGE gene, glycosylation of alpha-dystroglycan was restored. These results suggest that LARGE or a related molecule may represent a potential therapeutic target in treating patients with certain forms of MD (Barresi et al., 2004, *Nature Medicine* 10: 696-703).

Improvement of dystrophic phenotype in mdx mice by the growth factor heregulin: A recent study, funded in part by NIH, suggests that the growth factor heregulin may be able to alleviate some of the effects of DMD. Heregulin has been previously shown to upregulate utrophin, a dystrophin-related protein that can functionally compensate for the loss of the dystrophin protein. The investigators found that after injecting a fragment of the heregulin molecule into mdx mice for three months, the utrophin protein was upregulated. Moreover, there were also improvements in measurements of muscle structure and function. These results suggest that heregulin may be a promising therapeutic target in the treatment of DMD (Krag et al., 2004, *PNAS* 101: 13856-13860).

Loss of myostatin lessens muscle wasting in MD model: Myostatin is a protein that is thought to negatively regulate muscle growth. In genetically engineered mice that lack the myostatin gene, there is a dramatic increase in muscle mass compared to normal mice (see Zimmers et al., 2002, *Science* 296: 1486-1488). This suggests that blocking myostatin may represent an important therapeutic strategy for treating degenerative muscle diseases. A study funded by NIH shows that in an experimental model, loss of the myostatin gene reduces the severity of MD. The researchers genetically engineered mdx mice so they also lacked the myostatin gene. They found that these mice were stronger and more muscular than the "normal" mdx mice, which still had myostatin intact. This positive change was seen at 3, 6, and 9 months of age, suggesting that increased muscle mass is maintained over time (Wagner et al., 2002, *Annals of Neurology* 52: 832-836). A recent paper, funded in part by NIH, reports the first documented human case of a

myostatin mutation. The young German boy, who is now 4 ½ years old, has two mutated copies of the myostatin gene; his mother, a former professional athlete, has one mutated copy of the gene. The boy has had unusually pronounced muscles since birth and is now able to hold 7-pound weights with his arms extended (Schuelke, et al., 2004, *NEJM* 350: 2682-2688). These studies suggest that blocking myostatin may improve muscle health and strength and delay the progression of disease for patients with DMD and BMD.

Development of a reliable diagnostic test for myotonic dystrophy type 2: Myotonic dystrophy type 2 has historically been difficult to diagnose since many of its symptoms closely resemble myotonic dystrophy type 1. Previous work by NIH-funded researchers showed that myotonic dystrophy type 2 is caused by a repeat expansion (CCTG) in a region of the zinc finger protein 9 gene (*Science* 293: 864-867, 2001). This alteration is very unstable and varies dramatically in size from patient to patient. An NIH-funded researcher has now developed a new molecular diagnostic tool that can detect the region of the gene containing this repeat. Initial results using this new diagnostic tool indicate that myotonic dystrophy type 2 is much more common than previously thought, and suggests that, unlike myotonic dystrophy type 1, there is not a severe congenital form of myotonic dystrophy type 2. This study represents an important advance for detecting the disease and treating myotonic dystrophy type 2 patients in early stages of the disease (Day et al., 2003, *Neurology* 60: 657-664).

A rapid sequence gene test to diagnose DMD: Genetic tests to confirm a diagnosis of DMD fail to detect a gene mutation in about 35 percent of the cases. NIH-funded researchers have now developed an economical way to test for variations across the entire dystrophin gene. This approach can detect mutations responsible for both DMD and BMD. This research represents a very important advance in reliably diagnosing these disorders in the majority of patients. It has the potential to allow improved genetic counseling, better detection of female carriers whose mutations previously went undetected, and improved ability to measure severity and progression of the disease (Flanigan et al., 2003, *American Journal of Human Genetics* 72: 931-939).

Disruption of muscle membrane repair machinery implicated in MD: Mutations in the gene dysferlin are linked to both LGMD type 2B and Miyoshi myopathy, a form of MD initially identified in Japan with similarities to LGMD. However, the mechanism by which dysferlin deficiency leads to muscle degeneration is not known. A recent study, funded in part by NIH, shows that in mice lacking the dysferlin gene, the membranes of muscle cells cannot effectively repair themselves. In the absence of dysferlin, damaged muscle membranes do not efficiently reseal, normal muscle repair cannot occur, and the muscles degenerate as a result. This study highlights the importance of basic cellular function in various forms of MD and will help identify other proteins that may be involved in muscle membrane repair (Bansal et al., 2003, *Nature* 423: 168-172).

Conclusion

The NIH and CDC continue to implement the provisions of the MD-CARE Act. The MDCC has developed the Muscular Dystrophy Research and Education Plan for the NIH, and further implementation of the Plan will contribute to the goals of the MD-CARE Act. The challenges in MD research are formidable and varied, but scientific advances and collaborations and the commitment of the research and advocacy communities hold great promise for more and better treatments for individuals suffering from the muscular dystrophies.

Glossary: Guide to Acronyms Used in this Report:

AAV: Adeno-Associated Virus
BMD: Becker Muscular Dystrophy
CDBPM: Center for Developmental Biology and Perinatal Medicine
CDC: Centers for Disease Control and Prevention
DOD: Department of Defense
DMD: Duchenne Muscular Dystrophy
FSHD: Facioscapulohumeral Muscular Dystrophy
FY: Fiscal Year
HHS: Health and Human Services
LGMD: Limb-Girdle Muscular Dystrophy
MD: Muscular Dystrophy
MD-CARE Act: Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001
MD STARnet: Muscular Dystrophy Surveillance Tracking and Research Network
MDCC: Muscular Dystrophy Coordinating Committee
NCBDDD: National Center on Birth Defects and Developmental Disabilities
NCMRR: National Center for Medical Rehabilitation Research
NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD: National Institute of Child Health and Human Development
NIH: National Institutes of Health
NINDS: National Institute of Neurological Disorders and Stroke
PA: Program Announcement
RFA: Request for Applications
SP: Side Population

APPENDIX:

MUSCULAR DYSTROPHY
RESEARCH AND EDUCATION PLAN FOR NIH

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Muscular Dystrophy Interagency Coordinating Committee

Muscular Dystrophy Research and Education Plan for the National Institutes of Health

July 2004

Table of Contents

Executive Summary

The muscular dystrophies are a group of chronic diseases primarily characterized by weakness and progressive degeneration of skeletal muscles. There are many forms of MD, including Duchenne, Becker, limb-girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss dystrophies. MD can affect people of all ages; however, some forms first become apparent in childhood, while others appear later in life. While the genes responsible for some forms of the MDs have been identified, a causative gene has not been found for other forms. Currently, there is no treatment that can stop or reverse the progression of any form of MD, and symptomatic treatment is aimed at improving the quality of life for individuals with these disorders. Within the National Institutes of Health (NIH), the three institutes most involved in MD-related research activities are the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Child Health and Human Development (NICHD). These institutes support a wide range of research on many forms of MD ranging from studies to understand the basic mechanisms underlying the muscular dystrophies to translational and clinical research focused on finding therapies for these diseases.

In December 2001, the President signed into law the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (the MD-CARE Act, Public Law 107-84). Among the provisions of the law are that the Secretary, Department of Health and Human Services (DHHS), *shall establish a Muscular Dystrophy Coordinating Committee* (MDCC), and that the *Coordinating Committee shall develop a plan* for conducting and supporting research and education on muscular dystrophy through the national research institutes.

The MDCC, with input from a wide range of experts in the field of MD research, has developed a Research and Education Plan for MD for the NIH. The plan below provides background on the MDs, information on the development of the Plan, and a list of research priorities and goals for NIH, which fall under five broad headings: (1) Understanding Mechanisms of Disease; (2) Screening/Diagnosis; (3) Treatment Strategies; (4) Living with MD: Rehabilitation, Quality of Life, and Psychosocial Issues; and (5) Research Infrastructure Needs. The Plan encompasses many of the forms of the MDs; while some of the goals are specific to one form of MD, many apply to more than one dystrophy.

It is important to note that the MDCC designed this Plan to be a working document for the entire MD community: scientists, voluntary patient advocacy groups, the NIH, and other federal agencies. All these partners must work together to measure progress and redefine priorities, as science progresses and new opportunities emerge. The MDCC expects that all of these partners will play a role in the full implementation of many of these goals. As the NIH develops specific implementation strategies, NIH will work closely with its partners in the public and private sectors to ensure that all are fully engaged and that their respective expertise continues to complement that of NIH.

Exciting new opportunities are emerging in MD research. The NIH Research and Education Plan outlines a comprehensive set of research goals that will help to further advance MD research, and to develop or improve therapies for these devastating diseases.

INTRODUCTION

Background on the Muscular Dystrophies

The muscular dystrophies are a group of diseases that cause weakness and progressive degeneration of skeletal muscles, the muscles that help us move. As a group, the muscular dystrophies comprise over 30 disorders, which vary in age of onset, severity, mode of inheritance, and in the pattern of muscles affected. Muscular dystrophy (MD) can affect people of all ages; some forms first become apparent in infancy or childhood, while others may not appear until middle age or later. While the primary effect of MD is muscle weakness and degeneration, most types of MD are, in fact, multi-system disorders with manifestations in body systems including the heart, gastrointestinal tract, endocrine glands, skin, eyes, and other organs.

Types of Muscular Dystrophy

The various forms of MD include: Duchenne, Becker, limb-girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss dystrophies.

Duchenne muscular dystrophy (DMD) is the most common childhood form of muscular dystrophy. More than 15 years ago, researchers supported by the NIH and the Muscular Dystrophy Association (MDA) identified the gene for the protein dystrophin which, when absent, causes DMD. Dystrophin is part of a complex structure involving several other protein components. The "dystrophin-glycoprotein complex (DGC)" forms a link between the muscle cells, through the cells' outer membrane, to the surrounding cellular support structure. Defects in this assembly lead to structural problems in the muscle cells, which, in turn, are the most likely cause of the eventual muscle degeneration. The dystrophin gene is a very large gene, which can make treatment strategies that involve gene therapy more challenging to develop. Sporadic mutations in this gene occur frequently, accounting for a third of cases. The remaining two-thirds of cases are inherited in an X-linked recessive pattern, meaning that severe DMD affects boys almost exclusively. DMD usually becomes clinically evident at walking. Some of the first symptoms are often general weakness and fatigue, followed by progressive muscle damage. DMD affects many different portions of the body including the spine, legs, feet, joints, and tendons. Symptoms may include contractures (joint and tendon restriction), curvature of the spine, subtle behavioral and cognitive defects, heart failure, and respiratory problems. Boys who are affected typically require a wheelchair by age 10 to 12, and often die in their late teens or early 20's. Women who are carriers have milder symptoms. **Becker muscular dystrophy** is a less severe variant of the disease and is caused by the production of a truncated, but partially functional form of dystrophin.

The **limb-girdle muscular dystrophies (LGMDs)** all show a similar distribution of muscle weakness, affecting both upper arms and legs. Many forms of LGMD have been identified, showing different patterns of inheritance: autosomal recessive (designated LGMD1) or autosomal dominant (LGMD2). In an autosomal recessive pattern of inheritance, an individual receives two copies of the defective gene, one from each parent. In an autosomal dominant

disease, the disorder can occur in either sex when a person inherits a single defective gene from either parent. The recessive LGMDs are more frequent than the dominant forms, and may be more severe. LGMD can have a childhood onset, although more often symptoms appear in adolescence or young adulthood. The dominant LGMDs usually show adult onset. Some of the recessive forms have been associated with defects in proteins that make up the dystrophin-glycoprotein complex (DGC). Mutations in one component of the DGC, the sarcoglycan complex, can lead to the forms of LGMD known as LGMD2C, 2D, 2E, and 2F. Defects in caveolin-3, a protein that associates with the DGC, lead to LGMD1C, while mutations in dysferlin, a protein that is thought to interact with caveolin-3, cause LGMD2B. Mutations in genes not related to the DGC are implicated in other forms of LGMD. For example, mutations in the enzymatic protein calpain-3 lead to LGMD2A.

The **congenital muscular dystrophies** are a heterogeneous class of disorders, and include several disorders with a range of symptoms. Muscle degeneration can be mild or severe, and may be restricted to skeletal muscle, or paired with effects on the brain and other organs. Defects in the protein merosin are responsible for about half of the cases in the U.S. Mutations in one of the integrin proteins gives rise to another form of congenital muscular dystrophy. Defects in the proteins called fukutin and fukutin-related protein cause the most common forms of congenital muscular dystrophy found in Japan. All of these proteins are thought to have some relationship to the dystrophin-glycoprotein complex. Some forms of congenital MD, including Fukuyama MD, muscle-eye brain disease, and Walker-Warburg syndrome show severe brain malformations, such as lissencephaly (a "cobblestone" appearance to part of the brain) and hydrocephalus (an excessive accumulation of fluid in the brain). Other forms, including the merosin-absent form and rigid spine syndrome, do not have major brain malformations associated with the disease.

Facioscapulohumeral muscular dystrophy (FSHD) is also inherited in an autosomal dominant fashion. FSHD initially affects muscles of the face (facio), shoulders (scapulo), and upper arms (humeral) with progressive weakness. The weakening of facial muscles is often one of the first signs of disease, followed by weakness in the limb-girdle, abdominal, and pelvic muscles, which affect the individual's ability to walk. Symptoms usually develop in the teenage years. Life expectancy is normal, but some affected individuals become severely disabled. Mental retardation and seizures may also occur in rare cases.

Unlike Duchenne or myotonic dystrophy, the underlying genetic defect in FSHD is poorly understood. Most cases of FSHD are associated with a deletion near the end of chromosome 4. In a section of this chromosome, a region called 4q35, there is a reduced number of a DNA repeat known as the "D4Z4" repeat. In normal individuals, the number of this repeat varies from 11 to 150; in FHSD patients, however, there are fewer than 11 repeats. Despite this information about the location and type of genetic deletion, it has not yet been possible to identify a gene responsible for FSHD. However, studies have suggested a mechanism of FSHD in which the lack of D4Z4 repeats may cause changes in nearby genes, starting a cascade of molecular events that could lead to FSHD. One very important aspect of FSHD is the involvement of specific muscle groups; this suggests that the molecular defect might affect different muscles to different extents.

Myotonic muscular dystrophy (DM) is the most common adult form of muscular dystrophy. Symptoms include myotonia (an inability to relax muscles following contraction) as well as slowly progressive muscle wasting and weakness. DM varies in severity and manifestations, and affects many body systems in addition to skeletal muscle, including the heart, endocrine organs, eyes, and gastrointestinal tract. DM follows an autosomal dominant pattern of inheritance.

Two forms of DM have been identified: Myotonic dystrophy type 1 (DM1) and type 2 (DM2). In DM1, the inherited gene defect is an abnormally long repetition of a three-letter nucleotide "word" (CTG) in a region of a gene that encodes a "kinase," a class of proteins that helps regulate the function of other proteins. Normally, this "word" (CTG) is repeated a number of times, but in people with DM1, it is repeated many more times. Scientists have recently discovered that the gene defect in DM1 leads to an abnormal attachment (or "splicing") of a gene that encodes a protein called a chloride channel. In DM1, the abnormal chloride channels lead to muscle that is activated too easily, which could account for the abnormal muscle activity in DM1 and ultimately for muscle degeneration. DM2 is also caused by a repeat expansion (in this case, the repeated "code" is CCTG) in a region of a different gene.

Other forms of MD: Several other forms of MD also occur. **Oculopharyngeal MD**, which causes weakness in the eye, throat, and facial muscles, followed by pelvic and shoulder muscle weakness, has been attributed to a short triplet repeat expansion in the poly-A binding protein 2 gene (PAB2), a gene involved in translating the genetic code into functional proteins. This disease is most common in people of French-Canadian descent or people of Hispanic descent from certain regions of the Southwest, centered around New Mexico. **Miyoshi myopathy**, one of the **distal MDs**, causes initial weakness in the calf muscles, and is caused by defects in the protein dysferlin, which is the same gene responsible for LGMD2B, reinforcing the idea that progress against one form of MD should be informative to other areas of MD research as well. There are two forms of **Emery-Dreifuss MD** -- an X-linked and an autosomal dominant form. Emery-Dreifuss MD is characterized by weakness in the shoulder girdle and lower legs, as well as the development of contractures in regions of the body, particularly the elbows, Achilles tendons, and neck. Defects in proteins that make up the nucleus, including emerin, and lamin A/C, are implicated in the disorder.

Available Treatments

Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Symptomatic treatment, though not able to stop disease progression, may improve the quality of life for some individuals. Options include physical therapy, appliances used for support, corrective orthopedic surgery, and drugs. Steroids have been the standard of care for DMD, but side effects often limit their use. However, several therapeutic approaches have shown promise in animal models and some early trials in people have begun. Gene therapy is one promising avenue. In addition, a current clinical trial is exploring the use of the antibiotic gentamicin in DMD and LGMD patients. Other therapeutic approaches are also showing promise, including cell-based therapies; functional compensation for dystrophin by upregulation of certain proteins; and increasing muscle mass via inhibition of other proteins that negatively regulate muscle growth.

NIH Research Program in Muscular Dystrophy

Within NIH, the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Child Health and Human Development (NICHD) are the three institutes at NIH most involved in MD-related research and activities, although other institutes and centers at NIH support activities relevant to MD as well.

The National Institute of Neurological Disorders and Stroke (NINDS) supports intramural and extramural research on many forms of the muscular dystrophies ranging from basic studies of normal protein function, through projects on gene, stem cell, and drug therapies. The NINDS also supports a very active portfolio of basic research on the neuromuscular junction, the connection between a nerve cell and muscle fiber. Much of this basic research is critical to advancing our understanding of the mechanisms underlying the muscular dystrophies. Since the MDA and the NINDS supported the discovery, in 1987, that dystrophin mutations cause Duchenne and Becker MD, NINDS has supported much subsequent work on understanding the role and function of the dystrophin-glycoprotein complex in both normal and MD-affected muscle tissue. The NINDS funds research relevant to understanding the molecular and genetic basis of FSHD, as well as research relevant to myotonic dystrophy, congenital MD, limb-girdle MD, and other neuromuscular disorders. Another area of focus is the improved diagnosis of the muscular dystrophies. The NINDS has also been involved in and continues to fund clinical studies to test the potential of the compound gentamicin as a therapy for Duchenne MD.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) funds considerable research designed to improve our understanding of the dynamic molecular events that bring about and maintain the highly organized structures of skeletal muscle. This includes research on skeletal muscle structure and development, muscle growth and regeneration, and inflammation in muscle. Other work involves studies of genes associated with normal skeletal muscle components, and mechanisms of gene regulation and expression in normal muscle. Scientists supported by the Institute are also studying altered genes and proteins associated with muscle diseases and disorders. These efforts have increased our understanding of changes that occur during development and in disease states. In the area of muscle growth and regeneration, the NIAMS supports innovative research on muscle precursor cells. These specialized cells provide muscle with the ability to respond to increased activity and to damage from disease or injury. Important projects currently underway include the identification of factors controlling the activity of these precursor cells. This information will help guide efforts to use precursor cells to repair or replace tissue damaged by muscular dystrophy, other diseases, or muscle injuries.

The National Institute of Child Health and Human Development (NICHD) sponsors a portfolio of extramural research projects related to the muscular dystrophies and other neuromuscular disorders. Research related to MD is supported by two of the Institute's Centers: the National Center for Medical Rehabilitation Research (NCMRR) and the Center for Developmental

Biology and Perinatal Medicine (CDBPM). Current research topics include: cognitive disabilities in Duchenne MD; contractures (loss of mobility in joints) and molecular remodeling of muscle; muscular dystrophy response to stress; microsensors for intramuscular pressure measurement; motor control in muscle diseases; and the role of strength, body fat and energy cost for child mobility. In addition, NICHD is interested in issues related to newborn screening that may have relevance to the muscular dystrophies, and accepts applications for research on the non-skeletal manifestations of many of the muscular dystrophies. Finally, NICHD also sponsors several networks that are available to support MD research and research training, including the Pediatric Pharmacology Research Network, available for the conduct of trials of new pharmacotherapeutic agents; and the Pediatric Scientist Training Program, which can contribute to the training of new young investigators.

The NIH is also engaged in many other activities related to MD to help advance research and improve coordination and collaboration among members of the MD community. The recent funding by NIH of three Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers illustrates these collaborative efforts. Each of the Centers brings together expertise, infrastructure and resources focused on major questions about muscular dystrophy. The Centers promote side-by-side basic, translational, and clinical research, and provide resources that can be used by the national muscle biology and neuromuscular research communities. The NIH plans to fund two to three additional meritorious centers in FY 2005.

Other government agencies, including the Centers for Disease Control and Prevention (CDC) and the Department of Defense (DoD), fund activities related to MD as well. Agencies with an interest in MD research and education are represented on the inter-agency Muscular Dystrophy Coordinating Committee (MDCC), which coordinates activities across NIH and with other Federal health programs and activities relevant to the various forms of MD. Accordingly, the MDCC Research and Education Plan for MD cannot be addressed by NIH alone but will require the active engagement and expertise of CDC, DOD, and other Federal agencies to meet the plan objectives. The MDCC, with input from a scientific working group and other experts in the field of MD, has developed this Research and Education Plan for MD.

The Muscular Dystrophy Research and Education Plan for NIH

Background

In December 2001, the President signed into law the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (the MD-CARE Act, Public Law 107-84). The MD-CARE Act allowed the NIH to build upon existing activities and to enhance its relationships with other government agencies, as well as the scientific and patient voluntary communities in the area of MD. Among the provisions of the law are that the Secretary, Department of Health and Human Services (DHHS), *shall establish a Muscular Dystrophy Coordinating Committee* (MDCC), and that the *Coordinating Committee shall develop a plan* for conducting and supporting research and education on muscular dystrophy through the national research institutes.

The Secretary, DHHS, delegated authority to the NIH Director to establish the MDCC, but reserved the authority to appoint the members of the Committee, including the Chair. The NIH drafted the committee charter, solicited nominations, and developed a slate of recommended candidates. The Secretary gave final approval of and appointed all 15 members of the MDCC. In accordance with the MD-CARE Act, the MDCC is composed of two-thirds government and one-third public members. Government agencies with an interest in MD research and education, including components of DHHS, the Department of Education, and DoD are represented. Dr. Stephen Katz, NIAMS Director, chairs the MDCC. A roster of the MDCC is included in Appendix 1.

Process

The first meeting of the MDCC took place on July 1, 2003. Committee members each presented an overview of their organization's programs and/or personal interests in MD. The MDCC also discussed how to begin to develop the MD Research and Education Plan for NIH. The Committee recommended that a working group of the MDCC, consisting of prominent scientists in the field of MD research, should draft a plan to be submitted to the MDCC. Minutes from the first MDCC meeting are included in Appendix 2.

Based on these recommendations from the MDCC, a scientific working group of the Committee was formed to help develop the research and education plan for MD. Voluntary patient advocacy groups were asked to recommend scientists, whom they felt best represented their interests, to be included in the working group. The working group members included representatives from the MDCC (NIH, CDC, and DoD members or their designees) and leading scientists in the field of MD research. A roster of the scientific working group is included in Appendix 3.

The scientific working group met at NIH on October 8-9, 2003. Scientists present at the meeting discussed the state-of-the science for topic areas including etiology, diagnosis and screening, pathogenesis and sequelae, and treatment and therapeutic interventions, including rehabilitation,

for the muscular dystrophies. The participants identified the key challenges and opportunities in these areas, and discussed critical research goals. The discussions encompassed the many forms of MD, but also focused on biomedical research issues unique to specific forms of MD, including Duchenne and Becker MD, LGMD, congenital MD, FSHD, myotonic dystrophy, and Emery-Dreifuss MD.

Some topic areas were explored through further meetings and interactions with other experts in the field of MD. These areas included the surveillance, epidemiology, and screening for MD, where information was obtained through briefings and meetings with CDC, and psychosocial and rehabilitation issues, where input was solicited from scientists who are key players in the area of rehabilitation in MD and from MDCC patient representatives. As a result of these meetings, draft goals that would be a priority for the NIH were developed.

At the second meeting of the MDCC (March 22, 2004), the draft MD Research and Education Plan for the NIH was discussed. Many of the research goals are broad, and encompass multiple aims. These aims differ in the level of risk and time required to achieve them; as specific implementation strategies are developed for each aim, it will be important to take into account the time/risk factor for each. While the MD-CARE Act specified a Research and Education Plan for the national research institutes, it will be necessary for other federal agencies besides NIH to play a role in the full implementation of many of these goals, or to assume leadership in addressing other aspects of MD. Minutes from this meeting are included in Appendix 4.

Following minor changes, the final plan was cleared by the MDCC.

Research Goals

While the muscular dystrophies may appear to be a diverse group of disorders, with different causes and a range of symptoms, it is important to note that there are common themes among the different forms. While some of the goals below are specific to one form of MD, many of the goals apply to more than one dystrophy. It is important to keep in mind that research on one form of MD is likely to have an impact on our overall understanding of muscle structure and function, and the processes that contribute to muscle degeneration. This, in turn, will help lead to a fuller understanding of the disease process and aid in the development of new treatments for the entire group of muscular dystrophies.

BROAD HEADING 1: UNDERSTANDING MECHANISMS OF DISEASE

While we have a good understanding of the primary genetic and biochemical defects in many of the dystrophies, we have a very poor understanding of the downstream pathophysiological consequences leading to disease presentation and progression. There are common themes in the mechanisms of the muscular dystrophies (MDs). Most MDs are caused by mutations that result in the loss of specific skeletal muscle structural proteins. Many of these mutations disrupt the dystrophin-glycoprotein complex, a major component of muscle cells, and result in a variety of forms of MD, including DMD, Becker, and certain forms of the congenital and limb girdle muscle dystrophies (LGMD). In other cases, such as myotonic dystrophy, the disease is caused

by triplet repeat expansions in genes that disrupt the proper functioning of other proteins, such as ion channels (in the case of myotonic dystrophy type 1 (DM1)). For other forms of MD, such as facioscapulohumeral MD (FSHD), the pathobiology appears to be unique, in that in FSHD there is a reduced number of repeated sequences in a given region of chromosome 4. Whether through a common or unique mechanism, a more thorough understanding of these different mechanisms of disease is needed to effectively design treatments for each form of MD. Since there are common mechanisms for many of the forms of MD, it is likely that understanding the mechanism of disease for a particular form of MD may apply to other forms of MD as well.

Understand How Protein Deficiencies Lead to Disease

While it is known that protein deficiencies lead to a number of different forms of MD – for example, Duchenne and Becker dystrophies are caused by dystrophin abnormalities, and LGMD2B and Miyoshi myopathy are caused by dysferlin deficiency - there is a need to understand what dictates disease onset and progression.

Understand How Triplet Repeat Expansion Leads to Disease

Triplet repeat expansion has been implicated in the etiology of myotonic dystrophy and oculopharyngeal MD. It is important to understand both the cause of these repeat expansions as well as their role in the disease process. An understanding of these mechanisms of disease is needed and should include studies to determine how repeat expansion in non-coding regions leads to disease, what causes RNA-mediated toxicity (in the case of myotonic dystrophy), and the role of poly-alanine expansions in disease (in the case of oculopharyngeal MD).

Understand the Unique Pathobiology of FSHD, Emery-Dreifuss, and Other Dystrophies

There is a critical need to understand the molecular basis of FSHD. Specific targets for research include: identifying gene defects and additional FSHD loci; determining the mechanism by which the D4Z4 repeat causes disease; understanding specific changes in chromatin structure. In addition, the role of nuclear envelope proteins, and how they contribute to the pathophysiology of certain forms of MD, such as Emery-Dreifuss MD, also needs to be studied.

Identify Genetic and Environmental Modifier Factors

There is a need to identify genetic and environmental modifier factors, including gender differences and hormonal influences, and to understand how they may influence outcome and other variables associated with disease, including the variable susceptibility of different muscles to disease.

BROAD HEADING 2: SCREENING/DIAGNOSIS

In order to most effectively treat MD patients, reliable screening and diagnostic procedures need to be in place. One approach that needs to be re-examined is newborn screening for MD. Newborn screening is a program with many essential elements, not just the performance of a test; considerations include available treatment options, counseling, and ethical issues. Recent studies have yielded improved molecular diagnostics for DMD and myotonic dystrophy. However, although we know a number of the genes implicated in various other forms of MD, molecular diagnostics are not readily available for most forms of these diseases. For other forms of MD,

such as FSHD, where a gene has not been implicated in the disease, the development of molecular diagnostics is even more challenging. The development of improved molecular diagnostics are particularly challenging with regard to identifying tests with high sensitivity and specificity, low cost, and short turnaround time. As new genetic and molecular-based tests are released, the concerns of potential genetic discrimination against individuals must be addressed in order for patients to take advantage of available testing.

Epidemiological studies on the MDs are also needed to better understand risk factors, prevalence, phenotypes, and treatment outcomes. Collected data should be broad enough to be meaningful and should be collected in a reliable and uniform fashion. The development of comprehensive clinical data sets would also help to establish the natural history of MD. A number of patient registries are already collecting important data in this regard, but further activities are needed in this area.

Develop Effective Newborn Screening Strategies

Newborn screening has been focused on Duchenne MD, with creatine kinase tests showing high sensitivity, but with a high false positive rate requiring re-testing. A re-evaluation of neonatal testing for Duchenne MD is needed, with the development of less expensive follow-up re-screening methods. Small pilot studies could be used to determine the best technology and timing for screening. Once these details are worked out, screening of larger populations could be considered. In addition, ethical issues, including the lack of conclusive evidence that early treatment results in better outcomes, the psychosocial effects of test results on families, and issues of informed/parental consent, must be examined.

Improve Molecular Diagnostics

New and improved molecular diagnostic tests, which would be widely available, are needed for all forms of MD. This is particularly true for disease genes for which commercial diagnosis is not available (calpain, dysferlin, sarcoglycans). New methods of screening different regions of large genes (e.g. promoters and introns) should be developed. In addition, the identification of genes or genetic alterations implicated in other forms of MD, including FSHD, would aid in the development of molecular diagnostics for these dystrophies.

Conduct Natural History Studies

There is a need for updated natural history data to assess the health utilization needs in the face of current and future medical advances, including advanced supportive care (orthopedic and pulmonary support; cardiovascular management). Population-based natural history studies can aid in making medical predictions, designing therapeutic trials, and providing answers to questions about mechanism of disease and potential health disparities - for example racial, ethnic, gender, age, and geographic disparities - in the different forms of MD. There is also a need for longitudinal studies of carriers (or cross-sectional studies of populations of carriers at several ages) to define health status throughout their life span. Natural history studies should also examine genetic and environmental risk factors, which may help to explain the clinical heterogeneity among some categories of MD.

Develop Comprehensive Clinical Data Sets

There is a particular need for comprehensive clinical data sets that would include measurements of muscle dysfunction as well as pulmonary and cardiovascular function. Comprehensive clinical data sets would aid in appropriate genetic counseling, provide families with information needed for family planning, and give patients and families information needed for decisions about care and treatment. Clinical data sets are also needed for effective clinical trial design and standardization, and to establish natural history of muscle diseases of all types.

BROAD HEADING 3: TREATMENT STRATEGIES

While corticosteroids have been used for the past 15 years as a treatment for MD, it is one of the few interventions, aside from rehabilitation approaches to treat specific symptoms, available to MD patients today. New therapies that reduce side effects while preventing disease progression are needed for all forms of MD. There are three overall approaches to treatment: gene therapy, cell-based therapy, and pharmacological treatments. There have been some promising developments in many of these areas: we have a better understanding of the properties of muscle stem cells; gene therapy studies in animals have demonstrated that this approach may work well in humans; and new drugs, such as gentamicin, are being tested in clinical trials. As new therapies are being developed, it will be important to determine the appropriate timing and dosing for new and existing treatment regimens. While the primary goals of treatment should be to prevent muscle degeneration and improve muscle function, more inclusive treatment strategies should be developed that take into account the multisystem aspects of MD. Treatment protocols should also take into account the fact that both young and older populations are affected by the MDs.

Develop Effective Gene Therapy Techniques

Gene therapy: Large Animal Studies

Initial success with AAV vectors has set the stage for future animal trials. In the short-term, gene therapy testing should move into trials in dogs. Canine studies are needed to determine the safety, efficacy, and long-term expression of vectors. Colonies of large animals need to be supported and maintained in order for these studies to be conducted.

Gene Therapy: Develop a Clinical Grade Vector

While AAV vectors are showing great promise, additional resources are needed to explore and develop alternative vector systems, including targeted, non-viral delivery systems. In particular, development of systems with larger cloning capacities, and ones that can be grown easily in large quantities and which are safe in human muscle are needed. Methods to produce large amounts of clinical grade vector are needed for multicenter clinical trials to occur. Also needed are studies to define constructs for gene replacement, including the characterization of mini-dystrophin constructs. Alternatives to gene replacement – antisense oligonucleotides to promote exon skipping; introduction of other genes to improve muscle mass and strength, such as IGF-1 or modified myostatin – are also needed.

Gene Therapy: Serotype Issues

Determine pre-existing immunity and the potential immune response to different vectors in MD populations beginning with the dystrophinopathies and the LGMDs. This may be critical to the success of early human trials.

Optimize Potential Cell-Based Therapies

Basic studies are needed to evaluate cell transplantation as a viable therapeutic option. The best cell types for transplantation need to be determined; stem cells, such as those derived from bone marrow, including stromal or mesenchymal cells, as well as others from the skin, vasculature, and striated muscle should be considered. Methods must be developed for the isolation, growth and expansion of such cells. The potential of embryonic stem cells and somatic cell nuclear transfer should also be considered as tools to improve the potential use of cell-based therapies. Some key issues that need to be resolved include methods of delivery that could show therapeutic efficacy, the role of the local environment in determining cell survival and fate, and ways to avoid host rejection of transplanted cells.

Understand Mechanism of Action of Steroids

A better understanding of the mechanism of action of steroids in the treatment of dystrophinopathies, particularly DMD and Becker MD, will help us to understand the mechanisms of disease, refine steroid treatment regimens to increase effectiveness and reduce side effects, and facilitate the design of other potential therapies.

Optimize Steroid Dosing Regimen

Currently, there is no agreement among clinicians on the best dosing regimen for patients. The age of steroid introduction has been proposed as a critical factor in preventing disease progression. Clinical studies should be done to test whether earlier use of steroids leads to better outcomes. In addition, alternative regimens to daily steroid use have been proposed to reduce side effects. These include large weekly boluses or other schedules providing drug free periods. These alternative regimens should be tested in well-designed, controlled trials.

Pursue Pharmacological Treatment Approaches and Accelerate Drug Screening

Development of new pharmacological treatments should be pursued. Potential therapies that may hold promise include aminoglycosides or other agents that promote read-through of stop codons, functional compensation for dystrophin by utrophin upregulation, and increasing muscle mass via myostatin inhibition. Alternative regimens, including a cocktail approach, should also be pursued. In addition, assays for high throughput drug screening technologies also need to be developed.

Treatment of Complications / Co-Morbid Conditions

Treatments and/or treatment protocols should be developed that focus on cardiomyopathy, pulmonary function, osteoporosis, hearing loss, vision impairment, cognitive and behavioral issues, reproductive issues, and muscle wasting. With regard to cardiomyopathy, additional studies are needed on drugs currently used to treat and manage this condition.

BROAD HEADING 4: LIVING WITH MD: REHABILITATION, QUALITY OF LIFE, AND PSYCHOSOCIAL ISSUES

Patients with MD experience not only the principal effect of muscle degeneration, but also many secondary conditions, some of which are serious conditions of their own. Many body systems besides the musculoskeletal system are impacted by MD, and the "whole body" approach to the disease needs to be considered as rehabilitation measures and quality of life improvements are assessed and developed. The psychosocial effects of the disease, including the impact of the disease on the day-to-day lives of patients, should not be overlooked.

Determine the Extent of Cognitive Involvement in MD

It is important to study the relationship between etiology and cognitive/behavioral problems, and to determine the progression of cognitive problems.

Address Rehabilitation Challenges / Prevent Secondary Conditions

Rehabilitation research and the development of new and effective rehabilitation strategies are needed to address many areas including: maintenance of strength and management of muscle weakness and wasting; management of hearing and vision loss; speech rehabilitation and therapy; management of spine deformities; management of cardiomyopathy; nutritional concerns, including feeding issues and swallowing difficulties; and management of restrictive lung disease and respiratory weakness. Ways to prevent secondary conditions need to be developed, especially in slowly progressing forms of MD and conditions associated with both muscle overuse and with a sedentary lifestyle, including disuse atrophy, weight gain, contractures, and metabolic syndromes. More research is needed on the role of physical activity and exercise in preventing secondary problems.

Improve Quality of Life Measures

Instruments for objective measure of quality of life instruments are needed to determine appropriate interventions. Secondary outcome measures including blood pressure, body mass, and heart rate should also be improved.

BROAD HEADING 5: RESEARCH INFRASTRUCTURE NEEDS

There are many resources that are needed to advance the field of MD research. These include infrastructure needs and research resources, such as the development of better animal models, improved access to animal models and biological materials, and enhanced imaging methods. Collaboration and communication among the MD community should be further facilitated. Networks of patients, small meetings of researchers, and collaboration among government, industry, and the patient populations will help advance the field. In addition, young investigators should to be encouraged to work in areas of MD basic and clinical research.

Organize Patient Networks

Establish a centralized mechanism for collecting diagnostic and clinical data on all forms of MD. There should be an effort to enhance, supplement, and work with patient networks, organized in diverse geographical locations around the country, ensuring that all diagnoses are based on

common protocols and outcome measures. A major benefit would be the ability to collect accurate epidemiologic and natural history data. In addition, the networks would serve as an invaluable resource for researchers who wish to conduct clinical trials (e.g., for gene therapy or drug treatment).

Establish a North American Neuromuscular Working Group

Establish a mechanism – such as a North American Neuromuscular Working Group - to ensure communication and sharing of resources among all stakeholders in MD research and treatment. Either as a virtual or physical entity, such a group would allow scientists to meet frequently to discuss the latest data on new mutations, discuss ways to standardize diagnostic measures, publish common protocols, and set standards for trial design. Small, focused meetings that center around discussion, interaction and brainstorming on specific topics should be encouraged. Such a resource was identified as a critical need and one that could significantly advance the field.

Improve Access to Biological Materials

There is a need for collection and sharing of biological materials. Resources such as collections of newborn screening specimens, frozen tissue and cell lines, brain banks, and "biobanks" are identified needs.

Develop Better Animal Models

While animal models exist for dystrophinopathies, sarcoglycanopathies, and Emery-Dreifuss MD, there is a need to develop new and better animal models of FSHD and myotonic dystrophy. Creating animal models of these types of MD may be very challenging. Animal models would advance our understanding of the pathogenesis of disease and permit further study of experimental treatments. Animal models need to be made more readily available to investigators, and ease of sharing animals needs to be improved.

Develop Better Imaging Methods

More effective imaging technology is needed to better quantify muscle wasting and/or improvements in muscle mass in response to treatment. While some treatments, such as steroids, have become the standard of care, conclusive evidence is needed that they delay the progression of disease and preserve or increase muscle mass. New imaging technology should be developed, and uses of existing technology should be improved, to determine, for example, the best measurement parameters to use with current methods such as MRI. A need also exists for improved imaging methods to monitor, non-invasively, gene transfer and expression kinetics.

Facilitate Partnerships with Industry and Voluntary Patient Advocacy Groups

In many areas of MD research, it would be advantageous to establish government-academic-industrial partnerships, as well as partnerships with voluntary patient advocacy groups, to enhance therapeutics development. This is particularly true for gene therapy, where high cost is an issue. Partnerships with industry could also make genetic testing more readily available and affordable.

Increase the Number of Investigators in MD Research

There is a need to ensure an adequate number of highly skilled researchers to conduct basic, translational, and clinical research. Researchers who will promote multidsiciplinary and interdisciplinary approaches are needed to understand the disease process and pathophysiology, and to develop new therapies for all forms of MD. Training programs encompassing a wide range of scientific areas and clinical disciplines would be valuable to the field of MD.

Future Steps

There are many emerging opportunities in MD research. This NIH Research and Education Plan, which outlines comprehensive research goals that can help advance MD research, is meant to be a working document for the entire MD community. While it may be possible to accomplish some of these goals in the short term, many of the goals will take time to achieve. The NIH will work with its partners in government, academia, the private sector, and the patient community to develop implementation strategies for these goals, and will continue to work with these groups to measure progress and redefine priorities, as science progresses and new opportunities emerge. In accordance with the MD-CARE Act, the Research and Education Plan will be periodically reviewed and revised by the MDCC. The Plan, along with any revisions, will be included in the biennial report to the Congress, which will also include an update on research, education, and other activities on MD being conducted or supported through the DHHS, as well as a report of funding by DHHS with respect to various forms of MD. The first of these biennial reports will be sent to the Congress in July 2005.

APPENDICES

Appendix 1: COMMITTEE ROSTER
Muscular Dystrophy Coordinating Committee

Alexander, Duane F., M.D.
Director
National Institute of Child Health and Human Development
National Institutes of Health
Department of Health and Human Services

Bertram, Colonel Kenneth, M.D., Ph.D., FACP
Director
Congressionally Directed Medical Research Programs
US Army Research and Materiel Command
Department of Defense

Cordero, Jose F., M.D., M.P.H.
Assistant Surgeon General
U.S. Public Health Service
Director, National Center For Birth Defects
and Developmental Disabilities
Centers For Disease Control and Prevention
Department of Health and Human Services

Decker, Donavon R.
Patient Advocate

Duckett, Mary Jean
Director
Division of Benefits, Coverage, and Payment
Disabled and Elderly Health Programs Group
Center For Medicaid and State Operations
Centers For Medicare and Medicaid Services
Department of Health and Human Services

Furlong, Patricia A.
Patient Advocate
President, Parent Project Muscular Dystrophy

Hesterlee, Sharon E., Ph.D.
Director, Research Development
Muscular Dystrophy Association

Katz, Russell G., M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services

Katz, Stephen I., M.D., Ph.D., CHAIR
Director
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
Department of Health and Human Services

Landis, Story C., Ph.D.
Director
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Department of Health and Human Services

McPherson, Merle, M.D., M.P.H.
Director
Division of Services for Children With Special Health Needs
Maternal and Child Health Bureau
Health Resources and Services Administration
Department of Health and Human Services

Morrissey, Patricia A., Ph.D.
Commissioner
Administration on Developmental Disabilities
Administration for Children and Families
Department of Health and Human Services

Vacancy
Department of Education

Perez, Daniel P.
Patient Advocate
President and Chief Executive Officer
Facioscapulohumeral Society, Inc.

Stephenson, Bradley R.
Patient Advocate

Appendix 2: Minutes from July 1, 2003 MDCC Meeting

Muscular Dystrophy Coordinating Committee (MDCC)
July 1, 2003
Democracy II, 6707 Democracy Blvd., Bethesda, MD; Room 701

Attendees:
Kenneth Bertram, DOD
Coleen Boyle, CDC, MDCC ad hoc member
Calvin Carpenter, DOD
Daofen Chen, NINDS
Stephanie Clipper, NINDS
Donavon Decker, Patient advocate, MDCC member
Morgan Downey, FSH Society
Mary Jean Duckett, CMS, MDCC member
Marian Emr, NINDS
Lorraine Fitzsimmons, NINDS, MDCC Executive Secretary
Patricia Furlong, Parent Project MD, MDCC member
Stephen Groft, ORD
Katrina Gwinn-Hardy, NINDS
James Hanson, NICHD, MDCC ad hoc member
Steven Hausman, NIAMS
Sharon Hesterlee, MDA, MDCC member
Stephen Katz, NIAMS, MDCC Chair
Lisa Kaeser, NICHD
Cheryl Kitt, NIAMS
Anita Linde, NIAMS
Richard Lymn, NIAMS
Cynthia McCormick, NINDS
Merle McPherson, HRSA, MDCC member
Patricia Morrissey, Administration for Children and Families (ACF), MDCC member
Ralph Nitkin, NICHD
Robert Pasternack, Dept of Education, MDCC member
Audrey Penn, NINDS, MDCC member
Charles Perez, FSH Society
Daniel Perez, FSH Society, MDCC member
Heather Rieff, NINDS
Philip Sheridan, FDA, MDCC ad hoc member
Giovanna Spinella, ORD
Bradley Stephenson, Patient advocate, MDCC member
Fei Wang, NIAMS

Summary of meeting:

Ms. Lorraine Fitzsimmons, Executive Secretary, called the meeting to order at 9 am, reviewed the code of ethics considerations, and gave an overview of the agenda.

Dr. Stephen Katz, MDCC Chair and Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), welcomed the Committee members and thanked them for their service on the MDCC. He reviewed the Committee Charter and charge to the Committee, and noted that the Committee is required to develop and finalize a research plan one year from the time of the final appointment of all members to the MDCC. The Committee will likely meet one or two more times this year to develop this plan. Dr. Katz noted that much of this work can be done by e-mail and conference call.

During the morning session, members of the MDCC from government agencies presented an overview of their agencies' programs in muscular dystrophy (MD):

Dr. Audrey Penn, Acting Director, National Institute of Neurological Disorders and Stroke (NINDS), discussed NINDS's mission - to reduce the burden of neurological disease - in the context of MD. She gave a historical overview of the identification of MD and of the dystrophin-glycoprotein complex. She outlined the challenges for MD research including the elucidation of the defects in facioscapulohumeral muscular dystrophy (FSHD) and the use of gene therapy and stem cell therapy. Dr. Penn also discussed the establishment of the MD Cooperative Research Centers, and how these Centers are meant to advance research and treatment - the Centers overall goal is to advance research from the "bench to bedside and back."

Dr. Richard Lymn, Chief, Muscle Biology Branch, NIAMS, gave an overview of NIAMS's research programs in MD, which fall into three broad categories: skeletal muscle structure and development, muscle growth and regeneration, and inflammation in muscle. He discussed the role of the NIH MD Research Task Force in providing advice to the NIH about its research program. The Task Force has held two meetings, with different participants at each depending on topics discussed. The Task Force has discussed many issues including: identifying new capabilities to improve treatment; improving interactions among researchers and clinicians; and clinical research opportunities.

An overview of the National Institute of Child Health and Human Development's (NICHD) programs was provided by Dr. James Hanson, Acting Director, Center for Developmental Biology and Perinatal Medicine, NICHD, who was substituting for Dr. Duane Alexander, NICHD Director. Dr. Hanson highlighted the priority research areas of the National Center for Medical Rehabilitation Research, the Center for Developmental Biology and Perinatal Medicine, and the Center for Research for Mothers and Children, all of which support programs relevant to MD. He outlined areas of particular interest to NICHD including: cognitive disabilities in MD; newborn screening; non-muscle complications of MD resulting in mental retardation and developmental disabilities; rehabilitation; and family issues.
Dr. Philip Sheridan, substituting for Dr. Russell Katz (Director, Division of Neuropharmacological Drug Products, Office of Drug Evaluation 1, Center for Drug Evaluation and Research, FDA), described the role of the FDA in interactions with the pharmaceutical and biologics industries. He mentioned two important programs within the Center for Drug

Evaluation and Research: the Orphan Drug Development Program, and a new office, the Office of Counter-Terrorism and Pediatrics. FDA (along with NIH) is actively implementing the provisions of the Best Pharmaceuticals for Children Act of 2002. Dr. Sheridan explained his background in drug development in the area of epilepsy, and emphasized the availability of the FDA to advise the research community in drug development issues.

Ms. Mary Jean Duckett, Director of the Division of Benefits, Coverage, and Payment in the Disabled and Elderly Health Programs Group, Centers for Medicare and Medicaid Services, gave an overview of Medicaid services -- both home and institutional care -- that are available. Different programs offer flexibility from state to state to provide a variety of options including prescription drug reimbursement and rehabilitation services. One program, the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) Program, is a mandatory state Medicaid child health screening program. Members of the Committee expressed concern about the overall lack of uniformity from state to state in terms of services provided.

Dr. Coleen Boyle, Associate Director for Science and Public Health, National Center on Birth Defects and Developmental Disabilities at CDC, represented Dr. Jose Cordero (Director, National Center For Birth Defects and Developmental Disabilities, CDC), and gave an overview of the programs at the Center that focus on Duchenne MD (DMD). She highlighted a cooperative agreement program funded by CDC on DMD Surveillance and Tracking. The scope of this program ranges from biomedical and molecular-related research on DMD to data collection on practices of care for DMD patients. In FY 2003, two new states were added to the program. The program proposes to analyze a number of parameters including the incidence and prevalence of DMD, the early natural and diagnostic history of the disease, the impact of type of care on outcome, and the effects of different mutations and potential modifying factors. CDC is also funding a DMD family survey through the Children's National Medical Center to determine service needs and barriers to service, quality of life, and the impact of newborn screening on family-related issues. The survey is currently in development. For FY 2003, CDC is also considering funding a survey of female Duchenne and Becker MD carriers, and particularly examining their risk of cardiomyopathy.

Dr. Patricia Morrissey, Commissioner, Administration on Developmental Disabilities, Administration for Children and Families, discussed MD-related activities being undertaken by University Centers for Excellence on Developmental Disabilities. Eight of the Centers, which are authorized in the Developmental Disabilities Assistance and Bill of Rights Act of 2000, conduct research, provide training or clinical services, and/or collaborate with others on issues relevant to MD. Projects at these Centers range from biochemical and genetic research to clinical care, as well as a DMD surveillance and research program.

Dr. Robert Pasternack represented the Office of Special Education and Rehabilitative Services at the Department of Education. The Office of Special Education and Rehabilitative Services administers IDEA (Individuals with Disabilities Education Act) programs. IDEA programs provide parent support and training and address family issues relevant to special education needs. MD is not one of the special education categories per se, but rather falls under the "other health impairments" category. A system of vocational rehabilitation is in place to help individuals with

disabilities find employment. The National Institute on Disability and Rehabilitation Research supports basic and applied research to impact the lives of individuals with disabilities. A number of funded projects relate to the disabilities of patients with MD.

Dr. Merle McPherson, Director, Division of Services for Children with Special Health Needs, Maternal and Child Health Bureau at HRSA, discussed the work HRSA does related to the Presidents' New Freedom Initiative to provide community-based services for people with disabilities. A goal is to integrate and organize services and programs at the community level, although how to do this most effectively is a difficult challenge. Another goal of HRSA's programs is early diagnosis and early and continuous developmental/behavioral screening of all children.

Dr. Elias Zerhouni, NIH Director, spoke to the MDCC during the morning session of the meeting. He thanked the members for their commitment to the MDCC and acknowledged the leadership and energy that Dr. Katz will exercise in his role as Chair. Dr. Zerhouni recounted how one of his first activities as the new NIH Director was to meet with members of Congress about the implementation status of the MD-CARE Act. Dr. Zerhouni was accompanied by Dr. Katz, and they reassured the late Senator Wellstone and Senator Collins of the NIH's commitment to implementing the provisions of the MD-CARE Act.

Dr. Katz asked for public comment from members of the audience, and called upon two individuals to give an overview of their organizations' activities in MD:

Colonel Kenneth Bertram, whose appointment as the Department of Defense representative to the MDCC was pending, discussed the Congressionally Directed Medical Research Programs (CDMRP), US Army Medical Research and Materiel Command (USAMRMC). The mission of the USAMRMC is to shape the future of health care and conduct medical research and development projects to protect soldiers and their beneficiaries. Many medical developments and advances originally developed for military personnel and their families have been made available to and benefited the general public. The CDMRP was started in 1993 to fill a need for more research in breast cancer. It funds 'customer-focused,' product-driven research targeted to specific diseases. In FY 2003, the CDMRP received an appropriation of $3.4 million for muscular dystrophy research, all of which is expected to be committed in this fiscal year. Proposals are currently in peer review and include basic research, clinical research, and resource development. The review process includes both scientific and programmatic review to ensure relevance to MD and military relevance.

Dr. Stephen Groft, Director, Office of Rare Diseases at NIH, gave an overview of ORD's programs. ORD provides information and organizes workshops on rare diseases, in partnership with other NIH components. In addition, the doubling of the NIH budget has enabled a large increase in research on rare diseases and has allowed ORD to begin to implement some exciting programs. ORD recently issued a Request for Applications for Clinical Research Centers for Rare Diseases, and to date, has received approximately 80 letters of intent. ORD will fund up to four Centers as well as a data coordinating center. ORD is also thinking about ways to encourage translational research in rare diseases.

The Committee discussed ways to encourage companies to get involved in development of therapies for rare diseases and Dr. Groft highlighted the Small Business Innovative Research Grants (SBIR) and the Small Business Technology Transfer Grants (STTR) Programs at NIH, as well as the importance of continuing to increase the amount of basic research on these diseases coming down the pipeline.

The Committee also discussed the potential benefits of a patient registry and clinical network to aid in clinical and epidemiological studies. The Cystic Fibrosis Foundation patient network was cited as a model. There was enthusiasm expressed by several members about the potential for integrating muscular dystrophy knowledge into activities across different agencies. As an example, Mr. Perez noted that more information about the early natural history of FSH dystrophy should be made available to physical education teachers especially in middle and high schools when symptoms might be detected and diagnostic referrals made. Dr. Pasternack expressed great interest in this idea.

The meeting was recessed for lunch.

The afternoon session began with presentations from the public members of the MDCC:

Ms. Patricia Furlong discussed her family's personal experience with Duchenne MD as well as the efforts of her organization, Parent Project MD. She stressed the need for more education and widespread knowledge about DMD, and felt that effective partnerships need to be developed between government, academia, and pharmaceutical companies.

Dr. Sharon Hesterlee, Director of Research Development for the Muscular Dystrophy Association (MDA), gave an overview of MDA's programs including research funding, and patient and community services. She discussed MDA's new Translational Research Program. The goals of this program include supporting the development of infrastructure, providing a blueprint for conducting translational research through education and structured grants, addressing the shortage of clinical investigators, and strengthening relationships with the biotechnology and pharmaceutical industries. The program is still taking shape, but MDA plans to launch it soon.

Mr. Daniel Perez, patient advocate and President and CEO of the Facioscapulohumeral Society, Inc. (FSH Society), discussed the work of this organization to provide education on the unique nature of FSH dystrophy. The FSH Society reaches out to approximately 8,000 -10,000 individuals, and also funds post-doc grants. Mr. Perez also discussed the "whole body" issues of MD, and was pleased to see so many NIH Institutes participating in the meeting.

Mr. Donavon Decker, patient advocate, was the first patient to undergo gene therapy for limb girdle MD. He shared his experiences of having many family members afflicted with this disorder, including several family members. He described his experience working with Drs. Kevin Campbell and Jerry Mendell during the gene therapy trial, and expressed his strong support for the initiation of new gene therapy trials. He also commended the MDA for their strong support of patients with MD.

Mr. Bradley Stephenson, patient advocate with Becker MD, described the symptoms and progression of Becker MD and offered his suggestions for developing a research plan. He felt that the plan should contain specific action items for the NIH Institutes, and should draw upon the work of other groups such as the NIH MD Research Task Force, MDA, and other groups.

The Committee discussed how to approach their task of developing a research and education plan for NIH. Pat Furlong mentioned the need to look at a range of research options as well as care issues. Dan Perez was interested in an evaluation of the process of review of MD grants at NIH. He felt there was a mismatch between the research needs for particular disorders and the review process. The Committee may be interested in inviting Dr. Ellie Ehrenfeld, Director, NIH Center for Scientific Review, to a future MDCC meeting.

There was some discussion about how to include other agencies and groups with an interest in MD in the research plan, since the MD-CARE Act mandates that the MDCC develop a plan specifically for NIH ("...the Coordinating Committee shall develop a plan for conducting and supporting research and education of muscular dystrophy through the national research institutes..."). The Committee discussed that while we need to be aware of, and consider the activities of other groups, the first task of the Committee is to develop this plan for the NIH. Once the plan is developed, there will certainly be opportunities to discuss how other groups' activities fit with, or may build upon, this plan, and how NIH can work collaboratively and cooperatively with these other groups. It was envisioned that other agencies may wish to form their own working groups to expand upon issues identified by the MDCC for future program development.

Lorraine Fitzsimmons shared with the Committee examples of other research plans that have been developed at NIH: the "Benchmarks" for Epilepsy Research; the Report of the Brain Tumor Progress Review Group; and the Parkinson's Disease Matrix and corresponding narrative (she noted that a full Parkinson's Research Agenda is available on the web; see http://www.ninds.nih.gov/about_ninds/nihparkinsons_agenda.htm). Dr. Stephen Katz noted the important role that advocacy groups played in developing and revising these plans, once the initial input of the scientific research community had developed the core of the plan.
Ms. Fitzsimmons discussed one option for developing a plan, which is to use the Risk vs. Time Matrix format (an approached favored by Dr. Zerhouni) to identify research opportunities, needs, and roadblocks. Dr. Katz noted the importance of determining what the science needs are, rather than focusing on which specific mechanisms to use, or prescribing specific dollar amounts to advance the goals.

The Committee discussed using the expertise on the NIH MD Research Task Force to develop the plan. One idea is for some members of the MDCC to participate in the next Task Force meeting (tentatively scheduled for the fall) to work on a research plan. This 'working group' could further refine the plan via email and the full MDCC could meet in 5-6 months to discuss the plan and begin to finalize it. Sharon Hesterlee mentioned a Muscle Biology meeting, tentatively planned for January in San Diego, as a possible place to vet such a plan, depending on what stage of development the plan is in by then. Pat Furlong suggested that a website -

possibly a password-protected one - may facilitate the process of developing such a plan and distributing working documents and sharing comments during the plan's development.

The Committee was asked which other NIH components should be involved in developing the plan and Committee members cited the National Heart, Lung, and Blood Institute (NHLBI), the Office of Rare Diseases (ORD), the National Human Genome Research Institute (NHGRI), and the National Center for Research Resources (NCRR) as important players.

The meeting was adjourned at 3:30 pm.

Approved by:

_____/s/_____ September 25, 2003
Stephen I. Katz, M.D., Ph.D.,
Chair, MDCC

_____/s/_____ September 25, 2003
Lorraine G. Fitzsimmons,
MDCC Executive Secretary

Appendix 3: Scientific Working Group Roster

MDCC Members:

Dr. Stephen Katz, NIAMS, Chair, MDCC
Dr. Audrey Penn, NINDS
Col. Kenneth Bertram, DoD
Dr. Aileen Kenneson, CDC [for MDCC member Dr. Jose Cordero]

Other Members:

Jeffrey S. Chamberlain, Ph.D. (via phone)
University of Washington School of Medicine
Department of Neurology

Diana Escolar, M.D.
Children's National Medical Center
Research Center for Genetic Medicine

Kenneth Fischbeck, M.D.
Neurogenetics Branch
Division of Intramural Research
National Institute of Neurological Disorders and Stroke, NIH

Kevin Flanigan, M.D.
University of Utah
Departments of Human Genetics and Neurology

Dr. Rune R. Frants, Professor (by written communication)
Center for Human and Clinical Genetics
Leiden University Medical Center

Stephen Hauschka, Ph.D.
University of Washington
Department of Biochemistry

Veronica J. Hinton, Ph.D.
Columbia University
Cognitive Neuroscience Division
G.H. Sergievsky Center and Department of Neurology

Eric Hoffman, Ph.D.
Children's National Medical Center
Research Center for Genetic Medicine

David Housman, Ph.D.
Massachusetts Institutes of Technology
Center for Cancer Research

R. Rodney Howell, M.D.
University of Miami
Department of Pediatrics
National Institute of Child Health and Human Development, NIH

Johnny Huard, Ph.D.
Growth and Development Laboratory, Children's Hospital of Pittsburgh
Department of Orthopaedic Surgery, University of Pittsburgh

Louis Kunkel, Ph.D.
Harvard Medical School/Children's Hospital Boston
Department of Genetics and Pediatrics

Katherine Mathews, M.D.
University of Iowa Hospitals and Clinics
Departments of Pediatrics and Neurology

Craig M. McDonald, M.D.
University of California School of Medicine
Department of Physical Medicine and Rehabilitation

Elizabeth McNally, M.D., Ph.D.
University of Chicago
Department of Medicine, Section on Cardiology
Department of Human Genetics

Jerry Mendell, M.D.
Ohio State University
Department of Neurology

Paul Plotz, M.D.
Arthritis and Rheumatism Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH

H. Lee Sweeney, Ph.D.
University of Pennsylvania, School of Medicine

Stephen Tapscott, M.D., Ph.D.
Fred Hutchinson Cancer Research Center
Human Biology Division

Charles A. Thornton, M.D.
University of Rochester Medical Center
Department of Neurology

Appendix 4: Minutes from March 22, 2004 MDCC Meeting

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
MUSCULAR DYSTROPHY COORDINATING COMMITTEE
March 22, 2002
Summary of Meeting

The interagency Muscular Dystrophy Coordinating Committee (MDCC) was convened for its 2nd meeting on March 22, 2004, at the Marriott Suites Hotel, Bethesda, Maryland. Dr. Stephen Katz, Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), served as Chairperson.
In accordance with Public Law 92-463, the entire meeting was held in open session.

I. Call to Order and Opening Remarks

Dr. Stephen Katz called the meeting to order at 8:45 a.m. He welcomed the Committee members and explained the purpose of this meeting, which was to review the draft research and education plan. He then asked people to introduce themselves.

Ms. Lorraine Fitzsimmons, Executive Secretary, noted the following changes to the Committee: Dr. Story Landis, newly appointed Director of the National Institute of Neurological Disorders and Stroke (NINDS), replaced Dr. Audrey Penn, the NINDS Deputy Director. Dr. Robert Pasternack left the U.S. Department of Education, and a nomination for his replacement has been requested from ED.

Ms. Fitzsimmons reviewed the code of ethics considerations as well as the recusal policies and procedures. The minutes from the last MDCC meeting were circulated in September 2003, and there were no comments on them, so the minutes were accepted. The minutes, along with other Committee information, including future meeting agendas, will be posted on the MDCC Web site. The link, (http://www.ninds.nih.gov/research/muscular_dystrophy/coordinating_committee/index.htm), was distributed to participants.

Ms. Fitzsimmons then explained the process of developing the draft research and education plan. At the first MDCC meeting, Committee members suggested establishing a Working Group, comprised of scientific experts, to help draft the plan. The Working Group met in October 2003 to develop a plan for Muscular Dystrophy (MD) research and to identify research roadblocks and opportunities. Some of the goals developed were specific to particular forms of MD, whereas other goals were common to all forms of MD. As the goals were revised by the Working Group, many of them were broadened. As a result, the goals did not lend themselves to a time-risk matrix format, because many of them include multiple time-risk designations. Therefore, with the concurrence of the working group, the National Institutes of Health (NIH) will develop a matrix at the same time that it develops implementation strategies. Ms. Fitzsimmons also reiterated that, although the research plan is for NIH, there will be issues that go beyond NIH, and other Federal agencies will need to be involved as implementation strategies are developed.

Dr. Katz mentioned that, because this information is due to Congress in July, Committee members will need to pay strict attention to timelines to ensure the timely delivery of written materials.

II. Discussion of the Draft MD Research and Education Plan

The meeting was then turned over to Dr. Kenneth (Kurt) Fischbeck, Chief of the Neurogenetics Branch, NINDS, who gave an overview of *Broad Heading 1: Understanding Mechanisms of Disease.*

Under this heading, Dr. Fischbeck discussed genes for the various forms of MD that already have been identified. Different genes and different mechanisms may involve various treatments but may have commonalities. There remains a need to identify and understand critical pathways in the various forms of MD to be able to design effective treatments.

Common themes in MD include deficits in muscle structural proteins, altered gene expression and RNA processing, and the failure of compensatory mechanisms. Questions to be answered include the following:

- How do structural protein deficiencies lead to disease?
- How do triplet repeat expansions lead to disease?
- What are the mechanisms of other (not Duchenne) dystrophies?
- Are there genetic or environmental modifiers?

At this point in the discussion, Mr. Daniel Perez, an MDCC member, noted that the gene for FSH Dystrophy (FSHD) has not been identified. Dr. Sharon Hesterlee, an MDCC member, commented that for many congenital MDs, no genes have yet been identified; as a result, many patients remain undiagnosed for certain forms of MD. She stressed the importance of pursuing this area of research. Mr. Donavon Decker, an MDCC member who has undergone gene therapy for MD, said that he thought there is no need to hold up gene therapy trials just because research has not yet identified all the genes.

Dr. Katz charged the group to remember the broad heading, "Understanding Mechanisms of Disease," with the proviso that there are some unique understandings that researchers need that are critical to understanding how interactions occur. Ms. Patricia Furlong, an MDCC member, agreed with Dr. Katz that a multifaceted approach is needed.

Dr. Fischbeck discussed the current understanding of how triplet expansion leads to disease. He pointed to myotonic dystrophy type 1, thought to be caused by an mRNA toxicity mechanism. Dr. Hesterlee noted that it is important to understand what causes these repeat expansions as well as what the expansions do; this understanding could lead to targets for intervention. Dr. Fischbeck added that researchers in this area might apply lessons from similar processes seen in other diseases, such as Huntington's disease. He talked about understanding the unique pathobiology of other dystrophies. FSHD likely involves changes in gene expression caused by alterations in chromosome 4. Emery-Dreifuss MD, on the other hand, is caused by defects in nuclear envelope proteins.

Genetic and environmental modifiers were also discussed. These can be identified in patient or animal models and offer opportunities for therapeutic intervention. Modifiers may account for the variable susceptibility of different muscles. Mr. Decker stated that five of his family members are affected with MD of varying severity. Mr. Perez mentioned the importance of understanding why some muscles are affected and others are not.

Dr. Fischbeck talked about opportunities for therapeutic intervention:

- Correct the gene defect(s).
- Block deleterious effects of genetic defect(s).
- Replace defective gene(s).
- Block muscle degeneration.

- Enhance muscle regeneration.

Dr. Landis suggested that blocking muscle degeneration should be seen as the primary goal for treating all forms of MD. Dr. Hesterlee agreed and commented that it might be better to stop the process more "upstream" (e.g., block muscle degeneration) and perhaps that approach should be a research priority.

Dr. Fischbeck responded with common approaches to developing treatments:

- Using common mechanisms to allow more efficient use of research funds
- Studying other diseases to uncover possible common mechanisms
- Partnering with pharmaceutical companies regarding chances for commercial development. (He cited a joint project involving researchers at Johns Hopkins University and Wyeth Pharmaceuticals to investigate blocking myostatin as a therapeutic strategy.)

During the ensuing discussion, Mr. Morgan Downey raised questions from the audience, involving international monitoring and disease epidemiology. Dr. Giovanna Spinella, Office of Rare Diseases, NIH, suggested looking at nonskeletal muscle and other manifestations of disease (e.g., cardiomyopathy in cardiac muscle; brain manifestations) for clues to disease mechanisms.

Dr. Katz then introduced Dr. Eric Hoffman of Children's National Medical Center (via telephone) to speak about *Broad Heading 2: Screening/Diagnosis*, and to lead a discussion of developing effective newborn screening strategies. Dr. Hoffman suggested that Dr. Coleen Boyle, Associate Director for Science and Public Health, Centers for Disease Control and Prevention (CDC), update the Committee about a CDC meeting held two weeks earlier.

Dr. Boyle said that the meeting reviewed experiences with newborn screening programs and information from Wales, Germany, Belgium, France, and Cyprus. Of particular interest were issues of informed consent; psychosocial needs of families and individuals; and assessment of risks and benefits (i.e., efficacy of early intervention opportunities).

Outcomes and issues from the CDC meeting included the following:

- Research is making it possible to reduce the age of diagnosis of children with Duchenne MD (DMD), although newborn screening is not appropriate at this time.
- The issue of false-positive results has a negative impact on families.
- Newborn screening is a program with many essential elements, not just the performance of a test; system care, such as genetic counseling, and clinical care need to be considered.
- Questions remain about how beneficial early treatment with steroids is, and at what age such treatment should begin.

Ms. Furlong said that everyone recognizes the need for early diagnosis of MD. The information presented, she added, augments evidence about the importance of early diagnosis. When screening is delayed until the 12th month of life, 20 percent of the people are lost. Dr. James Hanson, National Institute of Child Health and Human Development (NICHD), mentioned the need for a cost-effective molecular test that can be applied in the newborn period, and Dr. Katz agreed with that statement.

The meeting was turned back to Dr. Hoffman, who indicated that approximately 1.5 million infants have been screened for DMD in the United States. The screening rate is lower than what is generally quoted, which is to be expected when the more familial cases are cancelled out, he said. To include DMD in newborn screening, better tests need to be developed or false positives need to be screened out; a system

is also needed to support parents and prospective patients by providing helpful care when a diagnosis is made.

Dr. Hoffman said that it is important to improve molecular diagnostics, because there are many patients with unknown genes or gene defects. That is a challenging task, he added, with regard to sensitivity, specificity, cost, and turnaround time. There might be some way to encourage laboratories to develop new methods to sequence all genes or to look for peripheral blood markers from small plasma samples. The use of microarray systems is possible; but this is expensive and technically challenging. About 200 laboratories offer dystrophin testing, but these find only about 60 percent of patients with DMD. Fewer labs (only about two or three in the United States) perform more specific testing, such as looking at duplication or small deletions.

Mr. Perez asked about FSH testing. This issue, said Dr. Hoffman, is particularly challenging, but methods have improved. Dr. Fischbeck stated that this is a moving target; the majority of MDs do not have genetic testing available. Dr. Hoffman noted that biochemical testing is not as reliable as genetic testing. Dr. Spinella mentioned an upcoming meeting to be held in May with CDC that pertains to genetic testing.

A colleague of Dr. Hoffman, Dr. Diana Escolar, Children's National Medical Center, addressed the issue of natural history studies by telephone. She pointed out the need for observational, population-based studies. Collected data should be broad enough to be meaningful and should be collected in a reliable and uniform fashion. Measures of muscle, pulmonary, and cardiovascular function should be collected as clinical data sets. In FSH, phenotype/genotype correlations are needed. It was suggested that an example of a clinical data set to emulate is the amyotrophic lateral sclerosis (ALS) observational database. Dr. Katz observed that it is difficult to standardize data but noted the cystic fibrosis (CF) community provides a good example of where this is being done. CF groups work together synergistically, and they develop good, standardized data collections.

Mr. Perez asked about the number of children screened for DMD. He said that he would like to see the section under newborn screening broadened to include all dystrophies and mentioned that preimplantation testing for FSHD is available outside the United States.

The issue of genetic discrimination was raised by Dr. Duane Alexander, Director of NICHD. Unless this is addressed, there will not be effective newborn screening processes. He felt that this issue should be highlighted as a potential obstacle needing congressional oversight.

Dr. Merle McPherson, Director of the Division of Services for Children with Special Health Needs, Maternal and Child Health Bureau, Health Resources and Services Administration, said that the health service delivery system must be engaged and that screening cannot occur in a vacuum. She urged the Committee to consider this point and how it relates to health care delivery. Dr. Katz responded that this is certainly an issue; the initial focus of the plan is on research, but as implementation strategies are developed, these issues, and the agencies involved with them will be critical.

Dr. Katz then introduced Dr. Jerry Mendell, Ohio State University, who talked via telephone about *Broad Heading 3: Treatment Strategies*.

There are three overall approaches to treatment: pharmacologic, gene therapy, and stem cell therapy. The forms of MD on which to focus initially are DMD, FSHD, and myotonic dystrophy. Success in any one of these will have an impact on other disorders.

The first approach discussed was gene therapy. There need to be more large animal studies in this area. Mouse studies are limited in the amount of muscle weakness that the animal can demonstrate; large animal models, like dogs, are better suited to address safety and efficacy issues, and the results are more applicable to humans. Large animal colonies are receding in supply and are expensive to maintain, so more money is needed to support them. Mr. Decker asked if pharmaceutical companies would participate if large animal studies were conducted. Dr. Mendell replied that it is very likely and that dog colonies are needed to demonstrate successes. Mr. Perez asked if there are primate models for MD, but Dr. Mendell said that there are no naturally occurring primate models for MD and that primate studies are very expensive to conduct.
Dr. Mendell then talked about the need to develop clinical grade vectors and that large amounts of vector are needed for multicenter clinical trials. Dr. Katz suggested that someone be brought in from the National Center for Research Resources (NCRR) to find out what is needed for large-scale vector production. Dr. Audrey Penn suggested involving the National Institute of General Medical Sciences (NIGMS). Dr. Hesterlee proposed reaching out to industry and remarked that many of these research areas (e.g., animal studies, vector development) should be pursued in parallel.

New viral vectors are able to reach remote sites after infection into the bloodstream. Adeno-associated viruses (AAV), retroviruses, lentiviruses, and herpesviruses are some of the vectors that hold promise; there are advantages and disadvantages to each. Mr. Perez asked about which dystrophies these vectors could be used to treat. Initially, DMD and limb girdle MD are most applicable, but they may eventually accommodate most MDs.

Dr. Mendell explained that gene therapy is not only the replacement of missing genes. Other promising strategies include the use of antisense oligonucleotides to promote exon skipping and to allow normal gene expression, as well as the introduction of other genes to improve muscle mass and strength (e.g., IGF-1, modification of myostatin). Combining gene replacement with some of these other approaches may be the most effective strategy.

Dr. Mendell commented that serotype issues are part of an exciting area that involves using subtypes of existing viruses as vectors. Some, such as AAV6 and AAV8, are known to cross the bloodstream into muscle. Some people's immune systems may have been previously exposed to these viruses, and the Food and Drug Administration (FDA) has restrictions on the use of vectors in patients with high titers of antibodies to these viruses. Dr. Mendell thought that the patient population needs to be surveyed to obtain a picture of their immune status and that this is important in light of future clinical studies.

When asked how close researchers are to conducting clinical trials, Dr. Mendell responded that scientists are on the verge of restarting gene therapy trials and there have been several discussions with the FDA.

Dr. Mendell said that, with regard to stem cell therapies, skin, muscle biopsies, and bone marrow might all be sources of stem cells. He addressed the difference between myoblasts (which do not appear to have the potential to differentiate) and muscle stem cells (which can differentiate, possibly into all the components of muscle). Much remains to be learned about cell therapy, including growing stem cells, cell delivery, and immunologic rejection.

MDCC member Bradley Stephenson indicated that he would like to see embryonic stem cells mentioned in this report. Dr. Hesterlee added that she does not know of any group that has used embryonic stem cells in MD research. Mr. Perez commented that he would like to see more research on embryonic tissue and muscle stem cells.

Mr. Stephenson asked about somatic cell nuclear transfer. Dr. Mendell advised that genetically competent (rather than affected) nuclei should be used. This is a line of research that has been largely neglected but would obviate the immunologic response. Mr. Stephenson thought that somatic cell nuclear transfer should be included in the section on cell therapy.

In the area of pharmacologic strategies, Dr. Mendell mentioned that corticosteroids have been used aggressively for the past 15 years and are the standard of treatment for MD. The challenge in terms of patient management concerns side effects. The mechanism of action of steroids needs to be studied, because this may help design other drugs that could work similarly but would lack the side effects.

Dr. Mendell stated that it is known that damage from MD is reduced when steroids are administered early and that there is more to learn about dosing regimens. Drug "holidays" may help patients avoid side effects, and it is possible that larger weekly doses are more suitable than daily doses. Dr. Katz asked if methods to measure benefits were available; Dr. Mendell replied that this is a complex issue.

There also are limited practice guidelines for the use of steroids and no standard of care. LT COL Calvin Carpenter, *ad hoc* MDCC member, noted that there need to be standards to which we can compare new therapies. The American Academy of Neurology is expected to release practice parameters for treating DMD with steroids in spring 2004.

Dr. Mendell then addressed other pharmaceutical treatment approaches and accelerated drug screening. One approach is to manipulate genes with pharmacologic agents. Studies are under way using aminoglycosides. Another area of study involves using monoclonal antibodies to inhibit myostatin, with a clinical trial now under way. Researchers also are looking at upregulation of other genes, including utrophin. High- throughput screening can help screen huge numbers of compounds for potential drugs. Dr. Katz mentioned that this type of technology has the power to benefit all MDs. There are aspects of the NIH Roadmap Initiative that address this issue.

Treatment options for complications and comorbid conditions were also addressed by Dr. Mendell. These can involve nonskeletal muscle, such as cardiac tissue. Other areas of concern include pulmonary issues and learning disabilities. Treatment strategies to address these issues should also take into account that younger and older populations are affected.

Mr. Perez raised a question involving hormonal changes in adolescents and young adults as well as the overall hormonal aspects of MDs (i.e., menopause and sex differences). Dr. Mendell noted that steroids delay adolescence and contribute to short stature and said that there are hormonal issues that likely have been understudied.

Dr. Hesterlee mentioned that comorbid factors in myotonic dystrophy (e.g., cardiomyopathy, diabetes) are very important and that muscle weakness in this disease process is almost the least of the problems. Ms. Furlong said that osteoporosis needs to be addressed in MD patients. Dr. Katz brought up bone scans in children, and Dr. Mendell replied that there are no standards for interpretation of bone scans in this population.

(The group broke for lunch at 12:30 p.m. and reconvened at 1:15 p.m.)

III. Update on the Senator Paul D. Wellstone MD Cooperative Research Centers

After the lunch break, Dr. Katz asked Dr. Richard Lymn, NIAMS, to discuss the Senator Paul D. Wellstone MD Cooperative Research Centers. Three Centers were recently funded, one each by NINDS, NIAMS, and NICHD. At the University of Pittsburgh, researchers are looking at potential gene and cell therapies (one involving cardiomyopathy). At the University of Rochester (New York), there is a focus on myotonic dystrophy and FSHD, and a clinical project is under way. At the University of Washington, researchers are investigating the means of developing and delivering adenoviruses and are looking at safety and efficacy issues in mice and dogs. Dr. Hesterlee said that the MDA, through a partnership with NIH, is providing a $500,000 supplement for research projects to each Wellstone Center.

IV. Continuation of the Discussion of the Draft MD Research and Education Plan

The discussion of the next broad topic area, *Broad Heading 4: Living With MD: Rehabilitation, Quality of Life, and Psychosocial Issues*, was led by Dr. Hanson of NICHD.
Dr. Hanson noted the need to determine the extent of cognitive involvement in MD. While cognitive and behavioral aspects have been documented in DMD, some congenital MDs, and myotonic dystrophy, less is known about cognitive and behavioral issues in other forms of MD, and much remains unknown about progressive changes in cognition and behavior in most forms of MD. Educational interventions need to be addressed, and the factors contributing to the variability of outcome also need to be understood.

Rehabilitation issues that need to be considered include improving functional mobility and promoting behavioral adaptability to functional loss, developing improved assistive technologies, and training scientists in the field of rehabilitation. Rehabilitation and the prevention of secondary conditions—manual strength, muscle weakness and wasting, spinal deformities, cardiomyopathy, respiratory problems, and nutritional concerns—also need to be addressed.

Quality-of-life measures need to be developed and applied to assess intervention strategies, Dr. Hanson said. He also mentioned that psychosocial issues relating to participation in the full range of societal activities (employment, education, transportation, and recreation) should be addressed.
Dr. Michael Weinrich, Director, National Center for Medical Rehabilitation Research, NICHD, addressed the issue of rehabilitation research. Nine NIH Institutes are participating in a recently issued joint program announcement on "Research Partnerships for Improving Functional Outcomes." The purpose of this initiative is to encourage basic, applied, and translational research directed toward improving the health of individuals with acute or chronic diseases who may benefit from rehabilitation, and MD is specifically included in the scope of research. Mr. Perez noted that rehabilitation is one of the few methods that we have to treat MD today. Ms. Furlong mentioned that physical therapy often is not covered by insurance, possibly due to the lack of ICD-9 codes.

Dr. Weinrich discussed the issue of exercise and said that there are no good guidelines for which exercises are therapeutic or harmful. Mr. Perez asked about the issue of setting guidelines in general. Patients have many questions: "Should I exercise? What kinds of exercise should I do? When should I consider a wheelchair?" Dr. Katz commented that the setting of guidelines is not necessarily part of the NIH mandate, however, there are times when a clinical consensus is needed. Dr. Hanson pointed out that NIH does not set guidelines (as this is more the province of medical societies and associations). However, it is important that research results be made available to specialists, and Dr. Katz added that translating knowledge into behavioral change is an important issue.

Dr. Katz asked about health disparities in MD, and questioned if there are racial and/or ethnic disparities in certain forms of MD. Dr. Hanson noted that there is a need to understand health disparities among subgroups of people with MD. Most of the MDs (other than DMD) have not really been studied epidemiologically around the world. Dr. Lymn noted that there are family and Tribal groupings, which

seem to be distinct subgroups. Dr. Hesterlee revealed that, in the case of oculopharyngeal MD, there seems to be a distinct French-Canadian grouping but that it is now also being seen more in people of Spanish descent.

Mr. Stephenson mentioned the issue of the management of cardiomyopathy. He said that, although the use of beta-blockers, or ACE inhibitors, can prevent or delay the onset of cardiomyopathy in MD, additional studies need to be conducted with these drugs. Dr. Katz said that cardiomyopathy could be considered a complication rather than a comorbid condition.

Dr. Katz and Dr. Landis then addressed *Broad Heading 5: Research Infrastructure Needs*. Dr. Landis noted the need to increase the number of investigators in MD—particularly pediatric neurologists, and that a variety of mechanisms could be used to increase the number of practitioners in this area. Mr. Perez asked if there was a way to stimulate the number of submitted applications. Dr. Katz explained that this is an issue that needs more than just money, as there is a general dearth in the number of practitioners in all pediatric subspecialties. Dr. Hesterlee noted that there was a real shortage of clinical researchers, and Dr. Landis added that a funding mechanism needs to be created to encourage the development of junior faculty at research centers, possibly through fellowship training and other awards.

Other matters concerning research infrastructure were addressed. Dr. Katz said that technology can be used to measure the efficacy of interventions and that new imaging methods should be pursued. The best type of imaging modality has not yet been defined regarding detection and surrogate markers of prevention. Dr. Landis recognized that the potential here is great, and that imaging has provided answers in multiple sclerosis (MS), and it could help significantly in MD.

Dr. Landis discussed the need to develop new animal models of disease, and to make current models more available. The NCRR has a major initiative in place to provide animal models to researchers, and NINDS provides funds for the distribution of mouse models.

Dr. Katz suggested developing centralized mechanisms for the collection of diagnostic and clinical data. Dr. Hesterlee remarked that she is leading a translational research program at the MDA, and was pleased to see that almost everything on the MDA's strategic plan for translational research was mirrored by the Working Group. An MDA clinical trials network working group will be meeting this summer, and it may address the issue of a patient registry. The MDA also will be looking for opportunities to partner with interested parties.

The issue of the collaboration and facilitation of research was raised. It was noted that the European groups do some things well, such as groups of 18 to 20 researchers who get together regularly to focus on specific issues. They also do a good job of taking interdisciplinary and trans-disciplinary approaches.

Mr. Decker asked if patient records could be made available as a shared database, and Dr. Hesterlee responded that the MDA does not keep patient records in that form. The issues of patient confidentiality and privacy also were addressed. Dr. Katz discussed improving access to biological materials but added that this has many challenges, such as privacy, sharing of clinical information, and consent.

Dr. Hesterlee suggested looking at industry as a potential partner in building patient networks. Dr. Katz noted that interested parties can explore using the power of NIH to bring the FDA to the table for the purpose of informing industry about what needs to be done, and mentioned that patient advocacy groups have the most clout in forming a link between NIH and patient networks. He cited the Cystic Fibrosis Foundation as an example of a group that has strong links to industry. Ms. Furlong mentioned a $1.5 million grant to PTC Therapeutics from Parent Project Muscular Dystrophy to initiate a high-throughput

screening, with the goal of identifying new drugs. Dr. Hanson noted that the MDA has experience collaborating with industry as well.

(A break was taken at 3:05 p.m.; the meeting reconvened at 3:15 p.m.)

The next section of the meeting focused on epidemiology. Dr. Richard Moxley, University of Rochester, joined the meeting by telephone to discuss the National Registry of Myotonic Dystrophy and FSHD patients and family members at the University of Rochester. This registry matches patients with researchers to join in trials. There are currently nine active research protocols that make use of the registry, and more protocols are expected to be approved soon. Approximately two-thirds of the protocols are located outside of Rochester, but some collaboration occurs between those sites and Rochester. He referred attendees to a registry newsletter and to other information that had been distributed prior to the meeting.

Dr. Moxley said that his group is brainstorming to develop general strategies that would improve patient recruitment and strategies for using existing members of the registry to recruit other family members. Forms and surveys for the registry are filled out annually to capture additional data. In response to a question about the role of the FSH Society in getting people to apply to a registry, Dr. Moxley said that the organization has played a major role and has been supportive in many ways. There is a critical role for patient groups in this activity, he added.

Dr. Boyle then talked about CDC activities, specifically the MD Surveillance Tracking and Research Network (MD STARnet). There are four State projects that are part of STARnet (Arizona, Colorado, Iowa, and western New York). These projects were funded in fiscal year (FY) 2003, and they are modeled after other programs to identify all cases of a particular disorder within a community. Funding in the amount of $500,000 was awarded to establish the surveillance piece. Neuromuscular clinics at which children, adolescents, or young adults up to age 20 are diagnosed and/or receive care were targeted. Information is collected and updated regularly. This project also contains a longitudinal component; families are interviewed to collect additional data. A pilot program—a "bio" bank, in which biological information is collected on each patient—is being added this year to improve the ability to understand the natural history of the disease and to correlate genotype and phenotype.

V. Next Steps

To conclude the meeting, Dr. Katz asked Ms. Fitzsimmons to discuss the next steps. Ms. Fitzsimmons said that comments from today's meeting would be reviewed and used to add to or modify existing goals. A revised document will be sent to MDCC members for review. Additional background will be added to the list of goals to help form a cohesive report. The entire document will be sent to the MDCC members for approval before it is submitted to Congress.

Dr. Hesterlee asked about implementation; Ms. Fitzsimmons responded that this will be addressed in subsequent reports, but that the subject document is more responsive to the charge from Congress. The MDCC is not involved in specific implementation strategies.

Mr. Perez initiated a brief discussion on funding. It was noted that patient advocates are expected to raise such issues, but the response to NIH actions overall is very favorable. Dr. Katz mentioned that, as the steward of research dollars, NIH needs to act responsibly and reasonably and for the greater good. Ms. Furlong mentioned that in the past few years, the MD community has come together to work more closely with NIH. She said that she feels progress is being made.

Dr. Katz said that at the end of FY 2005 there will be another report from the Committee updating Congress on the implementation of the report.

V. Adjournment

The meeting was adjourned at 4:15 p.m.

We certify that, to the best of our knowledge, the attachment and above minutes are accurate and complete.

__/s/_____

Lorraine G. Fitzsimmons
Executive Secretary, Muscular Dystrophy Coordinating Committee
Director, Office of Science Policy and Planning, National Institute of Neurological Disorders and Stroke

_/s/_____

Stephen I. Katz, M.D., Ph.D.
Chairperson, Muscular Dystrophy Coordinating Committee
Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases

June 4, 2004.

Attachment

Attendees

Duane Alexander, NICHD, MDCC member
Coleen Boyle, CDC, MDCC ad hoc member
Calvin Carpenter, DOD, MDCC ad hoc member
Daofen Chen, NINDS
Donavon Decker, Patient Advocate, MDCC member
Morgan Downey, FSH Society
Diana Escolar, Children's National Medical Center, *by telephone*
John Fakunding, NHLBI
Kenneth (Kurt) Fischbeck, NINDS
Lorraine Fitzsimmons, NINDS, MDCC Executive Secretary
Elizabeth Freedman, NIAMS
Patricia Furlong, Patient advocate, MDCC member
Katrina Gwinn-Hardy, NINDS
James Hanson, NICHD
Joanne Hawana, The Blue Sheet
Sharon Hesterlee, Patient/Professional Advocate, MDCC member
Eric Hoffman, Children's National Medical Center, *by telephone*
Troy Justeson, U.S. Department of Education
Stephen Katz, NIAMS, MDCC Chair
Lisa Kaeser, NICHD
Phil Kibak, Science Writer, MasiMax Resources, Inc.
Cheryl Kitt, NIAMS
Story Landis, NINDS, MDCC member
Anita Linde, NIAMS
Richard Lymn, NIAMS
Ophelia McLain, Administration for Children and Families, MDCC ad hoc member
Merle McPherson, HRSA, MDCC member
Jerry Mendell, Ohio State University, *by telephone*
Richard Moxley, University of Rochester, *by telephone*
Mary Lou Oster-Granite, NICHD
Audrey Penn, NINDS
Daniel Perez, Patient Advocate, MDCC member
Heather Rieff, NINDS
Susan Speesman, personal assistant to MDCC member Daniel Perez
Giovanna Spinella, ORD
Bradley Stephenson, Patient Advocate, MDCC member
Roger Stephenson, accompanying Bradley Stephenson
Brian Stutzman, personal assistant to MDCC member Donavon Decker
Philip Surine, Centers for Medicare and Medicaid Services, MDCC ad hoc member
Michael Weinrich, NICHD