DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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

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Executive Summary

The Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (the MD-CARE Act, Public Law 107-84) specified a number of provisions for expanding and intensifying research on muscular dystrophy, including that the National Institutes of Health (NIH) establish centers of excellence for research on muscular dystrophy, that the Secretary of Health and Human Services (HHS) establish a Muscular Dystrophy Coordinating Committee (MDCC), that the MDCC develop a plan for conducting and supporting research and education on muscular dystrophy, and that the Centers for Disease Control and Prevention (CDC) expand epidemiological activities regarding muscular dystrophy. The MD-CARE Act also specified that the HHS Secretary shall annually report to Congress on the implementation of the Act. This report, the fourth to date, is submitted in response to this request.

HHS has made significant progress in implementing the provisions of the MD-CARE Act. NIH currently funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers. These Centers promote side-by-side basic, translational, and clinical research and provide resources that can be used by the national muscle biology and neuromuscular research communities. They also serve as focal points for research collaborations in the muscular dystrophy field and provide training and advice about muscle diseases for basic and clinical researchers.

The Muscular Dystrophy Coordinating Committee, which has now met four times, has recently revised its original "Research and Education Plan for Muscular Dystrophy," into a more comprehensive "Action Plan for the Muscular Dystrophies." The Action Plan for the Muscular Dystrophies was developed as a document for the entire muscular dystrophy research and education community and emphasizes research on a broad range of topics; research objectives identified in the Action Plan touch upon all aspects of the muscular dystrophies, from identification of pathogenic mechanisms to clinical management of patients with these diseases. Implementation of the objectives in the Action Plan as well as tracking progress toward plan objectives will be facilitated by future efforts of the MDCC.

This report also describes other activities at NIH and CDC to expand research on muscular dystrophy. NIH has recently released a number of initiatives to encourage translational research in muscular dystrophy and to enhance training for basic and clinical researchers working to advance our understanding and treatment of the muscular dystrophies. CDC has a number of new and ongoing efforts related to the muscular dystrophies including the Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet), as well as projects to collect information about cardiac health in female carriers of Duchenne muscular dystrophy and to further research on issues related to newborn screening and diagnosis of Duchenne muscular dystrophy.

This report also describes a number of recent scientific advances funded in part by NIH related to muscular dystrophy.

Introduction

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

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

This report is presented as an annual report to Congress on the implementation of the Act. This is the fourth annual report, which highlights recent activities at NIH and CDC to advance our understanding and treatment of the muscular dystrophies.

Background

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

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

Myotonic dystrophy is the most common adult form of muscular dystrophy. It is marked by myotonia (an inability to relax muscles following contraction) as well as muscle wasting and weakness. Myotonic dystrophy varies in severity and manifestations and affects many body systems in addition to skeletal muscles, including the heart, endocrine organs, eyes, and gastrointestinal tract. Myotonic dystrophy follows an autosomal dominant pattern of inheritance. This means that the disorder can occur in either sex when a person inherits a single defective gene from either parent. Myotonic dystrophy results from the expansion of a short repeat in the DNA sequence (CTG in one gene or CCTG in another gene). More simply put, the inherited gene defect is an abnormally long repetition of a three- or four-letter "word" in the genetic code – normally, this "word" is repeated a number of times, but in people with myotonic dystrophy, it is repeated many more times. While the exact mechanism of action is not known, this molecular change may interfere with the production of important muscle proteins.

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

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

The **congenital muscular dystrophies**, another class of muscular dystrophies, also include several disorders with a range of symptoms. Muscle degeneration may be mild or severe. Problems may be restricted to skeletal muscle, or muscle degeneration may be paired with effects on the brain and other organ systems. A number of the forms of the congenital muscular dystrophies are caused by defects in proteins that are thought to have some relationship to the dystrophin-glycoprotein complex and to the connections between muscle cells and their surrounding cellular structure. Some forms of congenital muscular dystrophy show severe brain malformations, such as lissencephaly (a "smooth" appearance to the brain due to the absence of normal convolutions -or folds- in the brain) and hydrocephalus (an excessive accumulation of fluid in the brain).

Several other forms of muscular dystrophy also occur. **Oculopharyngeal muscular dystrophy**, which causes weakness in the eye, throat, and facial muscles, followed by pelvic and shoulder muscle weakness, has been attributed to a short repeat expansion in a gene which regulates the translation of the genetic code into functional proteins. **Emery-Dreifuss muscular dystrophy** is characterized by weakness in the shoulder girdle and lower legs, as well as the development of contractures (tightening or loss of motion) in regions of the body, particularly the elbows, Achilles tendons, and neck. Defects in proteins that make up the cell's nucleus are implicated in the disorder. **Miyoshi myopathy**, one of the distal muscular dystrophies, causes initial weakness in the calf muscles, and is caused by defects in the same gene responsible for one form of LGMD, suggesting that progress against one form of muscular dystrophy may lead to a better understanding of other forms as well.

Available Treatments: Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Symptomatic treatment, though not able to stop disease progression, may improve the quality of life for some individuals. Options include physical therapy, appliances used for support, corrective orthopedic surgery, and drugs. Steroids can slow the progression of DMD, but there are side effects. However, several therapeutic approaches have shown promise in cell-based approaches and in animal models and some early clinical trials in humans have begun. Gene therapy is one promising area of research, and efforts are underway to optimize gene delivery for potential use in humans. Other therapeutic approaches, which are also showing promise include the use of drugs to reduce muscle membrane damage, cell-based replacement therapies, functional compensation for dystrophin by upregulation of certain proteins, increasing muscle mass via inhibition of other proteins that negatively regulate muscle growth, inhibiting muscle protein degradation and genetic strategies to bypass the mutations that cause disease.

Overview of NIH Programs

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

National Institute of Neurological Disorders and Stroke (NINDS): The NINDS supports intramural and extramural research on many forms of muscular dystrophy ranging from basic studies of normal protein function through projects on gene, stem cell, and drug therapies at levels from the development of experimental therapeutics through clinical trials. The NINDS also continues to support a very active portfolio of basic research on the neuromuscular junction, the terminal between a nerve cell and muscle fiber. Much of this basic research is critical to advancing our understanding of the mechanisms underlying the muscular dystrophies. Since the Muscular Dystrophy Association and the NINDS supported the discovery in 1987 that dystrophin mutations cause DMD and BMD, NINDS has supported much subsequent work on understanding the role and function of the dystrophin-glycoprotein complex both in normal muscle and in muscular dystrophy-affected muscle tissue. The NINDS funds research relevant to understanding the molecular and genetic basis of FSHD, as well as research relevant to myotonic dystrophy, LGMD, and other forms of muscular dystrophy and neuromuscular disorders. Another area of focus is the improved diagnosis of the muscular dystrophies.

The NINDS also funds translational and clinical research on muscular dystrophy. Four projects relevant to muscular dystrophy have been funded through the NINDS Cooperative Program in Translational Research, a program to support milestone-driven projects focused on the identification and preclinical development of drugs, biologics, and devices in animals and cells. These projects focus on development of a class of compounds known as protease inhibitors to combat muscle degeneration, on gene modification strategies to bypass mutations in the dystrophin gene, on combined gene modification and cell therapy approaches, and on bringing gene therapy for DMD to readiness for clinical trials. In addition, NINDS also funds two clinical trials in muscular dystrophy. The aim of one trial is to test the potential of the compound gentamicin as a therapy for DMD and LGMD. A second trial at the University of Rochester Wellstone Center, which is funded by NINDS, is testing treatment with the growth factor IGF-1 in patients with myotonic dystrophy.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS): The NIAMS supports basic, translational and clinical studies on the muscular dystrophies and other muscle diseases and disorders. NIAMS funds considerable research to advance the understanding of the cellular and molecular mechanisms that underlie the muscle degeneration associated with the muscular dystrophies and to develop potential strategies for the treatment of these diseases. The NIAMS supports basic research projects to study normal muscle development and pathophysiology of muscle disorders using animal models and cells from human subjects. Basic studies investigating the capacity of healthy muscle tissue to regenerate after injury have led to the identification and characterization of muscle stem cells and other cell types that can serve as precursors for muscle. NIAMS-supported investigators continue to advance the understanding of inflammatory components in several forms of muscular dystrophy and the role of the immune system in disease progression. Discoveries from these basic projects have led to promising strategies for the treatment of degenerative muscle diseases including pharmacological, and gene- and cell-based therapies. NIAMS supports several translational research projects aimed at developing and testing recombinant viruses engineered to be vehicles for the delivery of therapeutic genes that may block or reverse muscle degeneration. For example, the Wellstone Center at the University of Pennsylvania is exploring gene therapy and muscle derived stem cell

therapies for the treatment of muscular dystrophies. Other areas of translational research include the identification and testing of potential drugs to block the enzymes that cause muscle degeneration and pharmacological methods to promote muscle growth. NIAMS supports clinical studies in DMD and LGMD, and facilitates clinical studies in myotonic dystrophy and FSHD through support of a registry of patient information, which is co-funded with NINDS (see p.12). The recently funded Wellstone Center at the University of Pennsylvania will be conducting a clinical trial on the efficacy of protease inhibitors for DMD; this study is in conjunction with intramural investigators at NINDS. Additionally, the institute supports extensive research in other areas of muscle biology, which may point to targeted interventions for the treatment of muscular dystrophies and other disorders.

National Institute of Child Health and Human Development (NICHD): The NICHD sponsors a portfolio of extramural research projects related to the muscular dystrophies and other neuromuscular disorders. Research topics related to muscular dystrophy are focused in two of the Institute's centers: the National Center for Medical Rehabilitation Research (NCMRR) and the Center for Developmental Biology and Perinatal Medicine (CDBPM). Several projects related to MD are being supported through the NCMRR. Current research topics include contractures (loss of mobility in joints) and molecular remodeling of muscle, canine muscular dystrophy response to stress, microsensors for intramuscular pressure measurement, motor control in muscle diseases, the role of strength, body fat, and energy cost for child mobility, and family and psychosocial issues including the effect on other family members such as carriers of X-linked disorders. Within the newly established CDBPM, the Mental Retardation and Developmental Disabilities Branch has supported research into cognitive disabilities in DMD and accepts applications for research on the nonskeletal manifestations of many of the muscular dystrophies. In addition, NICHD has been addressing issues related to newborn screening, which may have relevance to the muscular dystrophies and other neuromuscular disorders. Finally, NICHD also sponsors several networks that are available to support muscular dystrophy research and research training. These include the Pediatric Pharmacology Research Network, available for the conduct of trials of new pharmacotherapeutic agents, and the Pediatric Scientist Training Program, which can contribute to the training of new young investigators as soon as candidates are identified. Both of these programs are managed through the Center for Research for Mothers and Children, another component of the NICHD.

Muscular Dystrophy Coordinating Committee

The Secretary delegated authority to the NIH Director to establish the Muscular Dystrophy Coordinating Committee (MDCC) but reserved the authority to appoint the members of the Committee, including the Chair. The NIH drafted the Committee charter, solicited nominations, and developed a slate of recommended candidates, and the Secretary appointed the 15 members of the MDCC. In accordance with the MD-CARE Act, the Committee is composed of ten members from Government agencies and five members from the public. Government agencies with an interest in muscular dystrophy research and education, including components of HHS and the Department of Education, are represented. The Department of Defense (DOD) is also represented. Public members include representatives from the MDA, Parent Project MD, the FSH Society, and patient advocates for other forms of muscular dystrophy including Becker

muscular dystrophy and limb-girdle muscular dystrophy. Dr. Stephen Katz, NIAMS Director, chairs the MDCC. The most recent roster of the MDCC can be found on the MDCC's Web site: http://www.ninds.nih.gov/find_people/groups/mdcc/index.htm.

The MDCC has met four times. At the first meeting of the MDCC, which took place on July 1, 2003, committee members presented an overview of their organizations' programs or their personal interests in muscular dystrophy. The members also discussed how to develop a Research and Education Plan for NIH, and recommended that a working group of the MDCC, consisting of prominent scientists in the field of muscular dystrophy research, draft a plan to be submitted to the MDCC. A scientific working group met in October 2003, and developed research goals that formed the basis of the Muscular Dystrophy Research and Education Plan. At the second meeting of the MDCC on March 22, 2004, a draft of the Muscular Dystrophy Research and Education Plan for the NIH was reviewed and discussed. Comments from MDCC members were compiled, reviewed, and used to add to or modify the goals in the Plan.

The third meeting of the MDCC was held on December 1, 2004. One purpose of the meeting was to learn about activities and recent initiatives at various Federal agencies and within the muscular dystrophy scientific community. The Committee also discussed strategies to implement the Muscular Dystrophy Research and Education Plan for the NIH. The Committee agreed that the Research and Education Plan provided broad-based guidance, but that a second scientific working group should be convened to evaluate and refine the current plan and to develop and prioritize specific aims for the entire muscular dystrophy research community. MDCC members were asked to nominate individuals with the appropriate scientific expertise and commitment to serve on a second MDCC Scientific Working Group (MDCC SWG). Twenty-four basic and clinical researchers and physicians from outside the NIH participated in the MDCC SWG, which met on August 16-17, 2005. The final recommendations, including over 70 research objectives, formed the "Action Plan for the Muscular Dystrophies," a comprehensive document to help achieve the effective detection, diagnosis, treatment, and prevention of all types of muscular dystrophy.

The fourth meeting of the Committee took place on November 9, 2005. At this meeting, the Action Plan for the Muscular Dystrophies was discussed. The meeting also served as a forum to discuss translational research in the muscular dystrophies. Representatives from MDCC member organizations including NIH, Parent Project MD, the Muscular Dystrophy Association, and the Department of Defense, described in detail their translational research programs in muscular dystrophy. In addition, the committee heard presentations on recent advances in Emery-Dreifuss muscular dystrophy and FSHD.

Links to the agenda and minutes for the MDCC meetings are posted on the MDCC Web site (http://www.ninds.nih.gov/find_people/groups/mdcc/index.htm).

Muscular Dystrophy Research and Education Plan for the NIH/Action Plan for the Muscular Dystrophies

As part of its charge in the MD-CARE Act, the MDCC developed a Muscular Dystrophy Research and Education Plan for the NIH which was submitted to Congress in August 2004. The plan contains broad research goals relevant to all forms of muscular dystrophy organized into five broad categories: (1) Mechanisms of Muscular Dystrophy; (2) Diagnosis and Screening of Muscular Dystrophy; (3) Therapy of Muscular Dystrophy; (4) Living with Muscular Dystrophy; and (5) Research Infrastructure Needs for Muscular Dystrophy. The full Muscular Dystrophy Research and Education Plan for the NIH can be accessed through the MDCC Web site: http://www.ninds.nih.gov/find_people/groups/mdcc/index.htm.

As previously mentioned, a MDCC SWG met on August 16-17, 2005, to provide recommendations which formed a comprehensive "Action Plan for the Muscular Dystrophies." Some of the goals in the Action Plan are specific to one type of muscular dystrophy, while many of the goals are applicable to multiple forms or to all of the muscular dystrophies. The research objectives identified in the Action Plan touch upon all aspects of the muscular dystrophies, from identification of pathogenic mechanisms to clinical management of patients with these diseases. Objectives in the Action Plan are also aimed at improving communication and coordination of research, not only on a national level, but internationally as well.

The final draft report of the Action Plan was submitted to the MDCC and discussed at the November 9, 2005, MDCC meeting. Changes suggested by Committee members will be considered and added, as appropriate, prior to final approval by the Committee. Once it is approved by the Committee, the Action Plan will be posted on the MDCC Web site and included as part of the MDCC's biennial report to Congress.

The Action Plan for the Muscular Dystrophies was developed as a document for the entire muscular dystrophy research and education community and emphasizes research on a broad range of topics, including therapeutics. NIH has played a leading role in the basic science discoveries that will help drive therapeutic development. However, given the mission, expertise, and resources present at the Federal agencies that are represented on the MDCC, many aspects of the Action Plan are most appropriately addressed by agencies besides NIH. In addition, many of the activities that will be initiated as a result of the Action Plan will be facilitated by the leadership of the muscular dystrophy patient advocacy groups, particularly given their wide access to, and deep understanding of, the muscular dystrophy patient and family community. Indeed, many Federal agencies and advocacy organizations are already engaged in the types of activities that were identified as priorities by the MDCC SWG. Future activities may include the continuation and/or expansion of existing efforts, as well as the development of new initiatives by MDCC member agencies and organizations.

The Action Plan for the Muscular Dystrophies is not meant to be a static document, but is rather a snapshot at this point in time of the judgment of leading investigators in the field as to where current application of effort and resources can best address the most compelling opportunities. The Action Plan will require active tracking and assessment if it is to serve the purpose of

stimulating research in the field and guiding activities of the MDCC. NIH, together with its partner agencies and organizations in the MDCC, will ensure that progress relevant to the objectives in the Action Plan is tracked and made publicly available. Future accomplishments and initiatives by all MDCC member agencies and organizations relative to the Action Plan will be tracked by means of the MDCC public Web site. The Action Plan will be periodically reviewed and revised, and any revisions to the Action Plan will be included in the MDCC biennial report to Congress, as required in the MD-CARE Act. Reporting on progress made toward the Research Objectives will occur at future MDCC meetings as well.

Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

The MD-CARE Act authorized NIH to establish centers of excellence for muscular dystrophy research, and NIH currently funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (referred to here as "Wellstone Centers"). NINDS, NIAMS, and NICHD each fund two of the Centers. The award to each Center provides up to $1 million in direct costs per center per year for five years. In response to the first request for applications (RFA) to establish Wellstone Centers, NIH funded three Centers in October 2003: the University of Pittsburgh, the University of Washington, Seattle, and the University of Rochester, New York. Projects at the University of Pittsburgh and the University of Washington focus on gene therapy and research to advance muscle stem cells as potential therapies for DMD. These approaches may also be applicable to other muscular dystrophies. Projects at the University of Rochester focus on myotonic dystrophy and FSHD; researchers are studying these disorders at the cellular and molecular levels to examine which factors might contribute to these forms of muscular dystrophy. Additionally, this Center will soon begin a clinical trial to test the safety of the drug Somatokine in myotonic dystrophy patients who could potentially benefit from this treatment.

In response to a March 2004 reissue of the RFA for the Wellstone Centers, the NIH funded an additional Center at the University of Iowa in June 2005. This Center focuses on other gene and stem cell therapeutic strategies for Duchenne, limb girdle, and other muscular dystrophies. This Center also serves as a national resource for clinical researchers by providing diagnostic services and maintaining a repository of relevant patient tissues.

In February 2005, a notice was published in the *NIH Guide for Grants and Contracts* for limited competition of revised applications for the Wellstone Research Centers. Applications that were submitted in response to the March 2004 RFA, but not initially selected for funding, could be revised and resubmitted for further review. The review of these revised applications was completed in an expedited manner and NIH funded two additional Centers in September 2005--at the University of Pennsylvania and Children's National Medical Center (CNMC)--for the full complement of six Centers.

The Center at the University of Pennsylvania investigates strategies to promote muscle growth or to inhibit muscle protein degradation. These approaches could be applicable to a wide range of muscular dystrophies and other muscle diseases and disorders. The Center at CNMC is

analyzing genetic and cellular factors that contribute to DMD progression and the response of patients to treatment.

Each center brings together expertise, infrastructure, and resources focused on major questions about muscular dystrophy. The Wellstone Centers promote side-by-side basic, translational, and clinical research. The scientific cores the Centers provide resources--including biological samples such as cells and tissues--that can be used by the national muscle biology and neuromuscular research communities. They also serve as focal points for research collaborations in the muscular dystrophy field, and provide training and advice about muscle diseases for basic and clinical researchers. Taken together, the Wellstone Centers constitute a cohesive program operating under guidelines for NIH cooperative agreements, in which NIH staff are involved as partners with the investigators to provide coordination, guidance, and evaluation of the research at the Centers.

Muscular Dystrophy Association (MDA) Partnership: In May 2003, NINDS, NIAMS, and NICHD signed a Memorandum of Understanding with the MDA in which the MDA agreed to commit up to $1.5 million to enhance research activities at each of the three centers initially funded by NIH (U. Rochester, U. Washington, and U. Pittsburgh). The Muscular Dystrophy Association is now providing supplements of up to $500,000 per center per year for three years for additional projects to each of these three Centers.

Steering Committee: As part of the cooperative agreement, a Steering Committee ensures overall coordination of the Wellstone Centers program. The membership includes a public member in addition to the directors of each center and scientific program officers from NINDS, NIAMS, and NICHD. As part of its charge, the Steering Committee meets monthly either by teleconference or in person to share information, identify new research opportunities, and develop and implement collaborative activities that will accelerate muscular dystrophy research. Dr. Jeffrey Chamberlain (University of Washington) chairs the Steering Committee, and Dr. Richard Moxley (University of Rochester) is the cochair. A face-to-face meeting was held on March 4, 2005, during which the committee voted to recommend use of collaborative funds held by the Centers to provide additional support for the colonies of DMD dogs at the University of Missouri and at Fred Hutchinson Cancer Research Center, Seattle, WA. The Committee has also recommended support for a collaborative project between the Centers at the University of Rochester and the University of Washington to investigate the molecular mechanisms of myotonic dystrophy type 1. This collaboration will also test in mice a potential gene therapy strategy for treatment of this disease. The second face-to-face meeting of the Steering Committee took place February 7, 2006, at the University of Pittsburgh. The Committee reviewed and discussed the funded and ongoing projects at each Center, with a focus on understanding the breadth of efforts and identifying potential collaborative opportunities. The Committee also heard and discussed a summary of the new NIH initiatives in translational research in muscular dystrophy and discussed proposals for collaborative projects and coordination of research core facilities. Future face-to-face Steering Committee meetings will rotate among the Centers in order to provide a greater degree of interaction among Steering Committee members and other investigators at each of the Centers.

Efforts to Enhance Collaborative Activities at the Wellstone Centers: To enhance the ongoing activities at the Wellstone Centers, NIH recently released two notices announcing the availability of administrative supplements to the Centers. The first notice, "NIH Administrative Supplements for Senator Paul D. Wellstone Muscular Dystrophy Research Fellowships at Wellstone Muscular Dystrophy Cooperative Research Centers," are supplements to promote collaborations by the Centers and to maximize opportunities for career development among junior investigators affiliated with the Centers. The second notice, "Support for Muscular Dystrophy Workshops and Research Conferences," encourages the Directors of the Wellstone Centers, in collaboration with other muscular dystrophy researchers and/or representatives from voluntary health organizations, to apply for administrative supplements to support small workshops or conferences focused on specific topics in muscular dystrophy research. These workshops fill a specific need in the Muscular dystrophy field to bring investigators together to achieve a range of objectives, including developing collaborations, focusing efforts and resources, and reaching consensus on research and patient care strategies. The Steering Committee has begun discussing topics and plans for organizing these meetings. Both of these supplement programs also fill needs identified as priorities in the Action Plan for the Muscular Dystrophies.

Other Recent Efforts at NIH to Enhance Muscular Dystrophy Research

Solicitations

Translational Research Initiative:
As a result of an evaluation of the state-of-the science, as well as numerous discussions with representatives from patient advocacy groups who stressed an urgent need for translational research in the muscular dystrophies, NIH released two Program Announcements, with set-aside funds for: (1) "Exploratory/Developmental Program for Translational Research in Muscular Dystrophy" and (2) "Translational Research in Muscular Dystrophy."

The purpose of these initiatives is to implement a broad-based translational research program that will lead to new and more effective treatments for muscular dystrophy. The initiatives encourage translational research in all forms of muscular dystrophy, since it is likely that understanding and treating one form of muscular dystrophy may be applicable to other forms as well. This program has two components: exploratory/developmental research projects and cooperative agreements. Exploratory/ developmental projects will develop the tools and resources necessary for the subsequent conduct of a translational research program. Examples include: identification of targets for therapeutic intervention; development of assays that permit preliminary screening of candidate therapeutics; and development of tools and technologies that can be directly used for therapy development. Cooperative agreements are milestone-driven projects that focus on the identification and preclinical testing of therapies suitable for one or more of the muscular dystrophies. As part of the cooperative agreements, NIH staff will work closely with the applicant to help develop and guide the project. To ensure that grants are reviewed by individuals with the appropriate expertise, a special review panel convened by NINDS will review applications received through this program.

Initiatives to Increase the Number of Investigators in Muscular Dystrophy Research:
One of the goals of both the Muscular Dystrophy Research and Education Plan and the Action Plan for the Muscular Dystrophies is to increase the number of researchers working to understand the disease process and pathophysiology of muscular dystrophy and to develop new therapies for all forms of muscular dystrophy. In addition to the Supplements for Senator Paul D. Wellstone Muscular Dystrophy Research Fellowships (see above), NIH issued two program announcements in December 2005 to encourage training of scientists in muscle disease research. The first, "Ruth L. Kirschstein National Research Service Awards for Postdoctoral Fellowships in Muscle Disease Research," encourages postdoctoral fellows with diverse scientific interests to apply their expertise to enhance our understanding of the pathogenesis and treatment of muscle diseases and disorders, including the muscular dystrophies. Applicants are encouraged to develop innovative and novel approaches for studying and treating these diseases. The second program announcement, "Mentored Clinical Investigator Career Development Awards in Muscle Disease Research," was issued in recognition of the urgent need for highly skilled, interactive researchers who are able to integrate various disciplines and levels of expertise to successfully address the increasing challenges in the current research environment of muscular dystrophy and other muscle diseases. It is expected that these career development programs will increase the number of investigators in basic, translational, and clinical research on muscular dystrophy and other muscle diseases, and will also increase the quality of their research and training.

Muscular Dystrophy: Pathogenesis and Therapies: NIH issued a program announcement (PA) in October 2005 entitled "Muscular Dystrophy: Pathogenesis and Therapies" to encourage investigator-initiated research grant applications for projects studying pathogenesis and therapies for the muscular dystrophies. Responses to this announcement could include basic, translational, or patient-oriented studies of DMD, BMD, FSHD, myotonic dystrophy, or other forms of muscular dystrophy. It is the aim of this PA to promote research identified as priorities in the Muscular Dystrophy Research and Education Plan and the Action Plan for the Muscular Dystrophies. This PA is the third release and it updates two previous highly successful solicitations entitled "Therapeutic and Pathogenic Approaches for the Muscular Dystrophies," which was released in January 2001, and "Pathogenesis and Therapy of the Muscular Dystrophies," released in March 1998. Grants funded as a result of these solicitations include projects focused on: understanding the structure and function of the dystrophin-glycoprotein complex; elucidating the molecular and genetic mechanisms underlying myotonic dystrophy and LGMD; characterizing mutations in a large population of patients with DMD and Becker MD; understanding mechanisms of muscle membrane repair; developing vectors for potential use in DMD gene therapy and optimizing gene delivery techniques; exploring the use of the compound gentamicin as a therapy for DMD and LGMD; and developing gene alteration--such as exon skipping--approaches to therapy.

Workshops and Meetings

Workshop on Burden of Muscle Diseases: The NIAMS and the NIH Office of Rare Diseases hosted the "NIH Burden of Muscle Disease Workshop" on January 26-27, 2005, on the NIH campus in Bethesda, Maryland. The three main goals of the workshop were: 1) to identify the economic and psychosocial components of the totality of burden on individuals, families, and

societies resulting from chronic muscle diseases, particularly the muscular dystrophies; 2) to assess the available data and instruments for collecting data on these components; and 3) to recommend strategies for developing an assessment of the burden of muscle disease appropriate for use in strengthening and prioritizing research and health care activities. Speakers and attendees included muscle disease clinicians and researchers, health economists, epidemiologists, representatives of patient advocacy groups, and patients and their families. Workshop participants stressed the need to develop good measurement instruments as well as burden of disease survey methodology. A meeting summary is available at http://www.niams.nih.gov/ne/reports/sci_wrk/2005/muscle_dis_summ.htm.

New Directions in Biology and Disease of Skeletal Muscle: NIH, together with leading muscle researchers, organized a conference entitled "New Directions in Biology and Disease of Skeletal Muscle," which was held January 25-27, 2004, in San Diego. The purpose of this conference was to bring together researchers who focus on different aspects of muscle diseases. Until this point, there had been no national meeting with a focus on the functions and disorders of skeletal muscle, and the lack of a centrally focused meeting had become an impediment in understanding and treating important muscle diseases. With support from NIH, MDA, and other groups, the conference attracted clinical and basic researchers and provided an excellent forum for them to interact and share ideas and advance the field of muscular dystrophy and other muscle disease research. Based upon the success of the 2004 meeting, this conference is now planned to occur every two years, with the next meeting to be held in April 2006. This conference will retain the focus on cellular and molecular aspects of skeletal muscle as they relate to health, disease, and dysfunction. The conference is designed to bring together researchers who do not often attend the same meetings and to improve the treatment options for the muscular dystrophies.

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

Since September 2000, the NIAMS and NINDS have supported the National Registry of Myotonic Dystrophy and Facioscapulohumeral Dystrophy Patients and Family Members, a resource for the collection and analysis of clinical information from patients and their families to accelerate the advance of research on these diseases. NIH support for the registry was recently renewed for an additional 5 years. The long-term goal of the registry is to facilitate research in FSHD and myotonic dystrophy by serving as a liaison between families affected by these diseases who are eager to participate in research and investigators conducting specific projects relevant to these disorders. The registry, based at the University of Rochester, recruits and classifies patients and stores medical and family history data for individuals with clinically diagnosed FSHD and myotonic dystrophy. Genetic information is collected on individuals who provide their molecular diagnosis. The registry provides statistical analysis of the data, as well as access to the registry data for investigators with approved projects. The national registry serves as a resource for scientists seeking a treatment for these diseases, in addition to enhancing research to understand what changes occur in muscular dystrophy. To date ten research projects have utilized data from the registry.

Centers for Disease Control and Prevention Activities

In order to provide people with Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) and their families with better services, public health departments and health care providers need better information about these disorders. Using traditional public health research approaches, CDC is working with partners in State health departments and universities to answer questions about DMD and BMD including:

- How common are these disorders and are they equally common in different racial and ethnic groups?
- What are the early signs and symptoms of DMD and BMD?
- Does the type of care received affect the severity or course of DMD and BMD?
- Does the type of gene changes affect the severity or course of DMD and BMD?
- What medical and social services are families receiving?
- Do different groups of people receive different care?

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

Muscular Dystrophy Surveillance Tracking and Research Network: As part of the Muscular Dystrophy Surveillance Tracking and Research Network, or MD STARnet, CDC is working with researchers in Arizona, Colorado, Iowa, and western New York State to set up surveillance systems for DMD and BMD. The goal of the project is to find all DMD and BMD patients in these areas by using information from different sources, such as clinic medical records and hospital records. Information about each child's treatments and how he is doing medically will be collected from his medical records. The current HIPAA Privacy Rule allows protected health information to be obtained without individual authorization when the data are to be used for public health surveillance. MD STARnet activities fall within public health surveillance authorization and are in accordance with the HIPPA Privacy Rule. In accordance with the Privacy Act of 1974, safeguards have been provided for individuals and Establishments Against Invasion of Privacy. This public health monitoring activity does not involve gathering information from educational records; therefore, FERPA is not applicable to these activities. Because many DMD and BMD patients are seen in Muscular Dystrophy Association clinics, the researchers are working closely with the MDA clinics in their States. In addition, the researchers will be searching for DMD and BMD patients through other neuromuscular clinics, emergency rooms, pathology laboratories, orthopedists, and other muscular dystrophy associations to ensure that all patients with DMD and BMD are included in the project. The States have worked together to come up with a common system that can be used to find patients and collect information. Families who are identified in these areas will be asked to take part in interviews with public health workers to provide information related to DMD and BMD that might not be found in the medical records.

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

In April 2004, researchers began collecting information from medical records. The group has now developed and begun using a computer system for saving and combining the information collected and is also now developing the interview questionnaire. The four states began to pool de-identified data in FY 2005. Also in FY 2005, the state of Georgia, in collaboration with CDC intramural researchers, was added to the system. An independent quality assurance and control (QAQC) system contract was also awarded to the Titan Corporation in order to provide independent QAQC. CDC plans to add one additional State or geographic area to the system in order to achieve a sample that better reflects the racial/ethnic makeup of the general U.S. population. Current FY 2006 obligations do not allow for the addition of a State to MD STARnet for this fiscal year.

The MD STARnet project is intended to serve as a model and framework for future surveillance of other forms of muscular dystrophy. As MD STARnet has only been operational for a short period of time and given current financial obligations and constraints, the project at this time has not expanded to other forms of muscular dystrophy, but CDC has every intention of doing so when funding permits.

Also in FY 2005, CDC awarded a contract to Booz-Allen-Hamilton Corporation to transform the database of MD STARnet into a clinical tool that will be useful for physicians and that will allow collection and pooling of data into a national registry.

Cardiac Health in Female Carriers of Duchenne Muscular Dystrophy: Females who are DMD carriers sometimes have heart problems that leave them short of breath or unable to do moderate exercise later in adult life. The chance that a female carrier will develop heart problems is not known. However, such heart problems can be serious and life threatening. While there is no cure, there are a number of medications that might help reduce the effects of these heart problems. This project will use a large-scale, mailed, self-completed survey to collect information about what female DMD carriers know or believe about cardiac health care and how they act based on this information. The survey will be mailed to about 7,000 women who are on Muscular Dystrophy Association (MDA) or Parent Project Muscular Dystrophy (PPMD) mailing lists or are known by someone on one of the lists. Women will be eligible to complete the survey if they are at least 19 years old and have given birth to a son with DBMD or been told that they definitely or probably carry a genetic change that causes DBMD. The objectives of the project are (1) to find out what things affect the use of preventive cardiac health care by female carriers of DMD and (2) to develop new and workable plans that will increase preventive cardiac health care in this population. While there are currently no official recommendations for female carriers of DMD regarding cardiac testing and treatments, one of the goals of this project is to find ways to let women know about recommendations once they are available. It is likely that the results of this study can also be used to improve health messages to carriers of other X-linked conditions. Interviews and focus groups with carrier females and health care providers began in November 2004 and were completed in September 2005. Based on initial interviews and focus groups, and extensive literature review, CDC staff and researchers at Battelle developed a survey to assess the baseline activities of DMD carriers related to their heart health, as well as carriers' knowledge and beliefs about preventive cardiac care related to their DMD carrier status.

Information from this survey will be used to develop public health messages about cardiac health specifically to DMD carrier females. The baseline behavior data will allow us to evaluate the impact of such messages on carrier females' heart health related behavior. The survey is in both English and Spanish, and is available both in print and in a web-based format. The study protocol has completed Institutional Review Board (IRB) review and is in the process of Office of Management and Budget review. Survey administration is expected to begin in June 2006.

Newborn Screening for Duchenne Muscular Dystrophy

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

Early Screening and Diagnosis of Duchenne Muscular Dystrophy: To further research on the issues identified by the Newborn Screening for Duchenne Muscular Dystrophy Workgroup, the National Center on Birth Defects and Developmental Disabilities (NCBDDD) at CDC announced funding under a cooperative agreement for research in both infant and newborn screening for DMD in FY 2004 (*Federal Register*: June 24, 2004 (Volume 69, Number 121)). Two research groups were awarded cooperative agreements in September 2004, one for The Children's Research Institute in collaboration with the Ohio Department of Health in Ohio and another to Emory University in the state of Georgia. The Children's Research Institute in Ohio, in collaboration with the Ohio Department of Health, will pilot newborn screening for DMD and evaluate the informed consent process in the birth hospital. Emory University, in collaboration with local pediatric practices, will pilot infant screening for DMD and evaluate equity to screening as well as the informed consent process in a pediatric clinic setting. In addition, both programs will determine the number of false-positive and false-negative screening results, the types of problems false-positive screening results can cause, how families go through the screening process, and how pediatricians and other clinicians feel about the screening program. In FY 2005, both groups validated laboratory methodologies for bloodspot screening for DMD. Both groups have made significant progress toward the development of a screening protocol in their State, including informed consent procedures. In addition, Emory University conducted focus groups with parents of children with DMD and with parents of unaffected infant males. Both groups were asked to provide feedback on the type of information parents need in deciding on DMD screening and potential informational materials to be used in the informed consent process. Brochures on early screening for DMD were developed based on input from these groups. Implementation of screening is expected to begin in June 2006 in both states. IRB approvals for both groups are pending. In collaboration with both groups and with the National Center for Environmental Health Newborn Screening Quality Assurance Program, CDC program staff have developed a quality assurance protocol for screening in both States. Other countries that offer DMD screening will also be invited to participate in the quality assurance program.

Newborn Screening Decision Analysis: Newborn screening for Duchenne-Becker muscular dystrophy (DBMD) offers both advantages and disadvantages. Parents of children with DBMD often express an interest in newborn screening. However, it is not known if families of newborn males will also be interested in newborn screening for DBMD. In FY 2005, CDC awarded a contract to Research Triangle International to conduct literature reviews and focus groups to identify factors that parents may consider in making decisions about newborn screening. Research Triangle International will use these data to develop a survey-based method to evaluate how parents weigh the various factors. This information will help public health departments and policy makers to understand whether or not parents value newborn diagnosis of an incurable and fatal condition.

Parent and Provider Outreach Activities

Parent Project Muscular Dystrophy (PPMD): In accordance with Congressional intent, PPMD was awarded $500,000 in FY 2005 to develop and disseminate educational materials related to DBMD to a diverse audience through multiple media. Target audiences may include the general population, primary care providers, teachers, and peers of boys with DBMD.

Single Gene Resource Center: On July 19, 2005, CDC issued a request for proposals for a cooperative agreement (PA AA092) to develop a national resource network for single gene disorders. Initial funding will support projects related to DBMD and Fragile X syndrome (funds for the Fragile X activities were from a different source than the DBMD activities). The proposed National Network will have the capacity to expand to other single gene disorders. The cooperative agreement was awarded to the Genetic Alliance in September 2005. CDC staff will work closely with both Genetic Alliance and PPMD to ensure that education and outreach activities related to DBMD are coordinated with each other and with other federally-funded projects.

Duchenne/Becker Muscular Dystrophy Best Practices Conference:

CDC will sponsor a conference to present best practices for DBMD treatment, identify gaps in evidence for evidence-based medical practices, and develop care consideration guidelines for diagnosis and treatment of children with DBMD. In FY 2005, a contract was awarded to Booz-Allen-Hamilton Corporation to provide technical and administrative support for this process.

NIH and CDC Muscular Dystrophy Research Funding

NIH has devoted significant financial resources to muscular dystrophy research, and these commitments have increased substantially in the past few years. From FY 2000 to FY 2004, funding for muscular dystrophy research more than tripled, growing from $12.6 million in FY 2000 to $38.7 million in FY 2004. The funding for FY 2005 was $39.5 million, and the estimated funding for FY 2006 is $39.3 million. Beginning with FY 2004, NIH also began reporting spending broken down by three types of muscular dystrophy--DMD, FSHD, and myotonic dystrophy--as required by the MD-CARE Act. These categories are only part of the overall total of muscular dystrophy spending at NIH; the total Muscular Dystrophy number

includes these three categories as well as projects focused on other forms of muscular dystrophy and projects applicable to the muscular dystrophies in general. The funding amounts, with estimates for FY 2006, are listed below.

NIH Funding for Muscular Dystrophy:			
(Dollars in millions)	FY 2004 (actual)	FY 2005 (actual)	FY 2006 (estimate)
Duchenne/Becker MD	$ 17.6	$ 17.1	$ 17.1
FSHD	$ 2.0	$ 2.0	$ 2.0
Myotonic Dystrophy	$ 6.2	$ 6.4	$ 6.4
Muscular Dystrophy (total)	$ 38.7	$ 39.5	$ 39.3

CDC was appropriated $4.5 million (enacted amount) for muscular dystrophy research (all of which is devoted to Duchenne and Becker muscular dystrophy) in FY 2004. In FY 2005 CDC was appropriated $5.9 million (enacted amount) and the enacted funding for FY 2006 is $6.4 million.

Education and Training

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

HHS is committed to improving information and educational resources concerned with muscular dystrophy for health professionals, patients, and for the general public. The MDCC has a publicly available Web site (http://www.ninds.nih.gov/find_people/groups/mdcc/index.htm), which contains a Committee roster, the Committee charter, short biosketches of Committee members, agendas and minutes from Committee meetings, and the Muscular Dystrophy Research and Education Plan for NIH. In addition, the Action Plan for the Muscular Dystrophies, once approved by the MDCC, will be posted on the MDCC Web site, and progress toward each of the objectives in the Action Plan will be tracked on the site.

NIH also publishes summaries of muscular dystrophy workshops, descriptions of funding opportunities, and publications on the muscular dystrophies specifically developed for the public

on its Web sites, including links to information provided by voluntary health organizations. For example, the National Library of Medicine, a component of NIH, provides the MEDLINEplus.gov Web site. MEDLINEplus has many health-related information resources for professionals and the public, including the capability to search the extensive databases of the medical and scientific literature, in some cases with links to the full text of articles. The MEDLINEplus muscular dystrophy page at http://www.nlm.nih.gov/medlineplus/musculardystrophy.html provides links to sources of recent news, overviews, frequently asked questions, clinical trials, specific conditions, and other aspects of the muscular dystrophies from government agencies and private groups. The ClinicalTrials.gov Web site (http://clinicaltrials.gov) posts information about clinical trials as they become available for muscular dystrophy, as for other disorders.

Education and training are also goals of the Wellstone Research Centers program. The recently issued notice of supplements for "Senator Paul D. Wellstone Muscular Dystrophy Research Fellowships" will enhance training efforts at the Centers. In addition, as mentioned above (see p. 11), in December 2005, NIH issued two initiatives to enhance multidisciplinary and interdisciplinary research training of basic and clinical investigators in the area of muscular dystrophy.

Recent Scientific Advances

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

Gene therapy improves health and survival in animal models of muscular dystrophy: One of the biggest challenges in developing useful gene therapy for muscular dystrophy is finding a way to deliver the beneficial gene into a large number of skeletal muscles of the body to effectively treat the disease. Researchers funded by NIH have now shown in rodents that a virus called adeno-associated virus 8 (AAV8) can be used to systemically deliver genes to all the skeletal and cardiac muscles of the body. By introducing the gene for a marker called green fluorescent protein (GFP), they showed that AAV8 was able to deliver the marker gene to muscles throughout the body, including the forelimb, face, and heart muscles. The researchers then tested AAV8 to see if it could deliver a beneficial gene, delta-sarcoglycan, in a hamster model for one type of limb-girdle muscular dystrophy. In young adult hamsters, intravenous injections of AAV8 carrying the delta-sarcoglycan gene led to strong expression of the gene in the heart and leg muscles. A subsequent study showed that systemic delivery of delta-sarcoglycan markedly improved skeletal and cardiac muscle functions. In addition, the AAV8 treated animals were able to run the same distance as normal hamsters before tiring and to run for much longer than untreated animals with LGMD. Furthermore, all of the treated animals survived beyond the 48-week duration of the study while the untreated animals died of heart failure or other complications of LGMD at around 37 weeks.

In another recent study, the researchers found that delivery of a miniature version of the protein agrin to muscle cells using similar AAV vectors dramatically improved the health and survival of mice with a disorder that closely mimics a severe form of human congenital muscular dystrophy. The agrin compensated for the lost protective function of laminin, the protein that is defective in this disease. Following this therapy, the body weight of the treated mice improved by 80% at 6 weeks of age and the mice lived about four times as long as untreated mice. These results represent the first treatment that improves the health of animals with this severe form of muscular dystrophy. The next steps in this research are to study systemic delivery of therapeutic genes to muscles of a dog model for DMD using AAV vectors. If those experiments are successful, researchers might eventually be able to test AAV-based gene therapies in human clinical trials for muscular dystrophy and other related diseases. (Wang et al., 2005, *Nature Biotechnology* 23: 321- 328; Qiao et al., 2005, *PNAS* 102: 11999-12004; Zhu et al., 2005, *Circulation* 112:2650-2659.)

Toward stem cell therapy to repair diseased muscle: Questions remain regarding the potential use of muscle-derived stem cells (MDSCs) for the treatment of diseased muscle. One such question is whether MDSCs have the capacity to proliferate to the levels necessary to regenerate muscle tissue with high mass. NIH-supported researchers have developed a method for isolating MDSCs from young mice. These investigators found that colonies of MDSCs could be expanded in tissue culture for more than 200 doublings (two-fold increase in number of cells), which would theoretically provide enough cells for any clinical application. Furthermore, at up to about 200 doublings, the cells retained the ability to synthesize muscle specific proteins and to develop appropriate muscle cell structure in culture and when transplanted into mouse muscle tissue. This research demonstrates that MDSCs can be expanded in culture to the level necessary to show promise for the treatment of muscle diseases, and a high percentage of the cells can contribute to muscle regeneration. This level of expansion in culture, while maintaining the ability to differentiate, was previously attributed only to embryonic stem cells or cells in the bone marrow. (Deasy BM, et al., *Mol Biol Cell.* 2005 Jul;16(7):3323-33.)

Delivery of microdystrophin to mdx mouse muscle by muscle progenitor cells: Previous studies identified a population of muscle cells called side population (SP) cells from mouse skeletal muscle and showed that these cells are capable of regenerating muscle. A recent study funded by NIH showed that it may be possible to use these SP cells to deliver dystrophin, the protein that is absent in DMD, to muscle. The researchers introduced a portion of the human dystrophin gene using a virus-mediated method into SP cells and then transplanted these cells into mdx mice -a mouse model of DMD- via a tail vein. They found that the transplanted cells were able to move through the mouse's circulation and take up residence within the host muscles. Moreover, human dystrophin expression was detected in muscle fibers of all transplanted mice, demonstrating that delivery of the dystrophin construct to muscle fibers had occurred. These results show that transplantation of SP cells expressing a small part of the dystrophin gene represents a feasible way to systemically deliver human dystrophin to muscle. They also suggest that disease-damaged muscle is able to attract and recruit these cells to muscle from the circulation. These results have substantial implications for cell therapy in the treatment of human muscular dystrophy (Bachrach et al., 2004, *PNAS* 101: 3581-3586).

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

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

Conclusion

NIH and CDC continue to implement the provisions of the MD-CARE Act. The MDCC has developed an Action Plan for the Muscular Dystrophies, based on the broad goals of the Muscular Dystrophy Research and Education Plan for the NIH. Implementation of the objectives in the Action Plan will further contribute to the goals of the MD-CARE Act and will require the concerted effort of all agencies and organizations with an interest in muscular dystrophy. The challenges in muscular dystrophy research are formidable and varied, but scientific advances and collaborations and the commitment of the research and advocacy communities hold great promise for more and better treatments for individuals suffering from the muscular dystrophies.

GLOSSARY: Acronyms Used in this Report

AAV: Adeno-Associated Virus

BMD: Becker Muscular Dystrophy

CDBPM: Center for Developmental Biology and Perinatal Medicine

CDC: Centers for Disease Control and Prevention

CNMC: Children's National Medical Center

DBMD: Duchenne/Becker Muscular Dystrophy

DOD: Department of Defense

DMD: Duchenne Muscular Dystrophy

FSHD: Facioscapulohumeral Muscular Dystrophy

FSH Society: Facioscapulohumeral Muscular Dystrophy Society

FY: Fiscal Year

GFP: Green Fluorescent Protein

HHS: Department of Health and Human Services

IRB: Institutional Review Board

LGMD: Limb-Girdle Muscular Dystrophy

MD: Muscular Dystrophy

MD-CARE Act: Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001

MDA: Muscular Dystrophy Association

MDSC: Muscle Derived Stem Cells

MD STARnet: Muscular Dystrophy Surveillance Tracking and Research Network

MDCC: Muscular Dystrophy Coordinating Committee

MDCC SWG: Muscular Dystrophy Coordinating Committee Scientific Working Group

NCBDDD: National Center on Birth Defects and Developmental Disabilities

NCMRR: National Center for Medical Rehabilitation Research

NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases

NICHD: National Institute of Child Health and Human Development

NIH: National Institutes of Health

NINDS: National Institute of Neurological Disorders and Stroke

PA: Program Announcement

PPMD: Parent Project Muscular Dystrophy

QAQC: Quality Assurance and Control

RFA: Request for Applications

SP: Side Population