Virchows Arch. A Path. Anat. and Histol. 370, 307—321 (1976)


# Morton's Metatarsalgia

## Light and Electron Microscopic Observations and Their Relation to Entrapment Neuropathies

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Received February 4, 1976

*Summary.* The dissected plantar nerves of 105 patients with clinical symptoms of Morton's disease were examined under light and electron microscopy. Of the 105 cases, 75 showed characteristic neuronal lesions; in the others different pathologic substrates responsible for the clinical symptoms could be demonstrated. The nervous lesions are characterized by:

1. Thickening of the walls of the endoneurial vessels produced by multiple layers of basement membranes.
2. Edema and sclerosis of the endoneurium. In the electron microscope the endoneurium was filled by deposits of fibrils with a tubular substructure and a diameter of 100–110 Å.
3. Thickening of the perineurium.
4. Degeneration of the nerve fibers without signs of wallerian degeneration or obvious reactive Schwann's cell hyperplasia.

The possible pathogenetic mechanisms of Morton's disease and some clinical problems are discussed.

*Key words:* Morton's disease — Neuropathy — Peripheral nerve — Perineurium — Microfibrils.

*Zusammenfassung.* In 105 Fällen von Mortonscher Metatarsalgie mit typischer klinischer Symptomatik wurden lichtoptische und in einigen auch elektronenoptische Untersuchungen ausgeführt. In 75 dieser Fälle fanden sich in den chirurgisch entfernten Anteilen des Plantarnerven die für die Krankheit typischen neurohistologischen Veränderungen, während in den restlichen Fällen den klinischen Beschwerden unterschiedliche Befunde, wie Lipome, degenerative Gefäßprozesse mit thrombembolischem Verschluß und sekundärer Degeneration der nervösen Formationen sowie andere Krankheitsprozesse zugrunde lagen.

Die typischen Veränderungen bei Mortonscher Metatarsalgie sind durch folgende Befunde im betroffenen Plantarnerven gekennzeichnet:

1. Verdickung der Gefäßwände im Endoneurium durch Ausbildung zahlreicher Basalmembranen.
2. Ödem und bindegewebige Sklerose des Endoneuriums; letztere ist elektronenoptisch durch Fibrillen mit tubulärer Substruktur und einem Durchmesser von 100–110 Å charakterisiert.
3. Verdickung des Perineuriums.
4. Degeneration der neuralen Formationen ohne Zeichen Waller'scher Degeneration im Sinne eines langsam verlaufenden Prozesses.

Die den Veränderungen zugrunde liegenden pathogenetischen Mechanismen und einige klinische Probleme werden diskutiert.

## Introduction

Correct clinical diagnosis of Morton's disease has been rare up to now, although the syndrome first described by Durlacher in 1845 is characterized by distinct clinical symptoms. Patients complain of heavy pain of an electrical character

in one foot which begins in one of the intermetatarsal spaces during walking. Relief of pain follows immediately upon resting or removal of the shoe. The symptoms can be reproduced by pressing the affected nerve in the area between the toes. Since the disease is not well known the patients are commonly treated for vascular disturbances or by a great number of ineffective instep raisers. Nevertheless the only treatment leading to immediate and lasting relief of pain is resection of the interdigital nerve. Recurrences after operation have not been observed by us nor have such been reported by other authors.

In order to explain the pathogenetic mechanism of the disease, a wide spectrum of possibilities has been suggested in the literature, reaching from vascular lesions (Scotti, 1957), traumatic factors combined with abnormalities of the feet (Hauser, 1971), real neoplasms of the digital nerve (McElvenny, 1943), or formation of amputation neuromas (Baker and Kuhn, 1944). In a previous paper (Lassmann, 1968) we had a chance to examine the incipient stages of the alterations. They started in a spotted area of the normal interdigital nerve or one of its branches leading to a local knoblike enlargement. The first stages were characterized by thickening of the walls of the endoneurial vessels combined with local endoneurial edema, hypertrophy of neural connective tissue, and degeneration of nerve fibers. So we submitted that the designation *neuroma* is misleading and that the alterations are best described by the term endoneurial vascular fibrosis. On the other hand, the alterations of the vessels could not be discriminated clearly by routine or histochemical light microscopic techniques from the reaction of the neural connective tissue. Therefore we attempted to obtain new information about the pathogenetic mechanism of the disease by use of the electron microscope.

## Material and Methods

This study deals with the pathologic alterations in the resected material of 105 patients who presented the classical symptoms of Morton's disease. After plantar incision of the skin, the bifurcation of the digital nerve and the vessels were preparated and dissected. Only in advanced stages was it not possible to separate the nerve from the surrounding tissue and in these cases parts of the bursae had to be removed too. The specimens were fixed in 10% formalin and embedded in paraffin. Parts were fixed in formalin at a temperature of 0–4° C for 2 h for the visualization of biogenic amines (Sakharov). Sections were stained with H & E, Mallory, van Gieson elastica, peracetic acid-Gomori elastica stain for oxytalan fibers (Fulmer et al., 1958), Congo Red, Astrablue, cholinesterase (Root-Karnovsky), osmium zinc iodide (Maillet-Jabonero), and silver impregnation (Bodian, Cauna).

For electron microscopy 10 specimens were fixed in 3.5% glutaraldehyde buffered in 0.2 M cacodylate for 2 h. After rinsing in cacodylate they were postfixed in osmium tetroxide (Palade) and embedded in Epon 812. The staining procedure for the semithin sections included toluidine blue and alkaline fuchsin and after removal of the epoxy resin by sodium methoxate (Sheetz et al., 1973) Gomori elastica stain and the demonstration of oxytalan fibers (Sheetz et al., 1973). The ultrathin sections were stained with uranyl acetate and lead citrate and examined in a Philips EM 200 electron microscope. For quantitative evaluation of the myelinated and unmyelinated nerve fibers, cross sections of one digital nerve from different levels proximal to the bifurcation were prepared for light and electron microscopy. The quantitative analysis was performed as described by Sluga (1975) for myelinated fibers and by Ochoa and Mair (1969) for unmyelinated fibers. The results were compared with the histograms of two apparently normal digital nerves, which were selected from a control material of 82 digital nerves, gained by routine autopsy of 27 patients between 50 and 70 years of age with no clinical evidence of metatarsalgia.

## Results

A great many different pathologic conditions can produce the characteristic symptoms of Morton's metatarsalgia. On the other hand, about two-thirds of all clinical cases can be related to a typical pathologic substrate. In our material of 105 cases, 75 showed characteristic nervous lesions, whereas in 30 cases the symptoms were produced by other alterations. Thus our description of the alterations in Morton's disease will be focused only on the nervous lesions.

In the early stages of Morton's disease the alterations are dominated by the following characteristics (Fig. 2):

1. Thickening and hyalinization of the walls of the endoneurial vessels,
2. Sclerosis and edema in the endoneurium,
3. Thickening of the perineurium,
4. Demyelinization and degeneration of the nerve fibers without signs of wallerian degeneration.

The onset of the alterations of the endoneurial vessels is characterized by the formation of a hyaline-like envelope surrounding the vessels, sometimes combined with swelling of the endothelial cells (Figs. 1, 2). This coating is built up by an eosinophilic amorphous material which shows a negative reaction for amyloid, acid mucopolysaccharides, collagen, and elastica. Often concentric inner rings can be found in this material by using the PAS reaction (Fig. 1c). However, the peripheral parts lack a positive reaction. In the electron microscope multiple layers of basement membranes are visible around the endoneurial vessels (Fig. 5). Between these laminae may be found amorphous or sometimes granular, moderately electron-dense material and some pericytes. Besides the normal appearance of the muscle cells, similar alterations can be demonstrated in the endoneurial arterioles and venules (Fig. 5b). Reactive hyperplasia of endoneurial vessels forming loops and knobs sometimes occurs in more advanced stages of the disease. Perivascular infiltrations of inflammatory cells were detected only in three cases, combined with the deposition of iron pigment in the mesenchymal cells attached to the vessel walls.

Endoneurial edema and sclerosis is frequent in typical cases of the disease. The normal structure of the endoneurium seems to be filled with an eosinophilic amorphous material which often forms discs in cross sections (Figs. 1, 2) and cylindrical structures arranged in the long axis of the nerve. In advanced stages this material together with the similar appearing thickened walls of the vessels often fills the whole endoneurium and may even form primary denervated evaginations of the nerves. Attempts at a selective demonstration with special stains or histochemical reactions are unsuccessful. In connection with this material typical cells can be found (Fig. 2). Light-microscopically these cells have the characteristics of endoneurial fibroblasts with an ovoid chromatin-dense nucleus and scanty cytoplasmic processes. In the center of the material cellular debris can sometimes be found.

In the electron microscope the discs are built up by aggregates of filaments, which normally have a tubular substructure and a diameter of 100–110 Å (Fig. 3a, c). Sometimes collagen fibrils (endoneurial type) are intermingled with these microfibrils (Fig. 3a). The cells in between are small and spindle-shaped. Their flattened processes ramify freely without special arrangement in the endoneurium

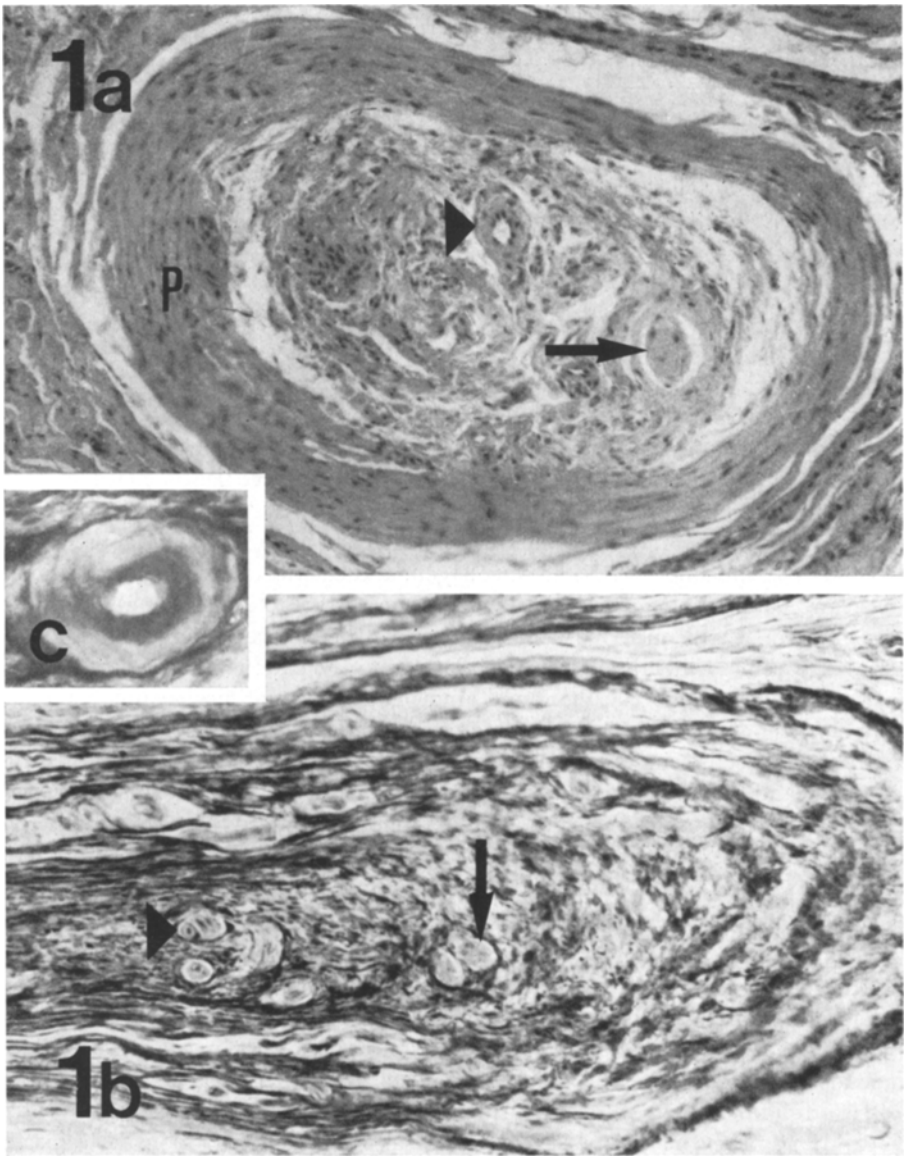



Fig. 1 (a) Female, age 36. Cross section through an affected nerve. Perineurium (*P*) is much thicker than normal. Endoneurium is edematous. Blood vessels (▶) are surrounded by a coat of eosinophilic material. In the endoneurium discs amorphous eosinophilic material (↑) can be found. H & E. × 150. (b) Female, age 68. Longitudinal section. Affected part of the nerve is distended. On the left side the normal structure of the digital nerve can be seen. Altered blood vessels (▶) and discs of amorphous material (↑) are frequent. Number of nerve fibers is decreased in the nodule. Osmium zinc iodide. × 100. (c) Female, age 63. Endoneurial blood vessel of an affected nerve. In the PAS reaction a concentric ring around the endothelial lining is clearly visible. PAS reaction. × 240

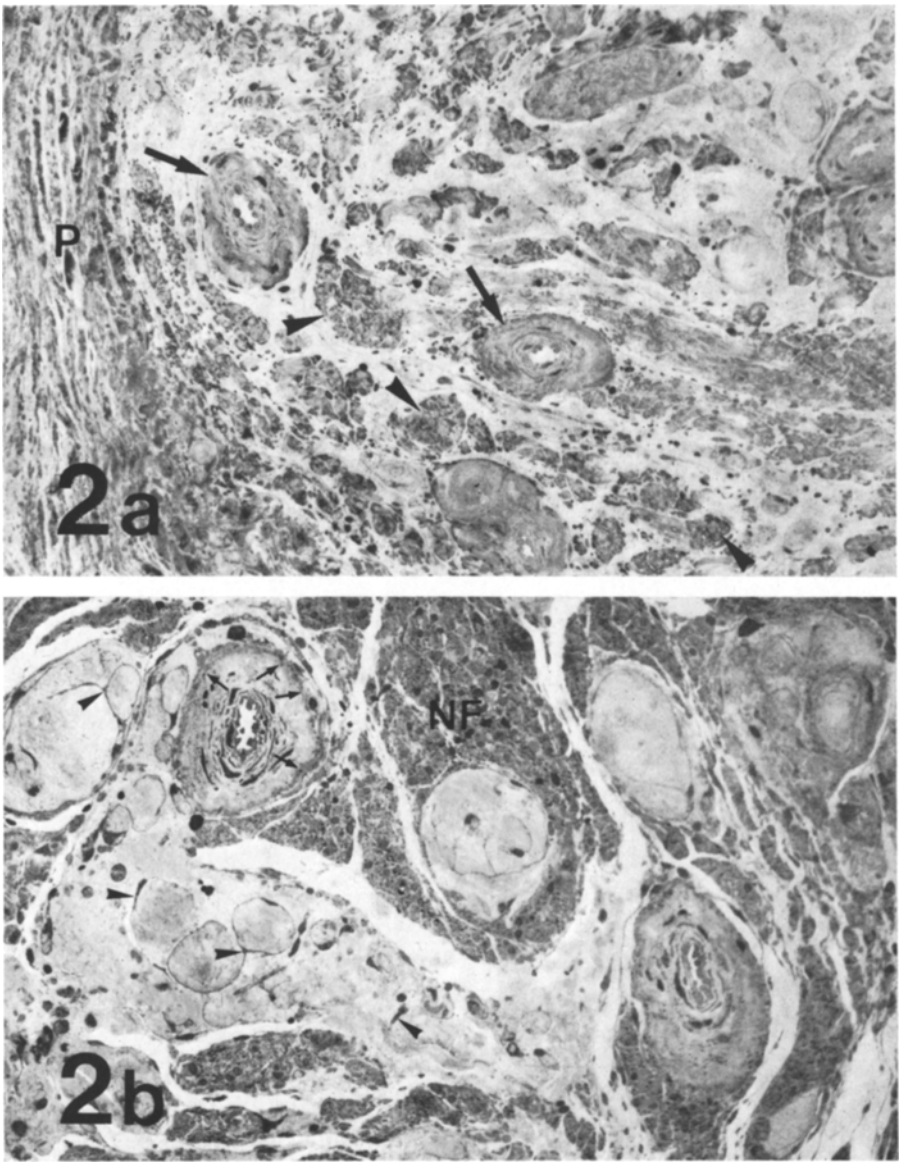
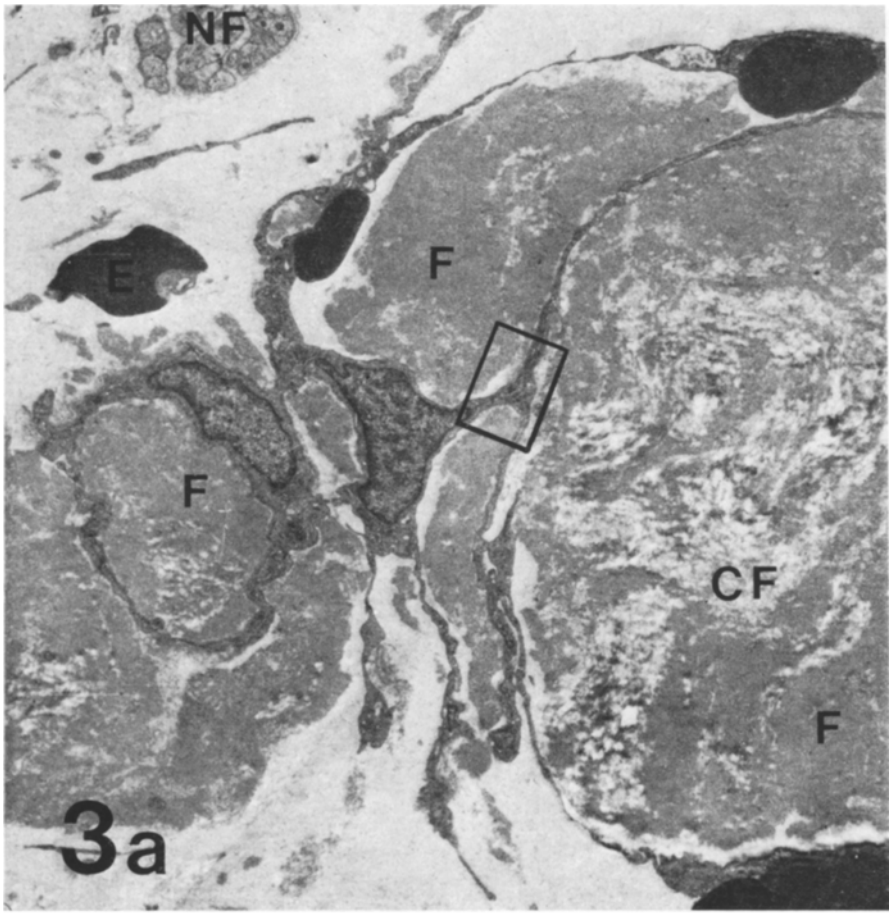



Fig. 2. (a) Female, age 49. Cross section through a digital nerve. Blood vessels are surrounded by a coat of amorphous material (↑). Edema of endoneurium is clearly visible. Nerve fibers are rare and packed in bundles (▲). No myelinated nerve fibers can be detected. Perineurium (*P*) is much thicker than normal. Semithin section, toluidine blue, alkaline fuchsin. × 180. (b) Female, age 49. Same nerve as (a). Coat around blood vessels shows a more intense staining reaction with alkaline fuchsin on its outer surface (↑). Endoneurium is partly filled with an amorphous unstained material. Between this material fibroblast-like cells with slender processes can be detected (▲). *NF*: Nerve fibers. Semithin section, toluidine blue, alkaline fuchsin. × 270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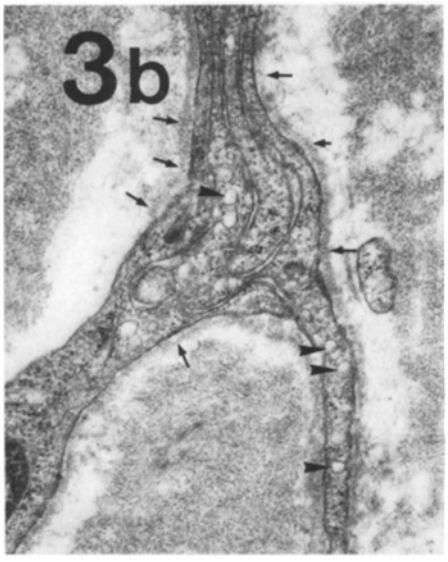
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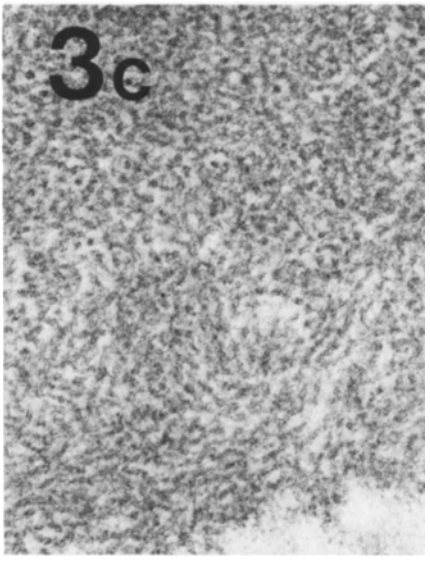

3c

(Fig. 3a). The ovoid chromatin-dense nucleus is surrounded by a small cytoplasmic margin. The cytoplasm contains primarily mitochondria, sometimes rough endoplasmic reticulum, and a Golgi apparatus. Small filaments are often found in the processes or around the nucleus. Some of the cells are surrounded by a continuous basement membrane, in others the basement membrane is discontinuous or even missing (Fig. 3b). Surface vesicles are frequent. Some recesses of the cells or their processes are filled with the extracellular filamentous material described above.

Compared with normal peripheral nerves the perineurium is much thicker and contains up to 20 lamellae of perineurial cells (Fig. 1a). Processes of these cells often accompany the endoneurial blood vessels or project freely into the endoneurium. Electron-microscopically no alterations in the individual cells can be detected. Between the perineurial lamellae a variable amount of collagen as well as some amorphous material can be found.

The degeneration of the nerve fibers as well as the other nervous lesions starts some distance proximal, reaching its maximum at the bifurcation of the digital nerve. In the Epon-embedded material in only one out of 10 dissected nerves is the amount of myelinated fibers enough for quantitative analysis. From this specimen external fiber diameter histograms were prepared from several levels above the bifurcation. Compared with the controls the histograms showed two characteristic alterations (Fig. 4):

1. Reduction of the amount of myelinated fibers, predominantly affecting the thick fibers,

2. Reduction of the diameter of the individual nerve fibers, due to attenuation of the myelin sheaths.

Regeneration clusters were rare; onion bulbs could not be detected in our material. The lack of signs of myelin catabolism was a constant finding.

Following a short stage of reactive hyperplasia the unmyelinated fibers were gradually destroyed too. In these stages the fibers seemed to be closely packed together by the compression of the filamentous material filling the endoneurium. The quantitative evaluation of the unmyelinated fibers, following the method described by Ochoa and Mair (1969a, b), is summarized in Figure 6. In contrast to the controls, which show a bimodal spectrum with peaks at 0.4 $\mu$ and 1.2 $\mu$, the affected nerves display a nearly unimodal distribution with a large peak at 0.4 $\mu$. Reactive hyperplasia of Schwann's cells or degenerative lesions in axons were not demonstrable in our material.

The biphasic spectrum of the unmyelinated fibers in the control nerves seems to be due to the advanced age of the patients (Ochoa and Mair, 1969b).

Fig. 3. (a) Female, age 50. Plaque in endoneurium of digital nerve. Normal structures are replaced by deposit of fibrillar material. In this material cells with a chromatin-dense nucleus and slender processes can be seen. *NF:* nerve fibers; *CF:* collagen fibrils; *F:* fibrillar material; *E:* free Erythrocytes. × 10,000. (b) Detail (a). Cell processes are in close contact with one another and contain numerous surface vesicles (▲). Basement membrane (↑) is discontinuous. Between cell processes fibrillar material can be found. × 27,000. (c) Detail (a). Microfibrils have a tubular substructure and a diameter of 100–110 Å. × 80,000

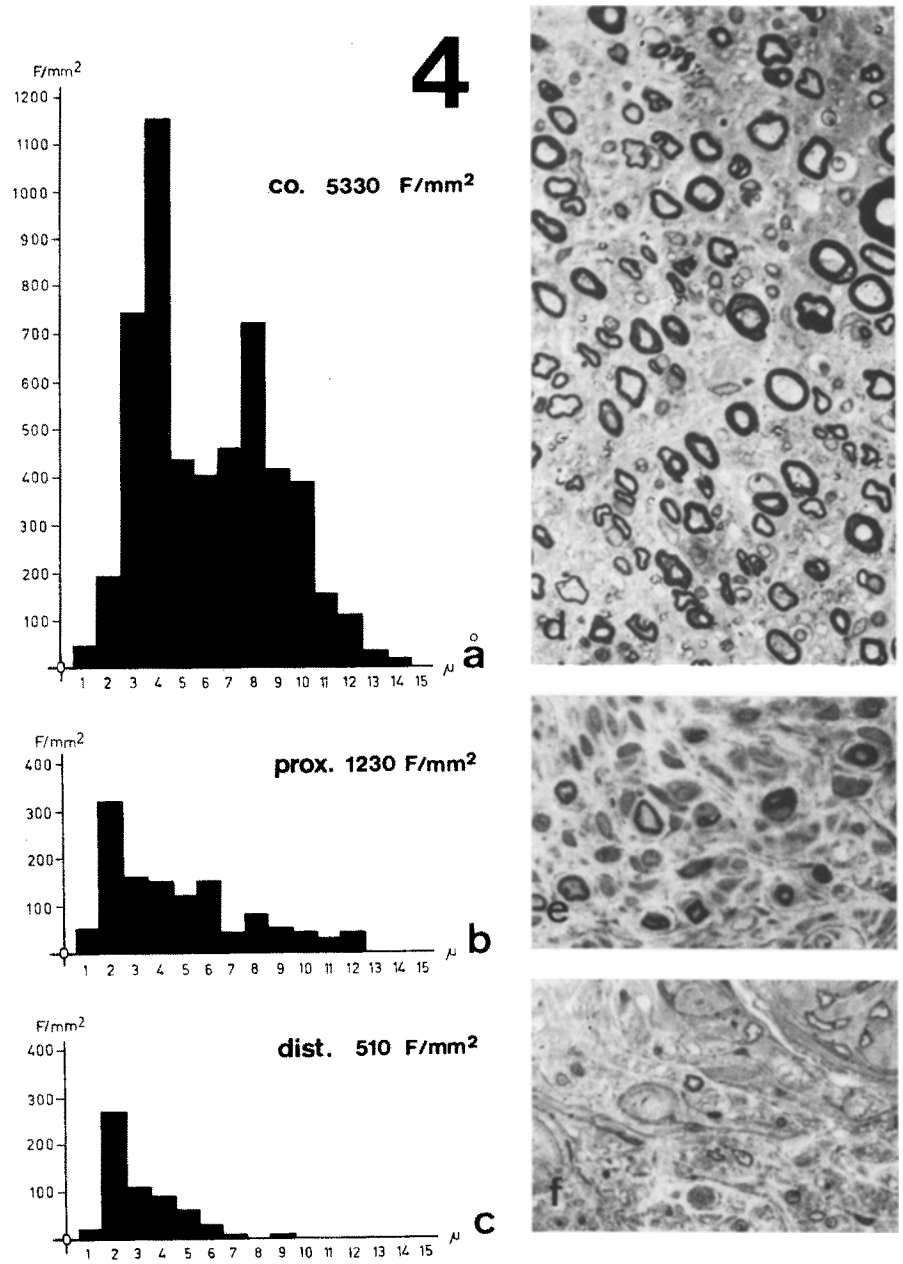
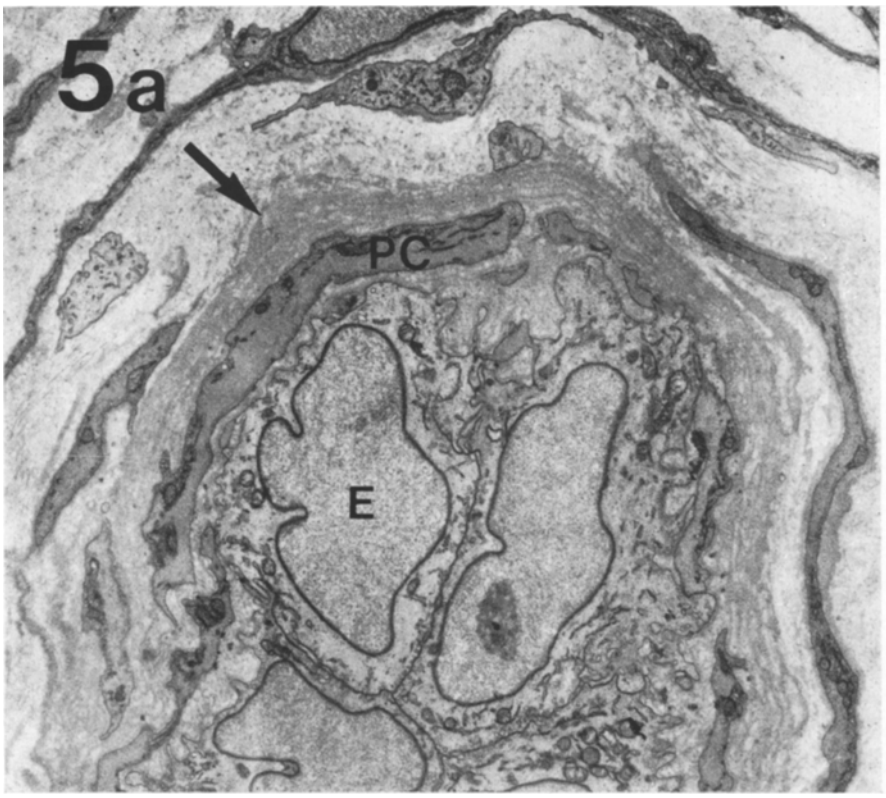



Fig. 4a—f. Histograms of myelinated nerve fibers with corresponding light microscopic figures of sections. (a, d) Control (female, age 64). (b, e) Metatarsalgia, proximal region (Nr. 15000, female, age 62). (c, f) Metatarsalgia, distal region (same Patient). (d, e, f) Toluidine blue. × 500

Fig. 5. (a) Female, age 50. Endoneurial capillary is surrounded by multiple layers of basement membranes (↑). *E:* endothelial cell; *PC:* pericyte × 6,000. (b) Female, age 50. Small endoneurial blood vessel. Between smooth muscle cells (*SM*) and endothelial cells (*E*) numerous layers of partly fragmented basement membranes (▲) can be found. × 17,000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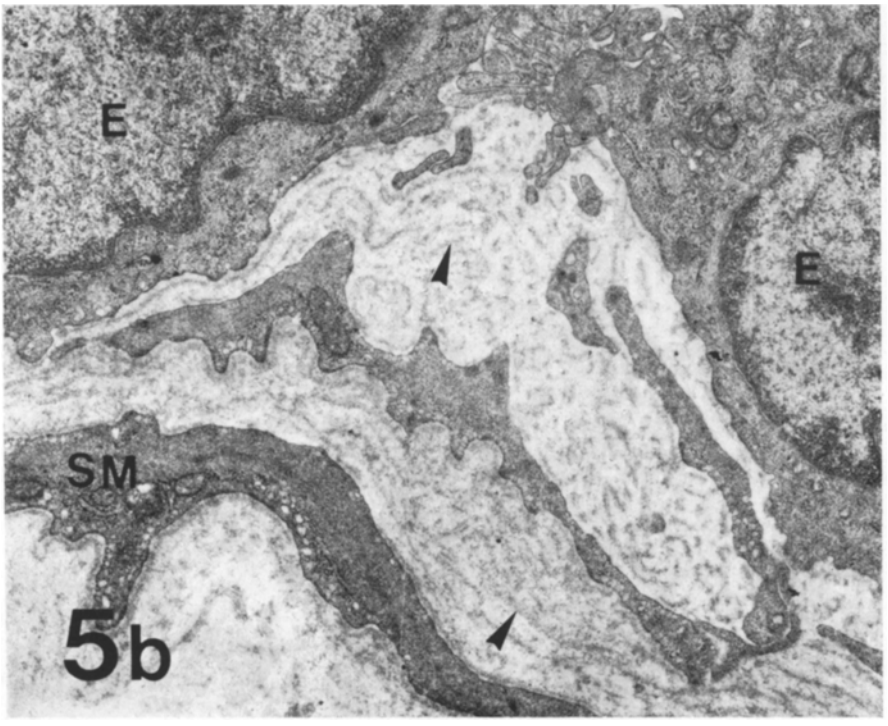
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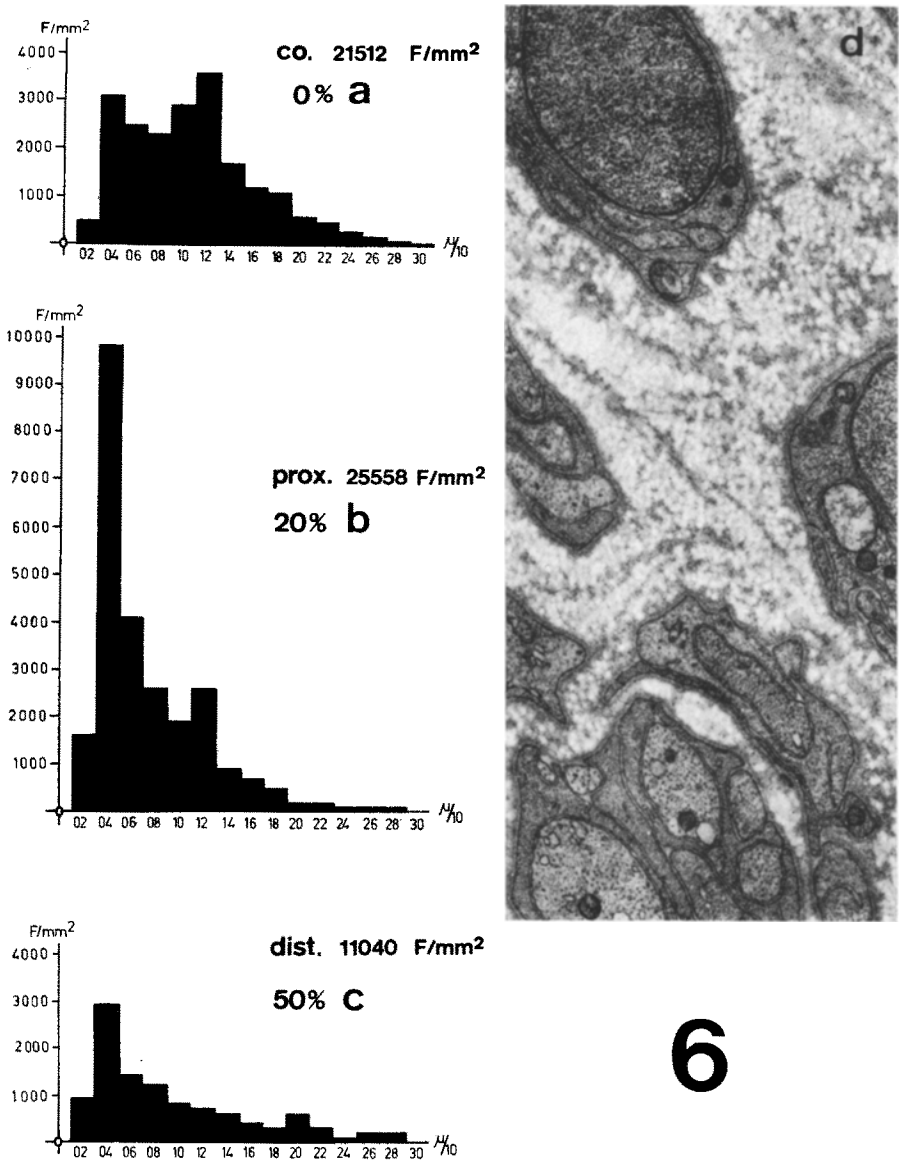


Fig. 6a—d. Histograms of unmyelinated nerve fibers. (a) Control (female, age 64). (b) Metatarsalgia, proximal region (female, age 62). (c) Metatarsalgia, distal region (same patient). Percentage data demonstrate area of nerve occupied by microfibrillary deposits. (d) Unmyelinated fibers in proximal area of digital nerve of patient with metatarsalgia. Small regeneration cluster can be seen in lower part of figure. × 17,000

In the region of the bifurcation of the nerve no further nerve fibers could be detected. The entire nerve was transformed into a cord of connective tissue, surrounded by a thickened perineurium, and filled by collagenous fibrils and microfibrillary material.

In general, the epineurial tissue shows no pathologic alterations in the early stages of the nervous lesions of Morton's disease. In advanced stages (stage 4, Lassmann and Machatschek, 1969) the denervated parts of the interdigital nerve together with the hypertrophic perineurium are absorbed by the surrounding connective tissue and the bursae are sometimes involved in these stages as well. The primary nervous origin of these structures can therefore only be recognized by the arrangement of the epineurial vessels. Then the characteristic nervous lesions can only be found in the proximal part of the nerve, whereas the nodule is built up by connective tissue alone. In electron microscopy the perineural cells seem to be intermingled with the epineural connective tissue cells, some of the cells containing remnants of basement membranes. Similar but smaller deposits of microfibrils, as described in the endoneurium, can also be found in these stages in the epineurium, sometimes in close contact with these cells. To date elastin has not been detected in the region of the microfibrils.

## Discussion

Ever since the first reports of the disease by Durlacher in 1845 and by Morton in 1876 a great many different descriptions of the underlying pathologic substrate have appeared together with attempts to explain the pathogenetic mechanism. Some of the authors referred the primary lesions to other than nervous structures. Reed and Bliss (1973) proposed the name "regressive and productive intermetatarsal elastofibrositis." They described mainly fibrosis and fibrinoid degeneration of the epineurium between the fascicles of the interdigital nerves. The alterations always involved the intermetatarsal bursa and the surrounding adipose tissue. In our material similar changes occurred only in advanced stages of the disease, but even in these cases the typical nervous lesions could be found in the proximal parts of the nerve.

Other authors (Scotti et al., 1957) have stressed vascular alterations and suggested that metatarsal ischemia plays an important role in the pathogenesis of the nervous lesions. In view of our material we find it impossible to maintain the view that Morton's disease is combined in every case with changes in the digital artery or vein. Our results apparently confirm that Morton's disease is not primarily induced by changes in the local vessels, but typical alterations of the nerves may, of course, also be combined with those of the vessels. This combination can be related to the fact that in elderly persons more or less distinct alterations of the peripheral vessels are a common finding.

Another etiologic factor which is discussed in the literature is an inflammatory process (Reed and Bliss, 1973; Hauser, 1971). On the contrary, other authors (Meachim and Abberton, 1971) emphasize that only a few specimens show leukocytic infiltration. In our material local inflammation as well as cellular infiltration were rare. Only in three cases lymphocytic infiltrations around the endoneurial vessels were found, in one case combined with deposition of iron pigment that was perhaps due to slight trauma. Therefore, we refused as early as our first study (Lassmann, 1968) an inflammatory process as being the pathogenetic mechanism of Morton's disease.

Contrary to McElvenny (1943), who stated that the nervous lesions are neurofibromata or angioneuromata, it is now generally accepted that no neoplastic reaction is causative. Even a reactive hyperplasia or an amputation neuroma, as suggested by Baker and Kuhn (1944), have been denied by several authors (Scotti, 1957; Lassmann, 1968; Meachim and Abberton, 1972).

In the early stages of Morton's disease especially, nervous lesions were prominent: primarily thickening of the walls of the endoneurial vessels, sclerosis and edema of the endoneurium, thickening of the perineurium, and degeneration of nerve fibers. Hyalinization of the vessel walls was described earlier by Scotti (1957), Lassmann (1968), Meachim and Abberton (1970) and others. On the other hand, Ringertz and Unander Scharin (1950) investigated control material obtained by autopsy of patients who had no clinical symptoms of Morton's disease and found that alterations of the endoneurial vessels and perineurial fibroses occurred with the same frequency in material from patients with Morton's disease and in the control material. Cottrell (1940) studied the histologic variations in apparently normal nerves and found a progressive thickening of the walls of the endoneurial vessels and the perineurium with aging. We were able to demonstrate that the thickening of the vessel walls is due to formation of multiple layers of basement membranes. Since these alterations of basement membranes are also found in other pathologic conditions, e.g., in diabetes mellitus or chronic venous congestion (David, 1967), they may represent an unspecific reaction. On the other hand, Vracko et al. (1968) found that similar basement membrane formations can also be produced by successive degeneration and regeneration of blood vessels.

Thickening of the perineurium has also been found by Ringertz and Unander-Scharin (1950) in the digital nerves of patients without Morton's disease. Sunderland and Bradley (1952) studied the thickness of perineurium in different nerves and found that it depends on the thickness of the individual fascicles as well as on the mechanical strain. The authors reported that in joint areas the perineurium is about twice as thick as in normal nerves. Therefore, it seems reasonable that the thickness of the perineurium of digital nerves may be due only to mechanical stress of the nerve. Nevertheless, in advanced stages of Morton's disease the perineurial cells were diffusely intermingled with epineurial tissue and therefore some proliferating process cannot be excluded.

Edema and sclerosis of the endoneurium is the characteristic lesion in Morton's disease. In electron microscopy large deposits of fibrillar material can be demonstrated between the nerve fibers. The individual fibril has a tubular substructure and a diameter of 100–110 Å. Nearly identical fibrils can be found also in normal peripheral nerves (Thomas, 1963) and in peripheral nerve tumors (Barton, 1962), but in Morton's disease these filaments occur to a much greater extent and often displace other endoneurial structures. Similar structures have also been described in the perivascular deposits in amyloidosis (David, 1967). On the other hand, the light-microscopic reaction of amyloid was negative. Nor were such fibrils found around blood vessels in our material. A striking feature of these filaments is also their similarity to elastic microfibrils (Greenley et al., 1966; Ross and Bornstein, 1969) and oxytalan fibers (Sheetz et al., 1973). Both are described as tubular filaments with a diameter of 110 Å and can be differentiated only by light-microscopic staining reactions (Fullmer and Lillie, 1958; Carmichael and Fullmer, 1966). On the other hand, the staining reaction for both oxytalan fibers and elastica was negative in our material. This contradiction could be explained by the fact that in our cases only microfibrils without interfibrillary substance—e.g., elastin, occurred, and elastin seems to play an important role in the light-microscopic staining reaction.

The cells between the fibrillar material have the appearance of fibroblasts in the light microscope. Nevertheless, in the electron microscope some of the cells contain a more or less complete basement membrane and surface vesicles. These

are characteristics of perineurial cells (Röhlich and Knoop, 1961; Shanta and Bourne, 1968).

Similar structures—deposits of microfibrils surrounded by spindle-shaped cells with slender processes—have been described as Renaut's bodies by Neary and Eames (1975) in one of their cases of ulnar nerve compression in man. However, in the light microscopic literature many different structures have been described as Renaut's bodies, including perineurial hyperplasia or mucinous degeneration of peripheral nerves (Renaut, 1881; Dick, 1901; Tretjakow, 1926; Schaffer, 1930; Krücke, 1955). In addition Renaut's bodies have always been believed not to interfere with nervous function. Therefore we do not believe that this term is descriptive of the lesions in metatarsalgia.

Comparing histograms of the myelinated and unmyelinated fibers of our material with the alterations in the carpal tunnel or ulnar nerve compression syndromes (Marie and Foix, 1913; Fullerton and Gilliat, 1967; Anderson et al., 1970; Thomas and Fullerton, 1970; Ochoa and Marotte, 1973; Marotte, 1974; Neary and Eames, 1975) it is tempting to classify Morton's metatarsalgia into the group of entrapment neuropathies. This view is also supported by the clinical results of Gauthier and Dutertre (1975). Nevertheless the constant occurrence of microfibrillary material in the endoneurium in nerves of patients with metatarsalgia, leading to a transformation of the nerve fascicles into cords filled by connective tissue, is in contrast to all descriptions of compression neuropathies. If, therefore, metatarsalgia should represent a compression neuropathy, the following explaination of the differences is suggested: the nerves in Morton's disease may be examined at a later, more advanced degenerative stage than those in the carpal tunnel or ulnar nerve compression syndromes.

One other possibility has to be considered with regard to the deposition of microfibrils as the primary pathogenetic mechanism. According to this view the degeneration pattern of the nerve fibers should be due to compression by endoneurial microfibrillar material. Factors responsible for the deposition of microfibrils in the endoneurium remain a matter of speculation. Because of the characteristic localization of the alterations in the region of the bifurcation of the digital nerve—a position in which the nerve is embedded between the metatarsophalangeal joints—a chronic traumatic factor must play an important role in the histogenesis of the disease. On the other hand, no clinical relation between the occurrence of the disease and orthopedic abnormalities of the feet could be worked out in our patients or in those of other authors. Furthermore, other factors causing special mechanical strain have been denied by the patients. Therefore, we believe that additionally a metabolic factor has to play a role in the development of the disease.

In addition to the theoretical problems concerning the pathogenetic mechanisms of the disease, it should be confirmed once again that surgical intervention is the only effective treatment for these cases and the only one that provides complete relief of pain. All other therapeutic efforts, such as orthopedic treatment or drug treatment for intermittent claudication are not causative and therefore useless. In this regard, it is interesting to note that neither in our patients nor in the material of other authors who have reported surgical treatment of Morton's disease has the formation of amputation neuromas or recurrences been observed, even after long follow-up as we done in the past 10 years.

Finally, the fact that the sensibility of the skin of the toe is restored 3–4 weeks after the operation requires further investigation.

We are greatly indebted to Miss J. Selbmann and Mrs. S. Kolassa for skilful technical assistance, to Mr. H. Wagner for preparing the photographs, and to Dr. M. Gootz for experienced technical advise.

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