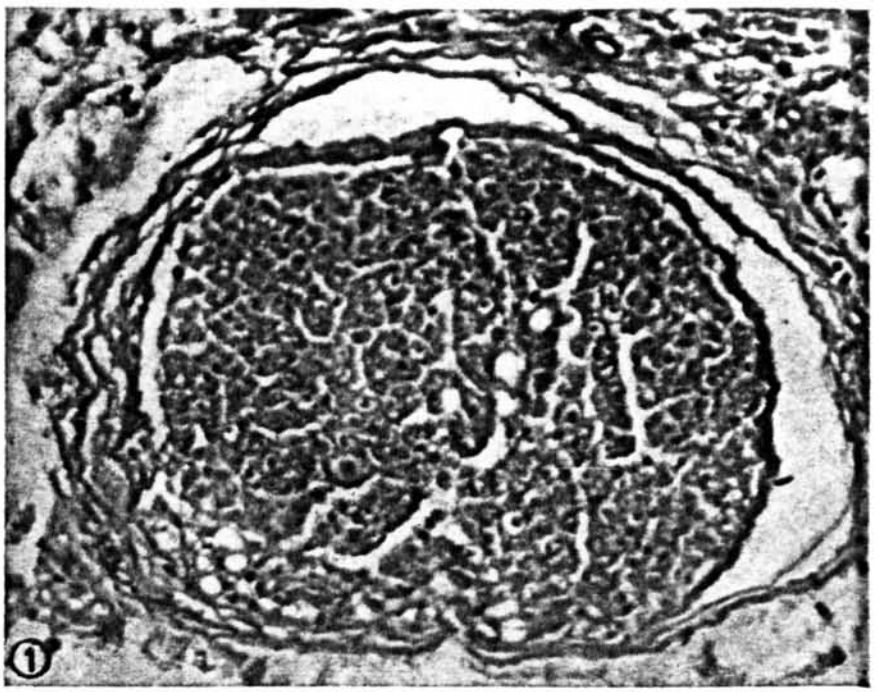

FIG. 1. Section of a nerve fascicle from a radial cutaneous nerve in lepromatous leprosy. There is only edema and minimal adhesion of the endoneurium with perineurium. Acid-fast stain of a serial section from the same block of nerve showed numerous *M. leprae* inside Schwann cells and macrophages. (H & E, x 260).

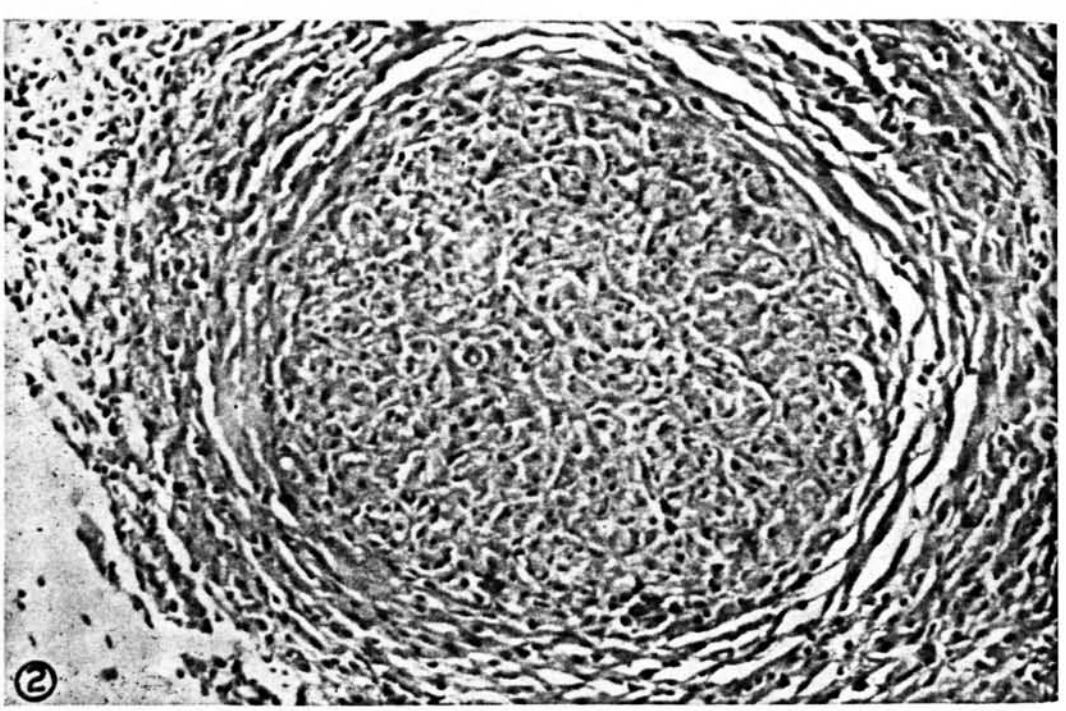

FIG. 2. Section of a nerve in the deeper dermis of a lepromatous skin lesion to show marked perineural thickening and gradual replacement of the nerve parenchyma with fibrous tissue. There is peri- and endoneurial infiltration with macrophages, plasma cells and lymphocytes (H & E, x 260).

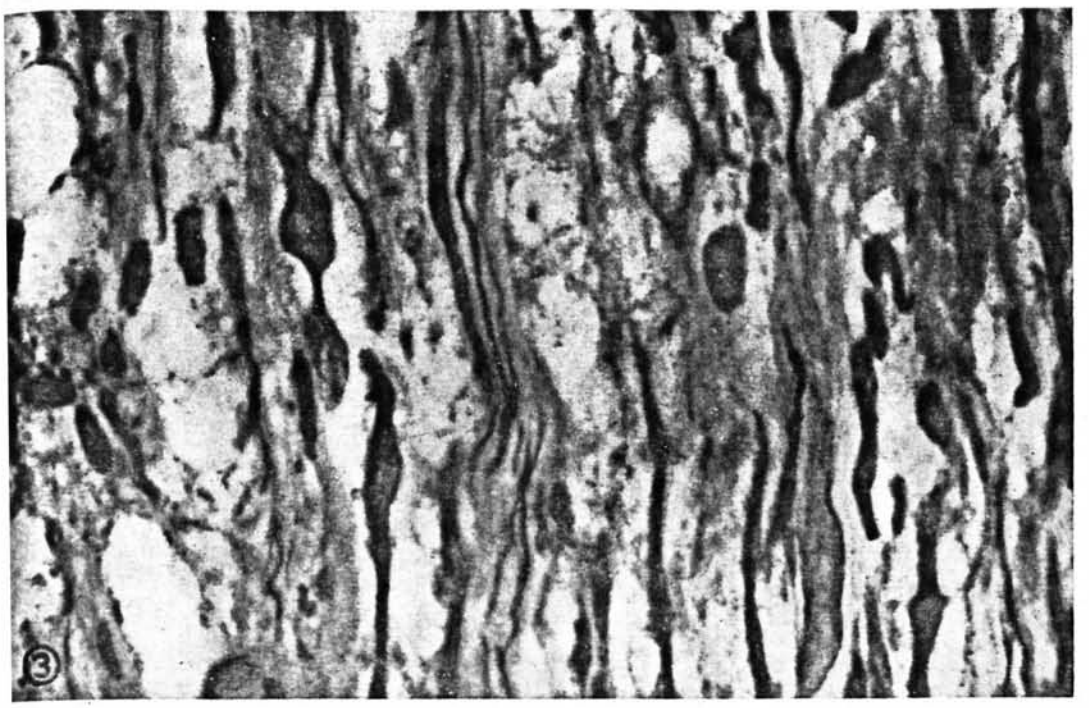

FIG. 3. High power photomicrograph of lepromatous nerve to show ballooning and fragmentation of axons (Bodian stain, x 1000).

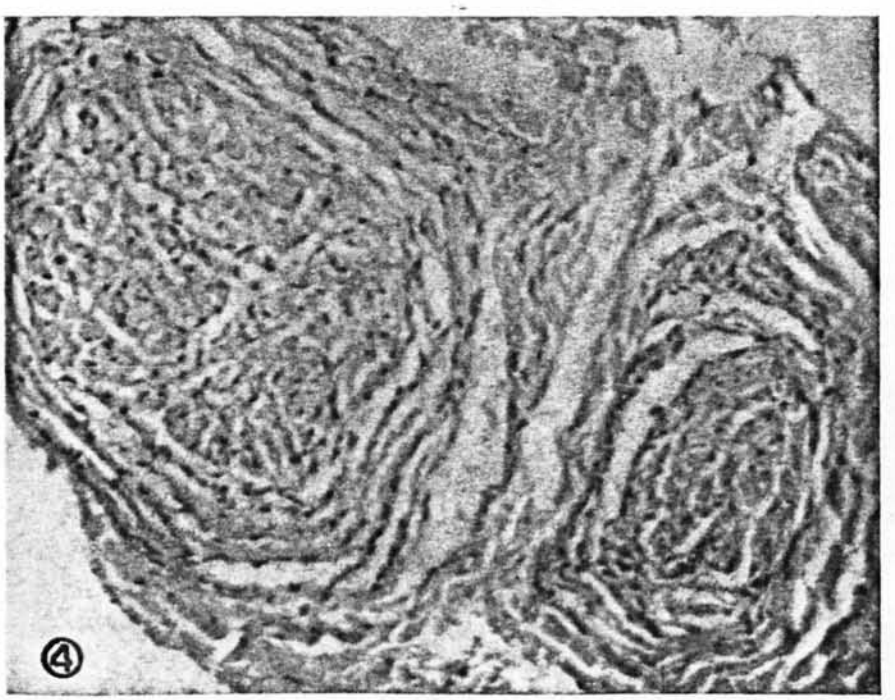

FIG. 4. Section through radial cutaneous nerve in an advanced case of lepromatous leprosy. The architecture of the nerve is totally lost and the nerve parenchyma and the perineurium are replaced by hyalinized fibrous tissue (H & E, x 260).

content increased there was commencing vacuolation of Schwann cells, macrophages and perineurial cells. However, the architecture of the nerve was well preserved.

In further stages, infiltration of the perineurium and nerve parenchyma with macrophages and occasional round cells became obvious. There was a progressive increase in perineurial and endoneurial fibrous connective tissue and also marked adhesions between the peri- and endoneurium. The "onion peel" appearance of the perineurium was very prominent (Fig. 2). Bacilliferous Schwann cells underwent marked foamy change, and ballooning and fragmentation of the axons were seen in Bodian stain (Fig. 3). Myelin stain showed extensive demyelination.

The whole nerve bundle need not necessarily be involved in this process at the same time, and very often a portion of the nerve was preserved. However, the disease process was progressive and in advanced cases the entire nerve bundle was replaced by fibrous tissue, followed by hyalinization (Fig. 4).

As the nerve parenchyma was being replaced by fibrous tissue there was a gradual reduction in their bacillary load, and with marked hyalinization of the nerve tissue the bacilli became very scanty. Even after attaining bacillary negativity of the skin, a few acid-fast bacilli still lingered inside the hyalinized nerves.

In two biopsies of radial cutaneous nerves obtained during an attack of erythema nodosum an unusual histopathologic appearance was seen. The nerve was infiltrated with collections of neutrophil polymorphs, forming several intraneural microabscessses (Fig. 5). The tissues in and around the abscesses were swollen and edematous, resulting in compression of the surrounding axons. Acid-fast stain showed scattered groups of bacilli inside Schwann cells and macrophages. Extensive demyelination of the entire nerve tissue was seen in the myelin stain. In the Bodian stain axons entering the abscess cavities were found to be fragmented and destroyed (Fig. 6).

Electron Microscopy: The ultrastructural

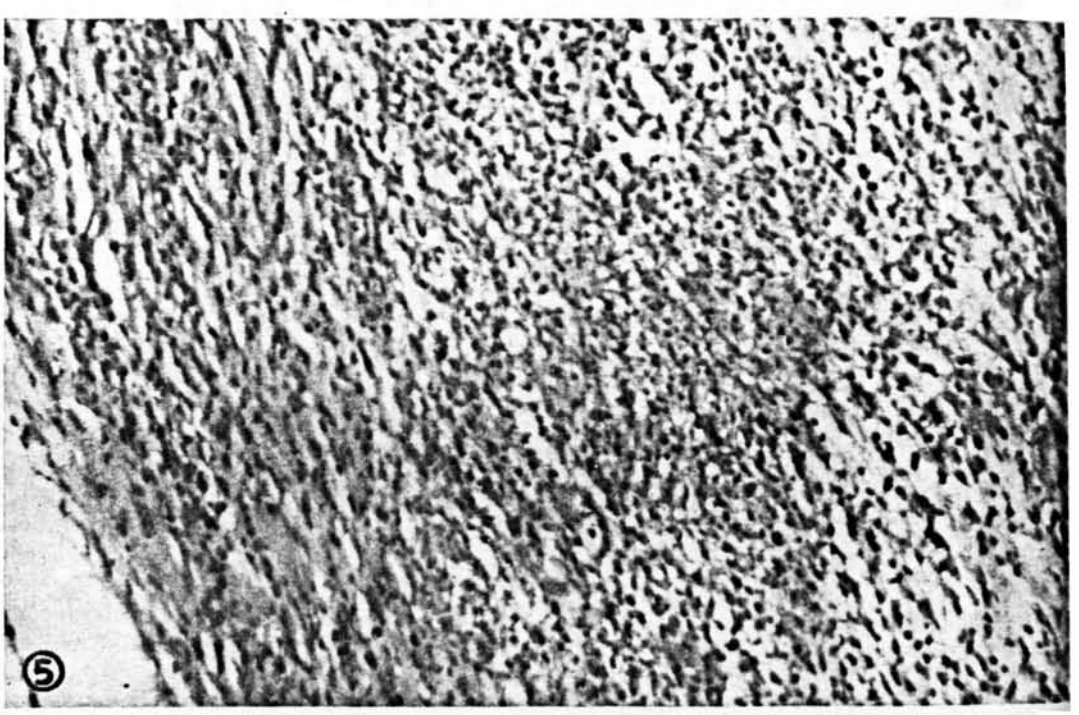

FIG. 5. Photomicrograph of the radial cutaneous nerve in lepromatous leprosy to show dense infiltration with neutrophil polymorphs and fibrinous exudate during the erythema nodosum phase. The nerve architecture is totally disrupted (H & E, x 260).

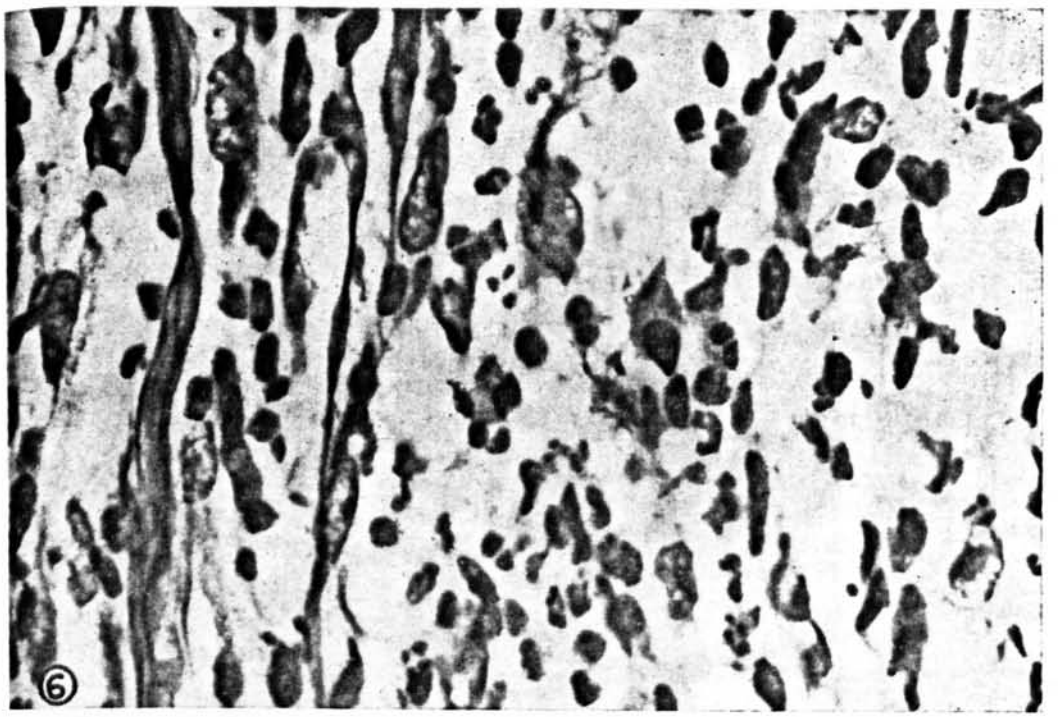

FIG. 6. Bodian stain of lepromatous nerve abscess to show extensive destruction of nerve fibers. Note the absence of axons in the abscess and swelling and ballooning of the remaining axons (Bodian stain, x 1000).

changes in nerves in lepromatous leprosy were characterized by degenerative and hypertrophic changes of Schwann cells and moderate to marked increase in endoneurial collagen fibrils. Schwann cells were identified by their basement membrane and intracytoplasmic fine filaments, and the degenerative changes seen in them were mainly due to the parasitization of their cytoplasm by *M. leprae*. *M. leprae* were recognized easily by their plasma membranes and markedly electron-dense and relatively homogeneous cytoplasm. ([12, 30]) (Fig. 7). The number of *M. leprae* present in Schwann cells varied from single ones to large aggregates. Some of the organisms evoked no reaction in the cell and appeared as if they were part of the many intracytoplasmic organelles, but most of the organisms had an electron-transparent halo around them. As the organisms proliferated to form large packs, they seemed to dissolve the Schwann cell cytoplasm and often there was no limiting membrane around them (Fig. 8). Less frequently these packs of organisms were contained in unit membrane-bound intracytoplasmic vacuoles. Numerous such vacuoles could be seen in a single cell giving rise to a foamy Schwann cell (Fig. 9). The presence of an organism in the Schwann cell has not produced any obvious change in the axon (Fig. 10). However, as the organisms increase in number, disruption of myelin may take place. The breakdown of the myelin occurred mostly from the Schwann cell side, with the myelin splitting away from an intact axon (Fig. 11). In some instances the Schwann cells containing an intact myelinated axon showed in their cytoplasm fragments of myelin with the lamellations still preserved (Fig. 12). Occasionally completely demyelinated axons were seen in Schwann cells (Fig. 13). In all these instances, despite the disintegrating myelin, the axons were intact.

The hypertrophic changes of the Schwann cells were characterized by the formation of numerous long and irregular

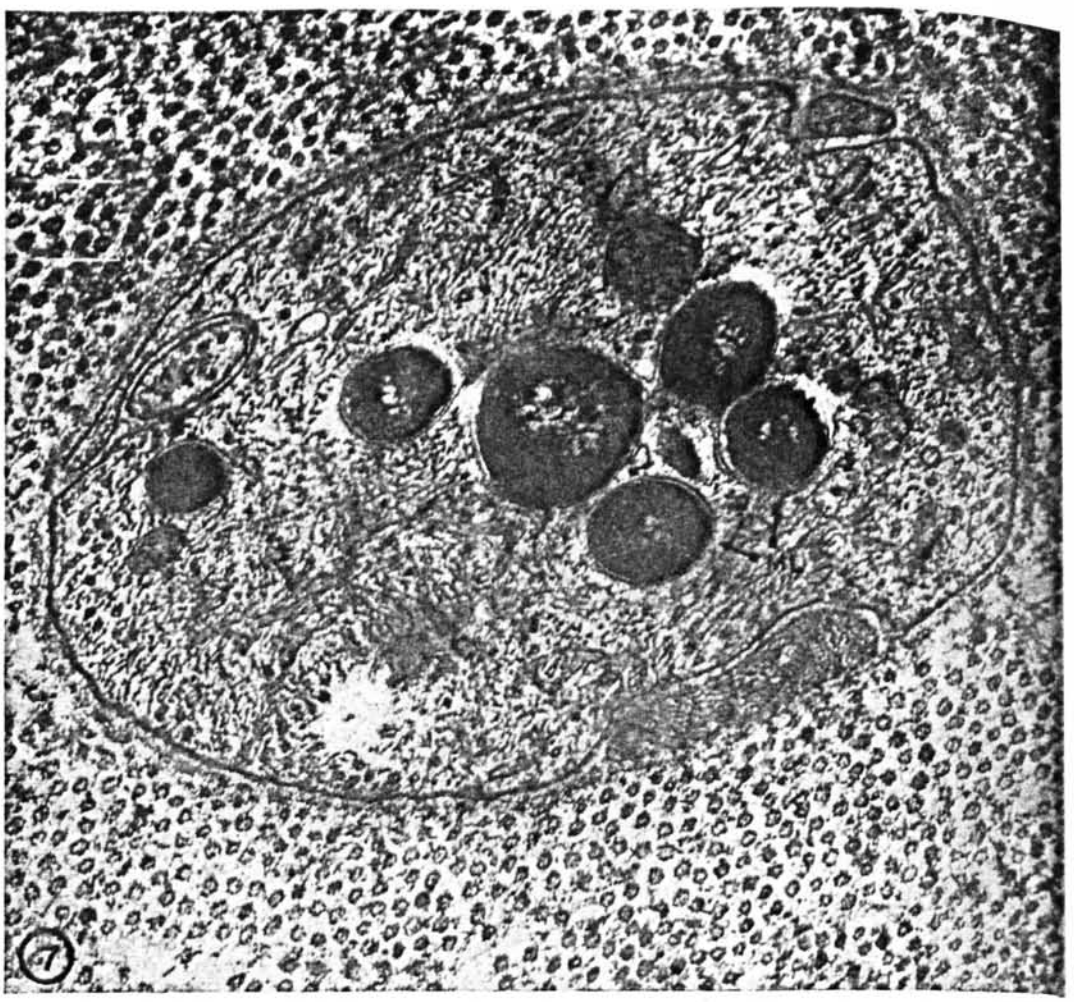

FIG 7. Cross section of a Schwann cell process surrounded by collagen fibrils containing a small nonmyelinated axon. There are six *M. leprae* (M.L.). with hardly any reaction around most of the organisms. The cytoplasm shows numerous fine filaments. (x 50,000).

processes (Fig. 14). Some of them showed marked increase in mitochondria, rough endoplasmic reticulum and fine filaments. In two cases Schwann cells, identified by the presence of their basement membranes, formed with their flattened processes what appeared to be "onion bulbs" (Fig. 15). The core of the onion bulbs consisted of myelinated axons most of the time, and in one instance of a nonmyelinated axon. The "onion bulb" was densely infiltrated by collagen fibrils.

Degenerating axons characterized by increase in dense bodies, edematous mitochondria, and clumping or absence of neurofilaments, were also seen. The myelin sheath of these axons showed splitting, fragmentation and loss of lamellar structure. The number of nonmyelinated fibers was far less than in normal nerves. In three cases *M. leprae* were seen inside the axoplasm in double membrane-bound vacuoles.

There was perineurial thickening with six to ten layers of perineurial cells in all the nerve biopsies studied. Some of the perineurial cells contained *M. leprae* in varying number. Many capillaries were present between the perineurial cells.

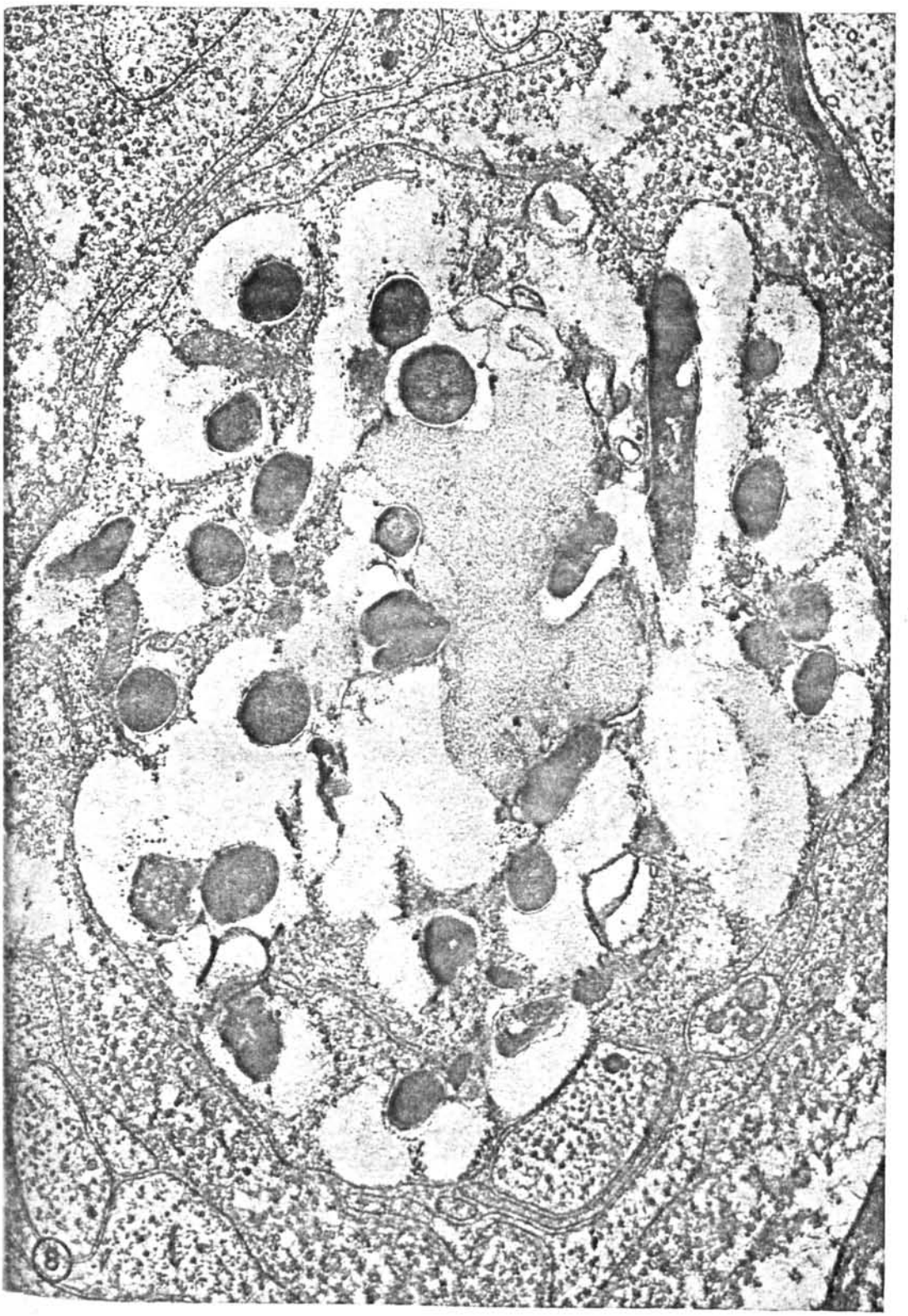

FIG. 8. Schwann cell containing a nonmyelinated axon and a large collection of *M. leprae* dissolving the cytoplasm (arrows) (x 46,000).

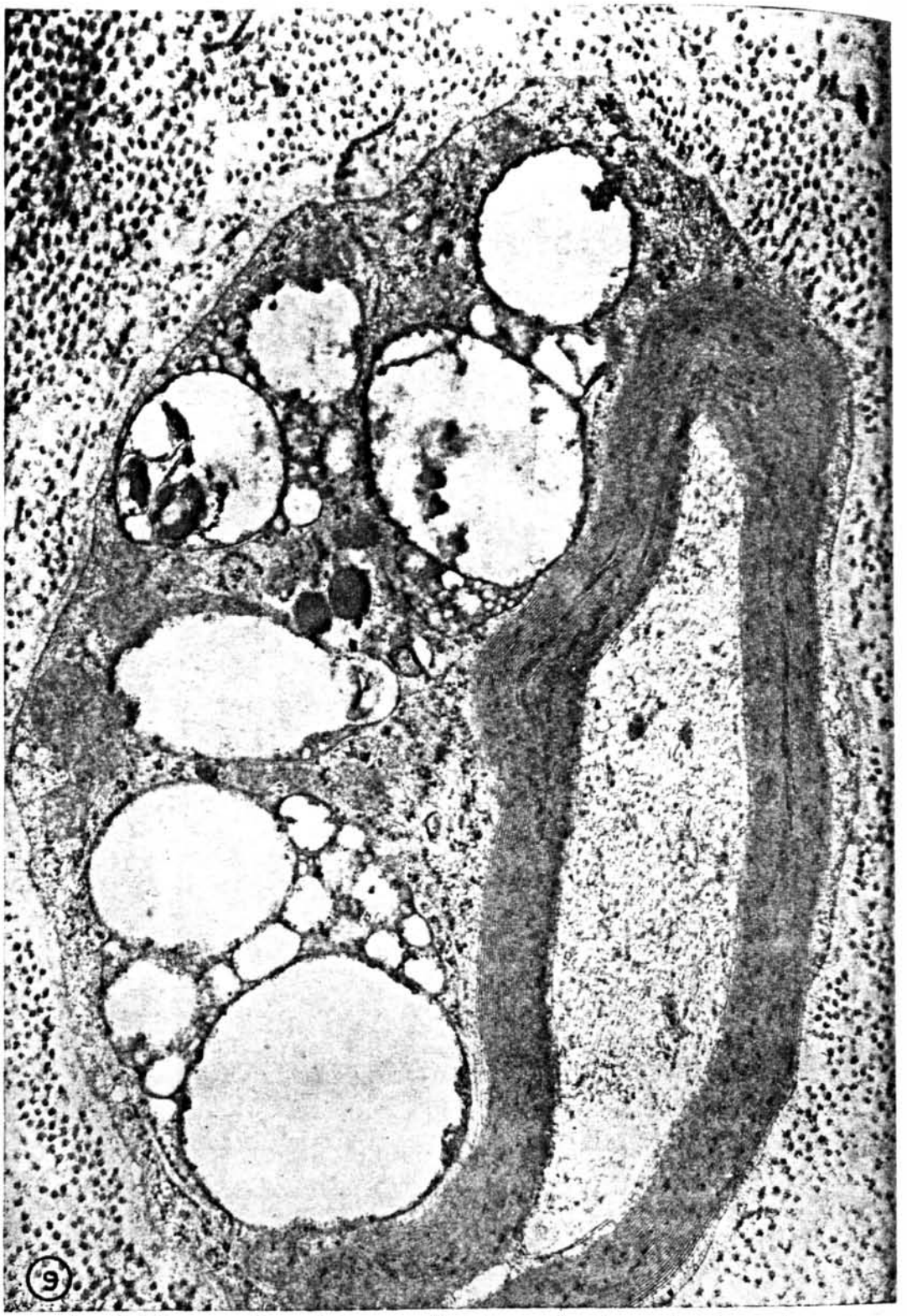

FIG. 9. Schwann cell containing a myelinated axon showing marked foamy degeneration following parasitization by *M. leprae*. In some vacuoles *M. leprae* can be seen. (x 33,000).

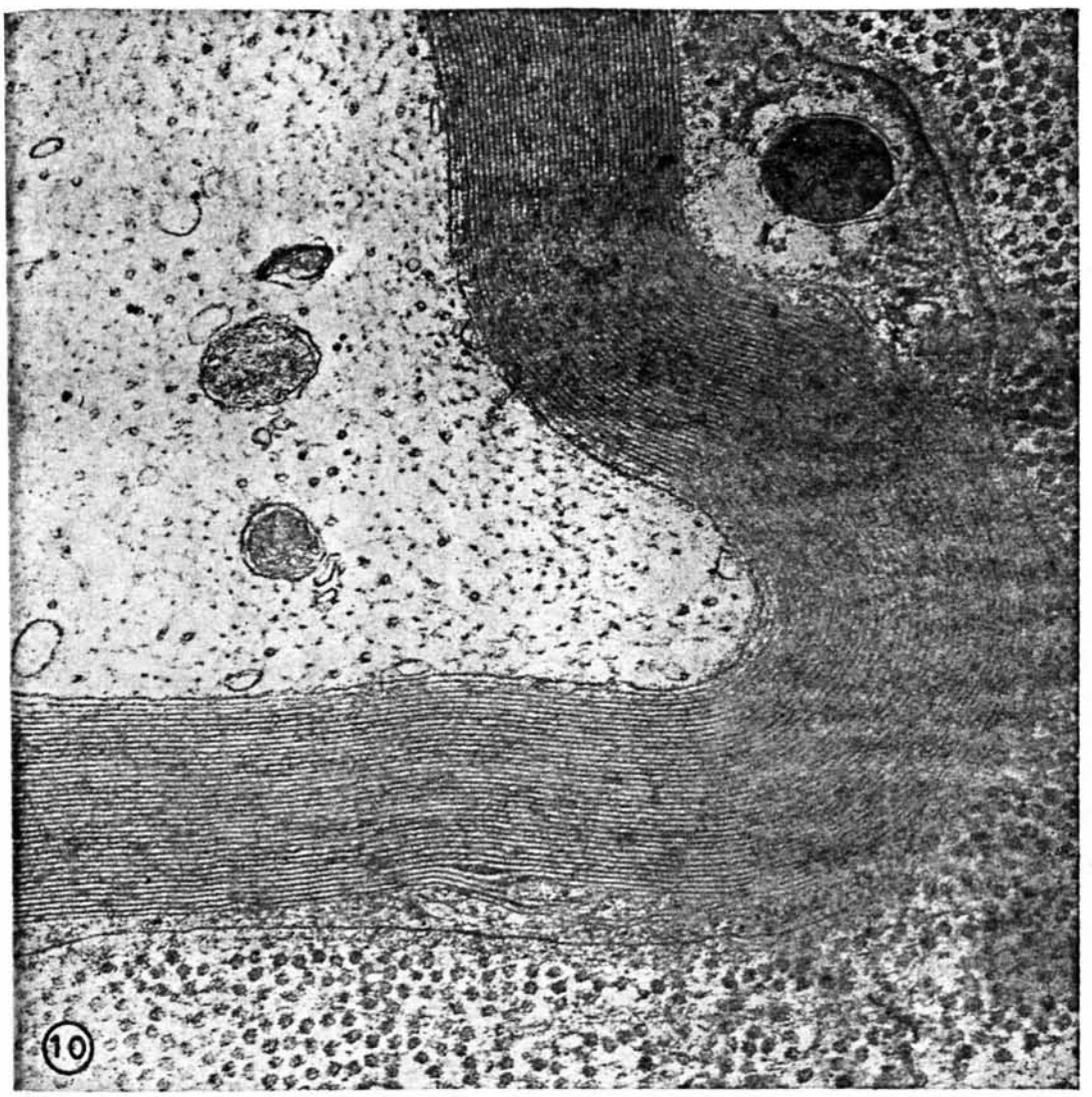

FIG. 10. Part of a Schwann cell showing a portion of a myelinated axon. A single organism is present in the Schwann cell cytoplasm with an electron-transparent zone around it. (x 54,000).

Scattered intraneurial macrophages, identified by the absence of basement membrane, their cytoplasm containing numerous mitochondria and active rough endoplasmic reticulum, were seen. They invariably contained vacuoles with aggregates of *M. leprae* undergoing degenerative changes. Lymphocytes and plasma cells, though very scanty, were also present.

Numerous intraneural blood vessels were seen in three cases and in one case the small capillaries showed pronounced hypertrophy of endothelium and thickening of the basement membrane. Occasionally the endothelial cells were invaded by *M. leprae*, with subsequent foamy degeneration of the cell (Fig. 16).

DISCUSSION

The histopathologic changes of nerve lesions in leprosy have been described by several authors [2, 5, 8, 10, 13, 16, 17, 23, 29]. However, the exact mechanism of production of nerve damage is not well understood.

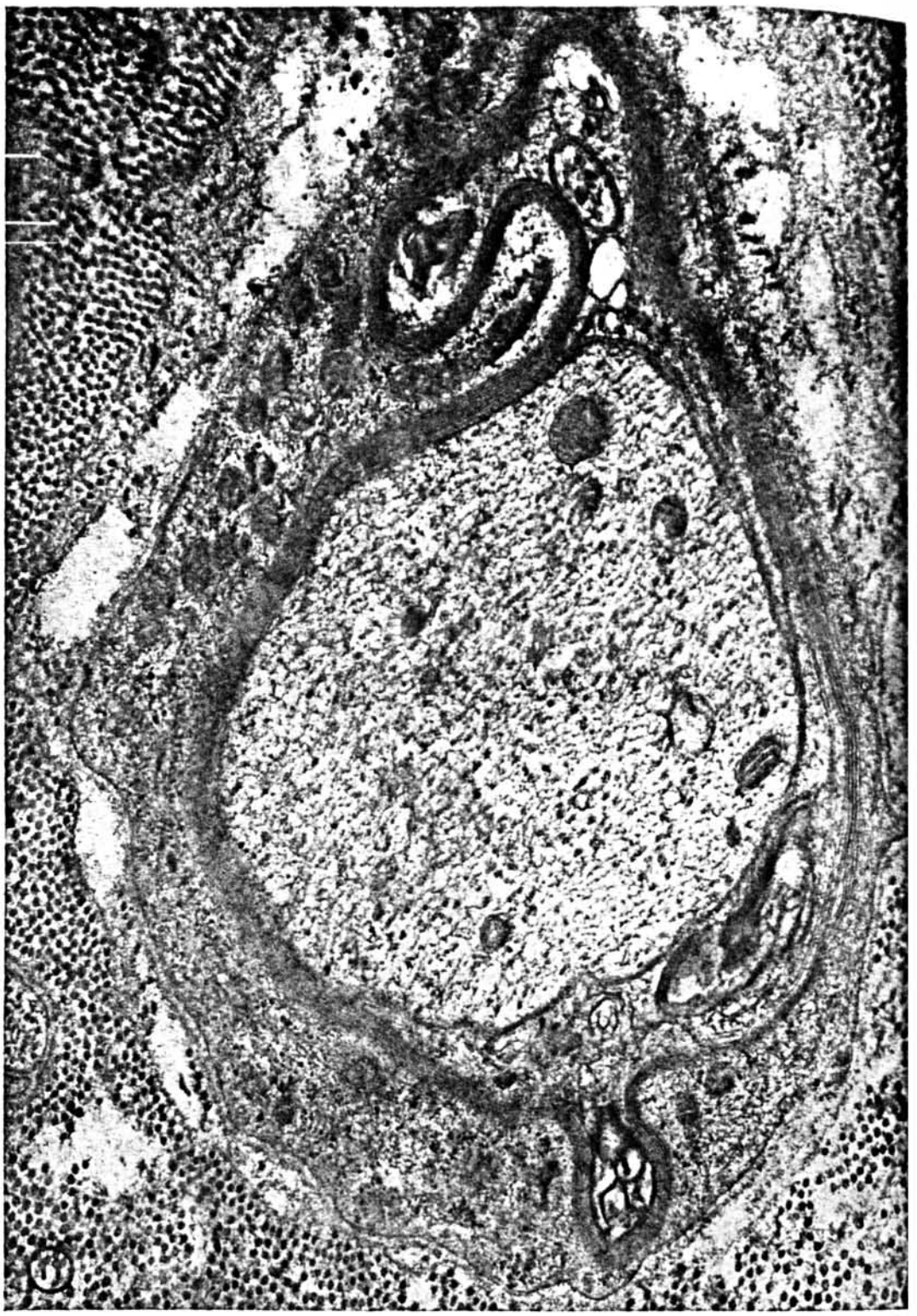

FIG. 11. Schwann cell with an axon showing marked splitting of the myelin lamellae breaking away from the axon. The Schwann cell cytoplasm shows numerous mitochondria. (x 32,000).

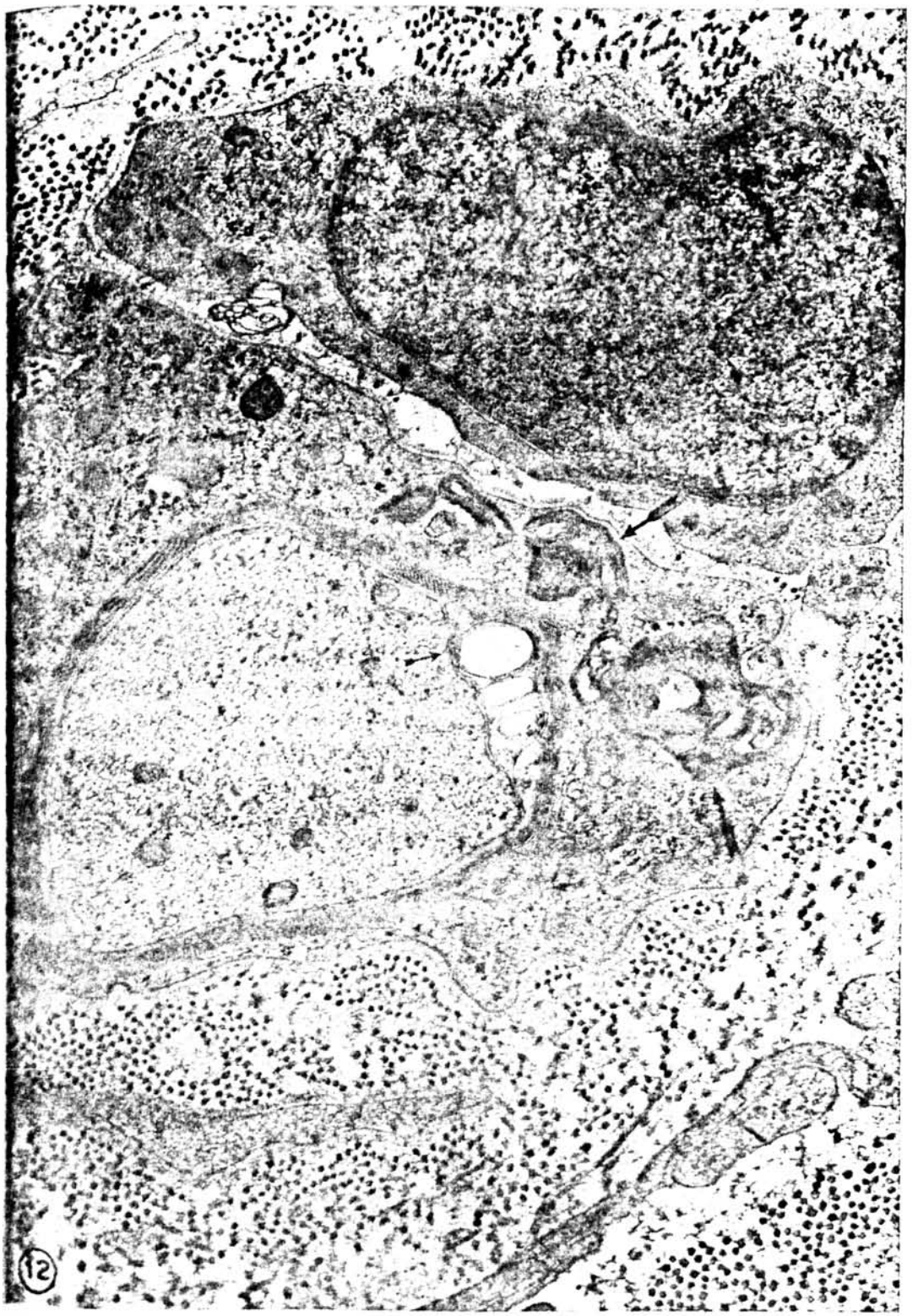

FIG. 12. Cross section of a Schwann cell with the myelin sheath separated from the axon by a few vacuoles (small arrow). In the cytoplasm are numerous myelin ovoids (large arrows) and in some of them the myelin rings can still be recognized. (x 23,000).

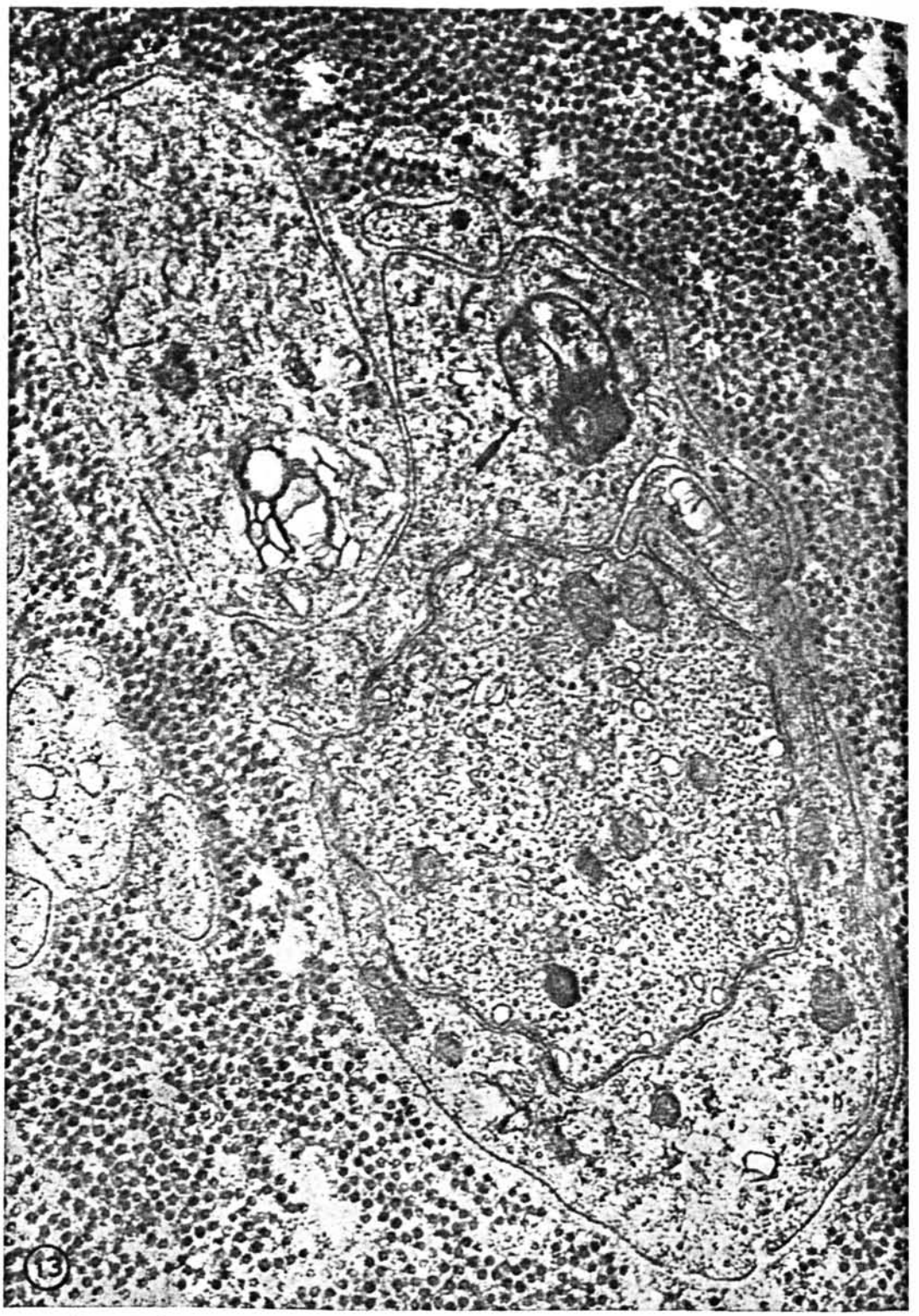

FIG. 13. Cross section of a Schwann cell containing a totally demyelinated axon. The Schwann cell cytoplasm contains a multivesicular body (arrow). The intact axon shows several mitochondria, a dense body and intact neurofilaments. (x 43,000).

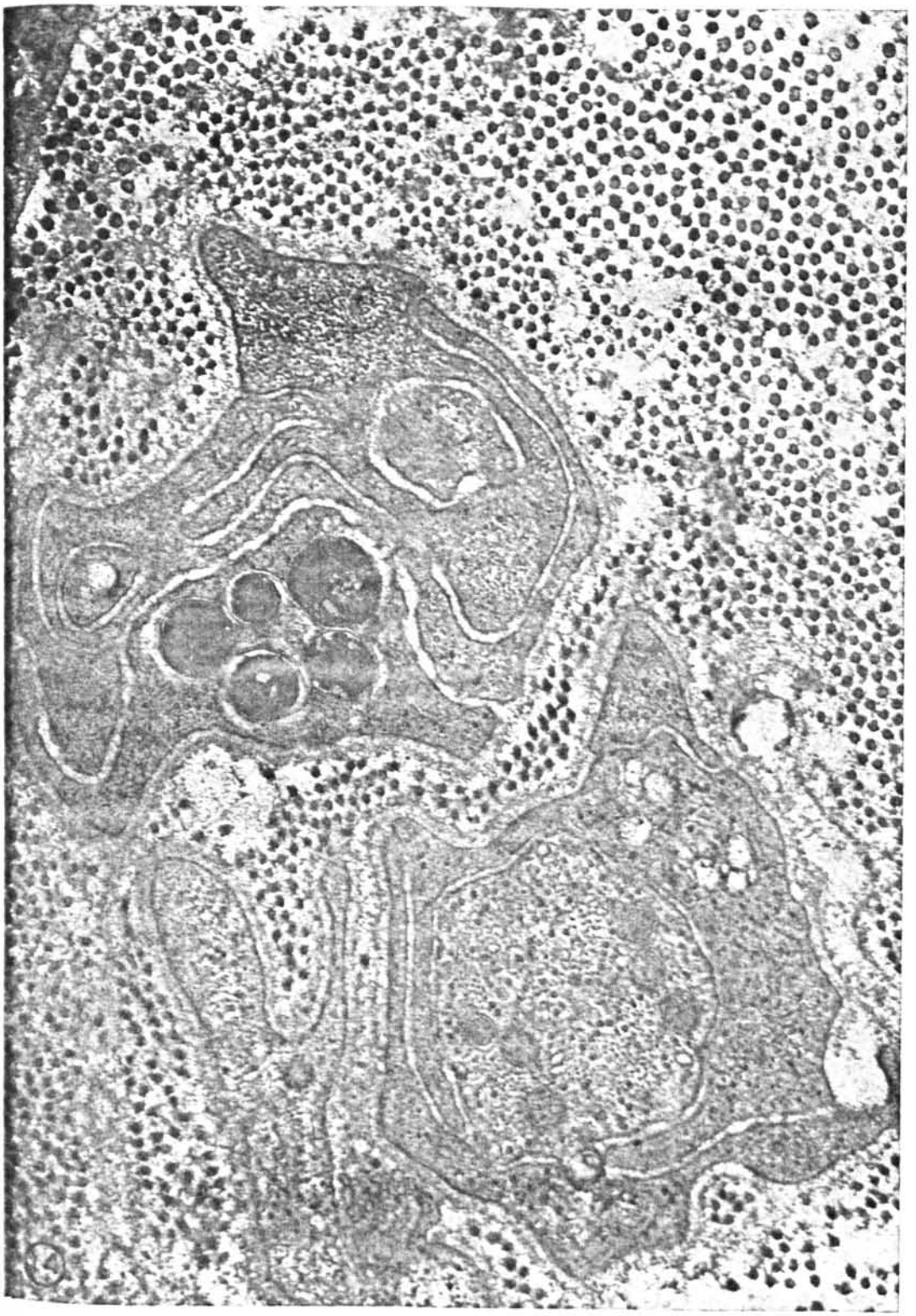

FIG. 14. Schwann cell including one nonmyelinated axon surrounded by collagen fibrils. There are several infoldings and irregular tongues of the Schwann cell cytoplasm. (x 40,000).

FIG. 15. Electron micrograph showing an "onion bulb" with a central core containing a myelinated axon surrounded by several flattened Schwann cell processes (SC) concentrically arranged around the axon (FB fibroblast) (x 20,000).

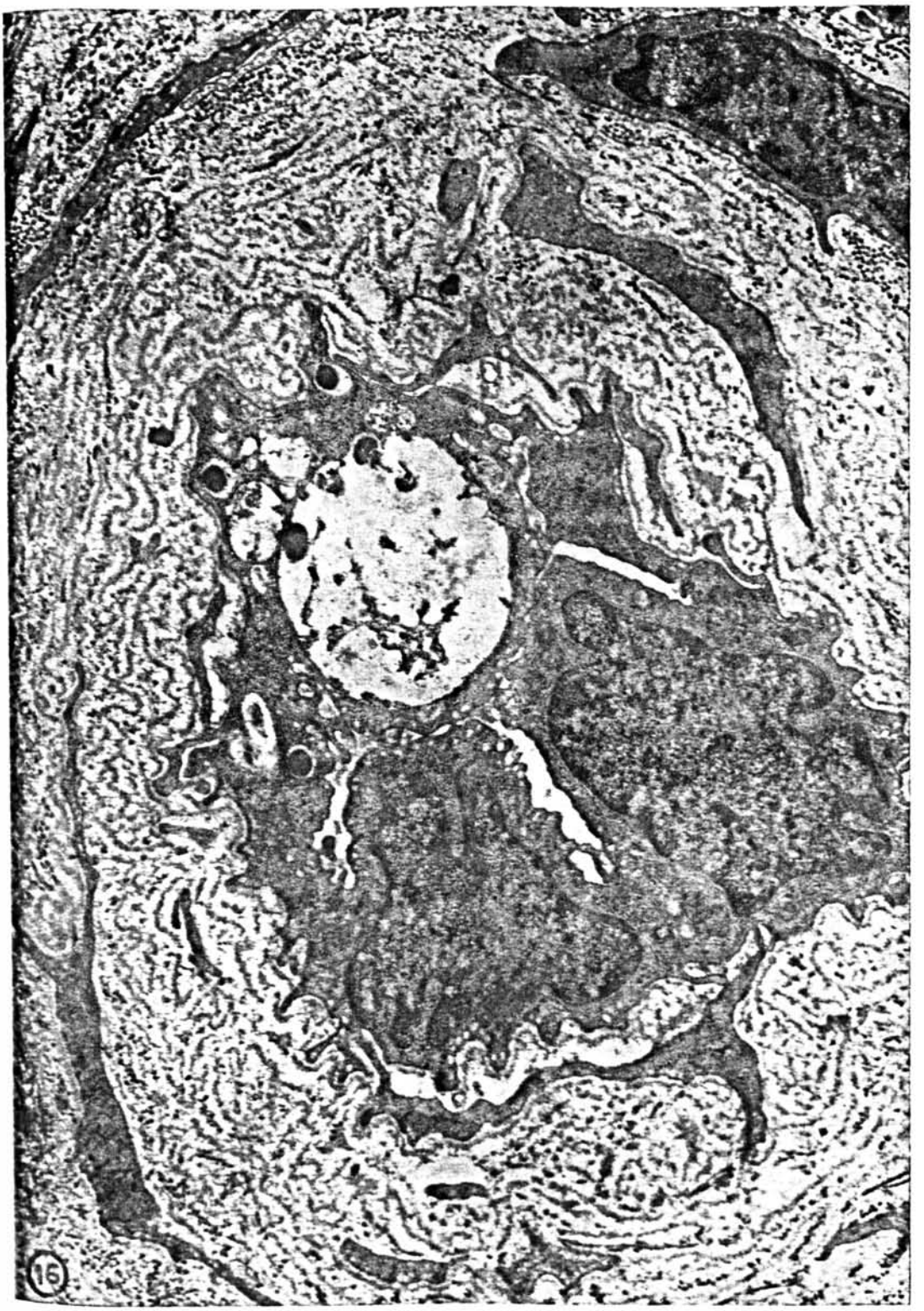

FIG. 16. Cross section of a blood vessel. The endothelial cells contain several *M. leprae* and there is commencing foamy change. The basement membrane shows edema and well marked thickening. (x 17,000).

In the foregoing description of the histopathologic changes in nerve lesions in lepromatous leprosy certain facts are clearly brought out. In the early stages a nerve infected with *M. leprae*, except for slight edema, may have a normal histologic appearance in a section stained with hematoxylin and eosin, though an acid-fast stain may reveal many bacilli in groups and clumps inside Schwann cells and macrophages. The infection may begin at a small part of the nerve fascicle, or may spread throughout the fascicle and later extend to involve the entire nerve. It is not uncommon to see a reactive proliferation of the perineurium giving rise to an "onion peel" appearance, and lepra bacilli may be present in large numbers in the perineurial cells. There may be infiltration of the nerve parenchyma and perineurial tissue with lymphocytes and plasma cells, and these inflammatory cells are very few when compared with the abundance of the organisms present.

The presence of *M. leprae* in perineurial cells produces reactive hyperplasia of the perineurium. The proliferation of organisms in Schwann cells results in their foamy degeneration, followed by disintegration of axons and endoneurial fibrosis. The growth of organisms inside intraneurial macrophages promotes the growth of the macrophage granuloma. The proliferation of perineurial cells, increase in endoneurial collagen and the steady growth of macrophage granuloma produce a pronounced thickening of the nerve, resulting in a significant elevation of intraneurial pressure and further degeneration of nerve parenchyma. Ultimately the entire nerve is fibrosed, followed by hyalinization. Even after the entire nerve is hyalinized a few organisms may persist and be detectable in the nerve.

During the phase of erythema nodosum leprosum, there may be dense infiltration of the nerve by polymorphonuclear leucocytes and acute abscesses may be formed, as seen in two cases reported here. Lepromatous abscess in the nerve can produce extensive destruction of nerve tissue. Acute abscess of nerve in lepromatous leprosy is not so common, though cases have been described earlier [11, 15, 20, 21]. However, infiltration of nerve with neutrophil polymorphs is quite possible during repeated attacks of erythema nodosum leprosum. The edema and the rapid destruction of tissue that accompany this condition may be responsible for the sudden onset of paralysis in patients with erythema nodosum leprosum. If the neurologic deterioration is due only to edema it may be transient, but if it is the result of neutrophilic infiltration and destruction of nerve parenchyma it is irreversible.

The ultrastructural changes observed in the cutaneous nerves of lepromatous leprosy have many points of similarity with the observations on diseases associated with a primary Schwann cell disease, as in diphtheritic neuropathy [20], lead neuropathy [18], and metachromatic leucodystrophy [28]. Disruption of outer myelin lamellae followed by demyelination of an intact axon was a prominent feature in lepromatous leprosy. In a previous paper it was reported that *M. leprae* proliferate inside the Schwann cells, producing a foamy degeneration in them [14]. It is quite possible that a parasitized Schwann cell may disintegrate with breaking up of its plasma membrane and basement lamina. Lampert *et al.* [18] emphasize the significance of the preservation of basement lamina, even after the destruction of Schwann cells, in serving as a scaffolding during the regenerative phase to guide the axonal sprouting.

In some instances the outer layers of myelin remained intact, whereas the inner part of the myelin sheath was disrupted to form several myelin ovoids. Clumping of axonal neurofilaments and disruption of axonal membrane, together with disruption of myelin, as described in Wallerian degeneration [19, 24], were also seen. It is reasonable to suggest that the destruction of axons in lepromatous leprosy is due primarily to irreversible damage caused by *M. leprae* in Schwann cells. The ensuing disruption of nerve architecture is further aggravated by marked increase of endoneurial collagen fibrils, proliferation of perineurial cells and infiltration with bacilliferous macrophages.

Formation of "onion bulbs," as described in chronic human neuropathies ([3, 7, 22, 25, 27]) was also seen in two cases. It is quite possible that some infected Schwann cells may recover and take part in the process of regeneration. Although the Schwann cell processes encircling the axons were found to be fewer, the mechanism of formation of the "onion bulbs" in leprosy may be due to repeated degeneration and proliferation of Schwann cells, as suggested in other chronic human neuropathies ([25]).

Since the process of destruction of nerve in lepromatous leprosy is directly related to the large number of organisms present in Schwann cells, and because the generation time of the organisms is inordinately long, the onset of paralysis is very slow and late in the natural history of the disease. It agrees very well with Iyer's findings that "The average mean duration of the development of the deformity is greater in lepromatous leprosy than in nonlepromatous leprosy." ([13])

SUMMARY

Skin biopsies and radial cutaneous nerve biopsies from 20 cases of lepromatous leprosy were studied with the light microscope, and in eight patients radial cutaneous nerves were examined with the electron microscope. It was found that *M. leprae* parasitize the Schwann cells, perineurial cells, macrophages and endothelial cells. A large number of infected Schwann cells, like the macrophages, undergo foamy degeneration and destruction, resulting in demyelination, axonal damage and irreversible destruction of nerve architecture. In erythema nodosum leprosum the destructive process of the nerve is accelerated by acute abscess formation.

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