Ultrastructural relationship of quadriceps muscle degeneration with a distant peroneal nerve conduction in human myotonia dystrophica*

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Summary. The association of motor nerve conduction velocity (MNCV) to (1) duration of symptoms, (2) deep tendon reflex responses, (3) clinical muscle atrophy, and (4) ultrastructure of quadriceps muscle was studied in 18 patients with myotonia dystrophica of Steinert and nine normal controls. These patients had neither diabetes mellitus nor any other type of muscle dystrophy. Ultrastructural features of muscle fibers and intercellular spaces between atrophic fibers provided a basis for identifying degenerative changes and evaluating them semi-quantitatively. Our study indicates presence of an association between the pattern of muscle degeneration and both MNCV (correlation coefficients, \( r = +0.60 \)) and duration of symptoms (\( r = -0.62 \)), but not between MNCV and duration of symptoms (\( r = +0.28 \)). Further analysis of the association between the degeneration of quadriceps and the MNCV of a distant peroneal nerve (which does not innervate quadriceps) suggested that the systemic nerve degeneration occurred in some groups of myotonia patients. Our study indicates that while in some patients the muscle degeneration may have been associated with the impairment of neurogenic elements, in others it occurred in the absence of any MNCV abnormality. Our findings favor the role of both neuropathic and myopathic factors in the muscle degeneration seen in myotonia dystrophica.

Key words: Myotonia Dystrophica - Muscle and Nerve degeneration - Peroneal Motor Nerve Conduction - Ultrastructure of Quadriceps

Introduction

Steinert's myotonia dystrophica of adults is a multisystem disease with a myriad of seemingly unrelated abnormalities, the most striking being the highly variable but progressive muscle weakness and wasting (Fardeau, 1969; Bosanquet et al., 1973; Roses et al., 1979). However, Iannaccone et al. (1986) showed delayed muscle fiber maturation in myotonia dystrophica of children. Studies of motor nerve conduction and neuropathology in adult myotonia patients (Caccia et al., 1972; Kalyanaraman et al., 1973; List and Lovelace, 1981), ultrastructural and cytological characteristics of myotonic muscles in adults and children (Samaha et al., 1967; Schroder and Adams, 1968; Santa, 1969; Schotland, 1970; Karpati et al., 1973), and muscle dystrophy in animal models (Atkinson et al., 1981; Kerr and Sperelakis, 1983), have lead to several hypotheses to explain the pathogenesis of the disease (Griggs, 1977; Panayiotopoulous and Scarpalezos, 1977; Tanaka, 1985). The above review also indicates that the previous ultrastructural studies on human myotonia dystrophica were based upon relatively few myotonic dystrophy patients (Samaha et al., 1967; Schroder and Adams, 1968; Schotland, 1970) and included patients with complications, such as diabetes (Samaha et al., 1967), and other dystrophies (Santa, 1967; Schotland, 1970; Karpati et al., 1973; Lanzi et al., 1982). In a series of myotonia patients, we have already reported that the muscle capillary basement membrane is thinner than normal (Olson et al., 1978; 1979; Olson, 1983), that a slowed motor nerve conduction velocity (MNCV) is unrelated to glucose intolerance (Olson et al., 1978), and that the slowed MNCV is not directly related to a reduced basement membrane width (Olson, 1983). In the same group of patients, we now report the association of ultrastructural patterns of quadriceps muscle degeneration with MNCV of a distant nerve (peroneal) in order to gain some clues into the involvement of a systemic nerve in this disease as opposed to the femoral nerve which innervates the muscle and might be affected due to muscle degeneration.

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*This research was supported by General Medical Research Funds of the Veterans Administration.
Materials and methods

Several needle biopsies of right quadriceps from 15 male and 3 female nondiabetic myotonia dystrophica patients (age 22 to 62 years) were studied and compared to those from 9 normal individuals who were potential kidney donors. Specimens were prepared, sectioned, stained and examined using standard electron microscopic techniques. Briefly, specimens were fixed for 2–3 hours in 3% glutaraldehyde in 0.1M phosphate buffer, washed in phosphate buffer, post fixed for 1-2 hours in 1% phosphate buffered osmiumtetroxide, dehydrated in graded ethyl alcohol and propylene oxide and embedded in Epon 812. From each biopsy several blocks were thin sectioned using an LKB Ultratome, stained with a combination uranyl acetate and lead citrate, and examined with an RCA EMU 3 or 4 electron microscope. The thick sections were stained with methylene or toluidine blue for light microscopy. Clinical evaluations (Olson et al., 1978) and MNCV (Johnson and Olsen, 1960) were performed as previously reported. All participants signed an informed consent designed according to the Helsinki agreement on human experimentation. The duration of myotonic dystrophy was obtained by patient and family interviews.

All sections and micrographs were analyzed to determine the pattern of muscle degeneration and numerical values were assigned to the biopsies. Likewise, the various clinical parameters were assigned numerical values to allow comparison of MNCV and biopsy results (Table 1). Values given are mean ± standard error of mean. Statistical evaluation was done using Student's test. A P value less than 0.05 was considered statistically significant. Correlations given between ultrastructural class, MNCV, and duration of symptoms were determined nonparametrically by Spearman’s ρ.

Results

The Ultrastructure of Normal Right Quadriceps Muscle

Although fine structure of normal skeletal muscles has been well documented (Price, 1974), a brief description is included for comparison with the myotonic muscles (Fig. 1). The light microscopic longitudinal sections of muscle fibers showed cross striations composed of alternating light (I) and dark (A) bands (Fig. 2). The connective tissue septa surrounding each muscle fiber was usually thin and contained capillaries, fibroblasts, lymphatics and nerves (Fig. 2). Ultrastructurally the quadriceps muscle fibers showed typical arrangements showing fibers containing numerous sarcomeres extending from Z to Z bands, numerous thick and thin myofibrils or myofilaments, peripheral nuclei, small Golgi complexes, mitochondria, polyribosomes, occasional lipid droplets, lipofuscin, and some glycogen granules.

Analysis of Myotonia Patients

When MNCV, age, duration of disease, and clinical parameters were arranged according to the ultrastructure (Table 1) the myotonia patients could be divided into four groups: (A) unimpaired MNCV showing minimum muscle degeneration, (B) unimpaired MNCV with moderate muscle degeneration, (C) slower MNCV with moderate muscle degeneration, and (D) slower MNCV with severe muscle degeneration.

The ultrastructural features indicative of muscle degeneration were: a) presence of ovoid nuclei in the central region of the muscle fiber in addition to the peripheral nuclei, b) pleomorphic, heterochromatic, central and/or internal nuclei, c) variable amounts of glycogen deposits surrounding nuclei, d) remnants of sarcomeres in the glycogen pools, e) mitochondria changed from the usual parallel orientation to a right angle orientation of the myofibrils, f) variable amounts of secondary lysosomes and lipofuscin granules, the latter usually associated with degenerating mitochondria, g) duplication and disorganization of Z bands, h) bizarre-shaped mitochondria often surrounded by large amounts of glycogen granules, i) loss of myofilament arrangements in portions of muscle fibers, and j) relatively thick plasma membranes but thin basement membranes; both of which were deficient in some areas of the fibers. When a muscle fiber showed three or less of the above characteristics, it was considered normal. However, when a fiber showed four or more of the above features, it was considered degenerating. Thus, a single ultrastructural feature was not used for distinguishing normal from degenerating muscle fibers.

(A) Ultrastructure of Quadriceps Muscle in Patients with Unimpaired MNCV and Minimum Muscle Degeneration.

The patients (Table 1, cases 1, 4, 5, 7 and 18) had MNCV comparable to the normal individuals (Table 2) (Fig. 1). These patients had myotonia ranging from 2 to 24 years (11.8 ± 3.9) of duration and showed variable degrees of reflex response and muscle weakness (Table 1). Analysis of the biopsies from these patients revealed that many muscle fibers were essentially normal, whereas some muscle fibers showed features of degenerating muscles which are described and illustrated in figures 3 and 4. Unlike the normal muscle, the interstitium surrounding the degenerating fibers contained variable amounts of flocculent material, fibroblasts, collagen fibers and connective tissues (Fig. 4).

B) Ultrastructure of Quadriceps Muscle in Patients with Unimpaired MNCV and Moderate Muscle Degeneration.

The patient (Table 1, cases 2, 3, 13 and 15) also showed MNCV comparable to the normal individuals (Table 2) (Fig. 1). In the group B, the duration of myotonia ranged from 10 to 30 years (19.0 ± 5.0).
However, in this group, many muscle fibers were degenerating fibers which were often surrounded by increased interstitial space containing fatty connective tissues (Fig. 5). The plasma membranes appeared thicker than the nondegenerating fibers. The degenerating muscle fibers contained relatively sparse myofilaments, indistinct arrangements of the A and I bands, pleomorphic and heterochromatic nuclei, and bizarre shaped mitochondria interspersed with some glycogen granules. Many muscle fibers contained large amounts of lipid droplets and lipofuscin granules (Fig. 5).

(C) Ultrastructure of Quadriceps Muscle in Patients with Slower MNCV and Moderate Muscle Degeneration

The patients (Table 1, cases 6, 8, 9 and 10) had significantly slower MNCV than the patients in the groups A and B and the controls (Table 2) (Fig. 1). The duration of myotonia varied from 9 to 21 (15.3 \pm 3.6) years. Analysis of muscle fibers showed many degenerating fibers containing many internal, pleomorphic, heterochromatin nuclei which were often surrounded by abundant glycogen granules. The muscle fiber had sparse myofilaments and thickened plasma membrane but relatively thin basement membrane both of which were deficient in some areas (Fig. 6). Many fibers lacked the typical arrangements of bands and they often contained pleomorphic, bizarre shaped mitochondria, variable amounts of lipid and lipofuscin granules. Some highly atrophic fibers had pleomorphic, heterochromatic nuclei and unidentified electron opaque masses (Fig. 7). These fibers were surrounded by the increased interstitial spaces and other fibers (Fig. 7). Many muscle fibers also had completed degeneration and were replaced by bundles of collagen fibers (Fig. 8).

(D) Ultrastructure of Quadriceps Muscle in Patients with Slower MNCV and Severe Muscle Degeneration

The patients (Table 1, cases 11, 12, 14, 16, and 17) also had significantly slower MNCV than the three groups described above (Table 2) (Fig. 1). The duration of myotonia ranged from 18 to 38 (30.2 \pm 4.1) years. Analysis of biopsies showed that numerous muscle fibers had degenerated. The atrophic muscle fibers contained numerous internal, highly pleomorphic and heterochromatic nuclei, completely disorganized sarcomeras, A, I and Z bands, isolated aggregates of myofilaments, thickened and deficient plasma membranes, many aggregated, dense glycogen granules, many lipid droplets, and lipofuscin granules (Figs. 9, 10). However, among the severely degenerated fibers some normal muscle fibers were innervated by apparently normal myelinated fibers (Fig. 11). These fibers were separated by relatively large interstitial spaces which were bordered with other degenerating fibers (Fig. 11). The connective tissue contained many large bundles of collagen fibers, floculent materials in the interstitium, and fibroblasts (Fig. 9).
Ultrastructure of quadriceps in myotonia

Fig. 2. The micrograph illustrates light (l) and dark (A) bands of normal muscle fibers separated by thin layers of connective tissues. Methylene blue stain. x515

Fig. 3. The electron micrograph from group A patient (case 18) shows peripheral portion of a muscle fiber with many large lipofuscin granules associated with lipid droplets and degenerating myofibrils (arrows). x10,680
Ultrastructure of quadriceps in myotonia

Fig. 4. The electron micrograph from group A patient (case 1) illustrates an essentially normal muscle fiber (F), a degenerating muscle fiber with a central nucleus (N) and capillary (C). A portion of the degenerating fiber contains highly disrupted myofibrils among the aggregates of glycogen granules (G), while the other portion shows typical myofibrils and bands. The basement membranes (arrows) around the degenerating and nondegenerating muscle fibers are thin and uniform. The fibers are separated by thin septal connective tissue. ×7,000

Fig. 5. The micrograph from a group B patient (case 5) shows several degenerating muscle fibers (D), some fibers containing large lipid (L) droplets and prominent interstitium. Methylene blue stain. ×540
Ultrastructure of quadriceps in myotonia

Fig. 6. The low power electron micrograph from a group C patient (case 9) shows portions of atrophied muscle fibers. A muscle fiber with nucleus (N) shows accumulations of dense granules (arrows) and some myofibrils. A degenerating muscle fiber (D) shows peripheral aggregates of glycogen granules, completely disrupted myofibrils, A, I and Z bands. The connective tissue spaces between the muscle fibers have increased in this patient. x7600

Table 1. The relationship of motor nerve conduction velocity (MNCV), age, duration of symptoms, hyporeflexia, and muscle atrophy arranged according to ultrastructural patterns of muscle degeneration in the biopsies of quadriceps muscle.

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient name (case #)</th>
<th>Classification of muscle degeneration by ultrastructure</th>
<th>Peroneal nerve MNCV (m/sec)</th>
<th>Duration of symptoms at biopsy (age at onset in years)</th>
<th>Age in years (sex)</th>
<th>Quadriceps patellar tendon reflex response</th>
<th>Quadriceps muscle mass strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>RC(18)</td>
<td>3</td>
<td>52</td>
<td>24(38)</td>
<td>62(m)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>RH (5)</td>
<td>3</td>
<td>45</td>
<td>10(17)</td>
<td>27(m)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>MF (6)</td>
<td>3</td>
<td>44</td>
<td>2(25)</td>
<td>27(f)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>JS (7)</td>
<td>3</td>
<td>44</td>
<td>6(30)</td>
<td>38(m)</td>
<td>3</td>
<td>3</td>
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<tr>
<td></td>
<td>PK (1)</td>
<td>3</td>
<td>42</td>
<td>17(5)</td>
<td>22(m)</td>
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<td>2</td>
</tr>
<tr>
<td>B</td>
<td>GG (2)</td>
<td>2</td>
<td>47</td>
<td>10(14)</td>
<td>24(m)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>KN (3)</td>
<td>2</td>
<td>47</td>
<td>11(15)</td>
<td>26(f)</td>
<td>0</td>
<td>3</td>
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<tr>
<td></td>
<td>HC(15)</td>
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<td>44</td>
<td>30(25)</td>
<td>50(m)</td>
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<td>1</td>
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<tr>
<td></td>
<td>RK(13)</td>
<td>2</td>
<td>--</td>
<td>25(29)</td>
<td>54(m)</td>
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<td>2</td>
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<tr>
<td>C</td>
<td>HH (8)</td>
<td>2</td>
<td>41</td>
<td>13(25)</td>
<td>38(m)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>GS(10)</td>
<td>2</td>
<td>41</td>
<td>7(36)</td>
<td>43(m)</td>
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<tr>
<td></td>
<td>JD (6)</td>
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<td>38</td>
<td>17(14)</td>
<td>31(m)</td>
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<td>3</td>
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<td></td>
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<td>39</td>
<td>24(15)</td>
<td>39(m)</td>
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<td>1</td>
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<tr>
<td>D</td>
<td>ES(17)</td>
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<td>--</td>
<td>36(25)</td>
<td>61(f)</td>
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<tr>
<td></td>
<td>RF(14)</td>
<td>1</td>
<td>44</td>
<td>38(15)</td>
<td>53(m)</td>
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<tr>
<td></td>
<td>VH(16)</td>
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<td>35</td>
<td>18(40)</td>
<td>58(m)</td>
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<tr>
<td></td>
<td>JK(12)</td>
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<td>35</td>
<td>36(14)</td>
<td>58(m)</td>
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<td>1</td>
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<tr>
<td></td>
<td>WN(11)</td>
<td>1</td>
<td>34</td>
<td>23(26)</td>
<td>49(m)</td>
<td>0</td>
<td>2</td>
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</tbody>
</table>

Footnotes: Numerical value was assigned to each of the following conditions: (a) severe = 1, hypoactive = 2, normal = 3; (c) marked atrophy/weakness = , mild to moderate = 2, normal = 3. Mean peroneal MNCV (N=24, control subjects) from Olson et al. (1978) = 46 ± 0.8 m/sec.
### Table 2. Segregate analysis of ultrastructure, MNCV, duration, age of onset and age of myotonic patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>Ultrastructural evaluation</th>
<th>MNCV</th>
<th>Duration</th>
<th>Age of onset</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3†</td>
<td>46.0 ± 0.8‡</td>
<td>0</td>
<td>23.0 ± 5.6</td>
<td>44.0 ± 3.5‡</td>
</tr>
<tr>
<td>A</td>
<td>3</td>
<td>45.4 ± 1.7*</td>
<td>11.8 ± 3.9</td>
<td>(n = 5)</td>
<td>34.8 ± 7.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 5)</td>
<td>(n = 5)</td>
<td></td>
<td>(n = 5)</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>46.0 ± 1.0*</td>
<td>19.0 ± 5.0</td>
<td>(n = 4)</td>
<td>39.8 ± 8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 3)</td>
<td>(n = 4)</td>
<td></td>
<td>(n = 4)</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>39.8 ± 0.8</td>
<td>15.3 ± 3.6</td>
<td>(n = 4)***</td>
<td>37.8 ± 2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 4)***</td>
<td>(n = 4)</td>
<td></td>
<td>(n = 4)</td>
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<tr>
<td>B&amp;C</td>
<td>2</td>
<td>42.4 ± 1.4</td>
<td>17.1 ± 2.9</td>
<td>(n = 4)***</td>
<td>38.8 ± 4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 7)**</td>
<td>(n = 4)***</td>
<td></td>
<td>(n = 8)</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>37.0 ± 2.3</td>
<td>30.2 ± 4.1</td>
<td>(n = 5)</td>
<td>54.2 ± 2.3</td>
</tr>
</tbody>
</table>

Footnotes: The statistical analysis of data in Table 1 showing mean ± standard error of mean, and numbers (n). † From 9 control subjects (see results). ‡ Data taken from Olson et al. (1978). *No difference from control; statistically significant **p < 0.05; 111 p < 0.005.

**Fig. 7.** The micrograph from group C patient (case 9) illustrates a highly atrophic muscle fiber with pleomorphic, heterochromatic nuclei and electron opaque masses (M). This muscle is surrounded by abundant interstitium and portions of other muscle fibers. × 3,300
Ultrastructure of quadriceps in myotonia

Fig. 8. The electron micrograph from group C patient (case 8) shows muscle fibers and a group of completely degenerated muscle fibers which have been replaced by bundles of collagen (CO) fibers yet they show remnants of perimysial (arrow heads) and endomysial (arrow) connective tissues. Although myofibrils, A, I and Z bands are not recognizable in these groups of fibers, remnants of lipofuscin and lipid droplets (L) are present. The interstitium between muscle fibers is prominent. ×6,640.

Fig. 9. The micrograph from group D patient (case 17) shows portions of three muscle fibers, two of which are in different stages of degeneration whereas the third muscle fiber is essentially normal morphologically. The interstitium is prominent and shows blood vessels and collagen fibers. ×3,415
Discussion

Previous evaluation of myotonia patients indicated a statistically insignificant relationship between MNCV and both age and duration of disease (Olson et al., 1978). The ultrastructural characteristics of degenerating muscles showed an association with duration of disease ($\gamma = -0.62$). Deep tendon reflex impairment and muscle weakness showed no apparent association with the duration of disease or ultrastructural features (Tables 1, 2). However, analysis of ultrastructural patterns of muscle degeneration indicated an association with a systemic nerve MNCV ($\gamma = +0.60$). In other words, impairment in a distant peroneal nerve occurred independent of the quadriceps function in a group of patients and the vice versa condition was observed in another group of myotonia patients (Tables 1, 2). Furthermore, the ultrastructural patterns of muscle degeneration appeared more related to MNCV and duration of symptoms than to age, age of onset, or clinical parameters.

We recognize and emphasize that except for the quantitative MNCV data, other values that we have analyzed are unfortunately subjective and semiquantitative. For example, dates for the onset of symptomatic diseases are imprecise because patients themselves were often vague and occasionally denied the presence of obvious muscle dysfunction or disability which was noted by other family members. In the present study we show that patterns of muscle degenerations were associated with MNCV of a distant nerve in some myotonia patients, and not in others. Further support to our conclusion comes from the studies of List and Lovelace (1981) who reported the presence of both normal and slowed MNCV in myotonia dystrophica patients. Recently, Bird et al. (1984) and Aminoff et al. (1985) also showed neuropathic changes in the automatic nervous system of myotonia dystrophy patients.

Ultrastructural analysis of quadriceps muscle in myotonia dystrophica patients indicated that the degenerating muscle fibers contained disintegrated and disoriented myofibrils, peripheral and internal,
occasionally pyknotic nuclei, thickened plasma membranes, thin basement membranes, fragmented and disrupted Z bands, abnormal mitochondria, variable amounts of glycogen granules and lipofuscin granules. Several studies have described the above ultrastructural features in other chronic myopathies as well as in myotonia dystrophica (Schröder and Adams, 1968; Santa, 1969; Schotland, 1970; Engel and MacDonald, 1970). For example, peripheral and/or internal nuclei have been reported to occur in different types of muscle dystrophy (Santa, 1969; Bosanquet et al., 1973; Vassilopoulos and Lumb, 1980). The centrally placed nuclei were more abundant in patients than in normal controls as is the case in primary neurogenic atrophy (Vassilopoulos and Lumb, 1980). Defects in the plasma and basement membranes have been reported in both murine (Kerr and Sperelakis, 1983) and human (Appel et al., 1977; Casanova and Jerusalem, 1979; Sandrini et al., 1982) muscular dystrophy and in the Z disk of human myotonia dystrophica (Engel, 1967). Our study indicates that in myotonia dystrophica patients, the degenerating muscles showed initial thickening of plasma membranes, followed by some disruption of basement membranes, Z bands and myofilaments, and internalization of nuclei. As the degeneration of muscle proceeded, there was an increased amount of septal connective tissue elements such as collagen fibers and flocculent material in the interstitium.

As in the other ultrastructural studies, we did not find a single ultrastructural feature of muscle degeneration that could indicate degeneration of an individual or groups of muscle fibers. Moreover the abnormalities identified did not correlate directly either in frequency or degree with slowing of MNCV, such as might occur with progressive neuropathic changes in motor units without any primary myopathy (McComas et al., 1971).

Recently, Rowland (1976) summarized three major hypotheses to explain the pathogenesis of muscular dystrophies, namely the vascular, neurogenic, and genetic membrane theories. The disruptions of muscles in myotonia dystrophica could be triggered by abnormal neuronal or nerve lesion as suggested by several workers (Caccia et al., 1972; Kalyanaraman et al., 1973), by genetic fault of the surface membrane (Rowland, 1976) or genetically inherited autosomal disease (see Tanaka, 1985), and/or by combined myopathic and neuropathic disturbances (Panayiotopoulos and Scarpalezos, 1977; List and Lovelace, 1981). Our study supports the idea that combined myopathic and neuropathic disturbances are involved in myotonia dystrophica as evidenced by the involvement of a systemic (peroneal) nerve which is distant from the degenerating quadriceps muscle.

References
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Accepted March 31, 1987