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## Conclusion

# Consensus Conference Summary

## Role of Physical Activity and Exercise Training in Neuromuscular Diseases

**ABSTRACT**

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The objective of the State of the Science Roundtable conference was to provide a responsible assessment of the state of the science regarding exercise training and fatigue in humans and animals with neuromuscular diseases. The conference comprised a nonfederal, nonadvocate, 20-member panel that brought together exercise scientists, neuromuscular disease investigators, and clinicians during a 2½ day workshop. The literature was searched using MEDLINE, and an extensive bibliography of references was created. Experts in each area presented reviews based on this literature. Scientific evidence was given precedence over clinical anecdotal experience. After the presentations, the panel answered predefined questions and developed conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel presented a draft statement during the conference and produced this revised statement after the conference.

**Key Words:** Muscular Dystrophy, Resistive Exercise, Aerobic Exercise

**N**euromuscular diseases (NMD) may be acquired or hereditary and are a very heterogeneous group of disorders caused by an abnormality of the anterior horn cell, peripheral nerve, neuromuscular junction, or muscle. Clinical syndromes continue to be rapidly redefined by molecular genetic advances, which have shown marked genetic heterogeneity within specific disorders (Table 1). Most exercise training or fatigue investigations used individuals with the acquired disorders, amyotrophic lateral sclerosis (ALS) or postpolio syndrome (PPS), and the heredity disorders, Duchenne (DMD) and Becker muscular dystrophy, myotonic muscular dystrophy, facioscapulo-humeral muscular dystrophy, spinal muscular atrophy (SMA), hereditary motor sensory neuropathy, and limb-girdle muscular dystrophy (LGMD). Spinal muscular atrophy, hereditary motor sensory neuropathy, and LGMD are really syndromes. Gene loci have been identified for at least nine autosomal recessive and nine autosomal dominant types of LGMD,

six types of spinal muscular atrophy, and six subtypes of hereditary motor sensory neuropathy, types 1 and 2 alone. The resulting gene product has been found in most types.

In view of the many different genotypes, it should not be surprising to also have considerable variation in muscle pathology. Clinical profiles, however, depend more on the degree and rate of progression of the skeletal muscle weakness than on the pathologic profiles. For this reason, and because of the relative rarity of each disease, researchers have usually grouped disorders together when investigating adaptations to exercise training. DMD and ALS have marked weakness and are rapidly progressive. Becker muscular dystrophy, myotonic muscular dystrophy, facioscapulo-humeral muscular dystrophy, hereditary motor sensory neuropathy types 1 and 2, spinal muscular atrophy types 2 and 3, and most types of LGMD are usually slowly progressive, with mild to moderate weakness. Because of the lengthy gap between the recovery from the initial acute polio and the later development of new weakness, postpolio syndrome

has been considered as a separate NMD in most investigations.

The two types of exercise training programs used in all investigations were either low-resistive cardio-pulmonary aerobic protocols or resistive strengthening exercise interventions. Most programs were at submaximal, low-intensity training levels for a few months' duration. Strengthening protocols were usually dynamic and concentric.

In evaluating studies, the roles of associated impairments, fatigue, and deconditioning were also addressed. In individuals with NMD and progressive weakness, there is objective evidence of muscle fatigue in myotonic muscular dystrophy, ALS, and postpolio syndrome. The combination of severe fatigue and weakness has, for example, prevented exercise interventions in individuals with ALS. Since individuals with NMD apparently represent a sedentary population, the resulting deconditioning affects both aerobic capacity and muscle strength. Thus, any response to exercise training may include a training effect on the atrophied muscle fibers.

**TABLE 1**

*Genotypes of some hereditary neuromuscular diseases with known gene products*

Disease	Inheritance	Gene Location	Affected Gene Product
Duchenne & Becker dystrophy	x-linked recessive	Xp21.2	Dystrophin and dystrophin-related proteins
Limb-girdle dystrophy			
1A	Autosomal dominant	5q22-q34	Myotilin
1B	Autosomal dominant	1q11-21	Lamin A/C
1C	Autosomal dominant	3p25	Caveolin-3
2A	Autosomal recessive	15q5.1-q21.1	Calpain-3
2B	Autosomal recessive	2p13	Dysferlin
2C	Autosomal recessive	13q12	$\gamma$ -sarcoglycan
2D	Autosomal recessive	17q12-q21.33	$\alpha$ -sarcoglycan
2E	Autosomal recessive	4q12	$\beta$ -sarcoglycan
2F	Autosomal recessive	5q33-q34	$\Delta$ -sarcoglycan
2G	Autosomal recessive	17q11-q12	Telethonin
2I	Autosomal recessive	19q-13.3	Fukutin
Myotonic dystrophy type 1	Autosomal dominant	19q13	Myotonin protein kinase
Hereditary motor sensory neuropathy			
CMT 1a	Autosomal dominant	17p11.2	Peripheral myelin protein P22
CMT 1b	Autosomal dominant	1q21-23	Peripheral myelin protein PO
Spinal muscular atrophy Kugelberg-Welander type	Autosomal dominant	5q11-q13	Survival motor neuron protein

**Quality of the Evidence.** The sources for evidence in individuals with NMD were very limited in both quantity and quality. There were only a few randomized controlled trials, and these were small in subject size. The evidence was mostly from outcomes of uncontrolled and nonrandomized trials and observational studies. Judgment, therefore, was primarily based on the consensus of the expert review panel.

In most exercise training studies, different types of NMD were considered as a single homogeneous disorder. The natural course of each disorder was usually ignored in terms of severity and rate of progression of weakness. There were marked variations in research design and measurement methodology. Most exercise training programs were nonsupervised home protocols of relatively short duration. Different types of exercise were used at various durations. Most studies used submaximal exercise training levels. Opposite nonexercised muscles were frequently used as controls in strengthening training interventions. The problem with this study design is that there is a confounding crossover training effect in the nonexercised control muscle. There was no attempt to determine if functional performance, the ultimate goal of any intervention, was affected by the training. The roles of neural adaptation and disuse secondary to a sedentary lifestyle were not addressed.

Muscle fatigue studies were primarily limited to evaluations of possible fatigue sites in a few diseases. There was considerable variation in fatigue-testing procedures and definitions of fatigue. Muscle fatigue and muscle endurance were considered to be synonymous in some studies, but in others, they were treated as separate measurements. Weakness and fatigue were sometimes confused.

In comparison with data from individuals with NMD, the quality of the evidence is excellent in nondisabled humans. There are many high-

quality, well controlled studies that have examined responses and adaptations at the organ system and cellular levels. In addition, there is good agreement between animal and human studies, and both exhibit similar types of tissue plasticity in response to conditioning and deconditioning.

**Adaptations to Strengthening Exercise Training.** The limited data available suggests that adaptations of the muscles of individuals with NMD to resistive strengthening exercise depend on the duration and intensity of the training and the stage of the disease. It has been shown that low-intensity training of a few months' duration increases strength in individuals with slowly progressive NMD and PPS if their weakness is not severe. These modest strength gains are especially evident in the early part of the training period. Although it has not been studied, increases in strength may be the result of neural adaptations or strengthening of muscles that have undergone disuse atrophy. In contrast to the modest strength gains observed in individuals with slowly progressive NMD, there is no convincing evidence that resistance training increases strength in those with rapidly progressive NMD such as DMD. In these individuals, however, exercise may briefly slow the anticipated progression of weakness. The relationship between initial strength and trainability indicates that the response to the training is poor in very weak muscles, regardless of the rate of progression of the disease.

Although there is no hard evidence that low- or moderate-intensity resistive exercise increases muscle weakness, some investigations have suggested that high-intensity resistance training may result in a reduction in strength. Since the exercise training programs were of short duration, it is unlikely that any decrease in strength secondary to accelerated muscle fiber degeneration

was due to overuse weakness. This poorly defined condition, reported in individuals with PPS and facioscapulothoracic muscular dystrophy, is associated with long-term sustained physical activity and not short-term exercise interventions. Significant decreases in strength from very high-intensity eccentric resistive exercise might, however, be related to contraction-induced muscle fiber injury, especially in muscles with advanced fiber degeneration. In intact skeletal muscle, the injury and rapid repair cycle observed in contraction-induced muscle injury experiments is considered to be a normal adaptation to increased utilization and stress production. However, if the extent of damage in diseased muscle is higher than in normal muscle, the balance between injury and repair may shift toward the former by lowering the threshold for repair and regenerative capacity.

**Responses to Cardiopulmonary Exercise Testing and Adaptations to Aerobic Exercise Training.** In the few studies reported, regardless of differences in methodology or the type of NMD, results during exercise testing showed significant impairment in cardiopulmonary measurements such as reduced oxygen uptake ( $VO_{2max}$ ), reduced work capacity, reduced endurance, decreased pulmonary ventilation, and decreased cardiac output. Testing was usually submaximal since weakness of lower limb muscles or fatigue frequently prevented exercise at the levels needed for maximal cardiopulmonary workloads. Although the data were limited, there was a correlation between leg strength and  $VO_{2max}$  in some investigations. This, of course, does not necessarily demonstrate a cause-and-effect relationship.

In some training studies,  $VO_{2max}$  and work capacity significantly increased, whereas there was no increase in leg strength. Many factors influence  $VO_{2max}$  and work capacity. These include the quantity of muscle

mass activated, the mode of exercise, body composition, sex, age, and the state of training at the time of measurement. Studies of aerobic exercise training, which were limited to individuals with slowly progressive NMD and PPS, were submaximal and of short duration. Regardless, cardiopulmonary adaptations, such as increases in  $VO_{2max}$ , were qualitatively similar to the adaptations observed in nontrained able-bodied controls.

**Role of Deconditioning on the Responses to Exercise Testing and the Training Effect.** Individuals with NMD represent a very sedentary and deconditioned population. Both total activity-associated energy expenditure and the ability to perform high-intensity physical activity for long durations are limited. A deconditioned state, such as that resulting from bed rest, has a profound effect on cardiopulmonary function and the muscle fibers in able-bodied individuals. Sedentary individuals have muscle fiber atrophy and decreased strength and reduced  $VO_{2max}$ , work capacity, and resting energy expenditure compared with active able-bodied individuals. They also have a greater age-related rate of decline in cardiopulmonary function and muscle mass.

Responses to cardiopulmonary exercise testing in individuals with NMD, and adaptations to aerobic training, are similar to those observed in sedentary, poorly conditioned, able-bodied individuals. Impairments in cardiopulmonary performance are probably due to both the disease and deconditioned state. It is also likely that the reduction in muscle mass in individuals with NMD is the result of both muscle fiber atrophy secondary to a sedentary life style and muscle fiber degeneration secondary to the disease. Therefore, strength increases in resistive training may be due, at least in part, to the training effect on the deconditioned and atrophied muscle fibers.

### **Role of Muscle Fatigue and Endurance in Limiting Physical Activity.**

Patients often state that their physical activity is limited by fatigue rather than by weakness. It is frequently described as a disabling exhaustion after minimal physical activity. Separating fatigue and weakness is difficult since fatigue and exhaustion, as expressed by patients, are subjective symptoms and not an objective finding like weakness. In addition, weakness and fatigue coexist in some NMDs, and the complex relationship between primary muscle fatigue from the NMD and secondary fatigue due to deconditioned muscles must be considered. Fatigue may result from prolonged endurance activity and from impairments at muscle, nerve, and central sites. As a measurable objective finding, muscle fatigue is usually defined as the loss of force output leading to a reduced performance output or the gradual linear loss of maximum force-generating capacity. Exhaustion is usually defined as when the target force can no longer be maintained at the required level.

The NMDs in which there is objective evidence of muscle fatigue include the metabolic myopathies, myasthenia gravis, the myotonic disorders, PPS, and ALS. Of these, ALS, myotonic muscular dystrophy, and PPS have significant and progressive weakness. If muscles are weak, they are forced to work at a higher percentage of their maximal strength to perform the same activity as a normal muscle. This will hasten the time of the muscle to fatigue and may be the source of fatigue in individuals with significant loss of muscle strength. There have only been a few studies regarding the effect of strengthening exercise training on muscle fatigue or endurance. In these investigations, the exercise training either had no effect or seemed to increase muscle endurance or reduce the fatigue.

**Future Areas of Research.** Since each NMD is relatively rare, multicenter investigations will be required to obtain a sufficient number of subjects to provide adequate statistical power to discern the effect of the exercise training. Study populations should be homogeneous, and diseases should not be grouped together. Treatment trials should be controlled and subjects randomized to an intervention or a control group. Control comparisons should be made using matched individuals with the same NMD. In addition to disease type, inclusion criteria should consider age, sex, physical activity level, degree of weakness, rates of progression of strength loss, reduction of cardiopulmonary capacity, and the presence of concomitant disorders.

Appropriate outcome measures should be specified in advance and not as midstudy additions. In addition to the usual measurements of fatigue, cardiopulmonary performance, and strength, outcome variables should include evaluations of functional performance and indicators of risk for chronic diseases such as high blood pressure, increased adiposity, and reduced bone density.

Intervention trials should be long enough to effect change given the type and intensity of the exercise protocol. To document the natural course of the disease, protocols should include adequate time for several preintervention and postintervention outcome measurements so that a comprehensive profile of rates of strength loss and rates of aerobic capacity changes can be obtained. Comparison of intervention results with rates of progression would be of greater value than the usual single preintervention and postintervention protocols. A review of past studies indicates that it is probably not realistic to expect significant increases in strength with moderate-intensity strength exercise training in individuals with continual progressive muscle fiber degeneration. Slowing the

rate of progression of weakness may be the best that can be expected.

Quantitative measurements and not manual muscle tests should be used to evaluate strength, especially dynamic concentric and eccentric measures. Whenever possible, strength changes due to psychological effects, disuse, and neural adaptations should be evaluated. Measurements of work capacity, strength, muscle mass, biomechanical efficiency and cardiopulmonary function should be standardized. Fatigue studies should compare whole-body fatigue and single-muscle fatigue. In these studies, parameters such as stimulation frequency, joint angle, and muscle length should be controlled. Variables should include maximum voluntary contraction, force production with both low- and high-frequency stimulation, determination of peak power, and recovery from fatigue.

The type of exercise training (concentric/eccentric, aerobic, static/dynamic strength), the intensity of training (submaximal/maximal), the frequency (sessions per week), duration (sets and repetitions per set in the case of strengthening exercise), and the rate of progression of the intensity of the training should be precisely defined. Home programs, when used, should be carefully supervised and should include a reliable record of compliance.

More comprehensive studies of individuals with specific NMD are needed. Because individual diseases are rare and generalizations regarding the exercise response for one disease may not be applicable to others, single-subject designs may be beneficial. Studies should also focus on a comprehensive battery of longitudinal measurements of small populations, as opposed to cross-sectional comparisons, with better understanding of the characteristics and progression of the diseases and the characteristics that remain unchanged with varying levels of physical activities. These studies should

include comprehensive measurements of the muscular system, sensory and motor systems, cardiopulmonary system, bone and connective tissue, hormonal responses, and neural and endocrine systems, using the same subject pool.

### **Exercise Training and Fatigue in Animal Models of NMDs**

In evaluating research of animal models, it should be recognized that investigations of exercise training, fatigue, and contraction-induced muscle injury had different purposes. The objective of studies on exercise training was primarily to evaluate its effect on function, muscle contractile properties, and muscle pathology. Most of the fatigue studies were designed to determine whether the fatigue responses of the animal models of NMD differed from their controls and to identify the sites of fatigue in each of the models. Typically, the primary objective of contraction-induced muscle injury experiments was to investigate the susceptibility of the muscle fiber membrane to injury. Most of these experiments attempted to elicit injury in the dystrophin-deficient muscle of the *mdx* mouse by either running the animals to exhaustion, by subjecting the animals to high-frequency electrical stimulation, or by increasing the load on the muscle through tenotomy of its synergistic muscles.

Some of the confusion that exists in the literature on the effect of exercise in animal models stems from the fact that there are several different animal models of NMD that have been utilized in these exercise experiments, and each of these has a different phenotype and genotype. Animal models of NMD subjected to various types of increased muscle activity include the cardiomyopathic hamster, the *dy/dy* mouse, the *mdx* mouse, and the CXMD dog. In all the models, fast-twitch muscle and type 2B fibers are the earliest and most severely affected. However, there is a

marked variation between the rodent models in organ system involvement and, of course, of the skeletal muscle fiber degeneration. The heart is more involved than skeletal muscle in the hamster, and the diaphragm is more severely involved than skeletal muscle in the *mdx* mouse. The peripheral nerves are also affected in the *dy/dy* mouse, which had the most severe and rapid muscle fiber degeneration. Skeletal muscle fiber degeneration in the *mdx* mouse is very mild, occurring primarily at 2–4 wk of age. The severity and progression of the muscle degeneration in the hamster and dog falls between that of the *dy/dy* and *mdx* mice. As a result of these differences, it is difficult to compare intervention results.

Although these animal models have the same genetic deficiencies as their human correlates (Table 2), their phenotypic expressions are quite different. For example, both the *mdx* mouse, the CXMD dog, and humans with DMD lack the subsarcolemmal protein dystrophin due to a defective or missing gene. Whereas in humans this results in progressive and severe fiber degeneration and replacement with fat and connective tissue, the *mdx* mice have a much milder response. In *mdx* mice, most of the skeletal muscle fibers undergo an acute bout of degeneration at 2–4 wk of age that is followed by rapid regeneration. After this regeneration, the *mdx* muscles are relatively stable, even though they have a continuous low level of degeneration and compensatory regeneration. However, the diaphragm of the *mdx* mouse displays continual fiber degeneration and some replacement with fat and connective tissue, as seen in the muscles of humans with DMD. Nevertheless, the *mdx* mice do not exhibit the severe and progressive clinical deterioration that is observed in DMD. Unlike the *mdx* mouse, the CXMD dog has progressive muscle fiber degeneration and replacement with fat

**TABLE 2***Genotypes of animal models of neuromuscular disease*

	<i>mdx</i> Mouse CXMD Dog	<i>dy/dy</i> Mouse	Hamster
Inheritance	x-linked recessive	Autosomal recessive	Autosomal recessive
Gene location	xp21.2	6q2	5q33-q34
Affected gene product	Dystrophin	Laminin $\alpha$ -2	$\delta$ -sarcoglycan
Model for human disease	Duchenne and Becker muscular dystrophy	Merosin-deficient type of congenital muscular dystrophy	One type of limb girdle muscular dystrophy

and connective tissue that is similar to DMD.

Phenotypic differences are also seen in the other animal models. Whereas both the dystrophic hamster and humans with LGMD lack normal  $\delta$ -sarcoglycan, the heart is more affected than the skeletal muscle in the dystrophic hamster, whereas only skeletal muscle is affected in LGMD. The 129 Rej *dy/dy* mouse, which was initially thought to be a model for DMD, was found to lack the gene for merosin and now serves as a model for one type of congenital muscular dystrophy. The *dy/dy* mouse has progressive muscle fiber degeneration that is more severe than that seen in humans with congenital muscular dystrophy, and the mouse also has peripheral nerve involvement. These phenotypic differences make it impossible to extrapolate experiments that examine the effect of exercise in animal models of NMD to humans. However, the models can be used to understand how exercise affects the pathophysiology of NMDs.

**Quality of the Evidence.** The difficulty in evaluating the results of the animal studies is the variety of animals, the variety of protocols used, and the various outcome measurements that were evaluated. Hence, judgment was primarily based on the consensus of the review panel. Regardless of the quality of the studies, there were a very limited number of experiments for each animal model within each type of study (exercise training, fatigue,

contraction-induced muscle injury). Outcome measurements differed between investigations. Some were contractile, others were histopathologic, and a few were metabolic. This, of course, further limited the number of studies available for comparison. Experiments were performed at various ages and, hence, at various stages of each disease. Therefore, different results might be expected even in one species. Muscles were evaluated by physiologic type (fast or slow twitch) based on fiber-type profiles, even though methods of fiber typing were not always reliable. Although there are a large number of high-quality, well controlled studies of normal animals examining the effects of exercise, comparisons are limited since the animal models of NMD are mice and most investigations on normal animals have been on other species.

In addition to the above general problems, exercise training experiments varied in intensity (submaximal, maximal), duration, and type. Almost all studies were limited to treadmill running, swimming, and voluntary wheel running. It is doubtful that the latter can be considered exercise training because it is actually "normal" rodent physical activity compared with a laboratory-imposed sedentary lifestyle. However, since the NMD population is generally sedentary, the voluntary wheel studies could be viewed as a method to evaluate the effect of an active life style on a sedentary model.

Most of the problems with fatigue studies are related to the use of different fatigue protocols, different muscle sizes or types, and experimental protocols at different temperatures. The variability of the results in contractile fatigue experiments in dystrophic animals has also been observed in normal rodents. Experiments were both in vitro and in situ, with marked differences in stimulus-related parameters, muscle size and type, and water bath or limb temperatures. Metabolic studies were primarily limited to the *mdx* mouse, and there were only a few investigations on adaptations to exercise training.

The major difficulty that limits comparisons in the contraction-induced muscle injury experiments was the extreme variability in the methods used to produce injury. In addition to the general problems described above, the cycles of fiber inflammation, regeneration, and repair that follow fiber degeneration in normal animals, and the effect of training on reducing the degree of degeneration, were not investigated.

The problems regarding the quality of the research described above apply only to animals with NMD. The quality of the evidence is excellent in normal animals. There is a large repository of high-quality, well controlled studies that have examined a variety of organ system, cellular and molecular adaptations, and responses. Studies have been conducted on several animal species. Tissue plasticity including fiber-type transformations and mito-

chondrial adaptations is similar in both humans and animals, although the time frame is often different and the magnitude of the adaptations to exercise is often less in humans than in animals.

**Adaptations to Exercise Training.** Regardless of species, the limited data available indicates that exercise training usually resulted in modest increases in total muscle contractile tension and size and a slight reduction in muscle fiber degeneration. These adaptations occurred mostly in slow-twitch muscle, probably because almost all experiments used aerobic running and swimming activities. Adaptations also typically occurred in younger animals or those not severely affected by the dystrophy. Decreases in muscle tension and increases in fiber necrosis sometimes occurred in fast-twitch muscle, especially in animals with marked muscle fiber degeneration. As in the human studies, outcomes seemed to be influenced by the severity of the weakness, the type of training, and the intensity of the exercise.

**Fatigue Responses and Adaptations.** Results of contractile fatigue-testing experiments were as variable as the many different types of fatigue protocols. However, based on in vitro studies, it seemed that both slow- and fast-twitch *dy/dy* mouse muscle had less fatigability (increased fatigue resistance) than normal control muscle. In the *mdx* mouse, most investigations showed that the fatigue response of the slow-twitch muscles was not different or was slightly less fatigable than that of the control animals. However, the fatigue results of the fast-twitch muscles were more variable. The results depended on the time of analysis of the fatigue measurement. In studies that examined the change in tension due to fatigue over time, the fast-twitch muscle fatigued much more rapidly during the first several minutes of the fatiguing protocol. However, at the end of

the protocol, when the tension produced was quite low compared with the initial tension, there was no difference between the *mdx* fast-twitch muscles and those of the controls. In most of the few exercise training experiments, fatigue resistance either slightly increased or showed no change after training. Metabolic studies have shown various nonspecific defects in energy metabolism.

**Responses in Contraction-Induced Experiments.** Regardless of the many methods used to produce injury, the purpose of most of these experiments was to investigate the susceptibility of the membrane of the dystrophin-deficient muscle of the *mdx* mouse. Slow- and fast-twitch muscles were subjected to static, dynamic concentric, or eccentric contractions, and the results were evaluated with contractile, histologic, or dye-penetration measurements. As in normal muscles, eccentric lengthening contractions resulted in greater injury than did static or concentric shortening contractions, and fast-twitch muscles were more affected than slow-twitch muscles. In most of the studies, there was a greater reduction in muscle tension, more necrosis, and greater dye penetration in *mdx* muscle when compared with normal control muscle.

**Future Areas of Research.** Future research first has to address the problems observed in past investigations. Comprehensive studies are needed in each of the three areas: exercise training, fatigue, and contraction-induced muscle injury. Research designs need to be standardized with similar outcome measurements. Studies should be designed to evaluate the effects of exercise on organ system, cellular, and molecular adaptations in short- and long-term experiments. The natural course of the disease in each animal model must be considered. In the *mdx* mouse, for example, experiments would be con-

ducted during the pre-necrotic stage, the necrotic phase, and the post-necrotic regeneration period. The entire animal, whole muscles, and single fibers should be evaluated. Exercise training protocols should be standardized as to intensity, duration, frequency, and type, with animals randomized to an exercise protocol or to a nonexercised control group. Normal animals, matched by age, should also be evaluated. In addition to skeletal muscles, outcomes should include measurements on the cardiopulmonary system, microvasculature, and exercise-hormone interactions. With high-repetitive training, concentric (uphill) and eccentric (downhill) running should be included. Resistive concentric and eccentric strengthening exercise methods need to be explored.

Fatigue and contraction-induced injury protocols should also be standardized. When this is done, the effect of training on fatigue can be addressed. The question of the relationship between contraction-induced injury and exercise training will not be answered until long-term experiments of contraction-induced injury in all animal models are conducted. Does the cycle of fiber necrosis, inflammation, regeneration, and repair occurring in normal animals also occur in the same way in animals with NMD? Is the threshold for regenerative capacity reduced? Does training affect the degree of necrosis resulting from the injury?

## Pathophysiology

One of the major limitations in determining the effects of exercise in NMD is that the pathophysiology of the major disorders is not understood well enough to produce a functional model of pathogenesis that is capable of providing a rational basis for therapeutic interventions. Although it is known that most of the dystrophies are genetic diseases that result in abnormal sarcolemma-associated proteins, such as dystrophin and the dys-

trophin-associated glycoproteins, the function of these proteins or the mechanisms by which their absence cause progressive muscle pathology is not understood. Without clearly understanding the pathogenesis of the disease, it is difficult to understand how the animal adapts to exercise.

Currently, there are five major theories of what causes the fiber degeneration in muscular dystrophy: (1) mechanical weakening of the sarcolemma, (2) inappropriate calcium influx, (3) aberrant cell signaling, (4) increased oxidative stress, and (5) recurrent muscle ischemia. Each of these mechanisms can be profoundly affected by eccentric and concentric, high-repetitive, or high-resistive exercise. Both structural evidence and physiologic investigations performed in vitro support the theory that muscles with abnormal sarcolemma-associated proteins are mechanically more susceptible to contraction-induced injury, especially as a response to eccentric exercise. Another possibility is that influx of intracellular calcium might trigger toxic or degradative pathways that lead to damage or death of the myofibers via apoptosis or necrosis. It is hypothesized that this influx may occur as a result of transient mechanical disruptions to the sarcolemma or through a calcium leak channel dysfunction that may be induced by calpain. However, it is not understood if abnormal calcium influx is a primary mechanism or simply a secondary phenomenon in a damaged muscle fiber that is about to undergo necrosis. There is a significant amount of indirect evidence that suggests that aberrant cell signaling may be responsible for the muscle pathophysiology seen in dystrophy. The sarcolemma-associated proteins have a number of characteristics, including ecto-adenosine triphosphatase activity, calmodulin-binding domains, and ability to be phosphorylated, which makes them good candidates for cell-signaling

functions. These functions could be involved in mechano-transduction, or they could be involved in the regulation of calcium- and sodium-channel activity. Oxidative stress has recently been implicated as both a primary and secondary mechanism of the pathology seen in muscular dystrophy. It may occur from inflammatory reactions, may be produced through abnormal calcium influx, or may result from fatiguing muscle contractions. Another possible mechanism that might be responsible for the injury seen in muscular dystrophy is recurrent muscle ischemia. It has been shown that when *mdx* mice and individuals with DMD are subjected to repetitive muscle contractions in vivo, they have recurrent localized muscle ischemia that leads to muscle necrosis.

## CONCLUSION

Until we have a better understanding of the pathophysiology of the different NMDs, both in human and animal models, it will be difficult to understand the adaptation of muscles with abnormal sarcolemmal-associated proteins to different types of exercise regimens. Comprehensive studies of exercise and pathophysiology in the animal models of NMD will require a multidisciplinary, coordinated consortium of investigators, just as an understanding of NMD in humans will require the cooperation of a consortium of centers. Although the data are limited, the following exercise recommendations are suggested for individuals with NMD:

- Adopt an active lifestyle. The benefits of regular physical activities for the able-bodied population are well known and include improved strength and endurance for daily activities and the modification of risk factors for cardiovascular disease, obesity, osteoporosis, and mental health problems. The same benefits would apply to the seden-

tary and deconditioned NMD population. Physical activities include, and probably should emphasize, recreational and sport experiences in combination with an active daily lifestyle and proper nutrition. Physical activity should be viewed as a way of improving quality of life and not just a tedious and exhausting set of exercises. The objectives of specific exercise training programs should be directed toward the goal of improving functional performance and daily activities.

- Moderate-intensity (defined by frequency, load, and duration) resistive strengthening exercise programs may be recommended and will usually result in modest increases in strength if the weakness is not severe and the disease progression is relatively slow. High-intensity resistance exercise has not been shown to have an advantage over more moderate-intensity programs and should be avoided since animal studies have shown that eccentric exercise or high-intensity exercise may result in a decrease in strength.
- Moderate aerobic exercise training programs may be recommended without concern about any deleterious effect. Modest cardiopulmonary adaptations qualitatively similar to those found in able-bodied individuals may be expected. Treadmill and bicycle programs will usually be self-limited to submaximal workloads due to lower limb weakness. The importance of a modest improvement in aerobic capacity is not known because aerobic capacity seldom limits a person's ability to perform daily activities.
- Individuals with NMD will have a variable response to training depending on their degree of weakness, the rate of progression of their weakness, their fatigability, and their level of conditioning. Fatigue can sometimes be reduced by using brief work-rest-interval training programs.

## APPENDIX

*Attendees.* R. Ted Abresch, MS, University of California–Davis; Susan Aitkens, MS, University of California–Davis;

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