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

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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