Striated Muscle in Four Categories of Leprosy. I. Histology and Histochemistry[1]

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Muscle changes in leprosy have been reported infrequently despite the fact that more than 20% of leprosy patients suffer from motor deficits and paralysis of muscles ([31]). In fact, according to the American Leprosy Missions, leprosy "causes more hand paralysis than all other diseases put together."

Hoggan ([20]) has been credited with the earliest report of muscular atrophy in leprosy. From their own considerable clinical and some pathological experience of nerve and muscle tissue in leprosy, Hansen and Looft ([18]), as far back as 1895, agreed with the suggestion of Hoggan that "the muscular affection in leprosy" was essentially an atrophy and secondary to the neuritis. The various stages of degeneration of the myoneural endings and denervation atrophy were described by Dastur ([4]). *M. leprae* have been reported in the muscle, mainly between striated muscle fibers, by Ishihara ([21]), Convit, *et al.* ([3]), and Pearson, *et al.* ([27]) and in intramuscular nerve twigs by Dastur ([4]). Harman ([19]) rightly stressed the frequent bacillation of smooth muscle fibers in the skin, the lips, and the nipple in lepromatous leprosy.

Most detailed reports dealing with pathological changes in nerves omit any mention of skeletal muscle changes. Convit, *et al.* ([3]) described degenerative changes in the muscle as "leprous myositis." In a study of muscles, intramuscular nerves, and nerve endings in leprosy, Dastur ([4,6]) stressed the relative infrequency of changes consistent with a leprous myositis (in less than 10% of specimens), which was at times secondary to intramuscular leprous neuritis. This has been reviewed recently ([23]). To the best of our knowledge, the histochemistry of muscle in leprosy has not been studied at all.

In the present study, histological changes, as seen in frozen and paraffin embedded sections of striated muscle, are reported. Ultrastructural examination of the muscle of the same cases has also been carried out and will be reported in the second paper of this series ([7]).

MATERIALS AND METHODS

Clinical material. The clinical material comprised 4 groups of leprosy patients. Except for group IV, all the patients were reporting as fresh, untreated cases to the outpatient department of Acworth Leprosy Hospital, where they were examined, selected, and biopsied.

The 7 patients of group I manifested very early non-lepromatous leprosy, generally of the early macular tuberculoid variety. They were bacteriologically negative as determined from smears of skin clips of the cutaneous lesion and the ear lobule. Each patient had only 1 or 2 small skin lesions, which were flat, hypopigmented, and hypesthetic to anesthetic. A full thickness biopsy of the periphery of the skin lesion, which included a part of the surrounding normal skin, was carried out in each case. The essential finding in variously stained paraffin sections of these biopsies was the presence of few or many inflammatory exudates consisting of small mononuclear cells with only a stray larger mononuclear cell. Epithelioid cells or giant cells were not seen. Lepra cells or bacilli were not encountered in any specimen. None of the patients had any signs or symptoms referable to the peripheral nerves except for

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slight tenderness of the ulnar nerve in 2 patients. None of them showed any weakness of the ulnar or median nerve supplied muscles of the hand or forearm nor wasting or weakness of the muscles of the lower limb.

The 2 patients of group II had untreated tuberculoid leprosy of long duration and were also bacteriologically negative on examination of skin smears or of the full thickness skin biopsies. There were multiple skin lesions which were small or large, generally pale, and occasionally well defined with raised edges. Paraffin sections of the biopsy specimen of 1 of these lesions showed a florid mononuclear cell reaction, with more large mononuclear cells than in biopsies of group I. One of the 2 specimens showed prominent epithelioid cells and a few giant cells organized to form "tubercles" and also clear infiltration of the deep dermal nerves. Of the peripheral nerves, the ulnar was most thickened, but other nerves of both the upper and lower limbs were also found thickened on palpation. The ulnar supplied hand muscles were found weak in both cases with wasting in 1 case (the one with the more severe reaction in the skin lesion described above).

Group III comprised 5 patients with established untreated lepromatous leprosy. They were bacteriologically positive with a large number of acid-fast bacilli in both the skin clip and nasal smears. Biopsy specimens of the skin from the edges of the incision on the hand showed a few exudates with lepra cells in addition to small mononuclears. There were no discrete lesions, but there was generalized infiltration of the skin, including thickening of the ear lobules. The ulnar, greater auricular, and other nerves were found thickened and tender. Two of the patients showed weakness and wasting of hand muscles with contractures of the medial fingers; one showed weakness but no wasting; and 2 others were unremarkable in respect to the power of these muscles.

The 7 patients of group IV were of the lepromatous type and had taken the prescribed course of treatment with dapsone (DDS), 100 mg daily for 6 days a week, continuously for 1½ to 6 years. The dapsone/creatinine ratio in urine was measured in all patients of this group and was found to be within normal limits for patients taking this dose of dapsone (35 and over) in 6 of them. In 1 patient (J/45), this ratio was markedly low (10.5), indicating that he alone was either not taking treatment adequately or not absorbing his dapsone. All patients were bacteriologically positive on skin clip and nasal smear examination with predominantly granular forms of AFB at the time of biopsy. At this time, 6 of the patients showed no overt cutaneous lesions. One patient (J/45) presented with ill-defined congestive lesions with a nodular surface over the ears, along the forearm, and on the hand, which probably represented either a form of reactive leprosy or an allergic reaction since these did not contain bacilli, and the patient was afebrile and asymptomatic. At operation, there were clear adhesions between the skin and the first dorsal interosseous muscle in these patients. Of the peripheral nerves, the ulnar was found thickened in all, and in 1 case, the radial and lateral popliteal nerves were also thickened. There was weakness of adduction/abduction of the thumb and fingers in 3 of the 7 patients (including J/45), the power of the hand muscles being normal in the others. Patient J/45 also showed wasting of these muscles.

Surgical procedure. The first dorsal interosseous muscle was biopsied in all the cases except 4 cases of group I where the flexor carpi ulnaris was biopsied. The former muscle was biopsied because the nerve selected for simultaneous study was the index branch of the radial cutaneous nerve from the dorsum of the hand, and the latter was biopsied along with 1 or 2 funiculi of the ulnar nerves in and above the elbow groove by the plastic surgeon (J.S.S.), assisted by the neuropathologist (D.K.D.). The other important reason for the selection of these particular pairs of nerve and muscle biopsies was the well-known fact that these 2 nerves, the radial ([6]) and the ulnar ([8]), are damaged early and selectively in leprosy of all types.

Laboratory methods. For routine histology the specimens were fixed in formalin, blocked in paraffin, and the sections stained with hematoxylin and eosin. For quantitation, the smallest fiber diameter in formalin fixed and frozen cross sections was measured by stage and eyepiece micrometry, and fiber size spectra were plotted.

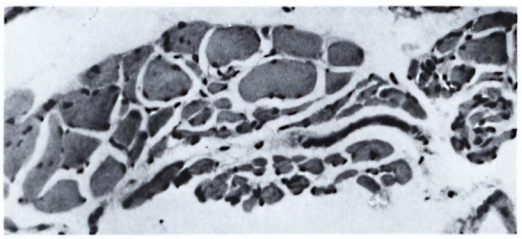

FIG. 1a. (NP/K/6): Weak muscle from a patient with lepromatous leprosy, showing muscle fascicles with small or large well-defined or ill-defined groups of atrophic fibers contrasting with the better preserved fibers. (H. & E., ×250)

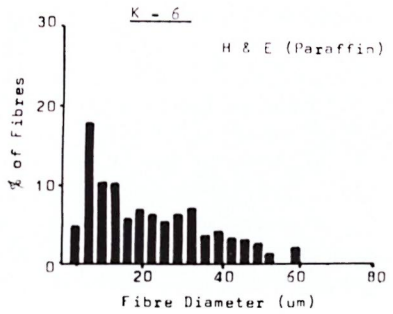

FIG. 1b. Histogram of fiber diameters of the same muscle shows a large proportion (56%) of small-sized fibers below 20 μm in size and a very small proportion (15%) above 40 μm.

A portion of the biopsy specimen was snap-frozen in isopentane cooled in dry ice, and 10 μm sections cut in a cryostat at −20°C. The histochemical reactions studied for determining fiber types were succinic dehydrogenase ([17]), adenosine triphosphatase ([25]), and phosphorylase ([29]). The thiolacetic acid esterase method of Wachstein, *et al.* ([30]) was followed for the demonstration of acetylcholinesterase at the motor end-plates.

RESULTS

Histology. Striated muscles from the patients in group I revealed a normal histology of well-organized fascicles with compactly arranged fibers. Fiber diameter measurements showed that there were no fibers smaller than than 34 μm in size, the average diameter being 52 μm in frozen sections and 40 μm in paraffin sections.

Of the 2 specimens in group II, atrophy was evidenced as a generalized reduction in the size of all the fibers in 1 case and as groups of small fibers in the other patient, who was clinically more severely affected and who showed the florid tuberculoid reaction in the skin. The average fiber diameter was lower than that in group I (25.5 μm in paraffin sections).

In group III, 2 patients who had no wasting or weakness of their hand muscles showed an essentially normal histological picture. The others, who presented with wasting, weakness, or clawing of fingers, showed atrophy (Figs. 1a and 1b), at times the entire muscle being made up of very small fibers and fascicles (Figs. 2a and 2b). Muscle fibers from the atrophic areas showed angularity and nuclear prominence.

In addition to the atrophy, 2 cases also showed some myopathic features. In some areas, there was moderate to marked variation of fiber size and rounding, some fibers showing central nucleation. Occasional muscle fibers undergoing necrosis, evidenced by collections of large mononuclear cells, were also seen (Fig. 3a) in the patient with moderate weakness of the hand muscles and early contractures (see clinical material).

The biopsies in group IV showed mainly large fascicles with compactly arranged fibers. These fibers showed little or no variation in size except in 1 case (with mild weakness of the hand muscles) where 1 or 2 groups of atrophic fibers were seen. The average frozen fiber diameter in these cases was 51 μm (comparable to that in group I) except in 1 specimen (NP/J/45, see clinical material), where all the fascicles were made up of highly atrophic fibers (average fiber diameter—20 μm). Slightly more than the usual variation in fiber size was found in specimens from 3 of the 7 cases of this group, all 3 of whom had clinically unaffected muscles.

Fite-Faracco stained sections showed acid-fast bacilli (AFB) in 3 of the 5 untreated lepromatous patients (group III). These bacilli were not within the muscle fibers but in an exudate between fibers in 1 case (Fig. 3b) and in endothelial cells of blood vessels in the other 2 cases (Fig. 3c). AFB were detected in the muscle in only 1 of the 7 treated lepromatous cases (group IV) and again in a vessel wall.

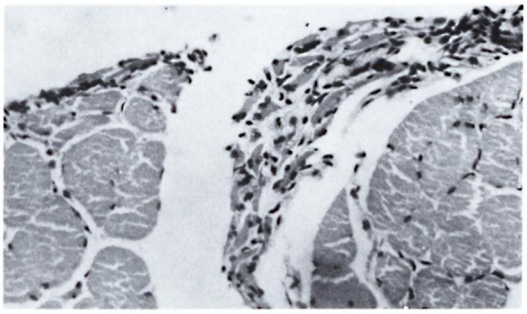

FIG. 2a. (NP/K/31): Weak muscle from a lepromatous patient; an entire fascicle made up of angulated atrophic fibers with apparent nuclear increase between 2 other fascicles with polygonal normal-sized fibers. (H. & E., ×250)

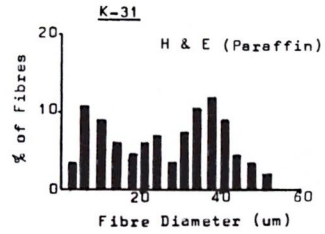

FIG. 2b. Histogram of fiber diameters, showing a wide range of size. The very small fibers (under 20 μm) represent the atrophic fascicle and the larger fibers the lateral fascicles in Fig. 2a.

Enzyme histochemistry. Histochemical preparations for succinic dehydrogenase (SDH), phosphorylase, and myosin adenosine triphosphatase (ATPase) revealed Type I and Type II fibers to be well distributed in a checkerboard pattern in all biopsies of group I, especially as seen by the ATPase reaction (Fig. 4a). An actual count showed the average ratio of Type I to Type II fibers to be 1:1.6 for the flexor carpi ulnaris (FCU) and 1:1 for the first dorsal interosseous muscles. The histograms for the diameters of the 2 fiber types confirmed the impression that there was no appreciable difference between the fiber types with respect to size.

Similar preparations of the specimens in group II showed a preponderance of Type I fibers (Type I:Type II = 1:0.4). In some areas the Type II fibers were grouped together, giving type grouping.

In group III, the muscle biopsies again showed type preponderance and type grouping. The graph of fiber types clearly shows the Type II fibers to include small and large sized fibers whereas the Type I fibers were of uniform size. In addition, the clinically weak muscles showing atrophy in paraffin sections contained small fibers of both types. Sometimes, there were groups of atrophic fibers all belonging to Type II, thereby manifesting type atrophy (Fig. 4b).

All the specimens of group IV showed a fairly constant picture of Type I preponderance, and most of them showed type grouping without atrophy (Fig. 5a). Thus, type grouping was encountered in clinically weak muscles as well as in those which were clinically unaffected. In the 1 muscle showing severe atrophy (NP/J/45), the atrophic fibers were of both types, but the larger fibers were mainly of Type II (Fig. 5b).

Preparations of cholinesterase reaction at motor end-plates revealed a rich spray of innervation in the muscles of group IV patients (Fig. 6a). In contrast, in the specimens showing fiber atrophy in groups II and III, the end-plates were scanty and tended to be abnormally expanded with outlying droplets of activity (Fig. 6b).

DISCUSSION

Histology. The most conspicuous change in the present material was a decrease in the size of the muscle fibers. The atrophied fibers occurred in well-defined or ill-defined groups, and many were angulated, conforming to the classical description of denervation [1], and were probably secondary to leprous neuritis. The only report on the

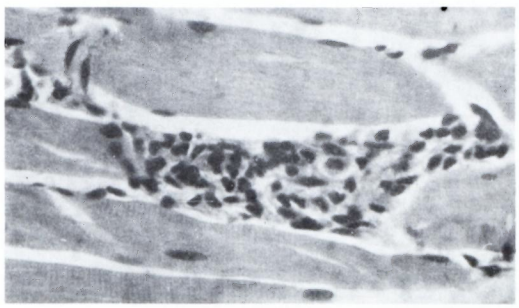

FIG. 3a. (NP/K/39): Slightly weak muscle from an untreated lepromatous patient, showing a longitudinal section of muscle fibers, 1 of them undergoing necrosis and replaced by a collection of large mononuclear cells (phagocytes). (H. & E., ×625)

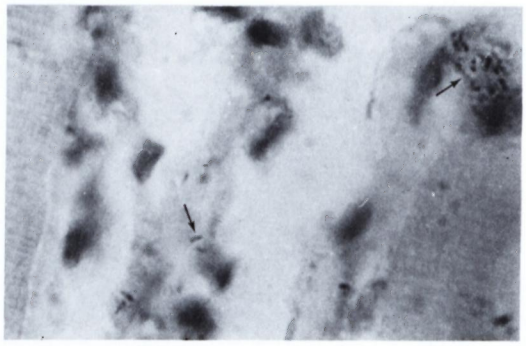

FIG. 3b. (NP/J/993): Perivascular exudate between muscle fibers, showing a number of acid-fast bacilli. Note the large cluster on the neurovascular bundle arching onto the fiber on the right (arrow). (Fite-Faracco, ×1400)

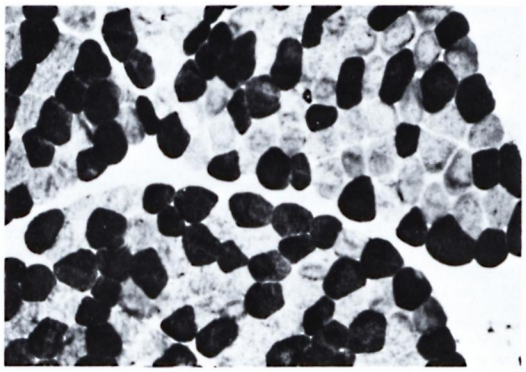

FIG. 4a. (NP/I/976): Muscle showing no clinical wasting or weakness; normal checkerboard pattern of dark Type II fibers and lightly stained Type I fibers. The 2 types of fibers are seen in equal proportions. (ATPase ×100)

correlation between clinical and histological features of skeletal muscle in leprosy is that of Dastur [4] on 60 patients, the majority of whom were non-lepromatous. The largest number of muscle specimens showing normal or only slightly affected histology was encountered among patients with clinically unaffected muscles (12 of 15). Correspondingly, the largest number of specimens showing pronounced pathological changes was derived from patients with clinically severely affected muscles (20 out of 28). Groups of atrophic fibers along with floccular and vacuolar change in the sarcoplasm were seen by Slotwiner, *et al.* [28] in muscles from patients with leprosy who were negative for acid fast bacilli.

For many years atrophy of muscle fibers was considered to be an effect of denervation only. The occurrence of sarcoplasmic changes in otherwise well-defined neurogenic disease with no evidence of any other process was subsequently noted by Engel [15] in spinal muscular atrophy. Drachman, *et al.* [9] have provided striking evidence of the myopathic histopathology of muscle in long standing neurogenic atrophy. Drachman, *et al.* [10] found many features of "myopathy," including inflammatory, degenerative, and regenerative changes within a month after experimental denervation of extraocular muscles.

In our observations reported here, only neurogenic changes were seen in the established tuberculoid group, the duration of

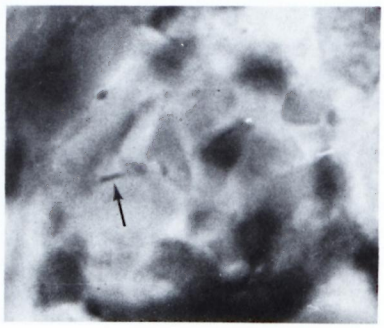

FIG. 3c. (NP/K/31): A single rod-shaped bacillus (arrow) in an endothelial cell of a blood vessel. (Fite-Faracco, ×1400)

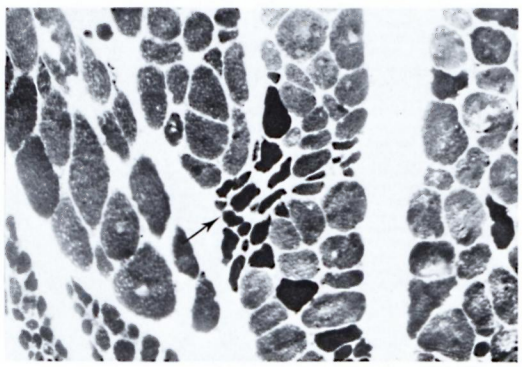

FIG. 4b. (NP/K/6): Better preserved fascicle made up of larger Type I fibers; a group of atrophic Type II fibers in the center (arrow) and parts of 2 fascicles with atrophic Type I fibers (in lower left corner), representing type atrophy in a clinically weak muscle from an untreated lepromatous patient. (ATPase ×100)

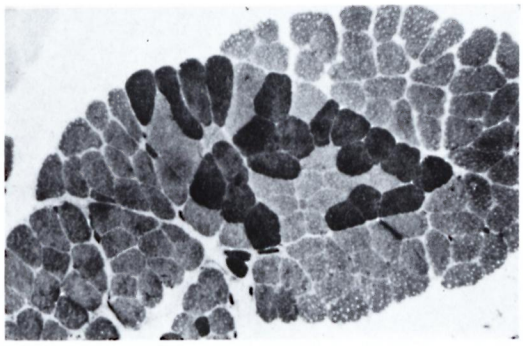

FIG. 5a. (NP/J/201): Clinically unaffected muscle; parts of 3–4 fascicles showing mainly pale Type I fibers. Note the central fascicle with a group of dark Type II fibers, suggesting type grouping without atrophy. (ATPase ×100)

symptoms being approximately the same in the untreated tuberculoid and lepromatous groups. Myopathic changes, i.e., fiber size variation, some rounding and occasional central nucleation, inflammation, and necrosis were encountered, in addition to considerable atrophy, in the lepromatous cases. Considering the light microscopic findings only, 2 of the 5 muscles from untreated lepromatous cases and 2 of the 7 from treated lepromatous patients showed acid-fast bacilli, generally in the inflammatory exudate between muscle fibers or fascicles. It may be recalled that 3 of the 6 lepromatous patients of Dastur ([4]) showed intramuscular bacilli, in 2 cases in interfascicular nerves and in 1 instance between muscle fibers. Likewise, of the 2 other instances when bacilli were seen in relation to intrafusal muscle fibers (within the "spindle"), by Patel, *et al.* ([26]) in a patient and by Edwards ([13]) in a mouse, they were clearly on the muscle fiber ([5]) (and not within it) and in the capsule cells of the spindle ([13]), respectively.

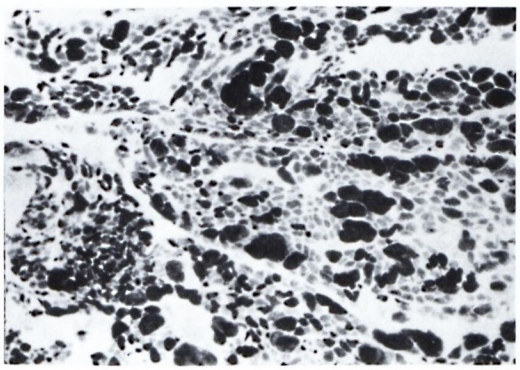

FIG. 5b. (NP/J/45): Clinically weak and wasted muscle, showing severe atrophy of fibers, both pale Type I and dark Type II fibers being atrophied except at lower left quadrant where there is a cluster of small Type II fibers representing type atrophy. Type II fibers constitute the majority of the better preserved fibers. (Phosphorylase ×100)

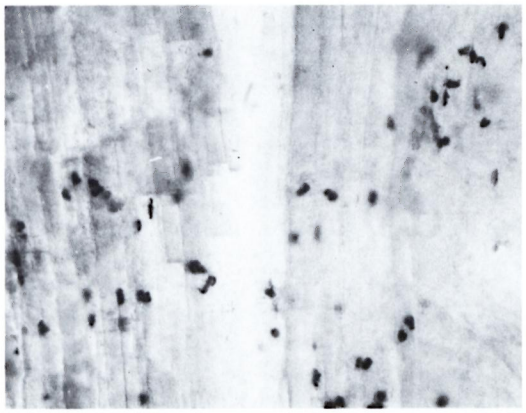

FIG. 6a. (NP/J/245): Clinically normal muscle from a treated lepromatous patient, showing a normal complement of motor end-plates. Note that there is generally 1 end-plate on 1 muscle fiber. (Cholinesterase ×100)

Histochemistry. There has been some argument whether a given denervative process acts selectively on 1 or another type of muscle fiber. In long standing denervation of muscle, the atrophic fibers are of both types histochemically, thus helping to

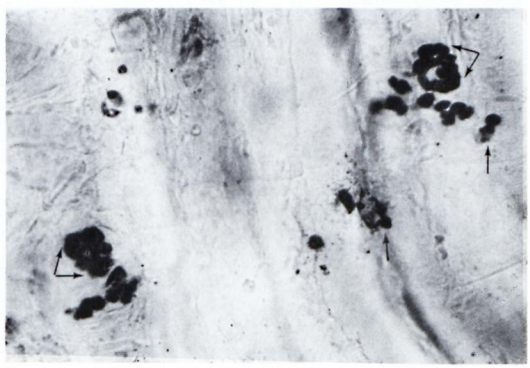

FIG. 6b. (NP/K/6): Weak muscle from a patient with lepromatous leprosy, showing motor end-plates of varying size and shape including some which appear expanded (split arrows) and some shrunken (arrows), the latter on atrophied fibers. (Cholinesterase ×320)

distinguish this condition from those with selective atrophy of 1 fiber type. "Type atrophy" of any fiber type is generally accepted to indicate a denervation process particularly affecting anterior horn cells ([16]). To the best of our knowledge, the present investigation reports for the first time histochemical findings on the striated muscle in leprosy.

In the present observations, there was no preferential atrophy of either type in the specimens of the tuberculoid group whereas some "type atrophy," especially of Type II fibers, was observed in the lepromatous group. Type II fiber atrophy has been recorded in such diverse situations as mental retardation ([2]) and collagen vascular disease ([14]). Perhaps this occurrence of Type II fiber atrophy should signify that the muscle is inactive. "Type grouping," another activity characteristic of denervation, probably represents a process of reinnervation of previously denervated fibers. It is usually a feature of long standing and relatively slowly progressive neuropathies. Type grouping was seen in our material in the lepromatous groups.

Histologically normal looking muscle revealed a rich supply of motor end-plates, demonstrated by their cholinesterase activity. In the atrophic muscles, the end-plates were scanty, and at times they could not be discerned at all in the severely affected cases. Lubinska ([22]) found an abrupt fall in cholinesterase activity after denervation of fast and slow muscles of the rat at birth. The slow muscles were more affected than the fast. Miledi and Slater ([24]) found that cholinesterase was clearly visible in both normal and denervated muscle even several months after nerve degeneration.

The elongated or multiple end-plates seen in myasthenia gravis might be caused by a change in the muscle fiber surface membrane consequent to the interruption of neuromuscular transmission ([12]). Duchen ([11]) has suggested that interruption of neuromuscular transmission may be responsible for axon sprouting. He observed marked sprouting following intramuscular injection of botulinum toxin. When the axonal sprouts make contact with the surface of a muscle fiber, they appear to induce in the sarcolemma, by invagination, the formation of a groove constituting a miniature synapse. The synapse formation is readily detected in acetylcholinesterase preparations because of the rich acetylcholinesterase activity of the invaginated sarcolemma. The development of new end-plates seems to result in the formation of a structure exceeding in size and complexity the original end-plates ([32]). The few end-plates which appear larger, with multiple droplets, in the leprosy muscle could therefore be due to reinnervation by axonal sprouting. Attempts at regeneration were reported as a rare occurrence in vitally stained whole-mount preparations in leprosy patients ([4]).

In these 4 groups, there was some correlation between clinically detected muscular weakness, on the one hand, and greater atrophy (in all groups) and degeneration (in groups III and IV) by all parameters of light microscopy, on the other. These findings are confirmed by subsequent electron-microscopic examinations ([7]).

SUMMARY

This histological and histochemical study of muscle in leprosy was carried out in view of the paucity of such studies despite the fact that leprosy is the single largest cause of motor deficit and paralysis. There were 21 patients who fell into 4 groups: those with very early non-lepromatous leprosy (group I, 7), untreated tuberculoid leprosy of long duration (group II, 2), untreated lepromatous leprosy (group III, 5), and treated lepromatous leprosy (group IV, 7). A normal histological and histochemical picture on paraffin and frozen sections stained for ATPase and succinic dehydrogenase (SDH) reactions was seen in group I. While groups II and III revealed muscle fiber atrophy and type preponderance, group III also showed degeneration of some fiber, inflammatory or necrotic reaction, and, histochemically, type atrophy or grouping. The treated lepromatous group showed similar but milder and less frequent changes. Fite-Faracco stained paraffin sections showed acid-fast-bacilli in and around blood vessels between muscle fiber in 2 specimens each of groups III and IV. In frozen sections stained for cholinesterase reaction, motor end-plates were well preserved in groups I and IV but appeared to be scanty in biopsies of group II and shrunken or expanded in group III. On the whole, lepromatous leprosy showed

the maximum changes in and around muscle fibers, and there was fair clinico-pathologic correlation in all the groups.

RESÚMEN

Este estudio histológico e histoquímico de los músculos en la lepra se realizó en vista de lo escaso de este tipo de estudios, no obstante que la lepra es la más importante causa única de disfunción motora y parálisis. Se estudiaron 21 pacientes organizados en 4 grupos: pacientes con lepra muy temprana no lepromatosa (grupo I, 7), pacientes con lepra tuberculoide de muy larga evolución y sin tratamiento (grupo II, 2), pacientes con lepra lepromatosa sin tratar (grupo III, 5), y pacientes con lepra lepromatosa tratada (grupo IV, 7). En el grupo I se observó un cuadro histológico e histoquímico normal en los cortes en parafina y en los cortes en congelación teñidos para visualizar la actividad de ATPasa y de SDH. Los grupos II y III mostraron evidencias de atrófia de la fibra muscular y preponderancia de tipo, el grupo III también mostró degeneración de algunas fibras, reacción inflamatoria o necrótica e, histoquímicamente, atrófia de tipo o agrupamiento. El grupo de los lepromatosos tratados mostró cambios similares pero moderados y menos frecuentes. En dos especímenes del grupo III y en dos del grupo IV, los cortes en parafina teñidos por Fite-Faracco mostraron la presencia de bacilos ácido resistentes en y alrrededor de los vasos sanguíneos, entre las fibras musculares. En los cortes en congelación teñidos para colinesterasa, las placas terminales motoras estuvieron bien preservadas en los grupos I y IV pero aparecieron escasas en los especímenes de los grupos II y III, con atrófia grupal.

RÉSUMÉ

On a décidé de procéder à une étude histologique et histochimique du muscle dans la lèpre, car de telles études sont rares, et ce, malgré le fait que la lèpre soit la principale cause de déficit moteur et de paralysie. On a considéré 21 malades, qui pouvaient être classés en quatre groupes. Le groupe I, composé de 7 malades, reprenait ceux avec une lèpre non lépromateuse très précoce. Le deuxième groupe était constitué par des malades atteints de lèpre tuberculoïde depuis longtemps, et non traités. Ce groupe se composait de 2 personnes. Le troisème groupe reprenait les malades souffrant de lèpre lépromateuse et non traités, soit 5 personnes. Quant au quatrième groupe, il s'agissait de lèpre lépromateuse traitée, 7 malades en tout. Dans le groupe I, on a observé des aspects histologiques et histochimiques normaux, dans des coupes congelées et enrobées de paraffine, colorées pour mettre en évidence les réactions à l'ATPase et à la SDH. Alors que les groupes II et III révélaient une atrophie des fibres musculaires, caractéristique du type de lèpre, le groupe III montrait également une dégénération de quelques fibres, de même qu'une réaction inflammatoire ou nécrotique et, du point de vue histochimique, de l'atrophie caractéristique du groupe. Le groupe lépromateux traité montrait des modifications analogues, mais plus discrètes et moins fréquentes. Les coupes colorées par la méthode de Fite-Faracco à la paraffine, révélaient des bacilles-acido-résistants dans les vaisseaux, de même qu'autour des vaisseaux, entre les fibres musculaires, et ceci dans deux échantillons appartenant effectivement aux groupes III et IV. Dans des coupes congelées, colorées pour mettre en évidence la réaction à la cholinesterase, les plaques terminales dans les muscles moteurs étaient bien préservées dans les malades des groupes I et IV, mais apparaissaient plus rares dans les biopsies provenant des groupes II et III montrant par ailleurs de l'atrophie caractéristique de ces groupes.

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