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Muscle Spindles in Rheumatoid Arthritis

An Ultrastructural Study

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Summary. Ultrastructural features of muscle spindles were studied in biopsy material from 100 patients suffering from classical rheumatoid arthritis. Thickening of the outer capsule, increased amount of extracellular ground substance within the inner capsule, and marked thickening of the basement membrane of capillary blood vessels supplying the muscle spindles were observed. Chronic inflammatory cells and macrophages were present within the spindles. Changes affecting the intrafusal muscle fibres were also seen. They were manifest as atrophy and degeneration of the intrafusal muscle fibres, absence of the specialised junctional complexes, and of the intercellular bridges, microladders and satellite cells. It is suggested that the changes affecting the intrafusal muscle fibres are probably secondary. Damage to the myelinated nerves was present, while the sensory and motor nerve endings were well preserved.

Key words: Rheumatoid arthritis – Muscle spindles – Neuromuscular spindles – Ultrastructure.

Introduction

Muscle spindles are richly innervated sensory-motor organs situated between the extrafusal muscle fibres found mainly in the perimysium. As seen by light microscopy the muscle spindle consists of a slender laminated capsule of connective tissue with an endothelial lining, containing specialised muscle fibres of two types; those of nuclear bag and nuclear chain fibres. It also contains sensory and motor nerve endings and blood vessels, supplying the spindle (Ruffini, 1898; Adams, 1975).

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It has been suggested by a number of investigators that the typical muscle changes observed in the course of rheumatoid arthritis such as muscle wasting, weakness and alteration in muscle tone may be due to the direct involvement of the neuromuscular system (Morrison et al., 1947; Moritz, 1964; Haslock et al., 1970). In view of this we have considered that changes in the muscle spindles may be of importance in this disease. In a previous study muscle spindles found in muscle biopsies from patients suffering from classical rheumatoid arthritis were examined by light microscopy (Magyar et al., 1973). The changes observed can be summarised as follows: 1) Marked thickening of the connective tissue capsule of the spindle. 2) Narrowing or even disappearance of the periaxial space of the muscle spindle, due to capsular thickening and proliferation of intracapsular connective tissue. 3) Damage to the fibrous septa within the periaxial space. 4) Decrease in the number of the intrafusal muscle fibres. 5) Degenerative changes within the muscle fibres. 6) Thickening of the wall and narrowing of the lumina of the blood vessels supplying the muscle spindle. 7) Damage to the innervation of the spindle and 8) Presence of inflammatory cells within the muscle spindle.

The majority of these abnormalities are similar to those of denervation changes affecting muscle spindles (Steinberg, 1960; Moritz, 1964; Cazzato and Walton, 1968; Patel et al., 1968; Magyar et al., 1973, 1977).

An ultrastructural study has been undertaken in order to obtain more detailed information and to establish whether, in cases of rheumatoid arthritis, there are changes in muscle spindles which can only be detected by electron microscopy.

Material and Methods

The present study has been carried out on biopsy material obtained from 100 cases of classical rheumatoid arthritis. During operations for joint reconstruction, muscle biopsies were taken mostly in a bloodless field at the beginning of the operation, from several muscles of the same patient. The muscles were: extensor carpi ulnaris, extensor carpi radialis, extensor digitorum brevis, biceps brachialis, vastus medialis and lateralis.

The fragments of muscle prepared for EM examination were fixed in 3% glutaraldehyde, in 0.1 M cacodylate buffer at pH 7.4 for 18 h at 0–4 C°. The material was rinsed in the same buffer for 24 h. It was subsequently postfixed in 1% Osmic acid for 4 h, dehydrated and embedded in Epon 812. The ultrathin sections were stained with 1% aqueous uranyl acetate for 30 min at room temperature, rinsed in a jet of distilled water and subsequently treated with lead citrate for 10 s, according to the method of Venable and Coggeshal (1965). The material was studied with Philips 300 electronmicroscope operating at 60 kV.

Fig. 1. Concentric layers of fibrocytes and collagen fibres are seen surrounding an intrafusal muscle fibre. Between the intrafusal muscle fibre and the peripheral collagen sheath, axons surrounded by Schwann cells and other fibrocytes are seen. The fibrous matrix has somewhat loose architecture. (Magn. ×8,160)

Fig. 2. Cross section of an atrophic nuclear bag fibre (presumably in the equatorial region). Inside the cell four approximately equally sized nuclei are present with heavily stained nuclear chromatin at the periphery. Some myofibrillar remnants are seen scattered in the cytoplasm (*arrows*). Outside the plasma membrane some nerve endings can be seen (*empty arrows*). They are separated from the bag fibre by extracellular material, which may indicate shrinkage of the bag fibre. (Magn. ×8,160)

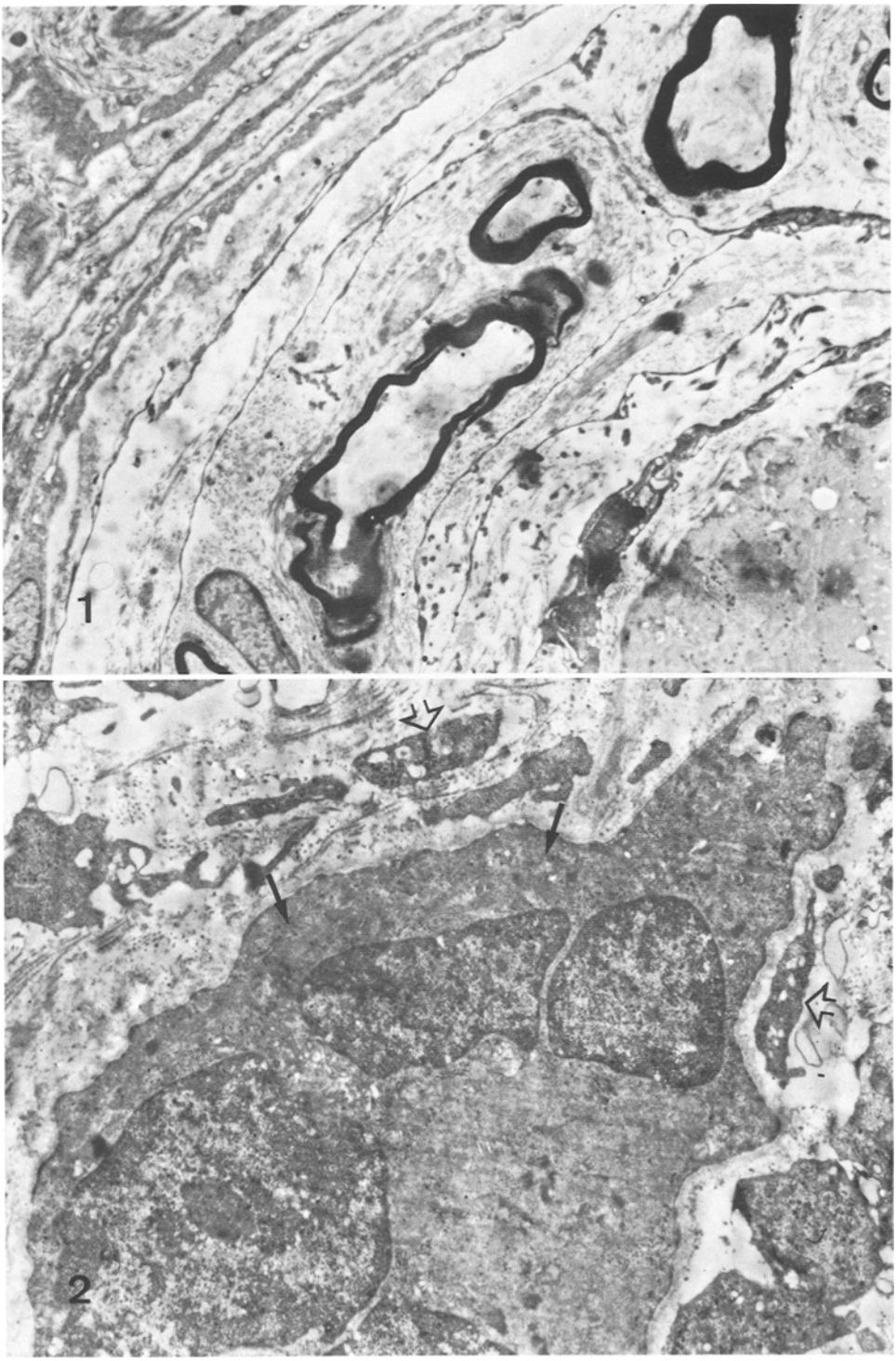
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Table 1. Ultrastructural features of the nuclear bag fibres in rheumatoid arthritis

Contractile elements	There is a chaotic array of myofibrillar material in the equatorial region. In some places the myosin and actin structure is preserved. In other areas the regular architecture is disrupted; the filaments are more loose and contain increasing amounts of glycogen, lipids and mitochondria. The plasma membrane is patent
Specialised junctional complexes	are absent
Components of the sarcoplasm	Glycogen particles and free ribosomes are present, as lipid droplets and dense bodies of various shapes and sizes
Sarcoplasmic reticulum and transverse tubular system	The plasma membrane shows some invaginations. Inside the cell only a small amount of sarcoplasmic reticulum is present
Sensory region	The nerve endings are well preserved. Within the sensory region atrophy and shrinkage of the bag fibres can be detected

Results

The majority of the spindles were surrounded by numerous concentric layers of elongated fibrocytes. Between these fibrocytes there was an extracellular ground substance in which collagen fibres were present. In places the fibrocytes contained an increased number of pinocytic vesicles. The fibrocytes were arranged in a closely parallel array and a small elongated channel appeared to be enclosed by them. More centrally this concentric architecture was absent and groups of axons, each apparently surrounded by a single layer of fibrocytes or Schwann cells (Fig. 1) were observed.

Damage to the fibrous septa within the periaxial space was evident. In some places the concentric array of fibrocytes was disturbed by the presence of somewhat pleomorphic fibrocytic cells, which were surrounded by large, irregularly arranged bundles of collagen fibres, disturbing the normal pattern.

The capsule contained capillary blood vessels. In some places the basement membrane was normal, while in others marked thickening was present.

The main findings concerning the nuclear bag fibres are summarised in Table 1. In most nuclear bag fibres the whole cytoplasm was filled almost completely by apparently normal myofilaments, separated by small mitochondria and very small amount of endoplasmic reticulum. The nucleus, or nuclei in most cases, were located eccentrically (Fig. 2). However, in some nuclear bag fibres the arrangement of the myofilaments was disturbed, although the number of mitochondria was not increased. In some cases this reduction of myofilamentous material was marked and apparently empty-looking cytoplasm was present containing only some small clusters of filamentous material. Satellite cells appeared to be absent. The specialised junctional complexes which appear as trilaminated structures were also absent.

Table 2. Ultrastructural features of the nuclear chain fibres in rheumatoid arthritis

Contractile elements	In some fibres the architecture of the cell is preserved. In others the architecture is disturbed and the fibres become increasingly intermingled with sarcoplasmic elements, leading to clustering. Empty-looking cytoplasm indicates fibrillar atrophy
Intercellular bridges	These foot-like processes could not be detected, and this may perhaps be an indication of the degeneration of the chain fibres
Microladders	Are not observed, and this may indicate muscle damage
Sarcoplasmic reticulum and transverse tubular system	In some places they are still patent, in others there is an apparent reduction in the transverse tubular system
Sensory region	The nerve endings show appearances within normal limits. The muscle fibres become atrophic, and the nuclei disappear

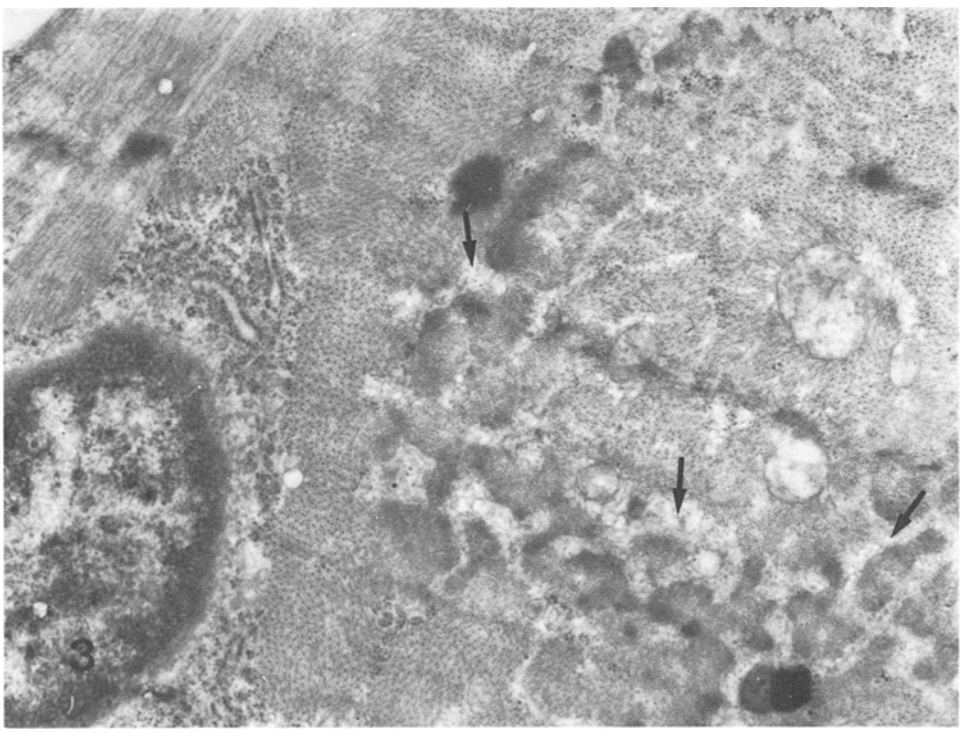

Fig. 3. Normal actin and myosin fibrils in a nuclear chain fibre. Around the nucleus there are some elements of the sarcoplasmic reticulum. In one place the normal regular structure of the actin myosin pattern is disrupted, forming empty-looking spaces between the myofibrils (*arrow*). (Magn. ×19,200)

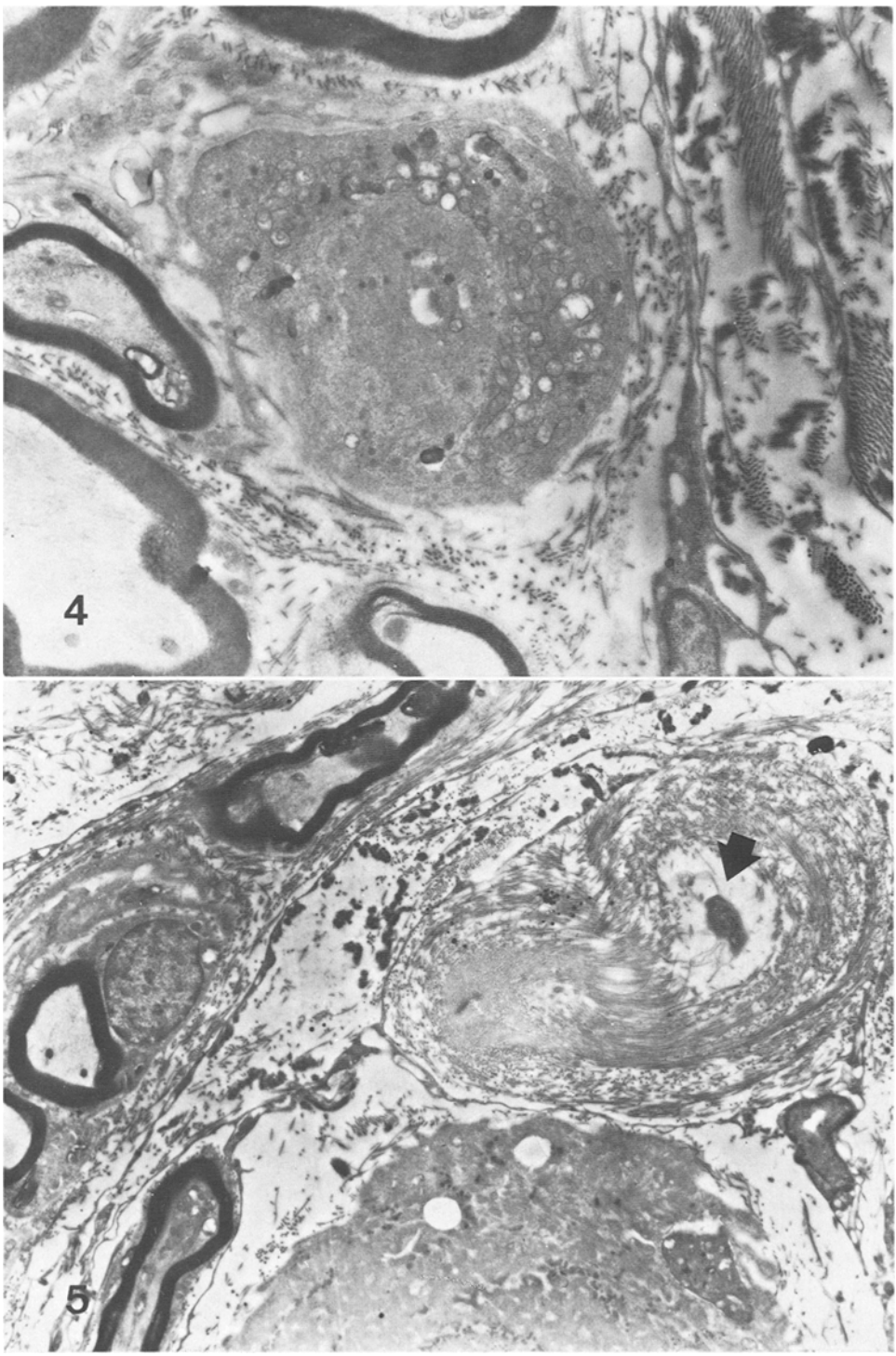

Fig. 4. Horseshoe shaped normal sensory nerve ending surrounding an atrophic nuclear chain fibre. (Magn. ×8,160)

Fig. 5. Nuclear chain fibre showing atrophic changes. Whorls of fibrous material are seen surrounding cytoplasmic remnants, which probably correspond to an atrophic nuclear chain fibre (*arrow*). (Magn. ×8,160)

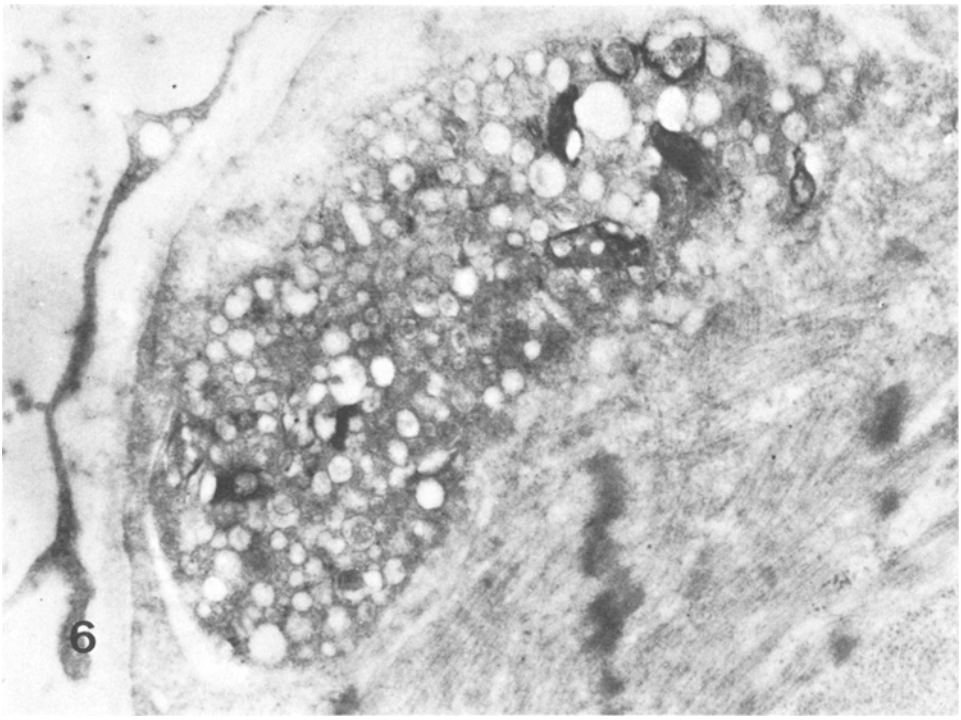

Fig. 6. Non-myelinated sensory nerve ending present on a nuclear bag fibre is seen. In this cross section the nerve ending is complete and surrounded by elements of the bag fibre. (Magn. ×28,000)

The findings concerning the nuclear chain fibres are shown in Table 2. At a high magnification the apparently normal arrangement of the thin actin filaments around the thick myosin filaments was not disturbed. However, in some places at a high magnification the regular arrangement of thin and thick myofilaments was disturbed, leading to a separation of the fibrils and a loose pattern. Glycogen was generally present in these sites (Fig. 3). In some areas the presence of whorls of collagen fibres surrounding some remnants of cytoplasmic material in the vicinity of chain fibres, suggests that muscle atrophy may be taking place in the spindles affected. Microladders were not found in the nuclear chain fibres and the intercellular bridges appeared to be absent completely. In some places normal horseshoe nerve endings were observed enclosing an atrophic remnant of a cell, which according to its cell content was considered to be a chain fibre (Figs. 4 and 5).

Nerve endings were frequently found on the surface of the nuclear bag as well as of the nuclear chain fibres. Primary and secondary sensory endings with numerous granular vesicles were observed, either within the basement membrane or completely surrounded by the elements of the nuclear bag fibre. The motor end plates located in the nuclear chain fibres appeared to be normal (Fig. 6).

The changes seen in the axons present in the muscle spindles were consistent with those of axon degeneration. In places the axons did not fit the space inside the myelin sheath, and irregularly shaped thick fragments of the myelin sheath were located in the cytoplasm of the Schwann cells. They appeared to be involved in a process of incorporation (Figs. 4 and 5).

Infiltrates composed of large lymphocytes and plasma cells were observed in the periaxial space of the muscle spindles, showing a mainly perivascular arrangement.

Discussion

Although the ultrastructural features of normal muscle spindles in different species have been described (Marrillees, 1960; Landon, 1966; Düring and Andres, 1969; Adal, 1969; Banker and Girvin, 1971) there is little information concerning the effect of various pathological conditions on the muscle spindles. In reviewing the literature we have failed to find any studies describing the fine structure of muscle spindles in rheumatoid arthritis.

The finding of an increased amount of extracellular collagenous material present within the inner capsule and of the thickening of the outer capsule observed in our material may be related to disturbances of transport, which may be followed by damage to the intrafusal muscle fibres. It has been shown that the outer capsule of the muscle spindle corresponds to the perineurium and its main role is transport (Banker and Girvin, 1971; Ovalle, 1976). The channels which open into the periaxial space are important from this point of view. The loose connective tissue, forming the inner capsule (fibrous septa) appears to function as a connecting link between the outer capsule and the intrafusal muscle fibres. The presence of chronic inflammatory cells and macrophages located in the capsule or in the periaxial space may also play a part by damaging the lamellae and channels. The thickening of the basement membrane of the capillaries causing considerable narrowing of the vascular lumina is also important, as it affects the blood supply to the spindles.

In view of the pathological changes mentioned above it is suggested that the abnormalities found in the intrafusal muscle fibres are probably secondary. The nuclear bag fibres did not contain specialised junctional complexes. These trilaminated structures are easy to recognise in normal muscle. Their function is the establishment of a low electrical potential in order to facilitate the spread of excitation (Barker, 1962). No intercellular bridges between the nuclear chain fibres were seen in our material. The function of these footlike processes is to maintain contact between the chain fibres. The microladders in normal smooth muscle cells and intrafusal muscle cells are approximately 1.5 μ in length, and are conspicuous. They are produced by nuclear activity, and represent early growth or regeneration of the intrafusal chain fibres (Katz, 1961). We could not detect these structures in our material. Banker and Girvin (1971) described the complete disappearance of microladders in muscles, which lost their efferent connection. They also observed abnormalities in the sarcoplasmic reticulum

and in the transverse tubular system. Reduction in the transverse tubular system in the intrafusal muscle fibres was also observed in our material.

The changes in the architecture of the axons in the muscle spindles examined in the present study resemble the changes produced by experimental denervation of mammalian spindles reported by Zelenà and Soukup (1974). Although the reduction in the axon diameter observed was related to the diameter of the myelin sheath, the microtubular organisation inside the axon was in most cases undisturbed. In the material examined the satellite cells appeared to be absent in the muscle spindles. Normally they are seen in association with the nuclear bag fibres, and play an important role in the innervation of these fibres (Banker and Girvin, 1971). It is of considerable interest that both the sensory and motor endings seen in our material were well preserved, and patent. It appears that in cases of rheumatoid arthritis the most resistant components of the spindles are the nerve endings.

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