ELECTRON MICROSCOPE STUDY OF CUTANEOUS NERVES IN LEPROSY

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Alteration of peripheral nerves is one of the characteristic features of leprosy infection. The importance of the role played by cutaneous nerves in the initial stages of the infection has long been a point of discussion. Although *M. leprae* and associated pathologic changes in cutaneous nerves have been studied over a long range of time, from Dehio in 1889 ([3]) to a number of workers in recent times (e.g., [29, 5, 1, 2, 6]), it has never been possible by histopathology to determine completely whether the bacilli were located in the axons or in the Schwann cells. The type of cytologic changes of the cutaneous nerve elements occurring during invasion by *M. leprae* could not be clarified, a consequence of the restrictions of the resolution of the light microscope.

More recently, electron microscope studies of leprosy lesions by Nishiura and associates ([19, 20, 21]) have revealed the details of cytopathologic changes in the peripheral nerve trunks, throwing light on the relationship between the leprosy bacillus and the various nerve elements. Cutaneous nerve branches, however, are so sparsely distributed that they are not easily encountered in ultrathin sections of the small fragments used in electron microscopic studies. Thus it is extremely difficult to describe the manner of invasion of such nerves by the bacillus. This problem can only be resolved by patient observation of many specimens of biopsy tissues, and by cutting fairly large areas of specimens facilitated by using a large-sized diamond knife.

The present study was undertaken to clarify the cytopathologic changes of the cutaneous nerves in leprosy, and also to discuss the occurrence of leprosy infection with special reference to cutaneous nerves.

MATERIAL AND METHOD

Biopsy specimens of skin lesions taken from 19 lepromatous, 8 tuberculoid, and 21 borderline leprosy patients were examined. The diagnoses of these patients were confirmed by clinical and histopathologic examinations and the Mitsuda test. The tuberculoid specimens comprised lesions of reactional tuberculoid leprosy, tuberculoid reactivation, and hypopigmented macules left after subsidence of erythematous lesions. In two cases there was total loss of sensation in the lesions, and in the others light hypoesthesia. The lepromatous and borderline cases showed little loss of sensation in the biopsied areas.

Tissue fragments were fixed with 1 per cent osmium tetroxide solution buffered with 2,4,6-collidine ([8]), and embedded in methacrylate by the usual methods. Ultrathin sections 1 to 1.5 mm. square were made with a diamond knife, stained with uranyl acetate solution ([34]) and observed with the Siemens Elmiskop I and the Hitachi HS-6 electron microscopes.

FINDINGS

TUBERCULOID LEPROSY

Reactional tuberculoid skin lesions are characterized by many infiltrating cells, mainly epithelioid cells and lymphocytes, and also by widened extracellular spaces representing intercellular edema (Fig. 1). This inflammation occurs within a short time as a result of the allergic phenomenon and is usually accompanied by a total loss of sensation.

The histologic examination of these lesions showed that the neural elements in the dermis are disorganized, explaining the sensory disturbance ([37]). On the other hand, fine regenerating nerve fibers apparently occur even in the center of fully developed lesions, suggesting the recovery of sensation. However, these changes in so small a unit of the structure as fine cutaneous nerves are not easily established at the light microscope level.

In electron microscopy of tuberculoid lesions of peripheral nerve trunks, the destruction of nerve elements and subsequent regeneration have been observed ([19, 21]). The degeneration process of skin nerves has not been found in the lesions examined in the present study, possibly due to the stage of evolution of the disease, and also to insufficient observation.

Distinct cutaneous nerves were encountered in the specimens from only two of our cases of tuberculoid reactivation, in which lesions bacilli were not found. The *preterminal* branch of the nerve consists of a group of Schwann cells surrounding variable numbers of axons, with endoneural collagen fibers embedded in fibrillar substance, the whole enclosed by laminate perineural cells (Fig. 1). The *terminal* branch, located in the subpapillary layer of the skin, has an appearance similar to the former, although it lacks perineural cells (Fig. 2). In both the preterminal and the terminal branches, Schwann cells and axons contain abundant cytoplasmic organelles. Frequently the axon is connected through the whorling mesaxon to the surface of the Schwann cell (Fig. 2).

According to Terry and Harkin ([28]) and Ohmi ([24]), nerve regeneration after Wallerian degeneration is characterized by the proliferation of Schwann cells with abundant cytoplasmic organelles, the prolonged mesaxon with a spiral wrapping movement around the axon, and increased neurilemmal collagen fibers. Since these features are all evident in the cutaneous nerves in tuberculoid lesions, it is believed that the preterminal and terminal branches observed here may represent the regeneration stage after complete destruction of nerves, which may occur in cutaneous nerves as in nerve trunks.

The so-called naked regenerating axons, devoid of Schwann-cell covering as observed in healthy skin ([25]), are not evident in tuberculoid lesions. The axons always either attach themselves to the Schwann cell surface, or are completely enwrapped by the Schwann cell. There

seems to be more opportunity of encountering free axons in this type of lesion, in which degeneration of nerve elements takes place. Therefore, it seems likely that regenerating axons never extend independently in the dermis but reach the terminal portion while wrapped by Schwann cells, as observed in the study of the regeneration of nerve trunks ([24]).

Large cells characterized by undulating cell membranes and also by abundant cytoplasmic organelles are sometimes observed in the endoneural space (Fig. 1). Their appearance is identical to that of the epithelioid cells which occur outside the nerve bundle. Possibly endoneural mesenchymal cells become epithelioid cells as an allergic phenomenon of tuberculoid leprosy ([14]). The outermost perineural cell layer is separated by these cells, and consequently the endoneural space directly faces the surrounding epithelioid tubercle.

Gass and Balasubrahmanyan ([6]) found that marked inflammatory reaction inside the nerve bundle in the dermis destroys the fibers by pressure. Although that process of cutaneous nerve degeneration is not confirmed by our present observations, the presence of large infiltrating epithelioid cells in the regenerating nerve bundle suggests that the mechanical factor of these cells may influence the nerve destruction.

Furthermore, the surrounding epithelioid tubercle, with the intercellular edema which occurs rapidly as a result of allergy, may also play a role as a mechanical factor causing nerve degeneration, especially in terminal branches.

LEPROMATOUS LEPROSY

Lepromatous skin lesions consist of many bacillated cells called "lepra cells" and a few infiltrating leucocytes ([38, 39]). These lesions are formed slowly with intracellular growth of *M. leprae,* and thus are different from tuberculoid lesions. The histology of the nerves in lepromatous skin lesions shows that the disorganization of cutaneous nerves is not so serious as that in tuberculoid lesions, but the average diameter of the axons is reduced by the surrounding infiltrate cells ([37]).

From electron microscopic observation of the peripheral nerve trunks in lepromatous leprosy it is clear that axons and myelin sheaths are destroyed, possibly by the direct invasion of the bacilli, and that the Schwann cells remain to form the cords of Büngner ([19-21]). The fine structure of cutaneous nerves in lepromatous lesions has an appearance similar to that of the nerve trunks. The preterminal branch consists of several Schwann cells, which normally include variable numbers of axons, abundant endoneural collagen fibers, and the perineural cells. This bundle is sometimes surrounded by lepromatous infiltration (Fig. 3). The Schwann cell cytoplasm has a filamentous substance, but the distribution of organelles is very sporadic, different from the cyto-

plasm of the Schwann cells in tuberculoid leprosy. The axon, having few cytoplasmic organelles, is usually connected to the mesaxon, which frequently shows a tendency to whorl around the axon.

Several endoneural cells contain many cytoplasmic organelles, particularly dilated ergastoplasms with amorphous or filamentous substance (Fig. 3). They, together with collagen fibers, surround the group of nerve elements in the endoneurium. Frequently the endoneural space is compacted by collagen fibers (Fig. 5). These small bundles are devoid of any indication of regeneration in the Schwann cells, i.e., increased cytoplasmic components. However, an abundance of endoneural collagen fibers and many endoneural cells are nevertheless signs of regeneration.

In lepromatous nerve trunks, destruction of Schwann cells usually does not occur, even after complete degeneration of both the axon and the myelin sheath. Regenerating axons are wrapped by the remaining Schwann cells, which are not characterized by copious distribution of cytoplasmic organelles ([19-21]). Furthermore, it has been shown that the regeneration of axons occurs even when the Schwann cell contains the bacilli which were released by the degenerating axon.

In the terminal branches within the subpapillary layer of the skin, some Schwann cells do not include axons (Fig. 4), indicating that the degeneration of axons leaves the Schwann cells intact.

In the preterminal branch, degenerated bacilli may be found in the cytoplasm of the Schwann cell which encompasses the axon connected by the mesaxon (Fig. 8). The bacilli in the Schwann cell, especially in the preterminal branch, may be discharged from the degenerating axon, as described later. This feature may indicate regeneration of the axon in the bacillated Schwann cell. However, nonmyelinated fibers—which are not affected by the disease—show sporadic distribution of the cytoplasmic components, and they are the main components of apical ends of cutaneous nerves ([25]). Therefore, it is difficult to determine which element of the terminal branches really corresponds to the regenerating stage.

Occasionally perineural cells contain a few degenerating bacilli surrounded by electron-transparent zones and foamy structures (Fig. 7), and dilated ergastoplasm containing fibrillar substance is noted, as in endoneural cells. These perineural cells are slightly distended by the bacilli, but they persist in a laminate arrangement around the nerve. Collagen bundles envelop these perineural cells, separating the nerve bundle from the surrounding lepromatous infiltration. In other words, there is no direct connection on the outside between nerve bundles and infiltrating cells. This differs from the condition in tuberculoid leprosy.

In addition, terminal branches are not surrounded by the lepromatous infiltrate, although small dense cells with ample distribution of

RNP particles and also with dilated ergastoplasms, possibly representing immature mesenchymal cells of the dermis, are located near the nerve elements (Figs. 4 and 6).

Takino ([27]) considered that the degeneration of cutaneous nerves in lepromatous leprosy does not occur by cell infiltration but by globus formation in the nerve element. Our evidence also suggests that the degeneration of cutaneous nerves may not be caused by pressure of the surrounding lepromatous infiltration, but by the direct bacterial invasion which may occur independently in each axon in the same branch. Thus some of the axons may still function, carrying stimuli, and consequently lepromatous lesions are not accompanied by a total loss of sensation but show a slight disturbance of sensation. This was suggested by Gass and Balasurbrahmanyan ([6]), although their conclusion is based on the idea that the separation of nerve fibers is produced by proliferating Schwann cells replacing the degenerated nerves. This has not been confirmed here, or in our previous studies of nerve trunks.

BORDERLINE LEPROSY

This form of leprosy is intermediate between the tuberculoid and lepromatous types, i.e., moderate tissue reactivity of the former still remains. The skin lesions are characterized by having both lepromatous and tuberculoid features ([31, 32]), and the infiltration is composed chiefly of epithelioid cells which are mostly bacillated ([13]).

Cutaneous nerves are not infrequently found in the lesions. The preterminal branches are composed mostly of nonmyelinated fibers, together with few myelinated ones (Fig. 10). Nonmyelinated fibers usually lack abundant cytoplasmic organelles, but their axons are connected with prolonged mesaxons, as observed in lepromatous cases. Some Schwann cells, occasionally containing bacilli and an ample distribution of cytoplasmic organelles, are larger than others (Figs. 10 and 12), suggesting that they really are proliferating in the regeneration stage, as discussed in tuberculoid cases.

Collagen fibers are richly distributed in the endoneural space, and the perineural cells enclose the bundle (Figs. 9 and 10). The proliferation of the perineural sheath observed by Wade and Perrin ([33]) has not been seen in the present study; but in their case that condition was found only in the deeper dermis where the lepromatous changes were concentrated.

Occasionally intact bacilli filled with their cytoplasm lie in the narrow axoplasms (Fig. 9). Furthermore, the rupture of the axon-Schwann membrane by the bacilli shown in Fig. 11 suggests that it takes place as a result of choking the narrow passage of the axons by the bacilli.

In the myelinated fibers, the accumulation of mitochondria is frequently noted in the axon, as seen in the lower right area of Fig. 10.

Webster ([35]) described the accumulation of mitochondria in the axon as one of the characteristic phenomena of the early stage of Wallerian degeneration in the distal portion of an injured nerve. In this instance, myelinated fibers observed in the bundle may also represent the early alteration of the axons, possibly caused by mechanical obstruction with the bacilli in the proximal portion of the nerve.

DISCUSSION

RELATIONSHIP BETWEEN CUTANEOUS NERVE AND EVOLUTION OF SKIN LESION

It was long believed that the peripheral nerves are primarily invaded by *M. leprae.* Dejerine and Leloir ([4]), in the early days of the study of leprosy lesions, believed that the cutaneous lesions depend on those of the peripheral nerves. Dehio ([3]) and Gerlach ([7]) also emphasized that the disease begins at the endings of peripheral nerves. Muir and Chatterji ([18]) suggested that the bacilli might pass into the nerve through the cutaneous neurovascular plexus without forming skin lesions.

In very early lesions (the "silent phase" of infection), Khanolkar ([15]) found the bacilli in both the Schwann cell and the axon of the fine nerve endings of the skin, while they were not encountered in other dermal regions. Studying these authors' results, it appears that the cutaneous nerve is always affected by the bacterial invasion, primarily or secondarily.

Weddell and Glees ([36]) and Weddell *et al.* ([37]) hold that "an axon surmounted by a growth cone having the morphologic characteristics of a regenerating nerve, was encountered in uninfected skin." Also, Hughes ([9]) showed, from tissue culture studies, that the function of fine pseudopodial processes of the ganglion cell with undulating membrane is comparable to that of macrophages. Based on his own findings, Nishiura ([21]) asserted that the growth cone of the naked stage of the regenerating axon in normal skin might engulf the leprosy bacilli and that these bacilli might provoke the disease.

On the other hand, Pease and Pallie ([25]) emphasized that there were no truly naked processes in normal skin. Ohmi ([24]) also observed in electron microscope study of nerve regeneration that there are no free regenerating axons, but that these axons are completely or partially enwrapped by regenerating Schwann cells.

Sometimes, however, axons have a free surface when they are partially enclosed by Schwann cells, especially in terminal branches, presumably of the regenerating stage (Fig. 6). The fact that the bacilli are found in the axoplasm of cutaneous nerves suggests that they enter directly into the axon, possibly through the free surface of regenerating axons, because entrance from the Schwann cell through the double axon-Schwann membrane, or through the myelin sheath, is unbelievable.

Concerning the bacilli in Schwann cells, it is assumed that bacilli

may be passively released from axons to the enclosing Schwann cells after the degeneration of axons and myelin sheath ([20, 21]). This was definitely confirmed in the present study (Fig. 11). Furthermore, regenerating Schwann cells contain the bacilli together with regenerating axon (Fig. 10). Ohmi ([24]) suggested that regenerating Schwann cells may much later become tightly covered with neurilemmal collagen fibers developing into thick compact bundles, implying the free movement of the surface of the Schwann cell in the early stage of regeneration. Therefore, Schwann cells may also phagocytose the bacilli in this early stage. Thus, the direct entrance of the bacilli into the nerve element may be not only through the free surface of regenerating axons, but also through regenerating Schwann cells.

The site of the bacterial invasion in leprosy is supposedly through the skin, at points of injury caused by other skin affections ([22, 26]) or by mechanical trauma. In the first invasion of the bacilli, they may be phagocytosed by the nerve element, as described, and also by the histiocytic cell which constitutes the natural defensive element of the dermis. The bacilli engulfed by nerve elements remain unchanged because of the absence of reaction in either the Schwann cell or the axon in this stage of infection. Khanolkar ([16, 17]) holds that the bacilli proliferate very slowly in nerves, moving centripetally through the axons.

The axons are very narrow tubes, especially those in cutaneous nerves, and their obstruction by the bacilli readily causes their degeneration and consequently the release of the bacilli into the Schwann cell. Since the Schwann cell is still bordered by the basement membrane and further enclosed by collagen fibers, the bacilli may not be released to the endoneural space. This stage may correspond to the silent phase of the infection. After repeating the same process, an allergic or anergic condition may arise in the individuals, and subsequent invasion may provoke tuberculoid or lepromatous leprosy, depending on tissue reactivity or the lack of it.

It is possible that the bacilli in nerve elements may play a role as the subsequent invasion to the dermis, even without any entrance through skin traumas. The bacilli may be discharged into the dermis from the nerve elements, by the injury caused by the traumas which occur in every-day life, or by pressure such as massage, etc. It is also possible that the bacilli may be freed from the axons through the nodes of Ranvier, which are not completely enclosed by Schwann cells and myelin sheaths ([30]). These released bacilli produce the lesion around the cutaneous nerves. Furthermore, these bacilli may be transported by macrophages through the blood and lymph vessels, thus spreading to other parts of the skin to establish the lesions.

On the other hand, the bacilli in dermal lesions are possibly phagocytosed by regenerating nerve elements, which have not yet been affected by the bacilli, forming new nerve lesions. Thus, two supposedly

contrary opinions regarding the spread of the lesions between cutaneous nerves and dermis reveal the truth.

M. leprae AND TISSUE REACTION IN CUTANEOUS NERVES

The morphologic feature of *M. leprae* in skin lesions depends on the type of leprosy. In lepromatous lesions the bacilli undergo lysis as a result of rapid growth in the nutritionally limited medium of the lepra cells. Therefore, details of the intact bacilli are revealed only in the primary stages of leproma formation ([12]), and most lepra cells contain degenerated bacilli ([12, 38, 39]).

In tuberculoid cases, the bacilli appear only in the early phase of the disease. In other words, the cellular reaction causes marked disintegration of the bacilli and forms epithelioid tubercles ([21]). In borderline cases, the bacterial activity and the tissue reactivity are balanced. Thus, many intact bacilli may be seen for a long time. ([11]) Usually the bacillated cells have abundant mitochondria, as in epithelioid cells in tuberculoid leprosy, suggesting a moderate reactivity to the bacilli ([13]).

In the study of leprous peripheral nerve trunks it was found that there are no degenerated bacilli in nerves, even in lepromatous cases ([21]). In borderline lesions, the intact bacterial structure is observed in both the Schwann cells and the axons of cutaneous nerves (Figs. 9 and 10). In lepromatous and some borderline lesions, however, Schwann cells contain degenerated bacilli (Figs. 8 and 12), occasionally together with the foamy structure (Fig. 12), as seen in mesenchymal host cells in the dermal lesion. The fact that, in Schwann cells, several degenerating bacilli are surrounded by the electron-transparent zone indicates that the bacterial degeneration probably occurs in the Schwann cells, because this zone shows the intimate relationship with the bacterial degeneration ([12]).

Based on these observations, it is possible to say that the bacterial appearance and environment in cutaneous nerve elements are not different from those in mesenchymal host cells. Therefore, once the skin lesion is formed, cutaneous nerves—especially their Schwann cells—may be influenced directly by infiltrating mesenchymal cells which are sites of tissue reaction. An abnormal lipid metabolism is supposedly one of the characteristics of the lepromatous type ([10]). This deviated metabolism may also appear in Schwann cells which have a capacity to digest lipids in noninfected conditions, as observed in Wallerian degeneration ([23]). Thus, the foamy structure and the electron transparent zone both contain lipids ([10]), as evidenced in Schwann cells.

In tuberculoid leprosy, the complete degeneration of nerve elements may, as said, be caused by the pressure of rapidly infiltrating cells. However, as far as we are aware total loss of sensation does not occur in other acute inflammations of the skin, which also may involve

pressure on the cutaneous nerves. Therefore, the nerve degeneration in tuberculoid lesions may be due not only to the pressure by infiltrating cells but also to the reaction of the Schwann cell to the bacilli, influenced by surrounding epithelioid cells. This would also explain the sensory disturbance in tuberculoid lesions which may take place in a very short time.

This hypothesis also explains the occurrence of both regeneration of Schwann cells with axons, and degeneration of axons in the same bundle (Fig. 10). This means that the degeneration may not be caused by the pressure of infiltrating cells either in the endoneural space or on the outside of the nerve bundle. Rather, it strongly suggests that the nerve elements may be affected, independently in each element, by a direct invasion of the bacilli. Furthermore, the feature of proliferation of the Schwann cell suggests that complete destruction of the nerve element has occurred previously. It is unlikely that degeneration results from the pressure in the nerve bundle. It is quite possible that the Schwann cell degeneration is caused by the cellular reaction to the bacilli as it occurs in mesenchymal cells, such as epithelioid cells, due to the moderate tissue reaction in borderline leprosy.

SUMMARY

Cutaneous nerves in the skin lesions in lepromatous, tuberculoid and borderline leprosy were examined by electron microscopy.

In tuberculoid cases, the regeneration of Schwann cells and axons possibly occurs after the complete degeneration of these nerve elements. Endoneural cells become epithelioid cells as a result of the allergic phenomenon, and laminate perineural cells are separated by these epithelioid cells. In lepromatous cases, the regeneration of axons takes place in the Schwann cells which remain after the degeneration of the axons. In borderline cases, both regenerating and degenerating processes may be seen in the same preterminal branch. This suggests that the alteration of each nerve element may occur independently in each fiber.

The bacterial appearance and environment in Schwann cells are identical with those of mesenchymal host cells. The electron transparent zone around degenerating bacilli is evident in Schwann cells in lepromatous lesions. Most of the bacilli in borderline leprosy show the same intact feature as in dermal lesions. Based on these findings, the hypothesis is offered that Schwann cells in cutaneous nerves may be influenced by the mesenchymal cell which is the site of the cellular reaction to the bacillus. This explains how the degeneration of nerve elements in tuberculoid cases may result, not only from the pressure of enlarged endoneural cells and the surrounding epithelioid tubercle, but also from the allergic reaction of the Schwann cells themselves.

The degeneration of axons in lepromatous leprosy may be caused

by mechanical obstruction by the bacilli. Generally the Schwann cell does not degenerate, because of the absence of tissue reaction to the bacillus in this type of leprosy. In borderline leprosy, the Schwann cells undergo degeneration independently in each fiber, because of the moderate tissue reaction in this form of leprosy.

M. leprae may enter the dermis through skin traumas and be engulfed, not only by the growth cone of a regenerating axon but also by the regenerating Schwann cell. The bacilli remain in these nerve elements. When these bacilli are released into the dermis, various types of dermal lesions may occur, depending on the reactivity of the mesenchymal cells which arises from the repeated bacterial invasion.

RESUMEN

Los nervios cutáneos en las lesiones cutáneas de la lepra lepromatosa, tuberculoidea y limítrofe fueron examinados con la electronomicroscopía. En los casos tuberculoideos, de las células de Schwann y de los cilindros-ejes ocurre posiblemente después de la degeneración total de estos elementos nerviosos. Las células endoneurales se vuelven epitelioides a consecuencia del fenómeno alérgico y las perineuraels laminadas quedan separadas por estas células epitelioideas. En los casos lepromatosos, la regeneración de los cilindros-ejes tiene lugar en las células de Schwann que restan después de la degeneración de los cilindros-ejes. En los casos limítrofes, pueden observarse procesos tanto regenerativos como degenerativos en la misma rama preterminal. Esto sugiere que la alteracíon de cada elemento nervo sopuede tener lugar independientemente en cada fibra.

La característica bacteriana y el ambiente son idénticos en las células de Schwann y en las células huéspedes del mesénquima. La transparente zona de electrones que rodea los bacilos en vías de degeneración es evidente en las células de Schwann en las lesiones lepromatosas. La mayoría de los bacilos en la lepra limítrofe muestra la mísma característica intacta que en las lesiones dérmicas. A base de estos hallazgos, se ofrece la hipótesis de que las células de Schwann en los nervios cutáneos pueden ser afectadas por la célula mesenquimatosa que es el asiento de la reacción celular al bacilo. Eso explica como puede sobrevenir la degeneracíon de los elementos nerviosos en casus tuberculoideos, no solamente debido a la presión de las hipertrofiadas células endoneurales y del circundante tubérculo epitelioideo, sino también a la reacción alérgica de las células de Schwann mismas. La degeneración de los cilindros-ejes en la lepra lepromatosa puede ser ocasionada por la oclusión mecánica producida por los bacilos. En general, la célula de Schwann no degenera, debido a la carencia de reacción histológica al bacilo en esta forma de lepra.

El *M. leprae* puede penetrar en la dermis a través de traumatismos cutáneos y ser absorbido, no tan sólo por el cono proliferante de un cilindro-eje en vías de regeneración por la célula de Schwann en regeneración. Los bacilos permanecen en estes elementos nerviosos. Cuando se liberan estos bacilos en la dermis, pueden presentarse varias formas de lesiones dérmicas, conforme a la reactividad de las células mesenquimatosas que se deriva de la repetida invasión bacteriana.

RESUMÉ

La microscopie électronique a été appliquée à l'étude des nerfs cutanés provenant de lésions de la peau chez das cas lépromateux, tuberculoïdes et border-line.

Chez les cas tuberculoïdes, la régénération des cellules de Schwann et des axones peut prendre place après la dégénérscence complète de ces éléments nerveux. Des cellules endoneurales subissent une transformation épithélioïde par suite du phénomène allergique,

et les cellules laminées périneurales sont dissociées par ces cellules épithélioïdes. Dans les cas lépromateux, la régénération des axones se produit dans les cellules de Schwann qui persistent après la dégénérescence de ceux-ci. Dans les cas border-line, des processus de régénération et de dégénérescence peuvent être à la fois observés dans le même filet préterminal. Ceci suggère que les altérations de chaque élément nerveux peuvent survenir de manière indépendante dans chaque fibre.

Les caractéristiques bactériologiques et l'environnement dans les cellules de Schwann sont identiques avec ce que l'on observe dans les cellules mésenchymateuses. La zone transparente aux électrons, qui entoure les bacilles en voie de dégénérescence, est bien apparente dans les cellules de Schwann au niveau des lésions lépromateuses. Dans la lèpre border-line, la plupart des bacilles montrent le même aspect intact qu'au niveau des lésions dermiques. L'hypothèse qui est émise à la suite de ces observations est la suivante: les cellules de Schwann dans les nerfs cutanés peuvent être influencées par les cellules mésenchymateuses qui constituent le site de da réaction cellulaire au bacille. Ceci explique comment la dégénérescence des élements nerveux dans les cas tuberculoïdes peut résulter, non seulement de la presion exercée par les cellules endoneurales augmentées de volume et par la structure tubreculoïde qui les entours, mais aussi provenir de la réaction allergique des cellules de Schwann elles-mêmes.

La dégénérescence des axones dans la lèpre lépromateuse peut être causée par l'obstruction mécanique due ou bacille. Géneralement, la cellule de Schwann ne dégénère pas, par suite de l'absence de réaction tissulaire au bacille dans ce type de lèpre. Pour ce qui est de la lèpre border-line, les cellules de Schwann dégénèrent de manière indépendate dans chaque fibre, car la réaction tissulaire est modérée dans cette forme de lèpre.

M. leprae peut pénétrer dans le derme à la suite de traumatismes cutanés et être alors enveloppé, non seulement par le cône de croissance d'un axone en voie de régénération, mais aussi par la cellule de Schwann en voie de régénération. Les bacilles persistent dans ces éléments nerveux. Quand les bacilles sont libérés dans le derme, des types différents de lésions dermiques peuvent prendre place, d'après la réactivité des cellules mésenchymateuses qui se produit à la suite de l'invasion bactérienne répétée.

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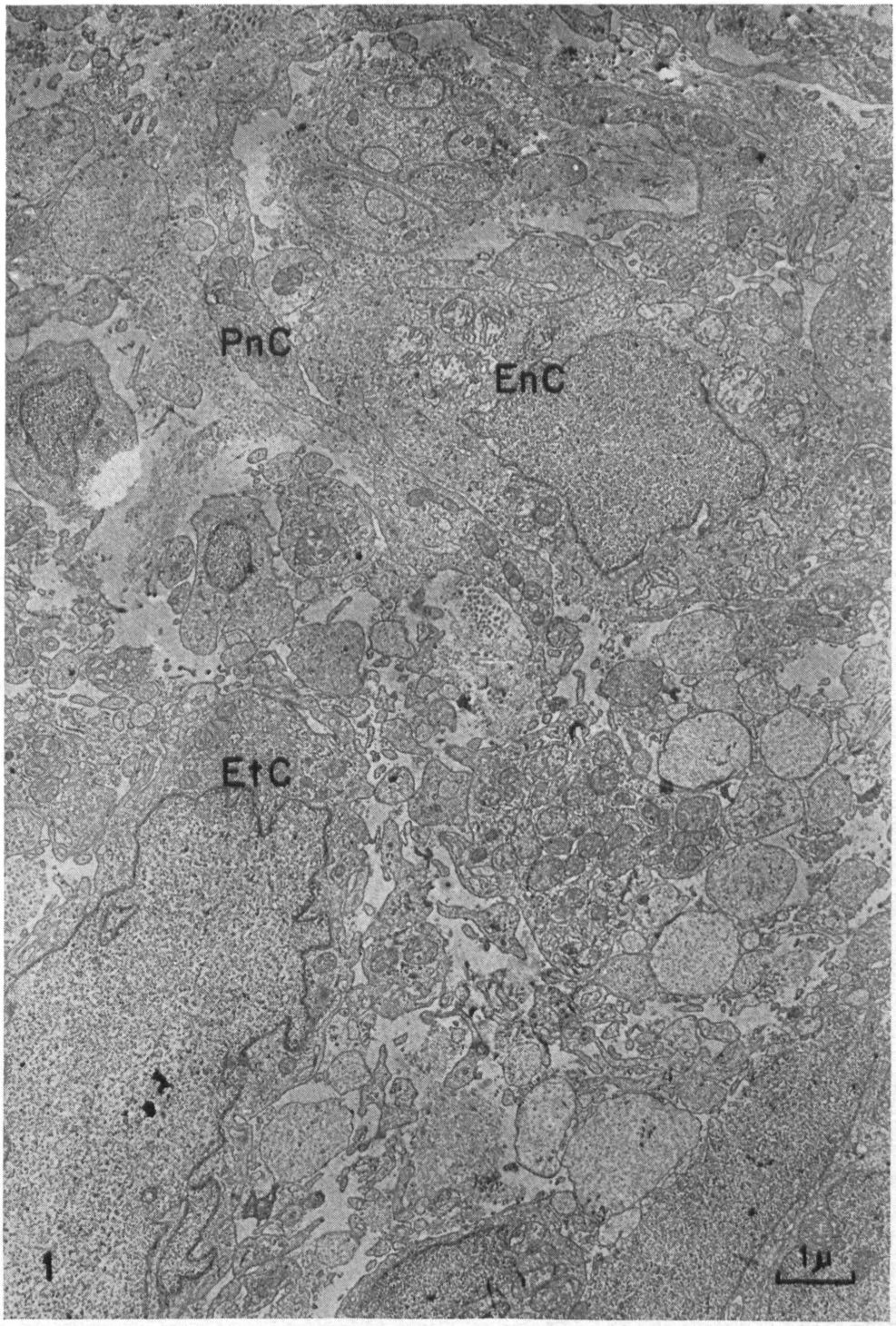


FIG. 1. A tuberculoid lesion. In the upper part of this picture, the preterminal branch of a cutaneous nerve is surrounded by the epithelioid tubercle. Regenerating Schwann cells including one or several axons are enclosed by endoneural collagen fibers. Laminate perineural cells (PnC) are separated by the enlarged endoneural cell (EnC) which in appearance is similar to the epithelioid cell (EtC) outside the nerve bundle.

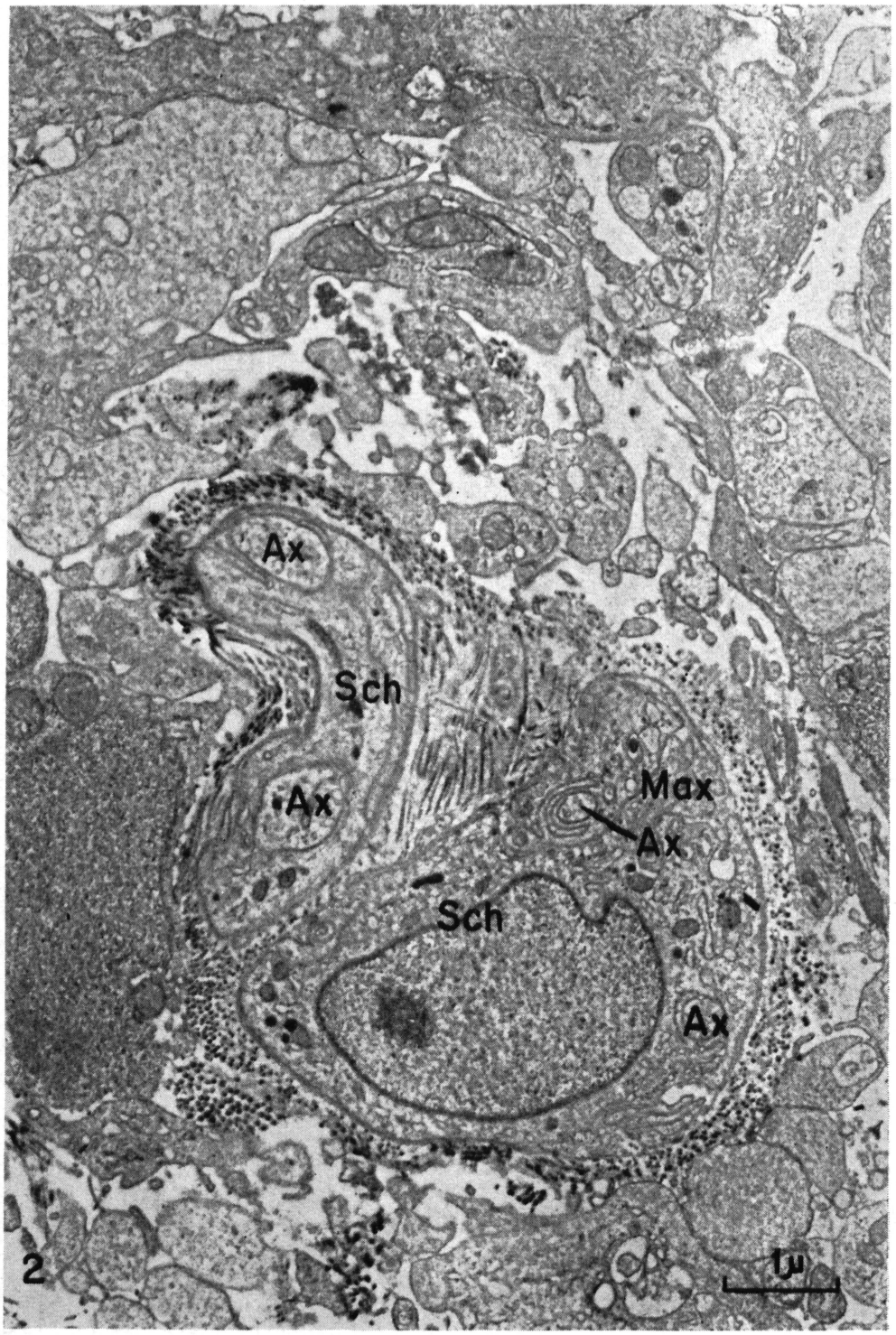


FIG. 2. A tuberculoid lesion. Regenerating Schwann cells (Sch) in the terminal branch are abundant in cytoplasmic organelles. Axons (Ax) are connected through whorling mesaxons (Max) to the surface of the Schwann cell. These nerve elements are surrounded by collagen fibers embedded in fine fibrillar substance.

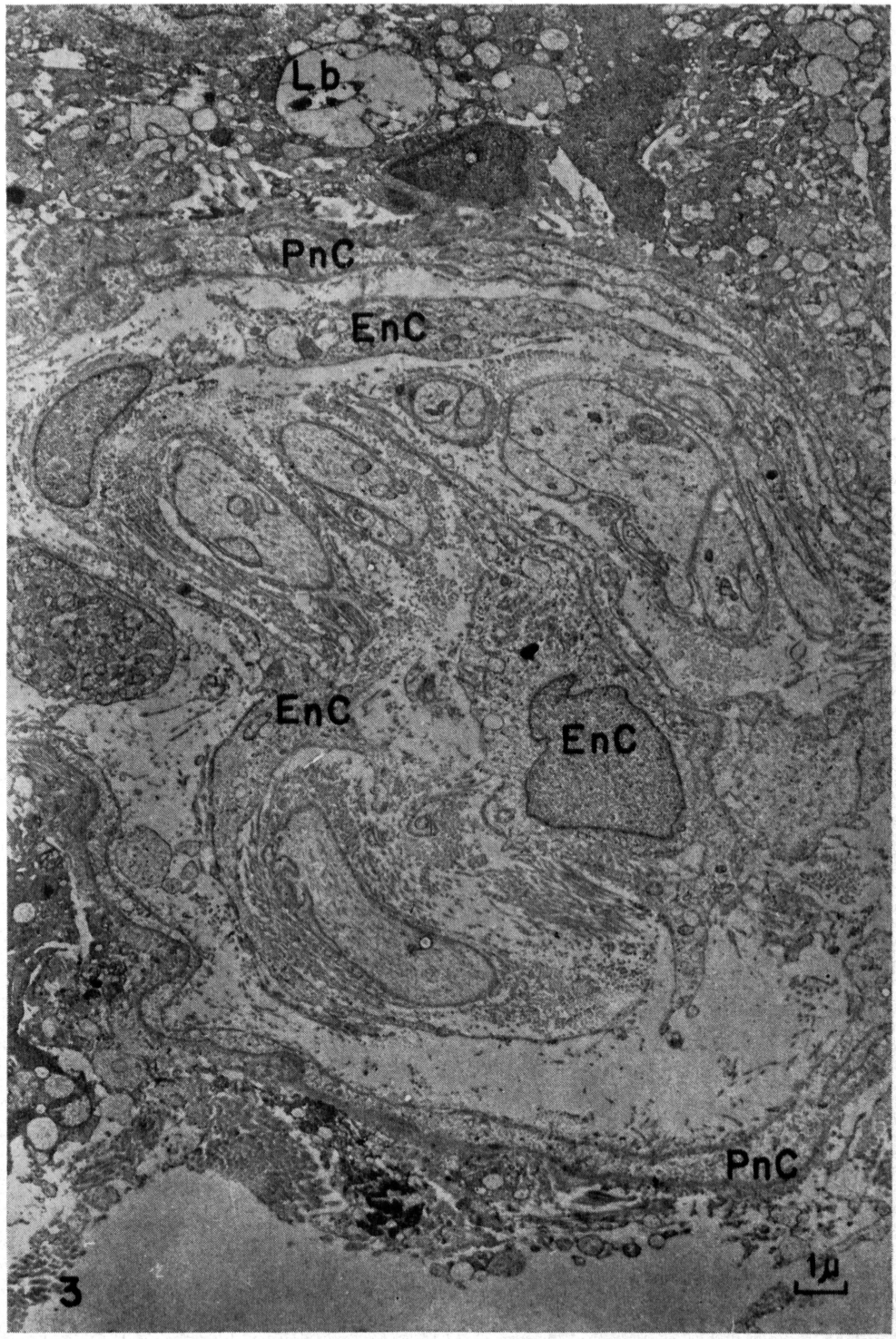


FIG. 3. In lepromatous infiltration of the cutaneous nerve, the preterminal branch is surrounded by lepra cells which contain bacilli (Lb). Schwann cells contain few cytoplasmic organelles. Some of them include axons connected through whorling mesaxons. Endoneural cells (EnC) containing dilated ergastoplasms, together with collagen fibers, enclose these Schwann cells. PnC: Perineural cell.

FIG. 4. A Schwann cell lobule representing the terminal branch is seen in the subpapillary layer, in the lower part of the picture. It is surrounded by a thick fibrillar substance. Dense cells, presumably representing immature mesenchymal cells, lie near the nerve bundle. Note that some of Schwann cells (Sch) do not include any axons.

Above that zone is the subepithelial intact connective-tissue zone common in lepromatous leprosy, composed almost entirely of collagen fibers. In the upper part of the picture is the lower level of the epidermis, here appearing too disorderly to be recognizable from the light microscope image. Between these two zones is a narrow, moderately dense layer which is the basement membrane of the epidermis.


Sch
4
1μ

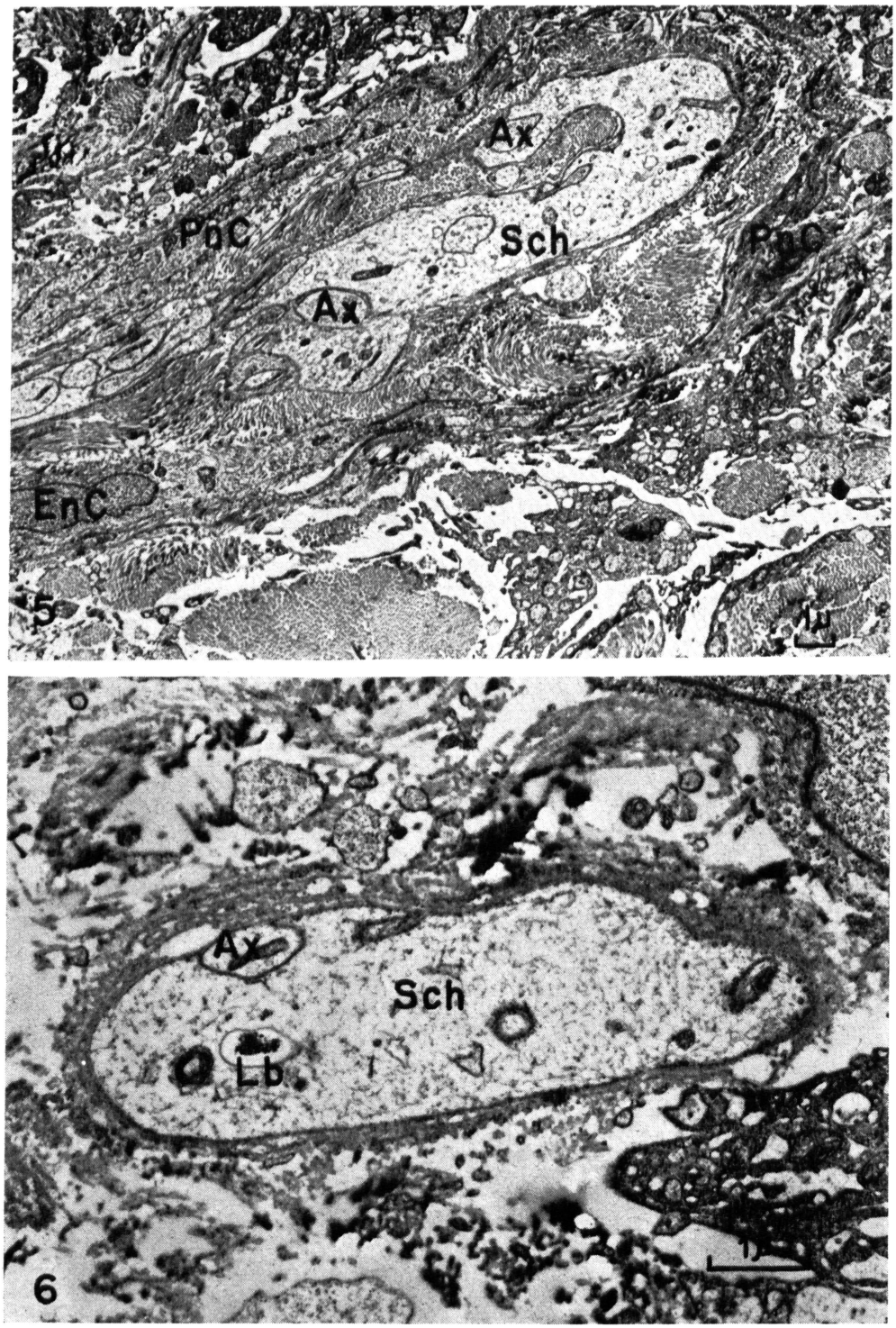
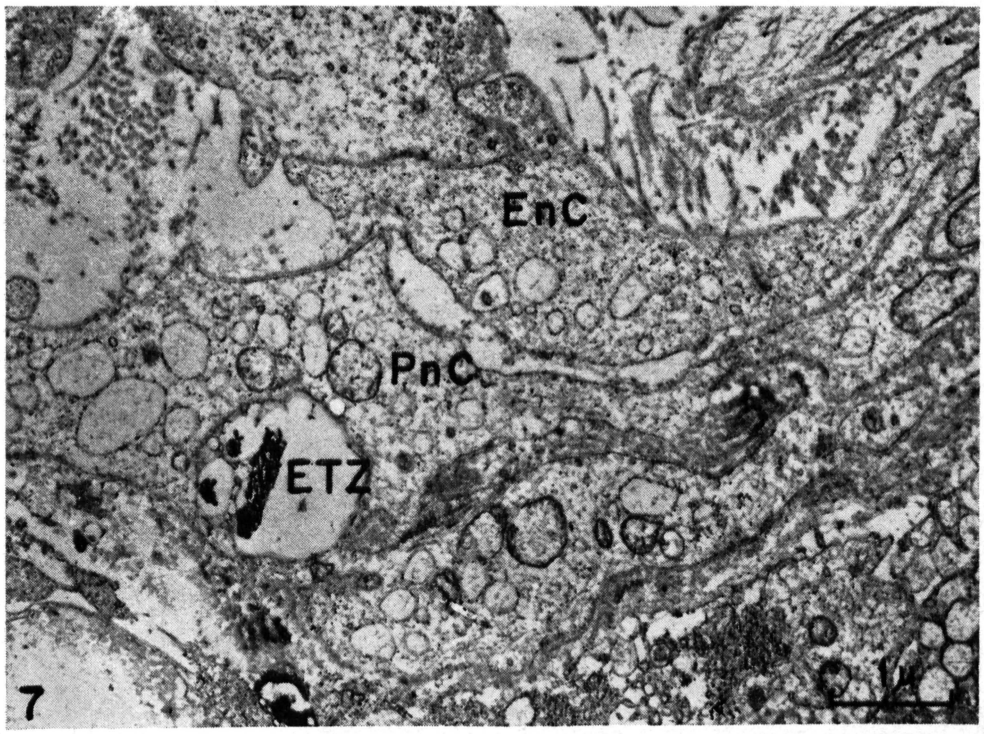


FIG. 5. A preterminal nerve branch in a lepromatous lesion. Note the abundant distribution of endoneural collagen. PnC: Perineural cell. EnC: Endoneural cell. Sch: Schwann cell.

FIG. 6. A terminal nerve branch in a lepromatous lesion. The Schwann cell (Sch) contains a degenerated bacillus (Lb), and partially surrounds the axon (Ax).



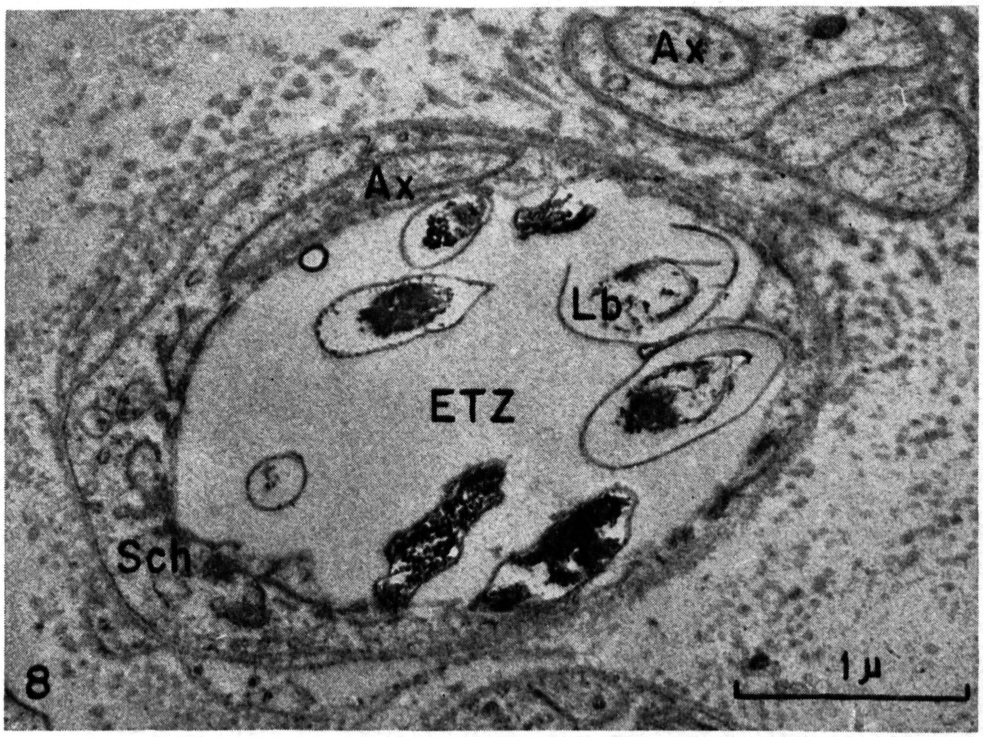


FIG. 7. The preterminal branch in a lepromatous lesion. The perineural cell (PnC) contains bacilli surrounded by an electron transparent zone (ETZ). EnC: Endoneural cell.

FIG. 8. The Schwann cell (Sch) in the preterminal branch in a lepromatous lesion contains degenerated bacilli (Lb), together with the axon (Ax). These bacilli are immersed in the electron transparent zone (ETZ).

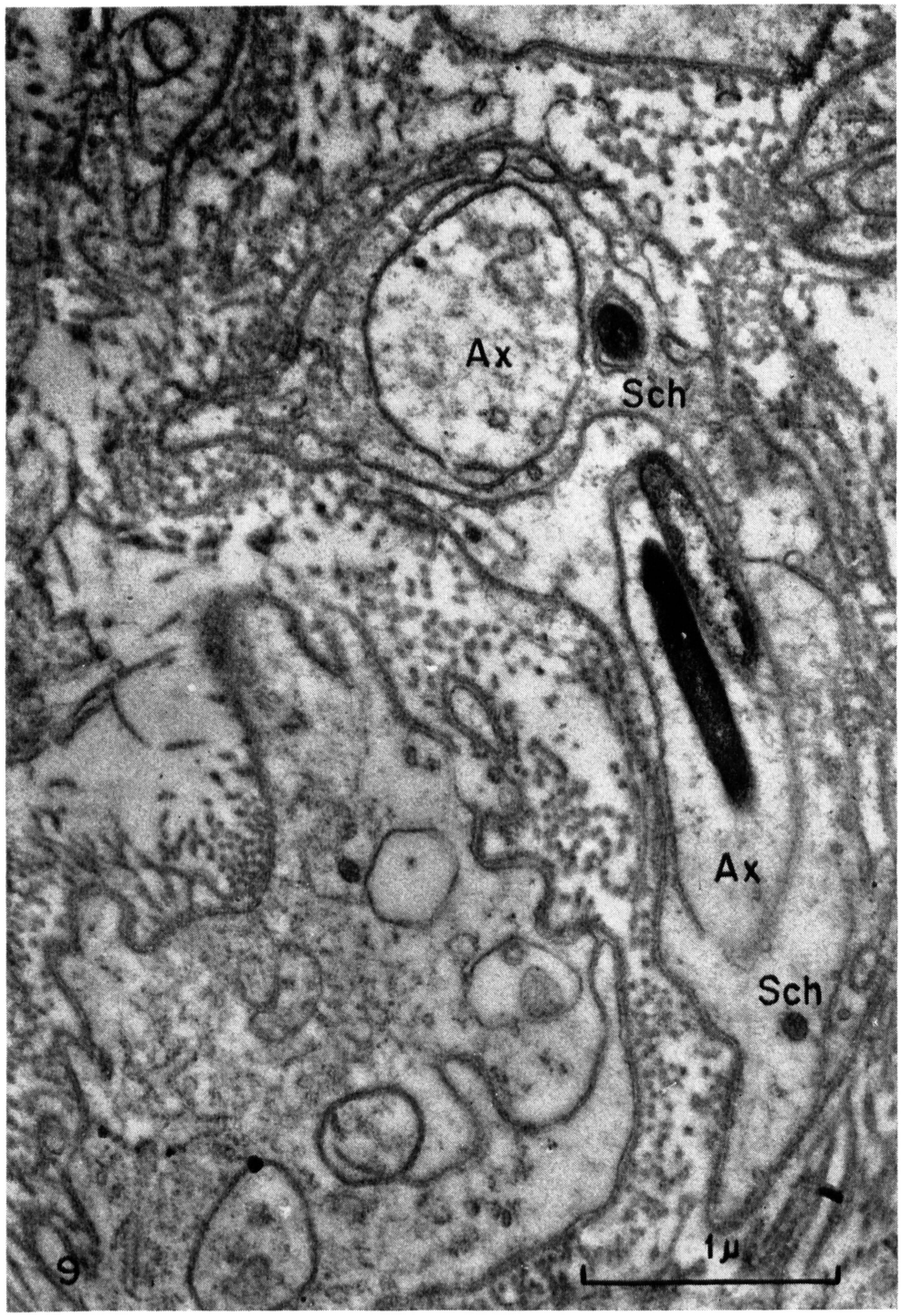


FIG. 9. A preterminal branch in a borderline lesion. Note the intact bacilli in axons (Ax), two cut longitudinally and one transversely. Sch: Schwann cell.

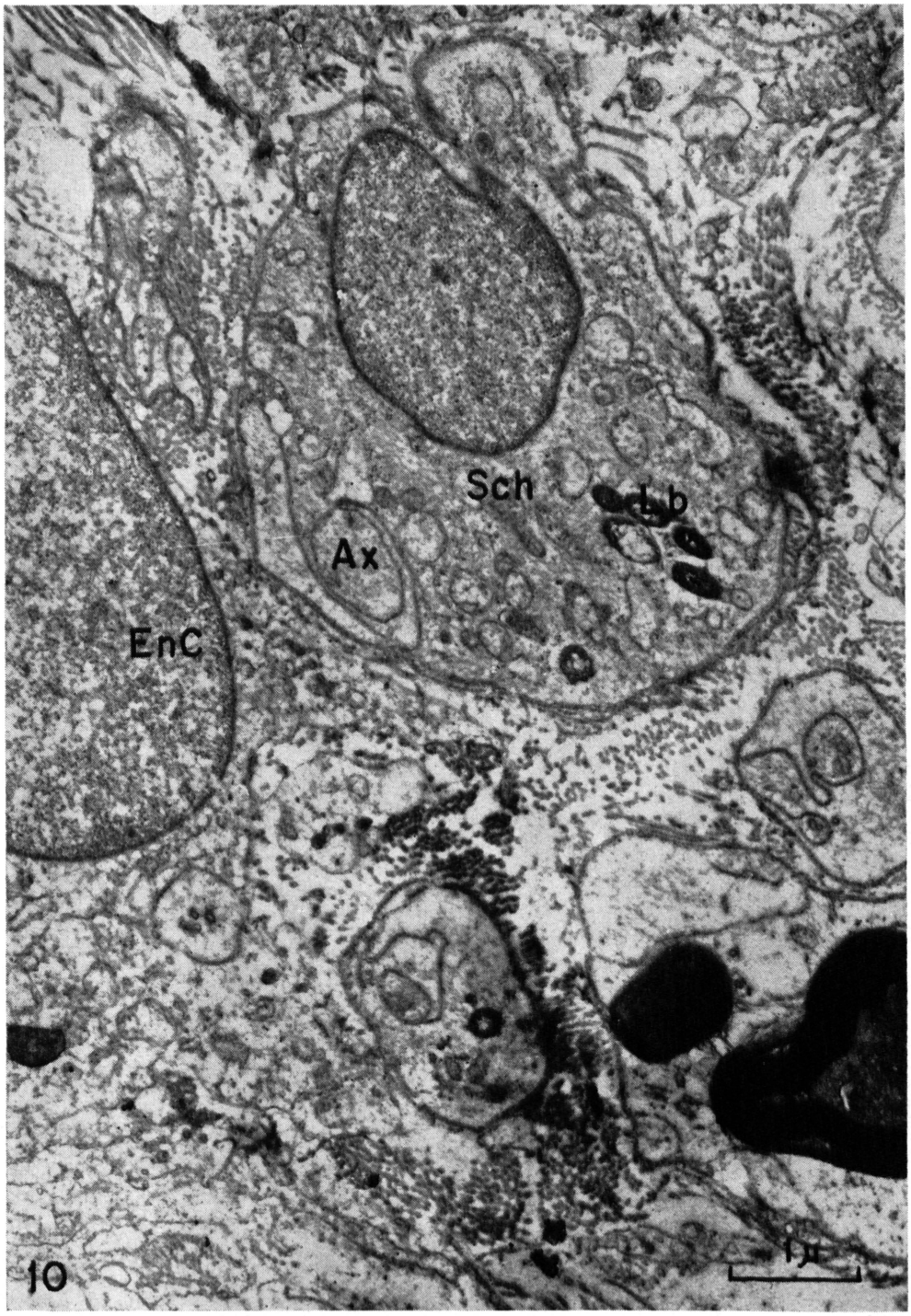
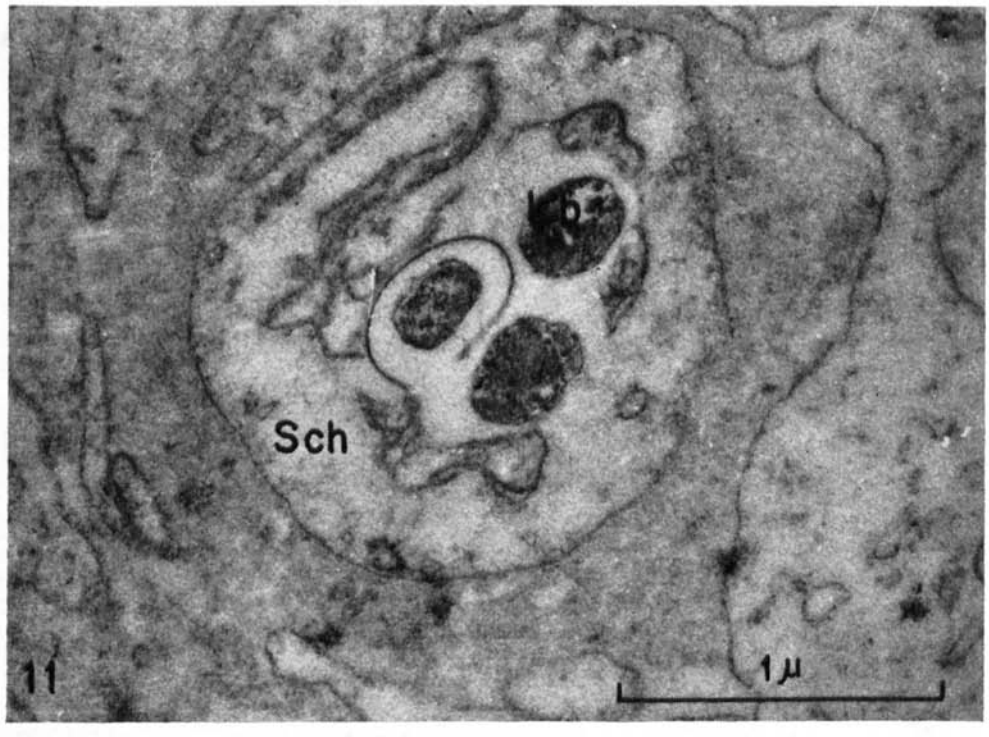


FIG. 10. The Schwann cell (Sch) contains an abundance of cytoplasmic organelles, and several intact bacilli (Lb). An axon (Ax) is connected through the whorling mesaxon. In the lower right corner, an accumulation of mitochondria in the axon of a myelinated fiber is to be seen. EnC: Endoneural cell.



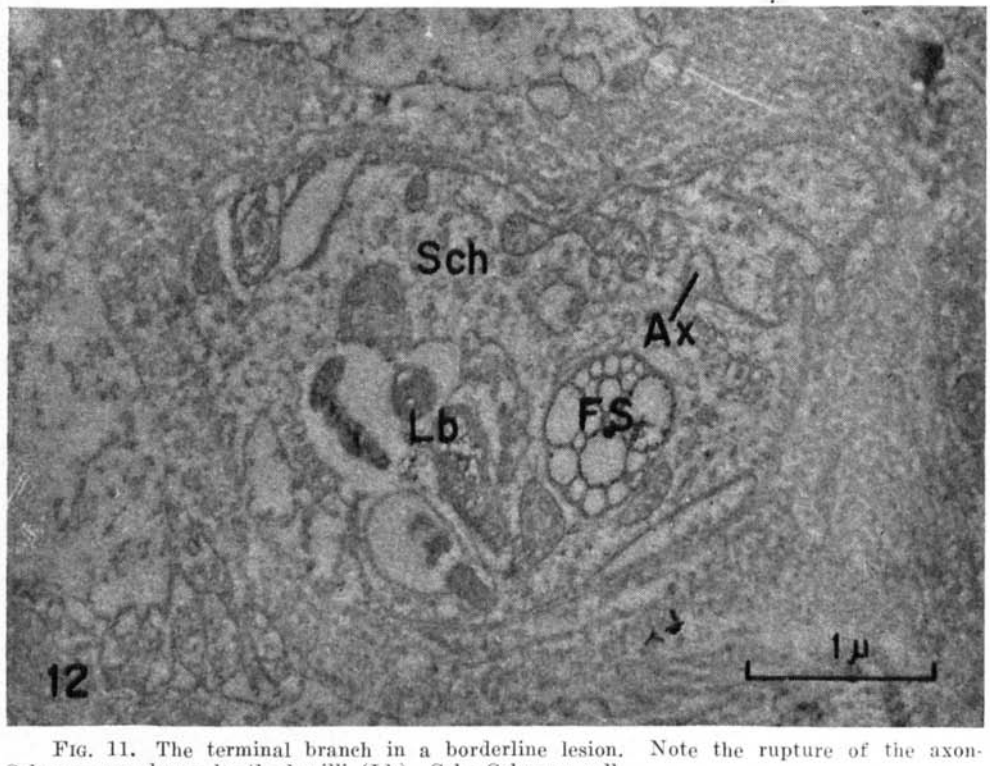


FIG. 11. The terminal branch in a borderline lesion. Note the rupture of the axon-Schwann membrane by the bacilli (Lb). Sch: Schwann cell.

FIG. 12. The Schwann cell (Sch) of the terminal branch in a borderline lesion, containing many degenerated bacilli (Lb), together with a foamy structure (FS). Ax: Axon.