New Horizons in Muscle Disease

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As information concerning the interactions between nerve and muscle increases, the concepts which divide disorders of the motor unit into the two basic categories of neurogenic atrophy and myopathy become less accurate. While it is still true that these concepts provide the clinical basis for classifying such disorders,\(^1\) they must be regarded as an oversimplification which establishes a point of reference for future understanding of these diseases. At present, attempts are made to isolate that portion of the motor unit, for example, anterior horn cell, axon (peripheral nerve), neuromuscular junction, and the muscle fibers innervated by that anterior horn cell, which can be primarily responsible for muscle weakness (Fig 1). To this end every patient so afflicted undergoes a series of evaluations which begins with a careful history and thorough examination.\(^3\) As part of this examination, muscles which are particularly affected are noted and graded as to size and strength. Next, serum is analyzed for the presence of enzymes which may "leak out" from the muscle, such as creatine phosphokinase, aldolase, and lactose dehydrogenase. Nerve conduction times, high- and low-frequency stimulation tests, and needle electrode studies constitute the electromyographic investigations which individually test each portion of the motor unit. Finally, a muscle biopsy, carefully removed from a moderately involved muscle, is analyzed with routine staining as well as a battery of histochemical techniques and, in selected cases, electron microscopy. When all of these data are assimilated, an attempt is made to identify this disorder which is then classified basically as neurogenic or myopathic.\(^3\) Yet, even after such a complete work-up, there are a number of ever-increasing cases where no categorization can be made and a noncommittal term such as "neuromyopathy" is used.

The reason for growing uncertainty in this entire field is an appreciation of the profound influence of the trophic effects of nerve on muscle.\(^4\) The most obvious of these is that there is a reduction in fiber diameter and collapse of the sarcolemmal membrane as denervated muscles atrophy (Figs 2, 3). Normally, the only area sensitive to acetylcholine resides in the junctional folds of the endplate region, but in denervated muscle, receptor sites can be identified over the entire sarcolemmal membrane. One can then infer that innervation is in some way responsible for the establishment and maintenance of fiber diameter as well as limiting the location of active acetylcholine receptor sites to the neuromuscular junction.\(^5\)

Aside from trophic influences on the size of muscle fibers, innervation affects the basic metabolic and physiologic characteristics of muscle fibers.\(^6\) Without offering unwarranted comparisons, it is known, either by taste or visual impression, that there is both light and dark meat on turkeys and other fowl. The light meat is found in the breasts and primarily functions to mobilize the wings; the dark meat is found in the legs and functions for support and posture. Lower mammals have been described in terms of red, slow or tonic muscle, and white, fast or phasic muscle. Physiologically, entire muscles seem to have one or the other characteristics. When stained histochemically for oxidative enzyme content, correlations were made for those muscles rich in oxidative enzymes with slow or "red" muscle, and those muscles which relied primarily on glycolytic pathways and were therefore low in oxidative enzymes, with fast or "white" muscle. By preparing human muscle

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Fig 1—Diagram showing four motor units with components including anterior horn cell, peripheral nerve (axon), neuromuscular junctions, and innervated muscle fibers.

Fig 2—Diagram showing focal atrophy due to denervation.

Fig 3—Photomicrograph showing focal atrophy.

Fig 4—Diagram showing four motor units stained histochemically. All of the fibers within the same motor unit are of the same type.
samples in a similar (Fig 4) fashion,\textsuperscript{6,8} it was seen that there are also two basic types of muscle fibers; Type I, rich in oxidative enzymes and staining darkly for mitochondrial nicotinamide-adenine dinucleotide (NADH) tetrazolium reductase (Fig 5) and Type II, low in oxidative enzymes but staining darkly for myofibrillar adenosinetriphosphatase (ATPase) (Fig 6).\textsuperscript{4} Subtypes have been identified with a wider variety of histochemical techniques. Several features concerning fibers stained by these techniques include: 1) the fiber type remains the same along the length of the fiber, 2) all of the muscle fibers within a given motor unit are of the same histochemical type so that there are Type I and Type II motor units, 3) the fibers of a motor unit are distributed in a random fashion throughout the muscle, mixing with, and dispersed among, muscle fibers of other units and, 4) both Type I and Type II muscle fibers are found within the same muscle in humans so that, normally, the randomized distribution of muscle fibers\textsuperscript{9} of the motor unit causes an alternating or “checkerboard” pattern of light and dark fibers when
Fig 8—Diagram showing reinnervation collateral of still intact motor units.

Fig 9—Diagram showing incorporation of reinnervated fibers into still intact motor units and conversion of innervating motor unit.

10—Photomicrograph showing a grouping of fiber types stained for myofibrillar ATPase. This grouping and loss of the "checkerboard" pattern indicates denervation-reinnervation has occurred.

The muscle is stained by histochemical techniques. In chronic disease states, such as neurogenic atrophy due either to anterior horn cell disease or peripheral neuropathy, there is both denervation and reinnervation by collateral sprouts of still intact axons (Figs 7, 8). If denervated muscle fibers are reinnervated by lateral sprouts from axons of motor units which are of a different type, the reinnervated fibers will assume the histochemical type of that motor unit on which they are reinnervated. There is then a loss of the "checkerboard" appearance as a grouping of fibers of the same type occurs (Figs 9, 10). This phenomenon is also observed in animal experiments which show that there is denervation and cross reinnervation from one muscle type to the other, and a subsequent organization of fiber types when reinnervation is complete. That the basic metabolic pathways of energy production in muscle are so drastically influenced by innervation must be considered when myopathies are viewed as primary derangements of muscle metabolism.

When the physiologic characteristics of the varia-
various types of motor units are studied, differences can be identified as to configuration of motor unit potentials, frequency of firing, duration of firing, and sequence of firing during voluntary contraction. Attempts to correlate these characteristics with histochemical differentiation are now in progress. Since there is no discernible difference between motoneurons which innervate different fiber types, it would seem that the influence may be purely physiological and depend upon firing rates as well as the frequency with which these neurons are called upon to perform. In that sense, the fiber type of a particular unit may be ultimately dependent upon the central organization which programs and controls motor function.

Many of these primary disorders of muscle, now subject to evaluation by histochemical techniques, are being either reinterpreted or at least held in their classification categories with less certainty. At present there is international debate regarding a primary neurogenic etiology for Duchenne's dystrophy. Many cases of limb girdle dystrophy are reclassified as motoneuron disease or as "neuromyopathy." Furthermore, myotonic dystrophy may not be 'dystrophy' at all, since the most obvious pathological finding is a selective atrophy of Type I fibers (Fig 11).

Histochemical techniques have permitted the identification of these pathological changes, which in the past were considered to be denervation atrophy, as 'type atrophy.' Selective atrophy of Type II fibers is seen in disuse atrophy, polymyalgia rheumatica, in steroid arthritis, oculopharyngeal dystrophy, and, as mentioned, myotonic dystrophy. In addition, there are a host of congenital myopathies in which specific histochemical changes are observed.

Currently, at the Medical College of Virginia, new techniques are being modified and applied in the evaluation of neuromuscular disorders. One of these is open biopsy electromyography, which permits a direct electrophysiological examination of a sample of muscle just prior to its removal. Information obtained in this way is being analyzed and correlated with the histochemical characteristics of the sampled muscle and has provided new as well as more precise interpretations.

Sophisticated physiological and histochemical information is accumulating at a rate which at present is faster than the clinician can assimilate. The
contributions made by electron microscopy further burden an overwhelming stockpile of data. In a true sense, many pieces to the puzzle have been found, and as these are cautiously put in place, a more complete understanding of muscle disease is foreseeable. One hopes that with better insight into the pathophysiology of muscle diseases, these new horizons will permit eventual treatment or cure for those suffering from these disorders.

REFERENCES


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