



THE NMD INFO



NEWS

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The mission of the Research and Training Center is to improve the lives of individuals with neuromuscular diseases by developing and evaluating new strategies that address lifelong needs for research-based medical care and counseling, psychosocial well-being, education, and independent living.

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Review of Neuromuscular Diseases and Current Research

In this and subsequent newsletters, this section will review the clinical and laboratory characterization, genetics, pathophysiology, management and current research of some of the major neuromuscular diseases. This issue will review Duchenne (DMD) and Becker (BMD) muscular dystrophies; the two most common dystrophinopathies.

DMD and BMD are caused by changes (mutations) of a gene on the X chromosome. This can happen sporadically for unknown reasons (a boy is affected, but his mother is not a carrier), or a boy can inherit the mutation from his mother. The gene regulates the production of the protein dystrophin, which is found in skeletal and cardiac muscle. Dystrophin plays an important role in maintaining the structure of these muscle cells. DMD is associated with a marked deficiency or absence of dystrophin. BMD is a milder pathology caused by a structural alteration and/or a lesser deficiency of dystrophin. Because the disease is milder, boys with BMD can reproduce. All daughters will be carriers of the dystrophin mutation. They (like the proband's mother, if she is a carrier) will have a 50% chance of passing along the mutation in each pregnancy.

Sons who inherit the mutation will develop the disease; daughters who inherit will be carriers.

Both DMD and BMD have x-linked inheritance. X-linked inheritance is a genetic trait or mutation that is carried on the X chromosome. The basis for X-linked inheritance is that females have two X chromosomes and males have only one X chromosome. Affected individuals generally are males, since their one X chromosome has the mutant gene. Mothers of the affected males are carriers, and the sisters of affected males may be either carriers or not carry the gene at all. Affected females are usually homozygous (that is, both X chromosomes, one each from the mother and father, have the mutant gene). Affected males transmit the gene to all daughters, but not to any of their sons. The daughters of an af-

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affected male will usually be a carrier (heterozygote, i.e., one copy of the mutant gene) and thus not show the trait. Sons of heterozygous females have a 50% (1 in 2) chance of receiving the gene and thus expressing the trait or condition.

In rare instances, females who carry a copy of the mutated gene (heterozygous carriers) may develop certain, typically milder symptoms associated with the disorder. However, there is no family history of the disease for some affected individuals.

Duchenne Muscular Dystrophy

Disease: Childhood muscular dystrophy, pseudohypertrophic muscular dystrophy, muscular dystrophy (classic X-linked recessive), Progressive muscular dystrophy of childhood

Inheritance Type: X-linked recessive

Protein: dystrophin

Gene Location: Xp21.2

Clinical Findings: DMD is the most common neuromuscular disease of childhood with prevalence rates ranging from 19 to 95 per million and an overall prevalence of 63 per million individuals.

Onset of Symptoms: Almost always between 18 months and 4 years. Mean age at onset is 3 ± 2 years.

Rate of progression (without prednisone treatment): Relentlessly progressive weakness leading to inability to walk within 7 to 13 years. Mean age of wheelchair use is 10 ± 3 years. Death is in the second or third decade from cardiac or respiratory failure. Mean age of death is 20 ± 5 years. With current long-term use of corticosteroids upright ambulation and length of life are increased by several years.

Distribution of Weakness: Early and selective involvement of the neck flexors with normal strength of the neck extensors during preschool years. Weakness is generalized and symmetrical, but predominantly proximal early in disease course. Pelvic girdle weakness

predates shoulder girdle weakness by several years. Ankle dorsiflexors are weaker than ankle flexors, ankle evertors are weaker than ankle invertors, knee extensors are weaker than knee flexors, hip extensors are weaker than hip flexors and hip abductors are weaker than hip adductors. In the upper extremities the serratus, pectoralis, and latissimus muscles are involved first and later the elbow flexors are involved.

In the early stages, Duchenne and Becker MD affect the pectoral muscles (which draw back the shoulders), the trunk, and the upper and lower legs. These weaknesses lead to difficulty in rising, climbing stairs and maintaining balance.



Other Clinical Characteristics: Unless there is mental retardation, developmental landmarks are normal followed by clumsiness in walking and especially in running or climbing stairs. Child then usually walks with a waddle, protrudes the abdomen with lordosis, and rises on the toes resulting in a Gower sign. At ages 4 or 5 years, growth may outstrip the progress of the disease, leading to a false impression of improvement. There is focal

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enlargement of muscles (pseudohypertrophy) secondary to increase in fat and connective tissue in calf muscles and deltoid; selective hypertrophy and wasting in different muscles of same region; dysarthria and dysphagia in late-stage; Increased fatigue and decreased endurance.

Secondary Conditions: Increase in body fat and obesity followed by cachexia in later stage. Joint contractures and scoliosis after end of upright ambulation. Osteoporosis and fractures, musculoskeletal pain, restrictive lung disease, decreased pulmonary function and decreased cardiopulmonary capacity. Cardiopulmonary (later onset with corticosteroids) and conduction defects. Mild mental retardation in about one third of the cases.

Differential Diagnosis: Severe childhood autosomal recessive limb-girdle

muscular dystrophy (SCARMD), some types of congenital muscular dystrophy and some of the congenital myopathies.

Detailed Impairment and Disability

Profile: One hundred and sixty two individuals followed in a regional neuromuscular disease clinic, 1987-1992, were reviewed. Mean age was 12 ± 6 years, mean age at onset of symptoms was 3 ± 2 years, and duration of disease was 9 ± 6 years at the time of the first evaluation. Age and disease duration were highly correlated. Fifty-eight percent were nonambulatory, and age at loss of ambulation in these 94 individuals was 10 ± 3 years. Only 9 boys had received long leg braces. Thirty-four percent were known to have died during the 10-year period with age at death of 20 ± 5 years in these 55 individuals. For profile go to: <http://nmdinfo.net/> , Publications, Research Reports, Impairment and Disability Profiles, Duchenne MD.

Becker Muscular Dystrophy

Disease: Benign juvenile muscular dystrophy; Progressive muscular dystrophy

Inheritance Type: x-linked recessive

Protein: dystrophin

Gene Location: Xp21.2

Clinical Findings: Compared to DMD BMD generally has a later onset and milder symptoms and is quite rare. Prevalence rates range from 12 to 27 cases per million individuals and an overall prevalence of 24 per million.

Onset of Symptoms: Usually between 5 and 25 years of age. Mildly affected patients with confirmatory Duchenne/Becker MD molecular ge-

netic studies and/or dystrophin studies on muscle biopsy have been classified as having either: 1) BMD with "subclinical" skeletal muscle involvement in the presence of elevated serum CK concentration, calf hypertrophy, muscle cramps, myalgia, and exertional myoglobinuria or 2) "benign" skeletal muscle involvement when "subclinical" findings are accompanied by muscle weakness in the pelvic girdle and/or shoulder girdle. It is now recognized that the mild end of the spectrum includes men with onset of symptoms after age 30 years who remain ambulatory even into their 60s.

Rate of Progression: Relatively gradual with inability to walk 25 years after the onset. Often have a normal life span.

Distribution of Weakness: Similar to DMD. Wasting of pelvic muscles and later of the shoulder girdle muscles and ankle dorsiflexors. The severity and rate of progression depends on how much dystrophin is available and how well it functions in the muscle.

Clinical Characteristics: Hypertrophy of deltoid and calf muscles are less common than in DMD. Contracture and spinal deformity are rare. Usually normal mentation and normal early development. Despite the relatively mild skeletal muscle involvement, heart failure from dilated cardiomyopathy is a common cause of morbidity and the

most common cause of death.

Differential Diagnosis: Late onset DMD; limb girdle dystrophy of early onset; spinal muscular atrophy type 2 and 3; some of the congenital myopathies.

Impairment and Disability Profile: Twenty individuals followed in a regional neuromuscular disease clinic, 1982-1992 were reviewed. Mean age was 26 ±17 years, age at onset 8.4 ± 8.5 years, and disease duration 20 ±14 years at the time of the first clinic visit. Only two individuals were non-ambulatory. Only one individual was known to have died during the 10-year period. For profile see: <http://www.rehabinfo.net/>, Publications, Research Reports, Impairment and Disability Profiles, Becker's MD.

Table 1. Clinical Signs: Duchenne and Becker Muscular Dystrophy

Clinical Signs	Duchenne Muscular Dystrophy	Becker Muscular Dystrophy
Onset of symptoms	toddler	child-adult
Skeletal muscle weakness	toddler	child-adult
Difficulty standing up	child	child-adult
Difficulty running & climbing stairs	child	child-adult
Focal atrophy	teen	adult
Focal enlargement of calf muscles	child	child
Gower's sign	child	child-adult
Weakness of shoulder & upper arm muscles	child	child-adult
Contractures	child	child-adult
Scoliosis	teen	adult (rare)
Cataracts	With steroids	
Respiratory distress	teen-adult	adult
Cardiac conduction defects	teen-adult	adult
Cardiac ventricular dysfunction	teen-adult	teen-adult
Dysphagia	teen-adult	adult
Gastrointestinal motility/ constipation	teen-adult	adult

Diagnostic Evaluation: DMD and BMD

Regardless of the recent advances in molecular genetics, a relevant patient and family history and a focused physical examination is necessary to direct subsequent laboratory tests for patients with DMD and BMD and carrier female relatives. Although many cases of DMD and BMD are isolated, a family history is critical. Evidence of progressive muscular dystrophy in the mother's brothers or maternal uncles strongly suggests an X-linked recessive inheritance pattern predominantly affecting males. In such cases, prognostic diagnosis usually can be based on the disease or the older male relatives. However, DNA testing should be done for the purpose of diagnosis verification and family genetic counseling. Also, 10% of isolated female dystrophy patients have a form of the disease and phenocopies exist of both DMD and BMD inherited as autosomal recessive conditions. In the X-linked recessive diseases, males on the maternal side of the family are affected in approximately 50% of instances and females are carriers in 50%.

An invariant laboratory finding is striking elevations of muscle creatine kinase (CK) in serum in DMD even in clinically normal infants. As the weakness and loss of muscle tissue progresses, CK levels decrease. CK levels are also elevated in BMD, but less than in DMD unless there is myoglobinuria.

Nerve conduction and electromy-

ography are an extension of the clinician's physical examination and help to guide such further studies as muscle biopsy and to focus subsequent molecular genetic analyses. Muscle biopsy is currently used primarily for quantitative dystrophin analysis. In DNA testing, blood samples are used as a source of patient DNA and the dystrophin gene is tested to determine whether it is intact or not. A positive DNA test result is diagnostic of a dystrophinopathy, but does not necessarily distinguish between DMD and BMD. Moreover, not all DMD or BMD patients have deletion mutations. In the patients testing negative for a gene deletion mutation, a dystrophin protein test is required on a muscle biopsy sample.

Other laboratory tests relate to the high incidence of cardiac disorders in both DMD and BMD and the severe restrictive lung disease in older boys with DMD. Electrocardiograms should be obtained on all patients with DMD and BMD. In the boys with DMD periodic pulmonary tests are indicated.

A family history is critical for diagnosing

DMD and BMD.

DNA testing should be done to verify diagnosis.



MANAGEMENT OF DUCHENNE AND BECKER MUSCULAR DYSTROPHY

With the possible exception of corticosteroids, there is no specific definitive treatment for DMD and BMD. Practice standards for corticosteroid treatment of DMD were recently established by the joint committee of the American Academy of Neurology and the Child Neurology Society¹.

Although currently incurable, DMD and BMD are not untreatable. Management is primarily directed at impairments and the objectives are to inhibit, prevent or treat physical deformity, treat pulmonary conditions and cardiac disorders and alleviate pain. Overall goals are to maximize functional capacities, prolong or maintain independent functional mobility and provide access to full integration into the community with good quality of life.

There are marked differences in secondary conditions between DMD and BMD. The former has rapidly progressive muscle degeneration and weakness leading to wheelchair ambulation at 9.5 ± 2.6 years of age without corticosteroid treatment; obesity in early adolescence followed by later underweight; multiple musculoskeletal complications such as contractures, spine deformity and osteoporosis; restrictive lung disease and cardiac disorders, and mild mental retardation in some boys. Boys with DMD also have reduced skeletal development, including decreased linear growth and bone mineral density. The latter is a factor in the development of osteoporosis. BMD is slowly progressive and the major secondary condition is cardiac disease in some individuals.

Obesity, Underweight and Nutrition.^{2,3,4}

Both DMD and BMD are associated with

loss of skeletal muscle, gain of excess body fat and changes in energy metabolism and physical activity over time. The changes, however, are far greater in DMD in whom there is a high prevalence of obesity. This excess body weight burdens already weakened muscles, makes breathing and mobility difficult. Older DMD patients, however, tend to lose weight near late adolescence as the disease progresses.

In obese boys there appears to be both excessive energy in take (food) and decreased energy expenditure (physical activity). The rapid decline in body weight in the later stages of DMD has been attributed to a hypermetabolic state resulting from an increased rate of muscle protein turnover (both increases in protein synthesis and degradation rates).

Weight management in overweight DMD boys is indicated, but weight reduction by dietary management and/or drug induced appetite suppression should be medically supervised, since reduction in caloric intake may lead to acceleration of loss of muscle tissue. Encouragement of greater physical activity is desirable. Studies of protein and branched chain amino acid supplements given in underweight patients have shown promising, but inconclusive results.

In later stages of the disease there can be difficulty swallowing and when this leads to aspiration and /or under nutrition, discussion of feeding by tube or percutaneous endoscopic gastrostomy is indicated. Symptomatic involvement of smooth muscle is not universal, but constipation is a relatively common problem in older DMD boys, who usu-

ally, respond to a combination of senna and docusate.

In BMD as in most individuals with slowly progress neuromuscular diseases, there is a reduction in fat-free mass and an increase in fat mass. While their basal metabolic rate is normal, energy expenditure is at least 25% lower than controls. This is due to a reduction in physical activity that far exceeds the degree of muscle weakness. Increased physical activity and a reduced caloric intake is recommended.

Weakness, Physical Activity and Exercise^{5,6,7}

Weakness due to muscle degeneration is, of course, the primary condition in most neuromuscular diseases. Weakness due to other causes such as decreased-use atrophy is a secondary condition. Reduced physical activity is a consequence of all neuromuscular diseases, which negatively impact quality of life and health outcomes. Improvement in physical fitness through increased physical activity is important for health maintenance and disease prevention (coronary artery disease, hypertension, diabetes, osteoporosis, anxiety and depression), and is likely to contribute to improved community integration and the ability to participate in recreational activities. Patterns of physical activity in childhood persist on to adult hood, and obesity, frequent in DMD, is due to a reduction in activity-associated energy expenditure and unchanged caloric intake.

Individuals with neuromuscular diseases represent a very sedentary and deconditioned population with responses to exercise testing similar to that found in poorly conditioned (bed-rest) able-bodied individuals and aging persons. It is likely, therefore, that the

reduction in functional muscle mass in DMD and BMD and the resulting functional impairments are the result of both sedentary imposed atrophy of disease and muscle degeneration secondary to the disease. In DMD, it is also known that even short periods of bed rest results in significant loss of strength and function that is often not reversible.

Evidence of low energy expenditure in individuals with neuromuscular diseases has been reported in several studies. In BMD, or in other ambulatory slowly progressive diseases, energy expenditure in physical activity was significantly lower than in control subjects. In addition, BMD patients reported exercise at lower intensity levels. In boys with DMD, who were still mobile, there were significantly lower levels of high intensity physical activities (continuous walking, running) compared to able-bodied boys, and far higher levels of low intensity physical activities and inactive sedentary time. Ambulatory boys with DMD also have decreased metabolic economy of movement (higher oxygen cost) during walking, lower oxygen uptake during comfortable movement and reduced velocities of walking.

At least to the extent that reduced physical activity is due to the effects of a sedentary lifestyle resulting in atrophy of disuse, exercise should be helpful to reverse the negative effects of the deconditioned state. Exercise training for individuals with neuromuscular diseases has long been a controversial issue. There are two types of exercise training: resistive strengthening exercise and aerobic exercise training (running, walking, and swimming).

In aerobic exercise testing studies (bicycle, treadmill), regardless of the

type of neuromuscular disease, there is improved cardio/pulmonary capacity (reduction of peak oxygen uptake, work capacity or rate, endurance and cardiac output). These responses are similar to deconditioned able-bodied individuals. While there are no studies of aerobic exercise training in DMD boys, several studies of training in individuals with slowly progressive neuromuscular diseases, including BMD, have reported positive responses. These improvements in cardiopulmonary adaptations are qualitatively similar to adaptations in able-bodied persons with no untoward effects.

Concern about increased muscle degeneration and further weakness induced by resistive strengthening exercise (overuse weakness) has led many physicians and therapists to avoid recommending it. There is, however, a significant difference between overuse weakness (found in post polio syndrome) and actual contraction-induced injury. The former appears to be secondary to long-term sustained physical activity of weak muscles, whereas, the latter occurs with a single bout, high intensity series of muscle contractions, usually eccentric. Resistive exercise training can be either concentric or eccentric. The former is when the exercised muscle shortens and the latter when it lengthens. Exercise, either aerobic or resistive, can also be sub maximal in intensity or maximal (to the point of fatigue). Regardless, most of the few studies of resistive exercise in both DMD and slowly progressive neuromuscular diseases such as BMD reported either a moderate increase in strength or a slight reduction in the progression of the weakness. The exception was in one study in which high intensity maximal resistive exercise was used to the point of fatigue.

The exercise recommendations made at a recent evidence-based consensus conference⁹ were:

(1) Adopt an active lifestyle. Physical activities should emphasize recreational and sport exercises in combination with an active daily lifestyle and proper nutrition. The goal should be improving functional performance and daily activities.

(2) Moderate-intensity resistive strengthening exercise programs can be recommended and will usually result in modest increases in strength. High-intensity resistive exercise and eccentric exercise should be avoided.

(3) Moderate aerobic exercise training can be recommended without concern about any deleterious effect.

(4) Fatigue can often be reduced by using brief work-rest-interval training programs.

Effect of Obesity and Sedentary Lifestyle⁸

The combination of increased adiposity and sedentary lifestyle in individuals with neuromuscular disease raises concerns about the development of medical conditions over time. In a recent study, a group of individuals with slowly progressive neuromuscular diseases were found to have multiple risk factors for cardiovascular disease and diabetes. These risk factors worsened over time. In addition, over 50% satisfied the criteria for metabolic syndrome (a constellation of risk factors that significantly increase the risk for coronary events and type 2 diabetes).

Mobility^{2; 3; 9; 10}

Cessation of walking, without interventions such as long leg bracing or treatment with corticosteroids, occurs at 9.5 ± 2.6 years of age in DMD boys. Loss of upright ambulation is variable in BMD, especially since there are two patterns of progression: a "typical" slowly progressive course and a more severe and rapidly progressive course. Mean age to wheelchair in the former is about 58 years of age and about 25 years in the latter.

Patients with proximal weakness involving the pelvic girdle muscles may rise off the floor using a "Gower sign" where a four-point stance on knees and hands is assumed. The knees are then forced into extension while leaning forward on the arms. The individual then pushes off the knees with the hands and sequentially moves the hands up the thigh until full hip extension is achieved. While not specific to any neuromuscular disease, it is a classic sign in DMD and BMD.

The pathomechanism of loss of upright standing and walking are a result of progressive weakness. Initially, weakness of the hip extensors produces anterior pelvic tilt and a tendency for the trunk to be positioned anterior to the hip joint. Patients compensate for this by going into lumbar lordosis, which changes their center of gravity to posterior to the hip joints. Eventually, weakness of the knee extensors results in knee buckling. Compensation for this is by decreasing stance-phase knee flexion and posturing the ankle into plantar flexion. Boys with DMD progressively demonstrate initial foot contact with the floor forward on the mid-foot and finally the forefoot as they reach the transitional phase of ambula-

tion. Eventually, weakness of the hip abductors produces lateral pelvic tilt and pelvic drop of the swing phase side. Patients compensate for this by lurching the trunk laterally over the stance-phase hip joint producing the so called "Trendelenburg gait pattern." By this time toe walking (foot drop) occurs with heel cord contractures and early equinovarus foot deformity. During this phase surgical heel cord release or short-leg braces to prevent foot drop will produce a precipitous increase in falls and even early cessation of ambulation since these interventions compromise the ability to stabilize the knee into extension with equine posturing of the plantar flexors.

Upright ambulation and standing ends when lower extremity strength has decreased to about 50% of normal levels and equinovarus deformity is present. Surgical release of contractures and / or orthotic (long leg braces) interventions in an attempt to prolong the upright position remain controversial. While the upright position can be maintained with braces, and bracing delays lower extremity hip and knee flexor contractures and may delay scoliosis, functional and useful upright ambulation is questionable.

While surgery and bracing should be offered as an option to patients, a wheelchair gives the DMD boy much more practical, independent mobility than does bracing and most children appear to take to the wheelchair with relief and even enthusiasm. When the decision regarding wheelchair use is reached, the goal should be to make the chair the passport to more rather than less activity. Electrically powered chairs are eventually required for most individuals, although hand operated

light high-mobility wheelchairs can delay the need for powered chairs for several years. Special wheelchair adaptations are usually necessary. These may be provided either through a combination of assistive devices attached to the chair or the patient or through a self-contained total-support system. Objectives of orthotic and assistive devices are to maintain a stable spine, reduce the progression of contractures in the legs, continue functional use of the arms and maintain comfort.

Musculoskeletal Complications^{2; 3}

Musculoskeletal conditions include limb contractures, spine deformity, pain and osteoporosis. Significant joint contractures occur in all DMD boys older than age 13, but are not a significant problem in BMD patients who remain ambulatory. The ultimate prevalence of scoliosis in DMD studies varied from 33% to 100%. This marked variability is due to the arbitrary retrospective selection for scoliosis and dissimilar age groups. Prevalence is strongly related to age and about 90% have clinical scoliosis by age 20 or 10 years from wheelchair reliance. Spinal deformity is very rare in BMD. Osteoporosis in the leg bones occurs at a relatively early age in most individuals who have lost upright ambulation.

Contractures and the Role of Stretching, Orthotics and Surgery¹¹

Contractures are shortening of muscle or the development of connective tissue around joints which prevent the normal range of movement and result in major impairments to walking and to the daily activities of living. Intrinsic muscle tissue alterations in dystrophic myopathies (muscle fibrosis) place these individuals at high risk for contracture formation. Weakness and in-

ability to achieve active joint mobilization through the full range is the most frequent factor contributing to the occurrence of fixed contractures. Fibrosis of muscles in a fixed position increases the tendency to form fixed contractures in the position of immobilization. In addition to static positioning and lack of full range of motion, contractures are enhanced by muscle imbalance; lack of upright weight bearing; compensatory postural changes used to stabilize joints for upright standing, and the functional anatomy of muscles and joints.

The most common contractures in DMD occur in the ankle plantar flexors, knee flexors, hip flexors, iliotibial band, elbow flexors and wrist flexors. Significant contractures are rare before age 9. Lower extremity contractures are strongly related to wheelchair reliance and develop soon after a sitting position for most of the day.

Management strategies for contractures include stretching, positioning, splinting, upright weight bearing, orthotics and surgery. If the individual has long-leg braces, a minimum of 2-3 hours of daily standing and walking is necessary in addition to passive stretching. For patients without braces, a standing table or frame with attachable desk top surface may be helpful for the prevention of hip, knee and ankle plantar flexion contractions. A program of passive stretching should be started as early as possible, should become a part of the patient's regular morning and evening routine and should be focused on the areas of contracture formations listed above. Care should be taken with stretching in the person with osteoporosis to avoid bone fractures.

Positioning is useful for preventing con-

tracture formation. For the lower extremities, legs are placed in a resting position that opposes the tendency for flexion contractures to develop. The prone-lying position is an effective method to stretch the hip flexors. Positioning in the upper extremities should emphasize wrist and finger extension.

Splinting is another measure. Any splinting should be used in conjunction with stretching and is usually at night. Stretching, positioning and splinting have limited roles in the management of hip and knee contractures in individuals who are in a wheelchair primarily. Night-time resting splints, which promote wrist extension and finger extension can, however, be helpful.

Braces with or without surgery for prolonged ambulation has been reviewed under mobility. Foot equinovarus and heel cord contractures after loss of upright ambulation can be managed with short leg braces or surgery. Heel cord tenotomies or muscle tendon transfers are not recommended while still ambulating independently. Indeed, surgical treatment of any contracture has not been shown to be of any benefit prior to the loss of upright ambulation. Weakness is of major cause of loss of walking and not contracture formation. Various assistive devices can be used for upper extremity weakness and contractures such as mobile arm supports.

Spine Deformity and the Role of Bracing and Surgery¹²

Spine deformity includes scoliosis, lordosis and kyphosis. Scoliosis is an appreciable lateral deviation (curve) in the normally straight vertical line of the spine when viewed from the back. Paralytic scoliosis as seen in DMD is a lateral curvature of the spine due to

muscle weakness. Lordosis is the concavity in the lumbar and cervical spine as viewed from the side. Abnormally increased lordosis is often called "hollow-back" or "saddle-back." Kyphosis is the abnormally increased convexity in the thoracic spine as viewed from the side ("hunchback"). The prevalence of scoliosis in DMD is strongly related to age. Fifty percent acquire scoliosis between ages 12 and 15, corresponding to the adolescent growth spurt in boys. Ten to 15% of older boys do not develop scoliosis or only have mild, non-progressive curves, and about 15% of DMD boys develop scoliosis before transition to a wheelchair. In those who develop severe scoliosis, the rate of progression of the lateral curve ranges from 11 to 42 degrees per year. There is no association between side of curvature convexity and hand dominance and no cause-and-effect relationship between onset of wheelchair reliance and occurrence of scoliosis. However, in individuals developing scoliosis, severity increases with age and length of time in a wheelchair. Wheelchair reliance and scoliosis are both, therefore, age-related.

When it occurs, there are three types of spine deformity. In Type 1 curves follow an unstable course and are characterized by progression of scoliosis concomitant with kyphosis. The progression leads to a collapsing spine, involving the sacrum and pelvis, and reaches greater than a 30 degree curvature before age 15. Surgical stabilization is indicated before the curve reaches 30 degrees and before vital capacity reaches 35% of predicted values. The type 2 curves are characterized by transition of the kyphosis to hyperlordosis with progression of the scoliosis curve.

The course is not uniform. Type 3 curves show minimum progression, a better prognosis for pulmonary function, and rarely any indication for surgical intervention.

In addition to marked deformity, scoliosis leads to restrictive lung disease. Even without scoliosis, severe and progressive lung disease occurs in DMD. The two conditions occur relatively early and reduce physical capacity and quality of life. In the advanced stages of DMD, pulmonary complications such as pneumonia, contribute significantly to death. Spine radiographs should be obtained every 4 months in DMD patients between the ages of 11 and 16 years if mild clinical scoliosis is present. In addition, pulmonary function tests should be obtained every 6 months during this age range.

Early management of scoliosis is directed toward keeping the spine extended and the pelvis level. Wheelchairs should have a firm, level pelvic seat with a top cushion. Because an erect spine is necessary for proper sitting balance, many different types of external spinal containment system or trunk supports have been advocated to retard the rate of scoliosis progression. In an attempt to prevent kyphosis and pelvic obliquity and to encourage an extended lordotic spine position, systems such as total wheelchair spinal support systems, lumbar pads and hyperextension braces have been advocated. While these systems may retard the progress of the scoliosis for a limited period of time if worn consistently, they are ineffective in changing the natural history of the scoliosis curves. Other approaches such as spinal exercises, electrical stimulation, and spinal manipulation have never been shown

to be effective. Spinal orthoses are uncomfortable and poorly tolerated and may slow the development of scoliosis until the pulmonary function levels have declined so low that spinal surgery is risky. Studies have shown surgical spinal instrumentation to be the only effective treatment for severe spinal deformity in DMD and other neuromuscular diseases. Surgery is indicated if the curve is greater than 25 degrees and progresses at a time when the vital capacity is greater than 50% of predicted.

Pain¹³⁻¹⁵

Recent reports indicate that chronic pain is a significant problem in many individuals with neuromuscular diseases. In adults with slowly progressive diseases, such as BMD, about 75% in one survey reported pain. Over 50% described the pain as severe. In boys with DMD and other youths, 58% reported experiencing chronic pain. In these reports, there was a lack of clear efficacy of any one of the pain treatments used (chiropractic care, nerve blocks, analgesics, physical therapy, etc.). This research also showed that pain had a significant impact on quality of life, and that the pain of persons with neuromuscular disease was under-treated. The lack of efficacy of any single treatment and under-treatment is not surprising, since this also occurs in the general population with musculoskeletal pain. Pain is rarely due directly to the neuromuscular disease and has many causes. Treatment is not specific and is highly individualized.

Osteoporosis and Fractures^{13; 16-20}

Disuse osteoporosis has been described in a variety of conditions in which the continuous weight-bearing stimulus, which is necessary for bone

remodeling, is substantially reduced. If such stimuli from muscular work are reduced in growth and development, as happens in DMD, the growing skeleton is deprived of one of the main factors of bone development and increase of bone mass. This reduction in bone mass, in which the bones become thin and demineralized, is well known to occur in wheelchair ambulatory DMD boys. If even normal external forces are applied, fractures can easily occur in the osteoporotic bone, especially in the femur and the spinal vertebra. The overall fracture rate has been reported to be about 45% with the rate increasing to about 65% in boys 14 years or more. Recently, it has been reported that bone density is also profoundly decreased in DMD boys who are still ambulatory (6-11 years). Prevention of fractures in this population is also critical since their occurrence can result in an acute loss of walking. Bone density is also reduced in BMD, but is less severe and rarely results in fractures. The problem of disuse osteoporosis is compounded by the current and long term use of corticosteroids (prednisone and deflazacort) in DMD. Long-term treatment with corticosteroids in other diseases has been proven to invariably induce osteoporosis and increase the rate of fragility fractures. In one study of DMD boys, bone mineral density and derangement of calcium metabolism was lower than normal for age in all boys, and even lower in those who were steroid treated.

It is now recommended that bone and mineral metabolism be periodically evaluated in DMD so that appropriate measures can be taken in order to reduce the risk of osteoporosis and its complications. Corticosteroids should

be reduced to the minimum effective dose. A high intake of calcium (at least the recommended daily allowance for age) is recommended especially in boys treated with steroids and vitamin D supplements. In some cases, the vitamin D metabolite, 25-OHD, and bisphosphonates are necessary.

Pulmonary Complications^{2; 3; 21-24}

Normal breathing depends on the function of the ventilatory pump, which consists of the central respiratory control center in the brain, the long bony rib cage, diaphragm and the intercostals and accessory muscles. Many neuromuscular disorders result in dysfunction of the ventilatory pump that can lead to acute or chronic respiratory failure and pneumonia. Breathing disorders represent the leading cause of death in DMD.

Respiratory failure results from: (1) respiratory muscle weakness and fatigue, (2) alterations in respiratory system mechanics and (3) impairment of the central control of respiration. In DMD and other neuromuscular diseases, progressive muscle weakness and fatigue of the diaphragm and chest muscles lead to what is called restrictive lung disease and ultimately to hypoventilation, hypercarbia and respiratory failure. Respiratory failure in DMD presents as a chronic worsening of gradually progressive muscle weakness. In addition to effects on muscle contraction by the muscle weakness, the disease increases elastic and resistive loads on the respiratory muscles. Both types of loads increase the work of breathing and hasten ventilatory failure. Kyphoscoliosis, usually present in DMD, also increases the work of breathing. The deformity of the back and thoracic cage increases chest wall stiffness and

produces mechanical misalignment of the respiratory muscles,, thus reducing this ability to operate effectively against the increased elastic and resistive loads.

Measurements of pulmonary function include forced vital capacity (FVC), forced expiratory volume, residual volume, maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), cough flow and on occasion, blood gases. In DMD reduced pulmonary function occurs in all individuals and the timing of significant compromise often occurs subsequent to wheelchair use. There is a linear decline in percent predicted FVC with an average rate of decline of only 0.3% per year between ages 7 and 10. Between 10 and 20 years of age the decline increases to 8.5% and between 9 and 21 years of age it reaches 25% per year. Significant respiratory complications such as pneumonia or acute respiratory failure occur at an increasing rate with age; only 7% at ages 3 to 8 to 61% at ages 21 and above. There is a high relationship between pulmonary complications and FVC. In BMD, compromised pulmonary function and respiratory complications are much less problematic and FVC is not substantially reduced until the fourth decade of life.

Appropriate interventions prevent complications and prolong life. In several studies, life was increased by about 6 years with aggressive management even before the current use of corticosteroids. There is some indication that there is sparing of pulmonary function with steroids. Comprehensive practice recommendations were recently developed in a n American Thoracic Society statement²³. These recommendations are very extensive and are only briefly

reviewed in this report:

- Surveillance: Serial pulmonary function measurements twice a year after confinement to a wheelchair, fall in vital capacity (FVC) below 80% and/or age 12 years. Evaluation for sleep disordered breathing. Pulmonary and a cardiac evaluation before surgeries. Nutritional and swallowing evaluations.
- Routine immunizations, pneumococcal vaccine and annual influenza vaccination. Prompt treatment of chest infections.
- Management of airway clearance. First by manual cough techniques, followed by mechanical methods (insufflators, exsufflators, mucus mobilization devices) when necessary.
- Noninvasive nocturnal ventilation. Nasal intermittent positive pressure ventilation for sleep-related upper airway obstruction and chronic respiratory insufficiency.
- Daytime noninvasive ventilation. Mouthpiece intermittent positive pressure ventilation when there is a state of constant hypoventilation.

Continuous invasive ventilation. Tracheostomy can be considered when there is severe bulbar dysfunction or there is patient aversion to noninvasive ventilation.

It has been known for many years that aggressive management significantly increases survival of DMD patients. However, there was also the assumption by physicians and other health care providers that ventilator-dependent individuals had a poor quality of life. It is now clear from several studies that this negative perception markedly underestimated the quality of life perceived by

ventilator dependent persons with DMD. The results of these studies have clearly shown that quality of life is either generally acceptable or actually improved among individuals with DMD who chose to use long-term mechanical ventilation.

Cardiac Complications^{2; 3; 25; 26}

Cardiac involvement is an almost universal complication of DMD and death may result from heart failure in 40% to 50% of patients or from sudden death in about 5%. The most serious major abnormality is cardiomyopathy, but cardiac conduction disturbances, premature ventricular contraction, sinus tachycardia and mitral valve prolapse also occur. Nearly all individuals over the age of 13 demonstrate abnormalities of the electrocardiogram. The cardiomyopathy, without routine screening, progresses asymptotically, until, when all cardiac reserve has been eroded, evidence of heart failure emerges. Development of clinical cardiomyopathy is a predictor of poor prognosis, with death occurring within a few years.

BMD shows many of the cardiac complications of DMD, although the resting tachycardia seen in DMD is not present. Electrocardiographic abnormalities become evident in the majority of patients during their lifetimes. Clinically evident cardiomyopathy is found in 15% of patients under 16 years of age, increasing to 73% in patients older than 40. Cardiomyopathy also has been reported to be the initial presentation of BMD in some individuals. In both DMD and BMD, cardiac involvement has also been reported in women with a close relationship to the patients (carriers).

Cardiac tests are indicated at diagnosis in both DMD and BMD, every 2 years

there after to age 10 in DMD and then annually if abnormalities are detected. Treatment with angiotensin converting enzyme (ACE) inhibitors and beta blockers should be initiated in the presence of cardiomyopathy with the addition of digitalis and diuretics, if necessary. In DMD in addition to reduction in the progression of muscle weakness and stabilized pulmonary function, corticosteroid therapy appears to alter the progressive decline in cardiac function.

Anesthesia Risks²⁷

Anyone having surgery should be aware of the risks associated with the surgical procedure and/or complications that may arise during and after it. For individuals with neuromuscular diseases, there are frequently added risks with the use of anesthesia. Anesthetic techniques should be tailored to minimize intra- and post-operative respiratory and cardiovascular depression. In DMD and BMD inhalation anesthetics, succinylcholine and anticholinesterase drugs should be avoided since they may provoke malignant hyperthermia, muscle breakdown and heart rhythm disturbances. Hypotensive anesthesia is often recommended, since dysfunction of smooth muscle may result in increased blood loss. Rapid deterioration of cardiac function is usually a contraindication to elective surgery. For patients with declining respiratory function it is desirable to familiarize the family with the use of non-invasive ventilation ahead of surgery. Caution is also indicated in procedures under sedation. For more information visit the RRTC web site: <http://nmdinfo.net/>

Cognitive and Psychosocial Issues^{2; 3; 28-30}

Since first described in 1872, it has been

commonly accepted that DMD is associated with diminished intellectual capacity. Many studies have shown that although IQ is normally distributed, it is shifted down by 2 standard deviations compared with the non-DMD population. Mean Full Scale IQs (FSIQ) fall in the low 80s, but with a substantial range in scores. On the average, the FSIQ among boys with DMD is about one standard deviation (15 points) below the normative mean (100). Because of the marked variability, patterns of cognitive impairments and their relationship to psychosocial and educational concerns are more important than FSIQ statistics.

Patterns of impairment include types and areas of function, causes of impairment and the course of impairment. Unfortunately, there is little consensus on any of these factors and some, while statistically significant, may have limited clinical meaning. Several studies have shown a relative and generalized deficit in verbal abilities with mean Verbal IQ (VIQ) lower than mean Performance IQ (PIQ). Other studies have shown age-related patterns: (1) an initial period of 8 to 9 years where there appears to be a progressive reduction of IQ scores associated with the maximum VIQ-PIQ difference; (2) a steady state of 4 and 5 years; (3) a final period of moderate IQ increase. Specific deficits have been reported in attention/concentration, verbal expression, short-term memory, visuoconstructional ability and higher syntax verbal mediated processes.

Although current data is limited by small numbers, it does not appear that BMD patients are at high risk for significant intellectual deficits. Some studies, however, have shown a "mild" or "mild to moderate" IQ impairment in individual subjects. The possibility exists that

the absence of dystrophin in the brain causes some downshift in IQ values in most DMD boys, and partial dystrophin abnormalities may cause mildly reduced intellectual performance in a subset of BMD individuals.

It is also clear from clinical experience that behavioral difficulties can be an issue in DMD and that these may be exacerbated by steroid treatment. Moreover, it is well known that individuals with progressively debilitating and often fatal illnesses, including those with a neuromuscular disease, are at risk for social, emotional and behavioral problems. In one study of DMD boys, a high percentage fell outside the accepted normal limits on most subscales of a personality assessment inventory. Indeed, 58% had scores that fell in the range for recommended psychological evaluation. These results, as well as reports from other studies should be viewed with caution. Many of the standardized measures used to evaluate personality and other psychological variables have not been standardized on disabled populations and, therefore, some elevated scale may actually be a realistic reflection of actual status rather than a deviation from the norm.

Fortunately, interventions targeted at these problems exist and can be appropriately implemented in programs designed to provide services to the individuals. There are three general areas of intervention. First, the need for a supportive therapeutic relationship with professionals providing health care should be emphasized. This includes the physician as a therapeutic agent; family therapy to assist the entire family in coping with the progressive loss involved in neuromuscular disease; and the supportive relationship of a peer

support group. Second, provision of education and information has been shown to diminish the psychological impact of DMD on the child as well as on the family. Finally, it is necessary to provide specific interventions based on the stage of the disease and the particular physical and psychosocial needs of the individual.

Educational and Vocational Concerns²⁸⁻³²

There is a well-documented relationship between DMD and learning difficulties associated with cognitive impairment and behavioral problems. Cognitive impairment frequently affects verbal short-term memory, reading comprehension and ability to process verbal data especially phonological processing defects. It should be noted that having a disease such as DMD that is associated with a cognitive impairment in some individuals does not necessarily mean that all individuals will have a learning disability or even a cognitive impairment. DMD boys are, however, at an increased risk for cognitive deficits and should be evaluated by a developmental neuropsychologist if any learning problems develop.

The child with DMD has two special education needs. The first relates to his physical impairments and the second to a learning problem, if present. While specific educational interventions for learning disorders is beyond the scope of this review, recommendations to improve their educational experience are essential. Schools must modify the physical environment to be barrier-free. Physical education activities must be modified. Children may need assistance to participate in the spontaneous social activities that take place in the

school environment and some may need assistance with the physical demands of completing assignments. The former is especially important for children who have problems with emotional interactions sometimes described as “emotional immaturity” or “a lack of connectedness with others.” The goal of adaptations should be to allow the child to learn in the best environment available for him, and should, when possible, remain in a mainstream classroom with his peers. Children and adults with BMD do not appear to have significant behavioral or educational problems. Recommendations for the education of children with neuromuscular diseases have been developed by the RRTC and are available on its website.

Until relatively recently, employment in the competitive labor market was not an issue with DMD individuals. Due to corticosteroid treatment and improved management of secondary conditions, it is no longer appropriate to look on DMD as a condition that is inevitably fatal in childhood as the majority can now be expected to reach adulthood. Therefore, they can be expected to have the same employment problems as adults with neuromuscular diseases.

In a RRTC study, 40% of 154 adult individuals with slowly progressive neuromuscular diseases were employed in the competitive labor market at the time of the survey. This was slightly higher than the 31 to 33% of employed work-disabled individuals reported in national surveys. Fifty percent had been employed in the past, 90% had been employed at some time and only 10% had never been employed. Of the total, 22% were employed part time. There was a disease-employment association and BMD individuals had the highest

level of employment (50%).

The RRTC study found significant consumer (self), and provider barriers to employment. Consumer factors associated with employment included type of occupations, education, intelligence, expressed interest in employment, reasons for unemployment, severity of physical impairments and disability, and psychosocial adjustment. Occupation clearly affected employment with the highest level of unemployment in less skilled and trained workers. Education, related to type of occupation, also had a significant effect on employment. Individuals who had received a college degree were usually in professional/management/technical occupations and were more likely to remain employed. Intelligence, associated with education, was a factor. Unemployed individuals had significantly lower IQs. Reasons for unemployment and interest in employment were related to physical disability. Sixty four percent of the individuals not employed believed that their physical disability (weakness) was the major or only limitation to employment. Of those not interested in a job, 89% gave the severity of their disability as the reason, but only 50% interested in obtaining employment considered disability as the reason. This is an interesting and important perception, since actual objective measurements of impairment and disability found that there was no significant difference between employed and unemployed individuals. There was also a significant association between psychosocial adjustment and unemployment. This, however, may be both the cause and result of unemployment.

Provider factors associated with employment included consumer awareness of public vocational rehabilitation

programs (DR); actual referral to DR (California); and DR (California) counselor and physicians attitudes toward persons with neuromuscular disease. Results from the RRTC survey indicated that most individuals with neuromuscular diseases were not aware of a state DR, and there was a low DR acceptance level and a low level of referral to DR by physicians. This was compounded by the lack of information and experience of vocational counselors and physicians with aspects of neuromuscular diseases. As a result many counselors and physicians believed that individuals with these diseases did not have employment potential.

Because of the negative attitude of many counselors, the RRTC developed and distributed a guide to neuromuscular diseases for counselors (also available on the RRTC web site). Every state has a vocational rehabilitation department to help disabled individuals obtain jobs.

Quality of Life Issues³³⁻³⁵

Quality of life is a broad concept that takes into consideration physical (health, physical functioning and independence, etc.), psychological (controlling one's life, life satisfaction and self-acceptance, self-esteem, etc.), social (social support resources, marital and family relations, standard of living, etc.), and financial attributes. From an impairment, function and participation standpoint, educational opportunities, employment opportunities, independent living and community integration, socialization, and family functioning lead to a satisfactory quality of life.

Life satisfaction psychometric assessment studies (very satisfactory, somewhat satisfactory, neither satisfactory

nor dissatisfactory, somewhat dissatisfactory) have shown that responses from control, non-disabled subjects ranged between very satisfied and somewhat satisfied with their life in general, whereas, responses from individuals with slowly progressive neuromuscular diseases, such as BMD, were somewhat satisfied. The latter were least satisfied with their recreational activities, sexual life, general health and money matters. Other areas with which they were less satisfied than controls were daily living tasks, employment and social life. They were most satisfied with housing and family life, neighborhood and spiritual life. The strongest association with life satisfaction was emotional well-being, perceived control, satisfaction with employment and self-assessed health. Impairment and disability, as measured by degree of mobility, dexterity and activities of daily living, didn't significantly affect life satisfaction.

Rather, quality of life depends on whether an individual receives adequate services, and whether he has the same choices and opportunities to participate freely in the community, not the level of physical disability. The greatest problems that individuals with neuromuscular diseases and their parents identified were: lack of information about their disease and available services; poor coordination of services; negative attitudes; and diminished expectations of their potential. Factors related to a good quality of life were related to perceived control and perceived health status. The more that people could do for themselves, either on their own or with personal care assistants, assistive devices and use of technology, the better their quality of life.

There were two other significant observations from these surveys of impor-

tance to individuals with neuromuscular diseases and their families. The first was that the quality of life perceived by people with neuromuscular diseases was substantially higher than that presumed by health care professionals. For boys with DMD, for example, quality of life was significantly underestimated by physicians, even in individuals with chronic ventilator dependence. The second problem experienced by many individuals was that they had no idea what services were available or how to obtain the services that are available. The RRTC web site, therefore, includes a directory of national resources for individuals with neuromuscular diseases. It should also be noted that most cities in the country have programs for their disabled citizens and many publish a directory of local services and resources.

Specific Treatment

Use of glucocorticosteroids (prednisone/prednisalone and deflazacort) is now the gold standard treatment for muscle weakness in ambulatory children with DMD. Randomized controlled trials have shown an increase in strength, and long-term cohort studies have been reported showing a striking improvement in function (ambulation prolonged to the mid teens) and a concomitant reduction in secondary conditions such as scoliosis. There is a marked improvement in respiratory function and some evidence of improvement in cardiac function.

The American Academy of Neurology (AAN) recently released a report on the use of corticosteroids in DMD.¹ A summary of the report concluded that:

- Prednisone and deflazacort (not available in the United States) are beneficial in the treatment of DMD. Seven high-quality studies showed a significant in-

crease in strength, timed motor function (such as time to climb stairs) and pulmonary function with these medications.

- Effective initial treatments are: 0.75 milligrams per kilogram of body weight per day for prednisone, or 0.9 milligrams per kilogram per day for deflazacort.

- The most frequent side effects are weight gain and the development of a Cushingoid facial appearance (rounded, puffy face).

- There are insufficient data comparing prednisone and deflazacort to determine whether deflazacort has fewer side effects.

- Maintaining a daily dosage of 0.75 milligrams of prednisone per kilogram is best, but if side effects require a decrease in dosage, a gradual tapering to as low as 0.3 milligrams per kilogram per day will still provide some improvement.

- Benefits and side effects of corticosteroid therapy need to be monitored. Timed function tests, pulmonary function tests and age at loss of independent walking are useful to assess benefits. An offer of treatment with corticosteroids should include a balanced discussion of potential risks.

- Possible side effects, such as weight gain, Cushingoid appearance, cataracts, short stature from slowed growth rate, acne, excessive hair growth, gastrointestinal symptoms and behavioral changes, need to be assessed. If a boy gains more than 20 percent over the estimated normal weight for his height

in a year, the dosage of prednisone should be decreased to 0.5 milligrams per kilogram per day, with a further decrease to 0.3 milligrams per kilogram after three to four months if excessive weight gain continues.

Deflazacort at 0.9 milligrams per kilogram per day can also be used for the treatment of DMD in countries where it's available. Patients taking deflazacort should be monitored for cataracts and weight gain.

To see the report for physicians and a version for families, go to "Practice Guidelines" on the AAN website at <http://www.aan.com> or the RRTC website at <http://nmdinfo.net>

Summary

The emphasis in this review is on the management of the secondary conditions found in DMD and BMD. The comprehensive management of all of the many clinical problems is an arduous task. For this reason, the multidisciplinary approach, found in most MDA supported neuromuscular disease clinics, is the most effective. Management is best carried out by a team consisting of physicians, social workers, psychologists and vocational counselors, among others.

This review represents practice parameters for the management of BMD and, especially, DMD. Evidence based practice guidelines have already been developed in other countries.³⁵ In the United States, the Centers for Disease Control is currently planning a conference to establish similar guidelines.

Reference List begins on page 26

Most effective approach to management is multidisciplinary

Dystrophinopathies

In addition to DMD and BMD, other diseases associated with primary abnormalities of dystrophin include exercise intolerance associated with myalgias, muscle cramps, or myoglobinuria; quadriceps myopathy; asymptomatic elevation of the serum creatine kinase (CK) level; cardiomyopathy with mild muscle weakness; and fatal X-linked dilated cardiomyopathy without muscle weakness. It is clear that primary muscle disorders due to inherited abnormalities of dystrophin (i.e. dystrophinopathies) represent a spectrum of disorders with a range of severity from DMD phenotypes to BMD phenotypes, to rare cases with exercise intolerance and muscle cramps. All these disorders are caused by varying gene defects at the same p21 locus, which in turn cause varying abnormalities in the protein dystrophin.

The Role of Dystrophin and the Dystrophin – Glycoprotein Complex:

Dystrophin is a cytoskeletal protein positioned on the inside of the muscle sarcolemmal membrane (muscle cell covering). It plays a critical role in maintaining the structural integrity of muscle fibers along with a series of glycoproteins which are positioned within and outside the muscle fiber membrane. The combination of dystrophin and this related complex of proteins is termed the "Dystrophin-Glycoprotein Complex." Dystrophin not only is attached to the dystrophin-associated glycoproteins, but also to actin filaments on the inside of muscle cell that function as internal structural scaffolding for muscle fibers. Outside the muscle fiber a protein called merosin anchors the glycoprotein complex to the basal lamina. Thus, the dystrophin-glycoprotein complex links

the internal actin filaments to the extracellular matrix outside the muscle membrane. This dystrophin-glycoprotein complex serves ultimately to protect the muscle membrane from stresses developed during muscle contraction and/or mechanical stretch.

Genetic abnormalities may lead to a primary and permanent deficiency in any one of the proteins of the Dystrophin-glycoprotein complex. However, dystrophin's absence (0-3% measured dystrophin as seen in DMD) appears particularly detrimental to survival of muscle fibers because a secondary, severe reduction in all dystrophin-associated glycoproteins occurs over time leading to severe instability of the membrane and susceptibility to muscle fiber injury. Eventually after cycles of injury and regeneration the muscle fiber undergoes irreversible death and is replaced by fat and connective tissue (scar tissue). This tissue replacement accounts for the pseudohypertrophy (enlargement) of some muscle groups and contracture formation when strength loss progresses to the point where limbs cannot actively be moved through their full range of motion.

There are individuals with normal length dystrophin who lack a critical region of the protein (the carboxy terminus end which connects to the dystrophin-associated glycoproteins) Despite essentially normal quantity of dystrophin, these individuals experience a severe progressive reduction of dystrophin associated glycoproteins and look clinically similar to DMD patients. Alternatively, there are a small subgroup of severe Becker Muscular Dystrophy (BMD)

(Dystrophinopathies—Continued on page 23)

patients with absent or severely reduced dystrophin by traditional analysis but intact carboxy ends of dystrophin. These individuals have a more slowly progressive dystrophy.

A subgroup of Duchenne dystrophy patients (referred to as "outlier" DMD) show later age of wheelchair reliance, less severe progressive scoliosis, less severe restrictive lung disease, and survival into the twenties or even thirties with supportive care. Some have been shown to have reduced amounts of dystrophin in the 3% to 20% range, while others have completely absent dystrophin as seen in more typical DMD.

Immunofluorescent stains of muscle tissue from BMD patients have shown reduce and/or patchy dystrophin staining along the sarcolemmal membrane, and immunoblot analysis has detected dystrophin of abnormal size and/or reduced quantity (in the 20-80% range). It appears that most BMD patients have dystrophin with intact carboxy-terminal domains (the region binding on to the glycoprotein complex). The enormous heterogeneity of severity seen among BMD patients relates to the varied partial structural abnormalities possible in dystrophin, which in turn leads to reductions of variable degree and variable rate in the dystrophin associated glycoprotein complex. Thus more severe BMD patients may present clinically in early childhood and transition to wheelchair reliance in the late teens or twenties. Mild BMD may present initially in adulthood with exercise intolerance or muscle cramps and these patients may maintain ambulatory skills into late adulthood. While determination of the quantity and molecular weight of dystrophin has substantially improved the early differentiation between BMD,

"outlier" DMD, and the more common and rapidly progressive DMD phenotype, one group of investigators found no clear correlation between abundance of dystrophin and clinical course within the BMD. Further analysis of the degree of abnormalities in the dystrophin associated glycoproteins in addition to dystrophin will likely prove useful in the prediction of disease course among DMD and BMD patients.

The Dystrophin Gene and Its Tissue Specific Expression:

The dystrophin gene is among the largest identified in the human genome. It makes up about 1 percent of the entire X chromosome and the coding sequence for the gene is made up of 79 exons, which are portions of DNA, which are read or transcribed. Variable gene expression leads to tissue specific dystrophin protein isoforms in skeletal muscle, cardiac muscle, smooth muscle and different regions of the brain. This tissue-specific expression explains the varied organ systems involved in the dystrophinopathies.

Identification of Dystrophin Mutations by Genomic DNA Analysis:

Mutations of the dystrophin gene can be either large rearrangements of DNA (deletions or duplications) or small mutations (e.g., single base changes or microdeletions). Current commercially available blood studies of the dystrophin gene utilize either polymerase chain reaction (PCR) techniques with primers constructed to amplify deletion-prone exons ("hotspots" which tend to be deleted) or by Southern blot analysis techniques using special cDNA probes for the dystrophin gene. Hotspots occur between exons 1 to 20 and 45 to 55. However, other exons may be involved. Large detectable gene ar-

rangements (deletions and duplications) account for about 70 percent of DMD cases and 85 percent of BMD cases. These cases show gene abnormalities on current commercially available DNA blood studies. Small mutations are technically difficult to detect because of the large size of the gene. These small mutations occur in about 30 percent of DMD cases and 15 percent of BMD cases and these cases have normal DNA blood studies. Much research is currently directed at developing techniques to identify small mutations. Currently a normal DNA blood test does not rule out either DMD or BMD.

Genotype-Phenotype Correlations in DMD and BMD: Currently DNA deletion/duplication information cannot definitively differentiate between DMD and BMD as there is no consistent correlation between the size or location of a deletion or duplication and severity of disease. The following correlations have been observed:

1) Frameshift mutations (a shift in mRNA translation reading by three nucleotides for each amino acid) result in premature termination of translation (protein construction). Frameshifting mutations typically lead to a shortened dystrophin molecule whose carboxy end is missing. Thus, dystrophin is not attached to the transmembrane glycoprotein complex and patients show a DMD pattern of progression.

2) Non-frameshifting mutations produce an internally deleted or endoduplicated dystrophin molecule (an extra amino acid sequence within the protein). These cases have less dystrophin deficiency, a preserved carboxy terminus on one end of their dystrophin, and a milder, more slowly progressive BMD disease course.

3) Non-frameshift deletions of the distal rod domain of dystrophin (that portion which does not attach to either intracellular actin or the dystrophin-associated glycoproteins) are associated with continued ambulation into the fifth decade and beyond. These patients show deletions involving exons 45 to 47, or 45 to 48, and may often show relatively high levels of dystrophin (40-70%).

4) Deletions of exons 48-49 in both DMD and BMD are correlated with more clinically evident cardiomyopathy and a statistical decrease in survival within the DMD cases.

5) A deletion isolated to the first muscle exon (exon 1) and the adjacent muscle promoter region may be associated with more severe cardiomyopathy and mild skeletal muscle involvement.

6) Frameshift mutations involving either deletions of exons 3 to 7 or exon 45 can result in variable severity (DMD, BMD, or "outlier" phenotype with 10-20% of normal dystrophin).

Genomic DNA analysis can confirm the presence of a dystrophinopathy in an affected individual, identify carrier status, and assist in the prenatal diagnosis of affected fetuses. However, prognostication of future clinical severity and differentiation of BMD from DMD cannot be currently determined solely from peripheral blood genomic DNA analysis.

Carrier Detection via mRNA Analysis: Carrier detection can usually be performed by a peripheral blood sample from patients, the potential carrier and other family members. Deletions of DNA in heterozygote female carriers are recognized by either a 50 percent reduction in band intensity in quantitative multiplex PCR analysis of genomic DNA or more commonly by analysis of altered mRNA transcripts from periph-

eral blood. If the above methods fail, carrier detection can be achieved by employing linkage analysis techniques.

Immunoblot Analysis of Muscle Tissue: The diagnosis of DMD or BMD can usually be confirmed or excluded by assay of the dystrophin protein in a muscle sample using immunoblotting techniques. Less than 3% dystrophin is associated with a DMD disease course; 3-20% is associated with an "outlier" DMD or severe BMD disease course; either 20-80% quantity or normal quantity and abnormal structure dystrophin is associated with variable BMD disease courses. The carbon-terminal antibody discriminates best between BMD and DMD, but tends to underestimate the amount of residual dystrophin. The immunoblot analysis is not 100% accurate, as approximately 5% of all severe BMD patients will show absent or severely reduced dystrophin.

Immunostaining of Muscle Tissue: Fluorescent immunostaining analysis is a qualitative technique that is reliable for nearly all cases of DMD. It is less reliable than quantitative immunoblot analysis for the diagnosis of BMD. Symptomatic female DMD and BMD carriers have been identified using immunostaining analysis of muscle biopsy specimens. This technique has rarely identified asymptomatic female carriers without weakness or muscle cramps.

Diagnostic Approach to DMD and BMD: While nearly all DMD patients develop observable clinical symptoms by 5-6 years of age, 80% of severe BMD patients are symptomatic by 6-7 years and over 20% of BMD patient have observable symptoms prior to age 5. Thus there is some overlap in age of presentation for DMD and severe BMD. Differentiation of DMD versus severe BMD often necessitates further diagnostic testing unless a family history for DMD or BMD exists. If affected family members did not have diagnostic confirmation by gene or dystrophin analysis, then further studies are warranted for the affected patient.

Peripheral blood genomic DNA analysis may provide confirmation of a dystrophinopathy in an affected individual in 70% of DMD cases and 85% of BMD cases. More definitive determination of DMD versus BMD requires that a muscle biopsy specimen be analyzed for dystrophin quantity and structure using immunoblot analysis. In rare instances patients with DMD may have an essentially normal quantity of dystrophin that is lacking primarily the carboxy terminus. Approximately 5% of BMD patients lack dystrophin on immunoblot analysis. Thus, clinical correlation is required for diagnosis.

Table 2. Dystrophin & Dystrophin Related Proteins in DMD and BMD

Phenotype	Dystrophin	Dystrophin Associated Proteins
Normal	+	+
DMD	-	Severe reduction
DMD	+ (Lacking C-terminal domains)	Severe reduction
BMD	Reduced and/or patchy amount	Reduced and/or patchy amount

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CURRENT RESEARCH

Muscular Dystrophy Association Research Meeting

Translating Basic Research into Clinical Strategies was the subject of a meeting held by the Muscular Dystrophy Association (MDA) in Tuscon, AZ November 17 through November 19, 2005. Attending the meeting were more than 200 MDA supported clinicians and scientists. Steve Wilton, H. Lee Sweeny and Jeffrey Chamberlain presented their work, each using a different approach to overcome the genetic problems that are found in Duchene muscular dystrophy.

- Dr. Wilton presented information on a technique called *exon skipping* which allows the cell to ignore DNA where errors are found during the production of the protein, dystrophin.
- Dr. Sweeny described work that used a method called *stop-codon read through* that works to prevent the formation of dystrophin molecules that are too short and, therefore, do not function as normal dystrophin does.

- Dr. Chamberlain used a method to insert “mini” dystrophin genes into the muscles in order to allow the muscles to produce a shortened form of dystrophin that did ease the symptoms of DMD.

For the report of this meeting and these studies go to the web site of the Muscular Dystrophy Association. http://www.mdaua.org/research/051208clinic_director_conf.html

The MDA has more detailed information on the techniques used in the above studies in its publication “Quest”. “Bridge over Troubled Waters” (<http://mdausa.org/publications/Quest/q121genetherapy.cfm>) in the Jan/Feb 2005 issue and “Changing the Code” (http://mdausa.org/publications/Quest/q122changing_code.cfm) in the March/April 2005 issue give excellent descriptions of the methods used.

Corticosteroid Use and Duchenne Muscular Dystrophy

The American Academy of Neurology (AAN) recently released a report on the use of corticosteroids (prednisone or deflazacort) in Duchenne muscular dystrophy (DMD). In a review of relevant literature published from 1966 to 2004 the group concluded that corticosteroids provide a benefit in DMD, but that there are drawbacks to their use. Pred-

nisone and deflazacort were included in the studies, but there is not a comparison of the two drugs. A summary of the report with recommendations and a discussion of the drawbacks to this treatment is on the website of the Muscular Dystrophy Assoc. (www.mdaua.com). The original paper is published in Neurology, 2005, 65, Jan (1 of 2)13-20.

The Cochrane Collaborative has published a review of the literature from January 1966 to October 2003 with a meta analysis of high quality clinical trials. The conclusion reached was that glucocorticoid corticosteroids significantly improve muscle strength and function in the short-term (six months to two years)

in DMD. Of the dose regimes tried, prednisolone 0.75 mg/kg/day is probably the most effective. This is in agreement with the recommendation of The American Academy of Neurology. The Cochrane review is in The Cochrane Library 2005, Issue 3 (www.thecochranelibrary.com).

Cardiac Improvement in Muscular Dystrophy

Both Duchenne and Becker muscular dystrophies are frequently associated with dilated cardiomyopathy (DCM) which leads to premature death. A recent study of 62 boys with DMD and 7 with BMD found that early diagnosis and treatment of the DCM with ACE inhibitors improved the course of the disorder. The average age of the first detectable abnormalities was 15.4. Treatment was begun at the first sign of abnormality. This preliminary study

suggests that a larger study to evaluate the early, even pre-symptomatic (as early as 8 or 10 years of age), use of ACE inhibitors is warranted. Further details of the study can be found on the web site of the Muscular Dystrophy Association (http://mdausa.org/research/051115dmd_bmd_cardiac.html). The original research is reported in the journal *Circulation*, 2005, Nov 1;112 (18):2799-804.

A retrospective study on the effect of steroid therapy on cardiac function examined echocardiograms performed from 1997 to 2004 for 111 subjects under 21 years of age (29 received prednisone and 19 received deflazacort). The findings suggested that the progressive decline in cardiac function of subjects

with DMD can be altered by steroid treatment and that the effect appears to be sustained beyond the duration of treatment. There was no difference between prednisone and deflazacort in the subgroups. *Pediatr Cardiol*. 2005 Jul 4 (epub ahead of print).

Osteoporosis

A common complication of DMD is a risk of bone fractures (20-25% of boys) and with glucocorticoid therapy, a risk of vertebral fracture. In 2004 two international workshops were organized to study the problem of osteoporosis in DMD. Experts in orthopedics, genetics, endocrinology, nutrition and rehabilitation met to review what is known about the prevalence and cause of bone fragility and to propose future directions for treatment. The two conferences, one in Birmingham, England (*Neuromusc Disord*. 2005, Jan;15(1)72-9) and the other in Cincinnati, Ohio (*Neuromusc Disord*. 2005, Jan;15(1)80-5) agreed on the need to address this problem. Weight-bearing physical activity, calcium intake and absorption, body mass and appropriate sex steroids and growth hormone are neces-

sary to maintain normal bone mass. The lack of exercise in DMD, vitamin D deficiency from lack of sun exposure and glucocorticoid therapy all threaten bone health in those with DMD. Both workshops concluded with a call to action to define the risk factors and the best treatment for osteoporosis in DMD. Monitoring various clinical and laboratory data and use of bone densitometry (DXA) every one or two years will provide information to begin evaluating the status of those with DMD. There must also be an agreement on the sites to be monitored by the DXA scans. If drugs (bisphosphonates) are to be administered, there must be an evaluation of their safety and efficacy in those with DMD through clinical trials. (*Neuromusc Disord*. 2005, Jan;15(1)86-7).

FOCUS

The focus section of the Newsletter for this RRTC Cycle emphasizes general management guidelines for neuromuscular diseases. Although their degree and severity or even occurrence can vary, the characteristics or complications of most of these disorders include the primary condition of progressive muscle weakness and atrophy and the secondary conditions of obesity or underweight, limb contractures, spine deformity, osteoporosis, pain, decreased pulmonary functions (restrictive lung disease), cardiac disorders and intellectual impairments.

Based on the World Health Organization classification of disablement, as applied to neuromuscular diseases, table below, impairment (body function), unless corrected or prevented, usually leads to activity limitation. This loss of

function, if not correctly managed, frequently results in participation restriction and reduced quality of life.

Although not strictly speaking a treatment modality, it is clear that proper treatment often depends on precise diagnosis. The addition of the utility of DNA and muscle biopsy analysis for genetic counseling purposes, it is now becoming clear that different diagnoses may carry specific implications for management. For example, some types of limb-girdle dystrophies are rarely associated with respiratory or cardiac impairment (LGMD 2A and 2B) while in LGMD 1B cardiac involvement is invariable and respiratory impairment is also common. Therefore, the following publications regarding diagnosis are included on the RRTC web site.

- C. M. McDonald: Clinical Approach to the Diagnostic Evaluation of Progressive Neuromuscular Diseases. Physical Medicine & Rehabilitation Clinics of North America, 1998. Reprinted by permission of W.S. Saunders Co.
- Genetic Inheritance Patterns. RRTC position paper
- P. F. Chance, et al: Molecular Basis of Neuromuscular Diseases. Physical Medicine and Rehabilitation Clinics of North America. 1998. Reprinted by permission of W. B. Saunders Co.

A link to the above references is : <http://www.nmdinfo.net/newsletter3.htm#focus>

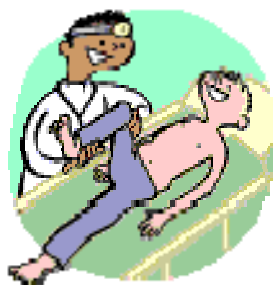
Table 3. on the following page gives a summary of the ways that NMD affect various body systems and their functions.

NIH Action Plan for Muscular Dystrophies

The Muscular Dystrophy Coordinating Committee Scientific Working Group (MDCCSWC), of which Dr. Craig McDonald of the RRTC-NMD was a part, was formed in 2005 and charged with developing recommendations for specific Research Objectives for the muscular dystrophies. The focus of the MDCCSWC was to identify scientific opportunities in the areas of disease mechanisms, diagnosis and screening, therapy, living with muscular dystrophy, and research infrastructure. This "Action Plan for the Muscular Dystrophies" (http://www.ninds.nih.gov/find_people/groups/mdcc/MDCC_Action_Plan.pdf or .doc) was designed to specifically identify currently feasible, high-priority Research Objectives that could be used by the Muscular Dystrophy Coordinating Committee and the muscular dystrophy scientific community to coordinate research activities in order to achieve the goal of timely detection, diagnosis, treatment, and prevention of all of the muscular dystrophies.

Table 3. Effect of Neuromuscular Diseases on Body Systems

BODY STRUCTURE	BODY FUNCTION (IMPAIRMENT)	ACTIVITY LIMITATION (FUNCTION)	PARTICIPATION RESTRICTION
Skeletal muscle	↓ Functional muscle mass ↑ Skeletal muscle fibrosis ↓ Strength ↓ Endurance ↑ Fatigue	↓ Mobility (walking, running, wheeling) ↓ Upper extremity tasks (reaching, throwing)	↓ Educational opportunities ↓ Employment opportunities ↓ Community integration ↓ Socialization ↓ Family functioning ↓ Recreation ↓ Quality of life
Body Composition	↑ Body fat & obesity ↓ Lean tissue	↓ Fine motor tasks (writing, typing, object manipulation)	
Bone & joint	↑ Joint Contractures ↑ Spine Deformity ↑ Osteoporosis ↑ Fractures ↑ Pain	↓ Self care & ADLs	
Lungs	↑ Restrictive Lung Disease ↓ Pulmonary function ↓ Cough/pulmonary toilet	↓ Communication ↓ Ability to undertake tasks	
Heart	↑ Cardiomyopathy ↑ Conduction defects ↓ Cardiopulmonary capacity	↓ Learning & applying knowledge	
Gastro Intestinal & Nutrition	↑ Dysphagia ↑ Constipation ↑ Cachexia (late onset)	↓ Psychosocial adjustment	
CNS	↓ Mental functions ↓ Intellectual capacity		



Duchenne Muscular Dystrophy Study

This Rehabilitation Research Center for the Study of Neuromuscular Diseases at the University of California, Davis, in partnership with the Center for Genetic Medicine at Children's Hospital in Washington D.C., is conducting a study of persons with Duchenne muscular dystrophy (DMD). This five-year study will document the natural course of the disease. It will collect the information that doctors usually acquire during routine examinations and use it to provide a picture of the abilities and impairments of those with DMD as the disease progresses. A study such as this has not been conducted since the 1980s. With improvements in clinical care in the last

15 – 20 years and advances in genetic analysis it is necessary to conduct another study that will update the documentation of the natural history of DMD. A second part of the study will examine the composition of the gene that is responsible for controlling the production of the dystrophin protein, the protein that is abnormal or lacking in DMD. With the genetic information that is available today, it will be possible to see if particular genetic abnormalities (single nucleotide polymorphisms) can be related to response to treatment or to particular characteristics of the disease progression.

For further information on this study visit the web site of the University of California, Davis Center for the Study of Neuromuscular Diseases (RRTC/NMD)

<http://www.nmdinfo.net/rrtc/clinicalstudies/>

or contact Ted Abresch at UC Davis, tabresch@ucdavis.edu.

The web site of Children's Hospital in Washington, D.C. also has information.

<http://www.cinrgresearch.org/UCD0305.shtml>,

The other partners in the cooperative International Neuromuscular Research Group (CINRG) will be accepting patients into this study in the future. Keep your eye on the UC Davis RRTC web site or the CINRG web site for announcement of their participation in this study.

Other Clinical Studies

Other clinical trials being conducted by CINRG are listed on their web site:

http://www.cinrgresearch.org/Genetic_research_muscular_dystrophy.shtml

For a listing of further clinical trials currently in progress for Duchenne and Becker muscular dystrophy, go to the <http://www.clinicaltrials.gov> web site. In the search window enter the name of the disease for which you are interested in finding trials. Click on the name of the trial that interests you and you will find details on the location of the trial, the qualifications for participation and who to contact for further information.

There is currently a Phase I/II clinical trial that is open for participation by those with Becker muscular dystrophy (also, facioscapulohumeral and limb girdle muscular dystrophies). This trial is to test the safety of an experimental compound, MYO-029, that looked promising in promoting muscle growth in mouse studies. It will now be tested for safety in patients.

Resources

Duchenne and Becker Muscular Dystrophy

Parent Project Muscular Dystrophy is a not-for-profit organization founded in 1994 by parents of children with Duchenne and Becker Muscular Dystrophy with primary goals to identify, fund and disseminate information about promising Duchenne and Becker MD research and to ensure that all affected by DMD have access to state-of-the-art information about treatment and care options for children with DMD and BMD.

Parent Project Muscular Dystrophy
1012 North University Boulevard
Middletown, Ohio 45042

Tel: 513-424-0696 800-714-5437
Fax: 513-425-9907
e-mail: pat@parentproject.org
Web site: www.parentprojectmd.org

MedlinePlus is a National Library of Medicine and National Institutes of Health web site that contains extensive information about individual diseases and is an excellent resource for a broad array of health and medical information. It contains Internet links to many valuable web sites.

Medline Plus information on Duchenne dystrophy:

<http://www.nlm.nih.gov/medlineplus/ency/article/000705.htm>

Medline Plus information on Becker's dystrophy:

<http://www.nlm.nih.gov/medlineplus/ency/article/000706.htm>

General Neuromuscular Disease Information

The **Muscular Dystrophy Association** is a voluntary health agency — a dedicated partnership between scientists and concerned citizens aimed at conquering neuromuscular diseases that affect more than a million Americans. MDA combats neuromuscular diseases through programs of worldwide research, comprehensive medical and community services, and far-reaching professional and public health education.

Muscular Dystrophy Association
3300 E. Sunrise Drive
Tucson, AZ 85718
800-572-1717, Fax: 520-529-5454

www.mdausa.org (U.S.)
www.muscle.ca/ (Canada)
www.mda.org.au (Australia)
www.muscular-dystrophy.org (England)
www.mdi.ie (Ireland)

The mission of the **Muscular Dystrophy Family Foundation** is to fund adaptive equipment. From wheelchairs to van lifts to communication devices and beyond, they can help get the equipment needed to live with No Boundaries®.

Muscular Dystrophy Family Foundation
2330 North Meridian Street
Indianapolis, IN 46208
mdff@mdff.org

Tel: 317-923-6333 800-544-1213
Fax: 317-923-6334
<http://www.mdff.org/>

Resources (cont.)

Neuromuscular Disease Center, Washington University, St. Louis, MO is a good web site with detailed information on genetic, clinical and pathological characteristics of neuromuscular diseases.

Neuromuscular Division
Box 8111-Neurology
660 South Euclid Avenue
Saint Louis, MO 63110

Phone: 314-362-6981
Fax: 314-362-3752
www.neuro.wustl.edu/neuromuscular

National Organization for Rare Disorders (NORD), a 501(c)3 organization, is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service. Information on more than 1150 rare diseases.

55 Kenosia Avenue
PO Box 1968
Danbury, CT 06813-1968

Phone: (203) 744-0100 or-
phan@rarediseases.org
<http://www.rarediseases.org/>

ABLEDATA is a web site with a database, sponsored by the National Institute on Disability Rehabilitation and Research, that contains information on thousands of assistive technology products. Each product contains a detailed description (including price).

ABLEDATA
30 Fenton Street, Suite 930
Silver Spring, MD 20910

1-800-227-0216
<http://www.abledata.com>

The **National Institute on Disability and Rehabilitation Research (NIDRR)** provides leadership and support for a comprehensive program of research related to the rehabilitation of individuals with disabilities. All of our programmatic efforts are aimed at improving the lives of individuals with disabilities from birth through adulthood.

National Institute on Disability
and Rehabilitation Research
U.S. Department of Education
400 Maryland Avenue, S.W.
Washington, DC 20202-2572

Voice/TTY : (202) 245-7640
<http://www.ed.gov/about/offices/list/osers/nidrr/index.html?src=mr>

Gene Tests A publicly funded medical genetics information resource developed for physicians, other healthcare providers, and researchers, available at no cost to all interested persons.

University of Washington
Seattle, WA

<http://genetests.org>

RRTC in the NEWS

Two people associated with the RRTC on Neuromuscular Diseases at the University of California, Davis were in the news in the fall of 2005.

The first was Amanda Smith, a recent high school graduate, who spent a week of her summer break as a counselor at the annual camp sponsored by the Muscular Dystrophy Association (MDA) in Susanville, California. The cover story of the September 4, 2005 edition of Parade magazine featured a photograph of Amanda and nine year old Caitlin Cox, the camper she assisted for the week. Amanda's mother, Wendee Smith is the Grants Administrator of the Rehabilitation Research and Training Center funded by the National Institute on Disability and Rehabilitation Research at UC Davis. This was the second summer that Amanda volunteered as a counselor at the camp. Her experience at the camp contributed toward her choice of a career and will serve her well as she goes off to the University of Washington in Seattle to pursue a career in nursing. The cover and the article about the MDA camps can be found on the web at: http://archive.parade.com/2005/0904/0904_index.html

The second person associated with the RRTC who made the news is Fred Hess, a member of the Advisory Committee. The following is an excerpt from a press release describing Fred's ambitious undertaking.

Disabled Sailor Plots Course to Italy for World Championship Regatta

Although he served as an officer in the Air Force, Fred Hess embodies a Marine Corps injunction: "Improvise! Adapt! Overcome!" The Stockton, California resident, who learned more than 20 years ago that he had muscular dystrophy, hasn't let his condition keep him from his passion for sailing. In October 2005, he competed in the Single Person Dinghy World Championship of the International Federation for Disabled Sailors.

Although Hess mounted his campaign under the auspices of the Stockton Sailing Club (<http://www.stocktonsc.org/>), the Tradewinds Foundation, a national nonprofit organization which has been sponsoring water safety and boating opportunities on both the East and West Coasts, also supported Hess. Any contributions to the campaign are tax deductible under Section 501(c)3 of the Internal Revenue Code.

Hess competed against approximately two dozen other disabled sailors from around the world in the open Mediterranean waters off San Felice Circeo, Italy which is south of Rome. The competition was held in Access Liberty dinghies. Although the boat is specially designed to allow people with very severe disabilities to sail solo, athletes with all levels of disabilities will be competing.

Information on the competition, the location, those participating and the results can be found on the Access Dinghy web site:

http://www.accessdinghy.org/2005sp_dinghyworlds/index.htm