

Muscle Mutability

Part 2. Adaptation to Drugs, Metabolic Factors, and Aging

JULES M. ROTHSTEIN
and STEVEN J. ROSE

Muscle fibers undergo changes in response to a variety of stimuli. This review examines metabolic, endocrine, and pharmacological factors that lead to alterations in muscle structure and function. These various stimuli may be considered nonphysical. This review also examines the interaction between physical stimuli (eg, exercise) and hormonal influences (eg, diabetes) on muscle. It is suggested that physical stimuli may often have a more potent effect on muscle than do nonphysical stimuli.

Key Words: *Aging, Muscle mutability, Muscular atrophy, Muscular hypertrophy.*

Normal human muscle fibers (cells) respond to a variety of stimuli by undergoing changes that may be either adaptive or maladaptive, depending on the nature of the stimulus and the context in which it occurs. Elsewhere in this issue, maladaptive changes such as "stretch weakness" and cast-immobilization atrophy have been discussed. Examples of adaptive changes are discussed in this issue by Rose and Rothstein in their review of the effects of altered patterns of use on muscle. Although these adaptive and maladaptive changes in muscle cells are different because of their functional significance, the stimuli are fundamentally similar. Exercise, disuse, and maintained lengths (shortened or lengthened) all provide muscle with physical stimuli. And in each case, through mechanisms that are not yet understood, the muscle cell's biochemical machinery responds to that physical stimulus. Somehow these stimuli trigger a series of signals that lead to changes in muscle fiber size, enzymatic profile, and muscle length. Physical stimuli are among the most obvious factors that influence muscle, but there are other stimuli that can dramatically alter cellular structure and function. Systemic metabolic factors, endocrine influences, drugs, and aging all lead to alterations of muscle. This review will focus on these nonphysical stimuli. The interaction of physical stimuli, such as exercises for the aged, diabetic, or steroid treated patient, will also be discussed.

DRUGS

General Observations

Although physical therapists do not prescribe medications, they may be able to play a critical role in the management of patients with drug-induced muscle disorders. Many medications induce either focal or global changes in muscle.¹ Frequently the only treatment for drug-induced muscle disorders is discontinuing the medication before serious disability develops.¹ Therefore, the early recognition of drug-induced muscle disorders is critical. Patients usually will be referred to physical therapy because they have pain or weakness. However, therapists may observe during evaluation and treatment the superimposed effects of drugs. Therefore, the physical therapist may be in a unique position to observe the first clinical signs of drug-induced muscle dysfunction in their patients.

According to Mastaglia and Argov some of the early signs of drug-induced muscle disease include 1) muscle involvement that is usually widespread and symmetrical, 2) proximal muscle involvement that is the most severe, and 3) sparing of muscles innervated by the cranial nerves.^{1(p873)} Therapists should also be aware of the focal effects of drugs, which may be caused by intramuscular injections. This local damage may consist of muscle fibrosis leading to induration,

TABLE
Drug-Induced Myopathies and Clinical Features^a

Disorder	Drugs	Clinical Features
Focal myopathy	intramuscular injections	Local tissue damage
Muscle fibrosis and contractures	antibiotics, pethidine, pentazocine, heroin	Swelling and contractures of injected muscle
Toxic effects (a painful proximal myopathy)	clofibrate, EACA, emetine, heroin, ethanol (acute abuse) vincristine	Pain and tenderness, proximal or generalized weakness Same as above but with loss of reflexes
Hypokalemia (a painful proximal myopathy)	clofibrils, isoetherine, danazol, cimetidine, metolazone, bumetadine, lithium salbutamol, cytotoxics	Pain, cramps, myokymia, weakness
Inflammatory myopathy (a painful proximal myopathy)	diuretics, purgatives, liquorice carbenoxolone, amphotericin B	Periodic weakness with depressed or absent reflexes
Acute rhabdomyolysis	penicillamine, procainamide, levodopa heroin, methadone, amphetamine, barbiturates, diazepam, meprobamate, isoniazid, amphotericin B, phenformin/fenfluramine, carbenoxolone	Proximal muscle weakness and pain with possible skin changes Severe muscle pain, swelling, flaccid quadriparesis, areflexia
Chronic painless proximal myopathy	corticosteroids chloroquine, heroin, perhexline	Predominant proximal weakness Same as above but with possible loss of reflexes due to associated neuropathy
Myotonic syndrome	20, 25 diazacholesterol (and analogues) suxamethonium, propranolol, (possibly other beta blockers)	Muscle cramps, weakness, myotonia May increase symptoms of myotonia
Malignant hyperpyrexia	suxamethonium, halothane, diethyl ether, cyclopropane chloroform, methoxyflurane, ketamine, enflurane, psychotropics	Rigidity, hyperpyrexia, acidosis, hyperkalemia, disseminated intravascular coagulation, renal failure

^a From Mastaglia and Argov.¹

with the possibility of contractures developing after repeated injections.¹

Only two drugs that commonly affect muscle, alcohol and steroids, will be discussed here. An overview of medications and their potential effects is presented in the Table. A complete discussion of drug-induced muscle and nerve diseases is provided in the comprehensive review of Mastaglia and Argov.¹

Alcohol

The deleterious effects of alcohol abuse on muscle have been documented² and have long been associated with life-threatening cardiomyopathies.^{3,4} Although the first report describing the effects of chronic ethanol ingestion on skeletal muscle appeared in 1822,⁵ alcoholic myopathy has not always been widely recognized clinically.⁶⁻⁸ The myopathic changes seen in the alcoholic patient have at times been attributed to malnutrition or disuse. Experimental evidence has demonstrated that even with nutritional support and prophylactic exercise normal subjects can develop alcoholic myopathy if they ingest large amounts of ethanol.^{9,10} Alcoholic myopathy has two clinical

phases: an acutely painful presentation that follows "binges" and a chronic phase that consists of morphological and functional alterations in muscle.^{2, 6, 8-15}

Binges by chronic alcoholics can result in an acute myopathy characterized by muscle cramps, muscle weakness and tenderness, myoglobinuria, reduced muscle phosphorylase activity, and decreased lactate response to ischemic exercise.^{2,7} These last two findings are also seen in McArdle's disease, a genetic deficiency in muscle phosphorylase.⁷ In McArdle's disease, the phosphorylase deficiency results in an inability to use glycogen stores. Therefore, even under ischemic conditions, the muscle will not produce lactate (called a decreased lactate response).¹³ Acute alcoholic myopathy, unlike McArdle's disease, is reversible. The two are clinically different: in McArdle's disease exercise can lead to pain fatigue and even contractures¹³ but in acute alcoholic myopathy exercise will lead to pain but not contractures. Exercise is contraindicated in acute myopathy and, in fact, whenever myoglobinuria is present because it may stress already compromised muscles.

Acute alcoholic myopathy has morphological features, such as fiber necrosis, intracellular edema, hem-

orrhage, and inflammatory changes, that can be detected under a light microscope.² These features are in contrast with those of chronic alcoholic myopathy, which are observable only under electron microscopic examination: intracellular edema, lipid droplets, excessive glycogen deposition, deranged elements of the sarcoplasmic reticulum, and abnormal mitochondria.^{2, 8, 10} The cellular changes observed in chronic alcoholics may also be seen in nonalcoholic subjects after one month of ethanol ingestion (42% of total caloric intake).⁹ The subcellular effects of ethanol in the nonalcoholic subjects and in alcoholics could not be prevented by nutritional support or exercise (use of a bicycle ergometer twice daily).^{9, 10} However, in most cases abstinence from alcohol appeared to lead to a return of a relatively normal morphological picture within a short period of time.^{2, 8}

Experimental studies have demonstrated that alcohol abuse inhibits calcium binding within muscle cells, which is probably associated with the derangement of the sarcoplasmic reticulum and the decreased number and the abnormality of the mitochondria.^{16, 17} In the myocardium of dogs, this alteration in calcium binding leads to a shift (down and to the left) in the force-velocity relationship.¹⁶ Alcohol apparently interferes with the calcium-dependent process of excitation-contraction coupling.¹⁶ In addition, Rubin has reported disruption of both contractile and regulatory proteins in alcoholic myopathy.²

Type II fiber atrophy also has been reported to be a sequela of chronic alcohol abuse.¹⁸ Hanid et al have shown that in 10 men and 5 women who reported ethanol intake of at least 80 g/day, type II atrophy was almost always present in biopsy samples from the vastus lateralis muscle.¹⁸ The only subject in the group who did not have a type II atrophy was one man who had been drinking heavily for less than six months. Type II atrophy was determined by comparing the mean muscle fiber areas (as inferred from measures of lesser diameter fibers) of the alcoholics with those of nonalcoholic subjects. Hanid et al's findings are in agreement with the observation of Kiessling and co-workers, who showed decreased areas of fast-twitch, glycolytic fibers in 11 patients hospitalized for severe alcohol abuse.¹⁹ Recently it has been suggested that in alcoholics primarily the type IIB fibers undergo atrophy.⁸

Although Hanid et al's subjects showed type II atrophy, the degree of atrophy did not correlate with clinical findings. Muscle wasting was absent in four of the subjects, mild or moderate in nine, and severe in two. Only one patient complained of weakness, although "clinically apparent weakness" was seen in seven. In addition, the pathological changes seen in biopsy specimens of the liver of these patients did not correlate with the degree of type II atrophy observed. However, Hanid et al speculated that because glyco-

gen deposits were observed in the muscle of alcoholics the type II atrophy may represent a selective lesion of glycogenolytic pathways.¹⁸ Such a lesion would interfere with glycogen use, which would most likely have a greater effect on the glycogen-rich type II fibers.

Except for the contraindication for exercise in acute alcoholic myopathy, the role of exercise has not been elucidated in ethanol-induced myopathies. It appears that in many patients abstinence leads to full recovery of muscle function,^{2, 6} whereas in other patients the injury may be more severe and resistant to treatment. Rubin has noted that under certain circumstances, ethanol abuse may lead to decreased energy metabolism (interference with metabolic pathways and destruction of mitochondria) and decreased protein synthesis to the point where the cell may not be able to maintain itself.² He asserts that the critical unanswered question relative to alcoholic myopathy, therefore, "concerns the relation between reversible alcohol-induced inhibition of important functions and the persistent injury found after chronic ethanol intoxication."^{2(p 32)} Questions regarding the rehabilitation of the alcoholic also remain to be answered. There is a need to understand the effect of exercise on the "persistent injury" in view of the weakness and visible signs of atrophy frequently observed in chronic alcoholics. The presence of type II fiber atrophy suggests the possibility that alcoholic patients may exhibit specific deficits in muscle performance such as an inability to generate tension rapidly and to produce power. Therapists working with alcoholics will need to determine whether these deficits do exist and whether exercise can play a role in patient management.

Corticosteroids

The widespread use of oral corticosteroid agents as anti-inflammatory and immunosuppressant agents has led to the observation of "steroid myopathy," an apparently reversible proximal weakness.^{1, 11, 20-27} Although steroid myopathy is most often of iatrogenic origin, it also occurs as a component of hyperadrenocorticism (Cushing's syndrome).^{20, 28, 29} Muscle weakness has been noted in up to 83 percent of patients with endogenous overproduction of corticosteroids (Cushing's syndrome).³⁰⁻³²

The primary biopsy finding in patients treated with prednisone-like steroids (eg, prednisone, prednisolone, and methylprednisolone) is a type II fiber atrophy (decreased cross-sectional area).¹ This reduction in fiber area is thought to be most pronounced in the type IIB fibers²⁰ and is believed to occur more often in women than men.³³ In the rat, Stern and Hannapel reported that atrophy has also been demonstrated in the histologically fast intrafusal nuclear bag fibers.³⁴

Because routine light microscopic analysis of muscle from patients treated with prednisone-like steroids reveals little more than a type II atrophy, the term "steroid-induced atrophy" may be more appropriate than "steroid myopathy." In muscle of patients and animals treated with triamcinolone and other synthetic steroids, the changes noted are disruption of mitochondria and the sarcoplasmic reticulum^{20, 35-41} and altered contraction characteristics.⁴¹⁻⁴⁴ With the use of synthetic steroids, especially fluorinated compounds (eg, triamcinolone), morphological changes are not limited to the type II fibers. Synthetic steroids apparently cause more generalized or "myopathic" changes in muscle than do prednisone-like compounds. Not surprisingly, clinicians have observed greater weakness in patients when fluorinated (halogenated) steroids have been used.⁴⁵

In view of the limited systemic (oral) use of synthetic steroids in clinical practice today, steroid-treated patients will most likely exhibit steroid atrophy rather than myopathy. The difference between the effects of synthetic and prednisone-like compounds must be kept in mind when reading older clinical literature or examining experimental reports. Researchers investigating the effects of steroids on animal muscle still use fluorinated compounds or other synthetic steroids such as dexamethasone or betamethasone.

Based on the observations of corticosteroid-induced type II atrophy and other experimental findings, Goldberg developed a conceptual model that can be used to describe many forms of muscle mutability.^{46, 47} He believes that with catabolic stimuli it is the pattern of muscle fiber use that determines which fibers will undergo atrophy. He notes that corticosteroids are potent catabolic stimuli. Corticosteroids are gluconeogenic agents that lead to the mobilization of available substrate, including muscle proteins, for the synthesis of glucose by the liver.^{48, 49} The atrophy caused by prolonged use of corticosteroids occurs because protein synthesis cannot keep pace with protein degradation.^{47, 49-51} In normal muscle the two processes occur at the same rate, whereas in muscle that is undergoing hypertrophy, synthesis exceeds degradation.^{47, 52, 53} Goldberg believes the pattern of atrophy seen with Cushing's syndrome and steroid-induced weakness is the result of a biological phenomenon that can be generalized. Atrophy, he observed, occurs in type II fibers, which are the least used muscle fibers. Therefore, the pattern of use of a muscle determines whether it will undergo atrophy in response to catabolic stimuli.^{46, 47} He argues that it is biologically useful for the body to maintain the most used muscles and to sacrifice the least used muscles when protein stores are mobilized.^{46, 47}

The size principle of Henneman⁵⁴ and the observations of Burke⁵⁵ strongly support the idea that type

I fibers are the first recruited during normal voluntary movements. Goldberg believes that the constant use of the type I fibers provides these fibers with a protective or "sparing" influence from the catabolic effects of steroids.^{46, 47} The type II fiber atrophy seen in animals suffering from malnutrition⁵⁶ and in the cachectic cancer patient^{57, 58} can also be explained by Goldberg's hypothesis. In both cases, muscle proteins must be used as a source of metabolic substrate.

When type II atrophy is severe, fiber proportions may change to the extent that physiological properties of whole muscle may be altered, that is, the muscle may become slower.⁴⁶ In a group of patients with rheumatic diseases who had undergone long-term steroid therapy, the quadriceps femoris muscle produced less power than did that of control subjects matched by age and activity.⁵⁹ A reduction in the slopes of the patient's power velocity curves also was noted (as the speed of isokinetic contraction increased, their power deficits increased).

Gardiner et al have demonstrated that in rats treated with triamcinolone some of the deleterious effects of steroids can be lessened through the use of a weight-lifting program.⁶⁰ The observation that exercise can lessen the effects of steroids supports Goldberg's hypothesis and has potential clinical significance. At present, the only known cure for iatrogenically induced steroid atrophy is to modify the use of medication.²⁰ Stern and Fagan maintain that normal muscle function can be expected to return within a year or, more often, within several months after steroid use has been stopped.²⁰ However, given the vital role of steroids in the management of so many diseases, it is often impossible to eliminate the medication in order to treat the atrophy. Attempts at limiting atrophy by altering the type of steroid and the dose regimen and by adding antagonistic agents, such as phenytoin sodium, have not always been effective.²⁰ In view of Gardiner et al's findings, future research will have to determine whether exercises can be used clinically to minimize the effects of steroids. If Goldberg's hypothesis is true, then exercises that consistently bring about the recruitment of type II muscle fibers (as in power training or any maximal effort) might also provide these fibers with protection from corticosteroid-induced atrophy.

Anabolic (Androgenic) Steroids

It has been suggested in the popular literature that muscle bulk, and therefore strength, can be increased by administering anabolic (androgenic) steroids.⁶¹ However, despite several decades of experimentation there are almost no valid studies that demonstrate improved function in men as a result of anabolic steroid use. As Ryan has noted, it is not ethically permissible to examine whether anabolic-androgenic

steroids can improve muscle bulk and function in women.⁶¹ Therefore, it is unlikely that the effects of anabolic steroids in female athletes can be determined. The use of anabolic steroids by humans remains controversial, despite the evidence that they do not improve muscle function and despite rather strong policy statements advising against their use.⁶² A full discussion of this area is beyond the scope of this review; the reader should consult the recent reviews by Ryan⁶¹ and Wright⁶³ to obtain bibliographies.

ENDOCRINE AND METABOLIC FACTORS

General Discussion

Primary metabolic defects in muscle are discussed by Wheeler in this issue. Skeletal muscle also undergoes alterations in response to changes in the overall metabolic and hormonal profile of the organism. Endocrine and nutritional influences are among the critical determinants of the amount and quality (eg, fiber type and biochemistry) of skeletal muscle. To understand how these factors affect muscle, one must know the physiological basis for contraction and the distribution of ions, metabolites, and precursors. Therefore, it is impossible to really understand the interaction between muscle and the endocrine system without first understanding general physiology.

Muscle contains most of the body's protein stores, and the heat generated during oxidative phosphorylation and excitation-contraction coupling is a major source of thermal energy.^{64, 65} Normal function requires the appropriate ionic milieu—especially relative to calcium, magnesium, and potassium.^{65, 66} Therefore, almost all systemic events will have some effect on muscle, and in turn, muscle disorders can affect other organs, as in kidney dysfunction secondary to acute rhabdomyolysis (breakdown of muscle).¹ A complete discussion of the interaction between muscle and other body systems is beyond the scope of this article. Stern and Fagan²⁰ elaborate on many of the issues that will be discussed here.

During ontogenetic development, muscle increases in size (both in length and cross-sectional area).^{47, 67} Many factors have been implicated in the way this process has been mediated such as the pattern of use during growth, the tension applied by growing long bones, and hormonal influences.⁶⁷ During normal development, all of these factors combine in such a manner that muscle develops similarly in all members of a given species. The growth of muscle during development is different from the hypertrophy in exercised muscle, especially relative to the need for hormonal influences.^{47, 53} Apparently, the underlying mechanisms for growth and work-induced hypertrophy are different.

Insulin normally plays a critical role in regulating protein balance in muscle. Plasma insulin levels de-

termine whether muscle will take up amino acids or release them.^{49, 68} In the absence of insulin in plasma, muscle wasting can be observed.⁶⁸ Not surprisingly, studies in animals have demonstrated that muscle growth during development requires pituitary growth hormones and insulin.^{47, 53} However, neither of these hormones is required for exercise-induced hypertrophy.^{47, 53} Goldberg has demonstrated that following tenotomy of the gastrocnemius muscle of rats the synergists (plantaris and soleus muscles) will undergo compensatory hypertrophy regardless of whether growth hormone or insulin is present.⁴⁷ Exercise can be effective in increasing muscle mass without the supportive influences of these two hormones.

Goldberg has come to the conclusion that exercise is one of the most potent stimuli available for muscle hypertrophy—probably more potent than endocrine factors.^{47, 53} He finds support for this concept in experiments that have shown exercise-induced muscle hypertrophy in animals that were starving (and were therefore in negative nitrogen balance).⁶⁹ In humans and animals, a normal response to malnutrition is muscle atrophy because proteins are mobilized for nutritional support. Somehow exercise appears capable of overriding catabolic signals, and as a result, working muscle can actually show a net gain in weight despite starvation.⁴⁷ A normal function of the endocrine system is to govern the rates of protein synthesis (associated with hypertrophy) and degradation (associated with atrophy) so that homeostasis can be maintained. However, the effect of these circulating factors can be altered by the local pattern of use of a muscle. This observation would explain Gardiner et al's findings that exercise can lessen the atrophy that occurs after the use of corticosteroids, a known catabolic agent.⁶⁰

Theoretically, it would appear possible to generate a hierarchical list of stimuli and how they affect muscle. However, many questions remain to be answered, and not all stimuli have been identified and examined. Goldberg believes that when such a hierarchy can be established it is likely that exercise will be high on the list. Some of the characteristics of some of the stimuli appear to have been identified. When stimuli lead to atrophy because of the mobilization of proteins, a type II fiber atrophy seems likely.⁴⁷ This appears to be the case whether the stimulus is starvation, endogenous corticosteroids, or exogenous corticosteroids. Other atrophy-provoking stimuli, such as cast immobilization, result in less clear-cut changes in muscle. These changes may be reflected both in diminished sizes of fibers and in metabolic alterations (eg, enzyme profiles).

Insulin

As was noted previously, plasma levels of insulin are thought to be a primary determinant of whether

muscle cells will take up amino acids for eventual incorporation (during protein synthesis) or release amino acids.⁶⁸ Therefore, insulin is a critical regulatory factor in protein synthesis and degradation. Insulin also stimulates the use of glucose for metabolism.⁷⁰ Normal resting muscle primarily metabolizes ketones and fatty acids; however, when insulin levels rise, as occurs after a meal, glucose uptake is enhanced. A major physiological function of insulin in skeletal muscle is to facilitate the transfer of glucose across cell membranes. The clinical consequences of insulin deficiency are well-known. In the patient with uncontrolled diabetes, muscle fibers and other cells cannot take up glucose and serum glucose levels remain high. Cells then undergo what has been called "starvation in the midst of plenty."⁷⁰ This starvation leads to the mobilization of other metabolic sources, especially muscle proteins, for nutritional support. Atrophy may result.

Recently, exercise has been shown to affect the insulin receptors on cell membranes.^{71, 72} It appears that exercise enhances a cell's capacity to bind and use insulin for glucose transport. Although this effect has not been localized to muscle cells and is most often demonstrated in red blood cells, it also appears to take place in skeletal muscle.⁷³ In athletes it has been shown that insulin sensitivity is correlated with $\dot{V}O_{2max}$.⁷¹ Based on the observation of increased insulin sensitivity with exercise, several research groups are now examining the effects of exercise on patients with diabetes. Initial evidence indicates that graded exercise can be an adjunct to other forms of therapy for diabetics. This appears to be especially true for insulin-resistant diabetes.^{73, 74} Therefore, exercise will have most likely two obvious effects on patients with diabetes. Initially, during the exercise, more glucose will be used by exercising muscle. And as an effect of training, insulin sensitivity may be increased. Because both of these factors will facilitate the lowering of serum glucose levels (one acutely and the other chronically), careful dietary and medical management must be a component of exercise training programs for patients with diabetes.

Growth Hormone

Weakness is common in patients with acromegaly. Although this weakness frequently may be the result of compromised neuronal structures, a myopathy has also been identified in many of these patients.²⁰ Early in the development of acromegaly, increases in muscle bulk and strength may be observed.¹¹ However, as the disease progresses, weakness develops and biopsy specimens reveal variable myopathic changes in muscle. Although most authors report that these changes, which include segmental degeneration, occur in both major fiber types, Stern and colleagues have described

a preferential atrophy of type IIB fibers in a patient with acromegaly.⁷⁵ Deficient amounts of growth hormone during development lead to dwarfism and associated poor muscular development.¹¹

Thyroid Hormone

Thyrotoxicosis (hyperthyroidism) occurs more commonly in women than in men, but men more often show the proximal muscular weakness associated with this disease.²⁰ Engel has noted that the weakness seen clinically appears to be out of proportion with the visible atrophy.¹¹ There is general agreement that light microscopic analysis of thyrotoxic muscle reveals few changes other than atrophy of all fiber types.^{76, 77} Under an electron microscope a variety of changes may be observed: mitochondrial hypertrophy, focal loss of mitochondria, focal dilation of the T-tubular system, and subsarcolemmic glycogen deposits.^{78, 79} In addition to structural changes, physiological alterations have been seen that may relate to the muscle's ability to effectively generate tension. Hyperthyroid muscle shows a lower than normal resting membrane potential, decreased membrane excitability, and a large hyperpolarization with a resultant increased refractory period.⁸⁰⁻⁸³

Fitts and colleagues induced thyrotoxicosis in rats and observed biochemical, physiological, and histochemical alterations in the soleus muscle.⁸⁴ They found that there was an increase in the number of type II fibers, especially the type IIC. A smaller increase was observed in the type IIA fibers. There are too few type IIB fibers in rat soleus muscle to determine if thyrotoxicosis had an effect on type IIB distribution. They observed the following changes with thyrotoxicosis: 1) decreased contraction time, 2) decreased one-half relaxation time, 3) increased frequency required for tetanic fusion, 4) no change in peak isometric tension, and 5) no change in the isotonic velocity of shortening. The effect of thyrotoxicosis on the rat soleus muscle was to increase the number of type II fibers and to make that muscle physiologically more like a type II or "fast muscle." This observation of speeding up in hyperthyroidism can be contrasted with observations of prolonged contraction and relaxation times with hypothyroidism.⁸⁰

Successful treatment of thyrotoxicosis leads to full recovery of strength, according to several investigators²⁰; however, Ramsay reports that the visible signs of atrophy take longer to disappear.⁸⁵ The effect of exercise during the uncontrolled and recovery phases of thyrotoxicosis has not been reported.

Hypothyroidism leads to weakness in 30 to 40 percent of adult patients with this disease.⁸⁶ Biopsy findings in patients with hypothyroidism have been variable but usually include focal necrosis, variable fiber sizes, and increase in the number of central

nuclei.²⁰ Spiro et al reported atrophy of the type I fibers⁸⁷ but McKeran et al described a type II loss and atrophy.⁸⁸ The primary symptoms with the disease are pain, cramps, and sluggishness of movement.²⁰ McKeran et al have reported reversal of the atrophy but no reversal of fiber loss after two years of hormone replacement therapy.⁸⁸

Parathyroid Hormone

Hyperparathyroidism does not usually lead to weakness, but weakness can be expected to develop in up to 80 percent of patients if the disease remains untreated.^{11,20} When weakness does occur it is more pronounced in proximal muscles and appears first in the lower extremities.²⁰ The deficits may be so severe that major disturbances in gait are common (eg, wide base of support with slow movements). Patients may exhibit poor endurance and have difficulty climbing stairs, walking on toes and heels, and carrying heavy objects. Although the changes in biopsy specimens have been called nonspecific, there is some evidence of atrophy and some disagreement in the literature.²⁰ Patten et al reported a type II atrophy but observed signs (when staining with a nonspecific esterase) that indicated possible denervation.⁸⁹ Chold, on the other hand, described changes under the electron microscope in the type I but not in the type II fibers.⁹⁰ Treatment of the underlying disease (surgical removal of parathyroid adenoma) has led to return of most muscle function.²⁰ Patten et al reported that six months postoperatively patients continued to show improvement, although residual weakness was found in the iliopsoas, gluteal, and hamstring muscles.⁸⁹

AGING

Cellular Changes

Cellular changes with aging can be found in all organs, though the rate of change varies greatly.⁹⁰ Among the most visible signs of aging are alterations in skin and the development of movement dysfunction.⁹¹⁻⁹³ As we age, strength and coordination decline and movements tend to become slower.⁹³ The etiology of these movement dysfunctions can be caused by disturbances in 1) peripheral and central synaptic mechanisms, 2) motivation, 3) skeletal disorders (eg, osteoarthritis), and 4) muscle.⁹³ Although several of these etiological factors may be occurring simultaneously, it appears that a general reaction to aging always involves a decline in muscular strength that is accompanied by visual signs of atrophy.^{91, 93}

Experimental evidence suggests that aging may affect certain muscles more than others. For example, the flexor muscles of the lower extremity and the extraocular muscles show age-related changes rela-

tively early.⁹³ The major fiber types also show a differential response to aging.^{91, 94, 95} Based on animal studies, Gutmann and Hanzlíková have characterized the essential features of the "senescent motor unit."⁹³ These features indicate that age-related changes are a distinct biological entity even though many of the changes are similar to those that occur with denervation.⁹³

In both aged and denervated muscle the following have been reported: decrease in the number and size of muscle fibers, proliferation of the T tubules and sarcoplasmic reticulum, and considerable histochemical evidence of fiber grouping.^{93, 96} (A description of fiber type grouping is presented by Wheeler in this issue.) In aged animal muscle biochemical changes consist of loss of activity of glycolytic and oxidative enzymes,⁹⁷ decreased concentrations of adenosine triphosphate, and a decreased rate of creatin phosphate resynthesis.⁹³ Structural changes resembling the early stages of denervation have also been found in the neuromuscular junction of aged animals.⁹³ However, despite the denervation-like structural changes reported in aged muscle, electrophysiological evidence of denervation with aging has not been demonstrated.⁹³ The degenerative changes in aged muscle have also been shown to occur before the degenerative changes that are known to occur randomly in aged motor axons.⁹³

Morphological examination of the neuromuscular junction has led to the conclusion that there is probably a primary disturbance in the neuromuscular connection in senile muscle atrophy.^{93, 96} These changes at the neuromuscular junction may lead to altered trophic interactions between muscle and nerve, and in addition they may compromise fast synaptic activity (eg, reduced end-plate potentials).

It has been suggested that some alterations in the aged muscle may be secondary to other age-related changes such as declining body weight. Because changes in the senescent motor unit usually become evident before the age-associated loss of body weight, it appears unlikely that muscle dysfunction is secondary to the development of a cachectic state.⁹³

Most of the research on the senescent motor unit has been done on animals. Recently, Larsson and colleagues in various studies have used a cross-sectional design to examine the effects of aging on the vastus lateralis muscle of humans.^{91, 97-100} In a series of experiments, histochemical, biochemical, and fine structural changes were studied in 55 healthy men 22 to 65 years of age who were sedentary office workers. Comparisons were made with data from studies of a group of 10 to 19 year old boys and from a group of active 66 to 76 year old men. Analysis of biopsy specimens from the vastus lateralis muscle revealed the following histochemical and biochemical data. Histochemical findings:

1. Decrease in the proportion of type II fibers with increasing age (50% in the 20–29-year-old group vs 45% in the 60–65-year-old group).
2. Similar proportions of the subclasses of type II fibers (types IIA, IIB, and IIC) in all age groups.
3. Decreased area of the type II fibers as a function of age.
4. No change in the type I fiber areas with aging.

Biochemical findings:

1. Increase in 3-hydroxyacyl-coenzyme A dehydrogenase (HAD, an oxidative enzyme) activity with aging.
2. Shift in lactate dehydrogenase (LDH) isoenzyme patterns with age that results in a decrease in the percentage of muscle specific enzymes.

To determine whether the observed biochemical and histochemical changes correlated with performance alterations, strength and endurance testing was carried out with a Cybex® isokinetic dynamometer. Subjects in this group were 10 to 69 years of age. Isometric endurance was defined as the time subjects could maintain a level of 50 percent of their maximal isometric force. Dynamic endurance was measured by having subjects perform 50 maximal isokinetic contractions at 180°/sec. Percent change was determined by dividing the mean torque of the last three contractions by the mean torque of the first three contractions.

An age-related decline was seen in isometric force when the knee was tested at 30, 60, and 90 degrees from full extension. Similarly an age-related decrease in peak isokinetic torque was found at all four velocities tested (30, 60, 90, and 120°/sec.). A decline in maximum knee extension speed was also observed. There was, however, no age-related difference in muscle mass, that is, thigh circumference. Endurance, both dynamic and isometric, was similar for all the age groups.

In summary, the force production of the quadriceps femoris muscle declined isometrically and isokinetically as a function of age but endurance did not. With age, force values linearly declined as did the proportion and area of the type II fibers in the vastus lateralis muscle. However, Larsson postulated, based on multiple regression analysis of the data, that type II fiber atrophy could not account for all of the decline in strength measures.⁹⁷ He suggested that other factors, such as age and activity levels, might account for decreased strength. The increased HAD activity, the shift in LDH isoenzyme pattern, the increased proportion of type I fibers, and the decreased areas of the type II fibers all combined to indicate that with aging there was an overall increase in oxidative capacity of the vastus lateralis muscle.

A peripheral, but possibly clinically significant, observation can be made from Larsson's findings of elevated enzyme activities in the older, active group

(the 70-year-olds) when compared with the younger, sedentary group. The increased enzyme levels in the elderly, active group raises the question of how "trainable" the aged motor unit is.

Effect of Training on Aging Skeletal Muscle

Recently, numerous studies have demonstrated that regular training produces significant cardiovascular adaptations in older individuals.^{92, 101–103} The improvement in cardiovascular response (an increased $\dot{V}O_{2max}$) is similar to that seen in young subjects but is of a lesser magnitude.⁹² Learning of this ability of the aged cardiovascular system to respond to training is an important finding; it had been thought previously that declining physical performance and decreased $\dot{V}O_{2max}$ were unalterable consequences of the aging process.¹⁰⁴ Although the evidence has been accumulating relative to cardiovascular training, there have only been a few studies that have examined training effects on skeletal muscle.^{105, 106}

Suominen and co-workers have demonstrated increased aerobic and anaerobic enzyme activity levels in the vastus lateralis muscle of subjects 50 to 70 years old after submaximal endurance training (3 to 5 one-hour exercise periods a week for eight weeks consisting of walking, jogging, swimming, gymnastics, and ball games).^{105, 106} Histochemical analysis was not performed in these studies so fiber specific changes were not documented. Suominen and co-workers' findings indicate that skeletal muscle is trainable in aged subjects.

Recently, Orlander and Aniansson reported the effects of a 12-week training program on the vastus lateralis muscle in five men aged 70 to 75 years.¹⁰⁴ Training sessions consisted of warm-up exercises (walking or jogging) followed by "various static and dynamic exercises." Resistance was body weight. The exercise program was designed by the authors to increase strength and endurance. Orlander and Aniansson estimated that the average work load during the training program was less than 70 percent of $\dot{V}O_{2max}$. They considered this level to be "moderately intense" for this age group. Histochemical and biochemical analyses were made from biopsy specimens taken from the vastus lateralis muscle before and after training. The results were as follows:

1. No significant changes in fiber type distributions.
2. No change in HAD or citrate synthetase (oxidative enzymes) activity.
3. Significant increases in LDH and cytochrome oxidase (oxidative enzymes) activity.
4. Significant increase in phosphofructokinase (a glycolytic enzyme) activity.

This study did not use a control group; however, the results suggest that aged human skeletal muscle can increase in oxidative and anaerobic capacity as a

result of training. Although no significant changes in fiber type distributions were shown, a trend was observed that led Aniansson et al to perform a follow-up study on a larger group.¹⁰⁷

In this follow-up study Aniansson et al compared the effects of training on muscle strength and fiber composition in two similar groups of twelve 70-year-old men.¹⁰⁷ One group trained for 45 minutes a day, three times a week for 12 weeks using "static and dynamic exercises," with body weight as the only resistance. The second group served as a control. Histochemical analysis was made from biopsy samples taken from the vastus lateralis muscle before and after training. Comparisons were made only within each group (exercise and control) using pretraining and posttraining measurement, with the following results:

1. Isometric torque increased significantly in the trained group.
2. Isokinetic peak torque (dynamic torque) increased significantly at all four isokinetic speeds tested (30, 60, 90, and 180°/second) in the trained group.
3. The number of type II fibers increased in the trained group.
4. Neither muscular strength nor fiber composition changed in the control group.

These studies on the effect of training can be criticized for using a small number of subjects,¹⁰⁶ using a pretest and posttest design without comparisons with a control group,^{106, 107} and perhaps most importantly for a failure to adequately describe training programs. However, these studies do demonstrate that force generation, enzyme activities, and fiber composition can be altered by training the aged mus-

cle. Further studies will be needed to confirm these findings and to adequately describe the training stimuli if this information is to become clinically useful.

Although the senescent motor unit differs from the motor units found in younger subjects, they share a common characteristic—both can respond to training. It appears that aging muscle fibers do not lose their capacity for change. There is some preliminary evidence that aged skeletal muscle, like cardiovascular response, can be altered by training but that the training effect may be different from that seen in younger subjects.^{106, 107}

SUMMARY

The response of skeletal muscle to physical stimuli, such as exercise and disuse, is well-known. This review has focused on muscle mutability in response to nonphysical stimuli such as drugs, aging, endocrine influences, and metabolic factors. As physical therapists treat patients, they frequently will have to account for changes in muscular performance that are not caused by physical stimuli. Therapists must, therefore, be aware of the issues raised in this review. In view of the possibility that some drug-induced muscle atrophy and age-related changes may be reduced through the use of exercise, therapists need to understand these phenomena. Although the role of exercise has not been described in the management of many of the diseases described in this review, future research may demonstrate new roles for therapists in the management of many dysfunctions caused by muscular changes of nonphysical origins such as steroid weakness or alcoholic myopathy.

REFERENCES

1. Mastaglia FL, Argov Z: Drug-induced neuromuscular disorders in man. In: Walton J (ed): *Disorders of Voluntary Muscle*, ed 4. Edinburgh, Scotland, Churchill Livingstone, 1981, p 873-906
2. Rubin E: Alcoholic myopathy in heart and skeletal muscle. *N Engl J Med* 301:28-33, 1979
3. Wood GB: *A Treatise on the Practice of Medicine*. Philadelphia, PA, Lippincott, Gambo and Co, 1847, vol 2
4. Regan TJ: Alcoholic cardiomyopathy. *Annu Rev Med* 22:125-132, 1971
5. Jackson J: On a peculiar disease resulting from the use of ardent spirits. *N Engl J Med Surg* 11:351-353, 1822
6. Perkoff GT, Dioso MM, Bleisch V, et al. A spectrum of myopathy associated with alcoholism. *Ann Intern Med* 67:481-492, 1967
7. Perkoff GT, Nardy P, Velez-Garcia E: Reversible acute muscular syndrome in chronic alcoholism. *N Engl J Med* 274:1277-1285
8. Martin FC, Slavin G, Levi AJ: Alcoholic muscle disease. *Br Med Bull* 38:53-56, 1982
9. Song SK, Rubin E: Ethanol produces muscle damage in human volunteers. *Science* 175:327-328, 1972
10. Rubin E, Katz AM, Lieber CS, et al: Muscle damage produced by chronic alcohol consumption. *Am J Pathol* 83:499-515, 1976
11. Engel AG: Metabolic and endocrine myopathies. In Walton J (ed): *Disorders of Voluntary Muscle*, ed 4. Edinburgh, Scotland, Churchill Livingstone, 1981, p 664-711
12. Hed R, Lundmark C, Fahlgren H, et al: Acute muscular syndrome in chronic alcoholics. *Acta Med Scand* 171:585-599, 1982
13. Brooke MH: *A Clinician's View of Neuromuscular Disease*. Baltimore, MD, The Williams & Wilkins Co, 1977
14. Faris AA, Reyes MG, Abrams BM: Subclinical alcoholic myopathy: Electromyographic and biopsy study. *Trans Am Neurol Assoc* 92:102-108, 1967
15. Teravainen H, Juntunen J, Eriksson K, et al: Myopathy associated with chronic alcohol drinking. *Virchows Arch (Pathol Anat)* 378:45-53, 1978
16. Pachinger O, Mao J, Fauvel J-M, et al: Mitochondrial function and excitation-contraction couplings in the development of alcoholic cardiomyopathy. In Fleckenstein and Dhalla (eds): *Recent Advances in Studies on Cardiac Structure and Metabolism*. Baltimore, MD, University Park Press, 1975, vol 5, pp 423-429
17. Kiessling K-H, Pilstrom L, Karlsson J, et al: Mitochondrial volume in skeletal muscle from young and old physically retrained and trained healthy men and from alcoholics. *Clin Sci* 44:547-554, 1973

18. Hanid A, Slavin G, Main W, et al: Fibre type changes in striated muscle of alcoholics. *J Clin Pathol* 34:991-995, 1981
19. Kiessling K-H, Pilstrom L, Bylund AC, et al: Effect of chronic ethanol abuse on structure and enzyme activities of skeletal muscle in man. *Scand J Clin Lab Invest* 35:601-607, 1975
20. Stern LZ, Fagan JM: The endocrine myopathies. In: Vinken PJ, Bruyn GW, Ringel SP (eds): *Handbook of Clinical Neurology Diseases of Muscle Part 2*. Amsterdam, The Netherlands, North Holland Publishing Co, 1979, vol 41, p 235-258
21. Faludi G, Gottlieb J, Meyers J: Factors influencing the development of steroid-induced myopathies. *Ann NY Acad Sci* 138:1, 61-72, 1966
22. Askari A, Vignos PJ, Moskowitz R: Steroid myopathy in connective tissue disease. *Am J Med* 61:485-492, 1976
23. Perkoff GT, Silber R, Tyler FN, et al: Myopathy due to the administration of therapeutic amounts of 17-hydroxycorticosteroids. *Am J Med* 26:891-898, 1959
24. Afifi AK, Bergman RA, Harvey JC: Steroid myopathy. *Johns Hopkins Med J* 123:158-173, 1968
25. Bullock GR, Carter EE, Elliott P, et al: Relative changes in the function of muscle ribosomes during the early phase of steroid-induced catabolism. *Biochem J* 127:881-892, 1972
26. Stern LZ, Gruener R, Kirkpatrick JB, et al: The fine structure of cortisone-induced myopathy. *Exp Neurol* 36:530-538, 1972
27. Yates DAH: Steroid myopathy. *Rheumatology and Physical Medicine* 11:28-33, 1971
28. Di Mauro S: Metabolic myopathies. In: Vinken DJ, Bruyn GW, Ringel SP (eds): *Handbook of Clinical Neurology, Disease of Muscle Part 2*, Amsterdam, The Netherlands, North Holland Publishing Co, 1979, vol 41, p 175-234
29. Pleasure DE, Walsh GO, Engel WK: Atrophy of skeletal muscle in patients with Cushing's syndrome. *Arch Neurol* 22:118-125, 1970
30. Golding DN, Murray SM, Pearce GW, et al: Corticosteroid myopathy. *Annals of Physical Medicine* 6:171-177, 1961
31. Plotz CM, Knowlton AI, Ragan C, et al: The natural history of Cushing's syndrome. *Am J Med* 13:597-614, 1952
32. Muller R, Kugelberg E: Myopathy in Cushing's syndrome. *J Neurol Neurosurg Psychiatry* 22:314-319, 1959
33. Bunch TW, Worthingham JW, Combs JJ, et al: Azathioprine with prednisone for polymyositis: A controlled clinical trial. *Ann Intern Med* 92:356-369, 1980
34. Stern LZ, Hannapel LK: The muscle spindle in cortisone-induced muscular atrophy. *Exp Neurol* 40:484-490, 1973
35. Shoji S, Takagi A, Sugita H, et al: Dysfunction of sarco-plasmic reticulum in rabbit and human steroid myopathy. *Exp Neurol* 51:304-309, 1976
36. Williams RS: Triamcinolone myopathy. *Lancet* 1:698-701, 1959
37. Golding DN, Begg TB: Dexamethasone myopathy. *Br Med J* 2:1129-1130, 1960
38. Koski CL, Rifkenberck DN, Max SR: Oxidative metabolism of skeletal muscle in steroid atrophy. *Arch Neurol* 31:407-410, 1974
39. Shoji S, Takagi A, Sugita H, et al: Muscle glycogen metabolism in steroid-induced myopathy of rabbits. *Exp Neurol* 45:1-7, 1974
40. Vignos PJ, Greene R: Oxidative respiration of skeletal muscle in experimental corticosteroid myopathy. *J Lab Clin Med* 81:365-378, 1973
41. Gardiner PF, Botterman BR, Eldred E, et al: Metabolic and contractile changes in fast and slow muscles of the cat after glucocorticoid-induced atrophy. *Exp Neurol* 82:241-255, 1978
42. Vignos PJ, Kirby AC, Marshalis PN: Contractile properties of rabbit fast and slow muscles in steroid myopathy. *Exp Neurol* 53:444-453, 1976
43. Gardiner PF, Edgerton VR: Contractile responses of rat fast-twitch and slow-twitch muscles to glucocorticoid treatment. *Muscle Nerve* 2:274-281, 1979
44. Grossie J, Albuquerque EX: Extensor muscle responses to triamcinolone. *Exp Neurol* 58:435-445, 1978
45. Byers RK, Bergman AB, Joseph MC, et al: Steroid myopathy. *Pediatrics* 29:26-36, 1962
46. Goldberg AL, Goodman HM: Relationship between cortisone and muscle work in determining muscle size. *J Physiol (Lond)* 200:667-675, 1969
47. Goldberg AL: Mechanisms of growth and atrophy of skeletal muscle. In: RG Cassens (ed): *Muscle Biology*. New York, NY, Marcel Dekker Inc, 1972, pp 89-118
48. Yates FE, Marsh DJ, Maran JW: The adrenal cortex. In: Mountcastle VB (ed): *Medical Physiology*, ed 14. St. Louis, MO, The CV Mosby Co, 1980, pp 1558-1601
49. Goldberg AL, Tischler M, DeMartino G, et al: Hormonal regulation of protein degradation and synthesis in skeletal muscle. *Fed Proc* 39:31-38, 1980
50. Millward DJ, Garlick PJ, Nnanyelugo DO, et al: The relative importance of muscle protein synthesis and breakdown in the regulation of muscle mass. *Biochem J* 156:185-188, 1976
51. Goldberg AL: Protein turnover in skeletal muscle. *J Biol Chem* 244:3217-3222, 1969
52. Goldspink DF: The influence of activity on muscle size and protein turnover. *J Physiol (Lond)* 264:283-296, 1977
53. Goldberg AL, Etlinger JD, Goldspink DF, et al: Mechanism of work-induced hypertrophy of skeletal muscle. *Medicine and Science in Sport* 7:185-198, 1975
54. Henneman E: Recruitment of motoneurons: The size principle. *Progress in Clinical Neurophysiology* 9:61-84, 1981
55. Burke RE: Motor units in mammalian muscle. In: Sumner AJ (ed): *The Physiology of Peripheral Nerve Disease*. Philadelphia, PA, WB Saunders Co, 1980, p 133
56. Goldspink G, Ward PS: Changes in rodent muscle fibre type during postnatal growth, undernutrition and exercise. *J Physiol (Lond)* 296:453-469, 1979
57. Henson RA: Neuromuscular disorders associated with malignant disease. In: Walton J (ed): *Disorders of Voluntary Muscle*, ed 4. Edinburgh, Scotland, Churchill Livingstone, 1981, pp 712-724
58. Kula R: Neuromuscular disorders associated with systemic neoplastic diseases. In: Vinken PJ, Bruyn GW, Ringel SP (eds): *Handbook of Clinical Neurology, Diseased Muscle Part 2*. Amsterdam, The Netherlands, North Holland Publishing Co, 1979, vol 41, p 317-403
59. Rothstein JM, Delitto A, Sinacore DR, et al: Muscle function in rheumatic disease patients treated with corticosteroids. *Muscle Nerve*, to be published
60. Gardiner PF, Hibl B, Simpson DR, et al: Effect of a mild weight lifting program on the progress of glucocorticoid-induced atrophy in rat hindlimb muscles. *Pflugers Arch* 385:147-153, 1980
61. Ryan AJ: Anabolic steroids are fool's gold. *Fed Proc* 40:2682-2688, 1981
62. American College of Sport Medicine Position statement on the use and abuse of anabolic-androgenic steroids in sport. *Medicine and Science in Sports* 9:xi-xiii, 1977
63. Wright JE: Anabolic steroids and athletes. *Exerc Sport Sci Rev* 8:149-202, 1980
64. Stryer L: Generation and storage of metabolic energy. In: Stryer L (ed): *Biochemistry*. San Francisco, CA, WH Freeman & Co Publishers, 1981
65. Gergely J: Biochemical aspect of muscular structure and function. In: Walton J (ed): *Disorders of Voluntary Muscle*, ed 4. Edinburgh, Scotland, Churchill Livingstone, 1981, pp 102-150
66. Dowben RM: Contractility, with special reference to skeletal muscle. In: Mountcastle VB (ed): *Medical Physiology*, ed 14. St. Louis, MO, The CV Mosby Co, 1980, p 82-119
67. Williams PE, Goldspink G: Longitudinal growth of striated muscle fibers. *J Cell Sci* 9:51-76, 1971
68. Goldberg AL: Influence of insulin and contractile activity on muscle size and protein balance. *Diabetes* 28:18-24, 1979
69. Li JB, Goldberg AL: Effect of food deprivation on protein synthesis and degradation in rat skeletal muscles. *Am J Physiol* 231:441-448, 1976
70. Goodman MH: The pancreas and regulation of metabolism. In: Mountcastle VB (ed): *Medical Physiology*, ed 14. St. Louis, MO, The CV Mosby Co, 1980, pp 1638-1673
71. Koivisto V, Soman V, Conrad P, et al: Insulin binding to monocytes in trained athletes. *J Clin Invest* 64:1011-1015, 1979

72. Soman V, Koivisto V, Grantham P, et al: Increased insulin binding to monocytes after acute exercise in normal man. *N Engl J Med* 271:220-225, 1964
73. Koivisto VA, Sherwin RS: Exercise in diabetics. *Postgrad Med* 66:87-96, 1979
74. Skyler JS: Diabetes and exercise: Clinical implications. *Diabetes Care* 2:307-311, 1979
75. Stern LZ, Payne CM, Hannapel LK: Acromegaly: Histochemical and electron microscopic changes in deltoid and intercostal muscle. *Neurology (Minneapolis)* 24:589-593, 1974
76. Hed R, Kirsten L, Lundmark C: Thyrotoxic myopathy. *J Neurol Neurosurg Psychiatry* 21:270-278, 1958
77. Havard CWH, Campbell EDR, Ross HB, et al: Electromyographic and histological findings in muscles of patient with thyrotoxicosis. *Q J Med* 32:145-163, 1963
78. Engel AG: Electron microscopic observations in primary hypokalemic and thyrotoxic periodic paralysis. *Mayo Clin Proc* 41:797-808, 1966
79. Engel AG: Electron microscopic observation in thyrotoxic and corticosteroid-induced myopathies. *Mayo Clin Proc* 41:785-796, 1966
80. Gold HK, Spann JF, Braunwald E: Effect of alterations in the thyroid state on the intrinsic contractile properties of isolated rat skeletal muscle. *J Clin Invest* 49:848-854, 1970
81. Denys EH, Hofmann WW: An in vitro study of biochemical changes produced by hypermetabolism and hypometabolism in skeletal muscle. *Neurology (Minneapolis)* 22:21-31, 1972
82. Stern LZ, Gruener R: Electrophysiological correlates of experimental hyperthyroidism. In: 2nd Annual Meeting of Society for Neuroscience, Abstract No 1519, 1972
83. Gruener R, Stern LA, Payne C, et al: Hyperthyroid myopathy intracellular electrophysiological measurements in biopsied human intercostal muscle. *J Neurol Sci* 24:339-349, 1975
84. Fitts RN, Winder WW, Brooke MN, et al: Contractile, biochemical, and histochemical properties of thyrotoxic rat soleus muscle. *Am J Physiol* 238:15-20, 1980
85. Ramsay ID: Muscle dysfunction in hyperthyroidism. *Lancet* 2:931-934, 1966
86. Ramsay ID: *Thyroid Disease and Muscle Dysfunction*. London, England, Heineman, 1974
87. Spiro AJ, Hirano A, Beilin RL, et al: Cretinism with muscular hypertrophy. *Arch Neurol* 23:340-349, 1970
88. McKeran RO, Slavin G, Andrews TM, et al: Muscle fibre type changes in hypothyroid myopathy. *J Clin Pathol* 28:659-663, 1975
89. Patten BM, Bilezikian JP, Mallette LE, et al: Neuromuscular disease in primary hyperparathyroidism. *Ann Intern Med* 80:182-193, 1974
90. Cholod EJ, Haust MD, Hudson AJ, et al: Myopathy in primary familial hyperparathyroidism: Clinical and morphological studies. *Am J Med* 48:700-707, 1970
91. Larsson L: Morphological and functional characteristics of the ageing skeletal muscle in man: A cross-sectional study. *Acta Physiol Scand (Suppl)* 457:1-36, 1978
92. Bassey JE: Age, inactivity and some physiological responses to exercise. *Gerontology* 24:66-77, 1978
93. Gutmann E, Hanzlíková V: Fast and slow motor units in ageing. *Gerontology* 22:280-300, 1976
94. Aniansson A, Grimby G, Hedberg M, et al: Muscle function in old age. *Scand J Rehabil Med* 56:43-49, 1978
95. Jennekens FGI, Tomlinson BE, Walton JN: Histochemical aspects of five limb muscles in old age: An autopsy study. *J Neurol Sci* 14:259-276, 1976
96. Tomonaga M: Histochemical and ultrastructural changes in senile human skeletal muscle. *J Am Geriatr Soc* 25:125-131, 1977
97. Larsson L, Sjodin B, Karlsson J: Histochemical and biochemical changes in human skeletal muscle with age in sedentary males, age 22-65 years. *Acta Physiol Scand* 103:31-39, 1978
98. Larsson L, Grimby G, Karlsson J: Muscle strength and speed of movement in relation to age and muscle morphology. *J Appl Physiol* 46:451-456, 1979
99. Larsson L, Karlsson J: Isometric and dynamic endurance as a function of age and skeletal muscle characteristics. *Acta Physiol Scand* 104:129-136, 1978
100. Orlander J, Kiessling KH, Larsson L, et al: Skeletal muscle metabolism and ultra structure in relation to age in sedentary men. *Acta Physiol Scand* 104:249-261, 1978
101. Sidney KH, Shephard RJ: Frequency and intensity of exercise training for elderly subjects. *Med and Sci in Sports and Exercise* 10:125-131, 1978
102. Stamford BA: Physiological effects of training upon institutionalized geriatric men. *J Gerontol* 27:451-455, 1972
103. Saltin B, Grimby G: Physiological analysis of middle aged and old former athletes. *Circulation* 38:1104-1113, 1968
104. Orlander J, Aniansson A: Effects of physical training on skeletal muscle metabolism and ultrastructure in 70 to 75-year-old-men. *Acta Physiol Scand* 108:149-154, 1980
105. Suominen H, Heikkinen E, Parkatti T: Effect of eight weeks physical training on muscle and connective tissue of the m. vastus lateralis in 69-year-old men and women. *J Gerontol* 32:33-37, 1977
106. Suominen H, Heikkinen E, Liesen H, et al: Effects of 8 weeks endurance training on skeletal muscle metabolism in 56-70-year-old sedentary men. *Eur J Applied Physiol* 37:173-180, 1977
107. Aniansson A, Grimby G, Rundgren H, et al: Physical training in old men. *Age and Ageing* 9:186-187, 1980