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PATHOLOGY AND PATHOGENESIS OF LEPROUS NEURITIS; A PREVENTABLE AND TREATABLE COMPLICATION

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The many recent advances made in the management of leprosy have helped to significantly reduce the prevalence of leprosy throughout the world. Yet the fear of the disease and the stigma attached to it continue to haunt the patients and their communities. The main reason for this appears to be the gross deformities that occur in leprosy, the major cause of which is neuritis. Much work has been done during the past three decades to understand the pathology and pathogenesis of leprous neuritis which has helped greatly in its management. In this presentation, an account of the pathology and pathogenesis of leprous neuritis and also a short note on its management and prevention will be given. For a detailed study of the subject readers are referred to an excellent monograph by Antia and Shetty ([1]) and a recent exhaustive review by Naafs ([13]).

Histology of nerve

The complex pathological changes in a nerve trunk will be better appreciated if the histology of a normal nerve is clearly understood by studying its cross section. There are three major parts to a normal nerve: 1) the epineurium consisting of fibrous connective tissue and fat with blood vessels and lymphatics, 2) the perineurium formed by layers of perineurial cells and dense fibrous connective tissue and 3) the endoneurium composed of axons, collagen fibrils and fibroblasts and blood vessels. The axons, the basic units of a nerve along with blood vessels and collagen fibrils, are bound together by a tight perineurium to form a nerve fascicle. Several fascicles are bound together by epineurium to form a nerve trunk. The axons are either myelinated or nonmyelinated. Several nonmyelinated axons are invested by one Schwann cell; whereas each and every myelinated fiber is covered by only one Schwann cell. There are one or more fascicles at every level of a nerve trunk in its course in the extremity. It is interesting that the fascicles of major nerve trunks divide, branch and realign to form a new set of fascicles which contain a different group of axons several times in its course through the upper and lower extremities ([18]).

Schwann cells and *M. leprae*

The affinity of *Mycobacterium leprae* to Schwann cells has been repeatedly affirmed by many studies ([6, 8]). It has been observed that in the early stage of the disease *M. leprae* are almost exclusively found in Schwann cells. Perhaps Schwann cells offer a protective environment for the bacilli, a place to hide from the immune system of the individual and multiply. It is suggested that *M. leprae* make their entry into the body through Schwann cells. Destruction of Schwann cells by *M. leprae* and their antigens is a major factor in leprous neuritis, leading to paralysis and deformity. Apparently *M. leprae* invade Schwann cells containing nonmyelinated axons earlier and more often than those having myelinated axons. Whether there is a preSchwann cell phase in leprosy where *M. leprae* proliferate in the cells of the reticuloendothelial system, as in experimental animals such as nine-banded armadillos and nude mice, is not known.

Definition of leprous neuritis

Neuritis in leprosy is manifested in two forms, namely, the "active" and the "silent." In active neuritis there is inflammation of the nerve with edema, increased vascularity and cellular infiltration accompanied by signs and symptoms of acute, subacute or chronic inflammation, followed by active destruction of nerve parenchyma. In some instances, the nerve may be paralyzed in 24 hr accompanied by acute pain and swelling of the nerve. In silent neuritis there is continued presence of *M. leprae* and its antigens in Schwann cells, minimal intraneural edema and advancing reactive fibrosis. The affected Schwann cell gradually degenerates, dies and is replaced by fibrous tissue. There is no inflammatory change or active signs and symptoms of neuritis. However, progressive paralysis of the nerve is noticed. Over the course of time the nerve is imperceptibly replaced by fibrous tissue and paralyzed.

Entry of *M. leprae* into the nerve

There are four suggested ways through which *M. leprae* may enter the nerve: 1) through the naked axons in the epidermal region, 2) through the Schwann cells in the upper dermis, 3) through the perineurium, and 4) through the intraneural capillaries.

Entry through naked axons. In a detailed study by Khanolkar ([12]) of early skin lesions in children, *M. leprae* were found in axons in the dermis, and it was suggested that the organisms spread centripetally along the axons. This upward movement along the axon is compared to "fish swimming against the stream." In recent electron microscopic studies intraaxonal *M. leprae* are rare.

Entry through Schwann cells. Schwann cells are found to phagocytose easily *M. leprae* both *in vivo* and *in vitro,* and a selective affinity for Schwann cells to *M. leprae* is suggested. Recent studies have shown that alpha-Dystroglycon found in the basal lamina of Schwann cells serves as a receptor and binds to the surface-protein of *M. leprae* ([14]). This hypothesis must be considered in light of other observations which negate the theory of special affinity of *M. leprae* to Schwann cells. It is shown in an experimental study in the nine-banded armadillo that in addition to macrophages other parenchymal cells, such as hepatocytes, striated muscle cells, cells of adrenal cortex and medulla, can phagocytose *M. leprae* and offer a suitable environment in which they can multiply ([11]). Further, it has been shown that *M. leprae* cannot establish themselves and multiply in any cell, including phagocytes, in the flanks of highly susceptible nude mice where the temperature is high ([7]). It is reasonable to state that the environment more than the type of cell determines the entry of *M. leprae.* Schwann cells are present in abundance in the superficial parts of the skin of the cooler regions of the body, and they may serve as entry points of *M. leprae.* Surely the shared components between the surface protein of *M. leprae* and the basement membrane of Schwann cells will facilitate their entry.

Entry through perineurium. In an ultrastructural study of early skin lesions, it was found that in all types of leprosy macrophages containing *M. leprae* are more frequently found in the epineurial tissue ([5]). In an experimental study where rabbit tibial nerve was traumatized and *M. leprae* were introduced in that area, the gaps in the perineurium allowed macrophages containing *M. leprae* to migrate from the epineurium into the endoneurium ([4]). Further, *M. leprae* have been demonstrated inside perineurial cells. It is possible that organisms from perineurial cells can be shed into the endoneurium.

Entry through intraneural capillaries. During bacteremia, circulating *M. leprae* get lodged in small peri- and endoneurial capillaries and, thus, are carried into the endoneurium and presented to the Schwann cells. In a very elegant study of peripheral nerves of nine-banded armadillos, Scollard, *et al.* demonstrated very clearly the role of epi- and perineurial blood vessels in infecting nerves with *M. leprae* ([15]). There is no doubt that in lepromatous leprosy generalized infection of all susceptible peripheral nerves takes place by the hematogenous route.

Distribution of nerve lesions

Dermal and cutaneous nerves. The dermal nerves in all skin lesions of different types of leprosy are infected by *M. leprae,* causing varying degrees of loss of sensa-

tion. In tuberculoid leprosy it is limited to the skin patch; in lepromatous leprosy it is generalized and may involve large portions of the skin. Some of the cutaneous nerves adjacent to tuberculoid skin lesions are known to be directly affected, most probably due to the spread of *M. leprae* from skin lesions.

Peripheral nerve trunks. The mixed nerve trunks of the upper and lower extremities and the face are involved in segments which are subcutaneously placed and have a cooler temperature than that of the body. The hypothesis that *M. leprae* multiply in the cooler region of the nerve put forth by Brand ([2]) is proved beyond doubt in a study by Job and Desikan ([9]). It was shown that the segments of ulnar nerve above the medial epicondyle, median nerve above the carpal tunnel and radial nerve at the spiral grove are selectively infected by *M. leprae,* resulting in destruction of nerve parenchyma at these sites. Similarly, in the lower extremity the common peroneal nerve at the neck of the fibula, the posterior tibial nerve above the flexor retinaculum are involved. The facial nerve is affected as it crosses the zygomatic bone. It is now well accepted that segments of peripheral nerves that are subcutaneously placed have a cooler environment and, therefore, support the growth of *M. leprae,* resulting in the destruction of nerves localized to these sites.

Pathology of neuritis

The pathologic changes of nerves usually reflect those found in skin and may be a little more serious ([17]) since nerve offers somewhat a protective environment to *M. leprae* from the immunologic defense of the host. Just as described in skin, the pathologic picture is a spectrum varying from a localized disease confined to one nerve, or even a small portion of a fascicle as in tuberculoid leprosy, to a generalized involvement of most of the dermal nerves and all the peripheral nerve trunks in the body, as in polar lepromatous leprosy.

Tuberculoid neuritis. Neuritis in tuberculoid leprosy is often a localized disease confined to nerves in the skin patch. The dermal nerves are infiltrated intraneurally by a granuloma composed of epithelioid cells and lymphocytes, and are gradually destroyed (Fig. 1). Often only fragments of Schwann cells are left behind in the lesion, and it may need special procedures which stain S-100 protein to make the remnants of Schwann cells visible. Acid-fast stain usually does not reveal any organisms. Occasionally, a rare intraneural acid-fast organism (AFB) may be seen in an active lesion (Fig. 2). In the healed skin lesion small nerves in the superficial dermis usually disappear; some of the nerves in the deep dermis may be seen as fibrosed, hyalinized structures.

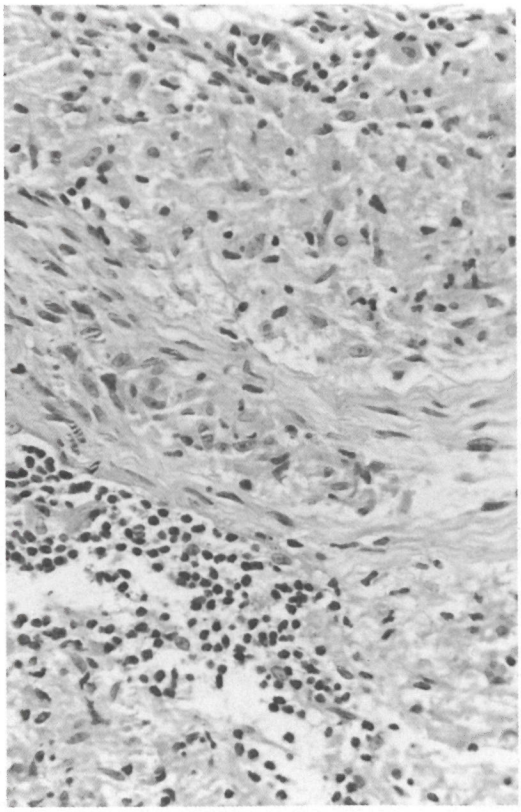

FIG. 1. Tuberculoid leprosy: Dermal nerve is infiltrated by epithelioid cell granuloma (H&E ×400).

In nerve trunks composed of several fascicles a part of one fascicle or all the fascicles may be involved by granulomatous inflammation (Fig. 3). There is thickening and lamination of the perineurium of the affected fascicle. The granuloma is composed of mostly epithelioid cells, lymphocytes and occasional Langhans' giant cells (Fig. 4). Focal areas of caseous necrosis may be seen or an entire fascicle may be destroyed by caseation (Fig. 5). The granulomatous

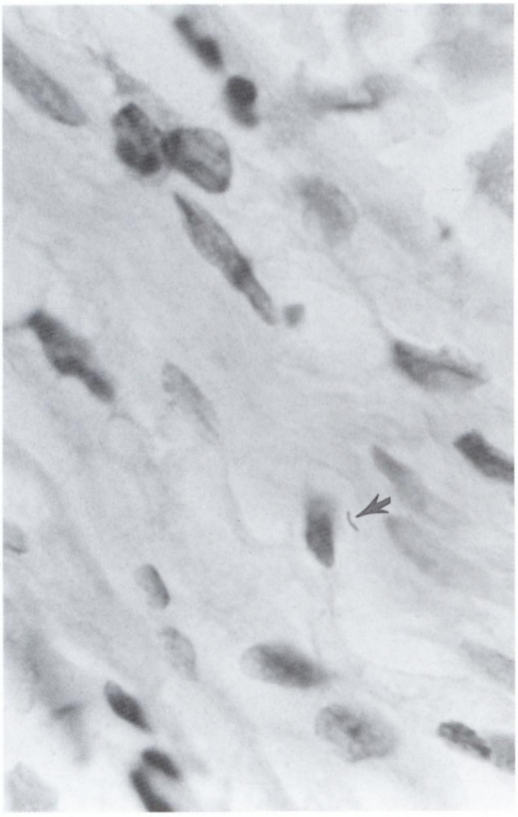

FIG. 2. Tuberculoid leprosy: One AFB is seen in a Schwann cell of a dermal nerve infiltrated by granuloma (modified Fite ×800).

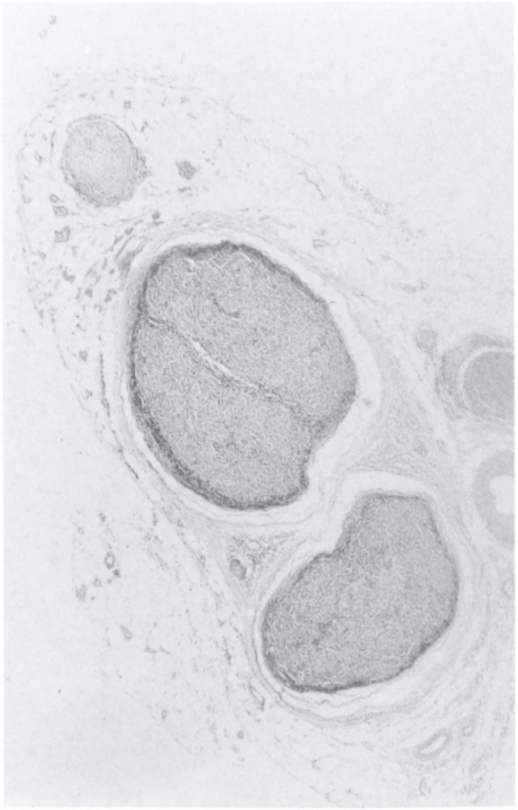

FIG. 3. Tuberculoid leprosy: All four fascicles from a radial cutaneous nerve infiltrated by granuloma. There is perineurial lamination and thickening (H&E ×40).

reaction is immunologically mediated in response to the antigens of *M. leprae.* In some cases all the fascicles may be irreversibly destroyed, and the nerve loses its function. It is also possible that only one or a portion of a fascicle may be destroyed by granuloma with practically no noticeable functional change, or a transient functional loss as a result of increase in intraneural pressure and ischemia.

Lepromatous neuritis. In generalized lepromatous leprosy in which a major portion of the skin over the extremities, trunk and face is involved by the disease, almost all dermal nerves in the affected areas are infected by *M. leprae.* The perineurium of the deep dermal nerves may appear normal or may show intense reactive proliferation, forming many layers of perineurial cells. The endoneurium may appear normal but may show an occasional macrophage and a rare lymphocyte. Acid-fast stain shows numerous bacilli inside macrophages, perineurial cells and Schwann cells (Fig. 6). In the early stage of the disease there is no appreciable loss of sensations. As the disease advances, there is gradual destruction of Schwann cells by intracellular proliferation of *M. leprae,* resulting in extensive sensory loss in the skin.

In nerve trunks all fascicles are invariably affected. There is reactive proliferation of perineurial cells, resulting in thickening and lamination of perineurium. Initially, there is minimal infiltration by lymphocytes and macrophages (Fig. 7). *M. leprae* are present in Schwann cells in large numbers (Fig. 8). As the disease progresses a number of macrophages invade the endoneurium (Fig. 9). The nerve parenchyma is gradually destroyed and replaced by fibrous tissue. In addition to this *M. leprae* invade endothelial cells of capillaries and produce endothelial swelling and narrowing of their

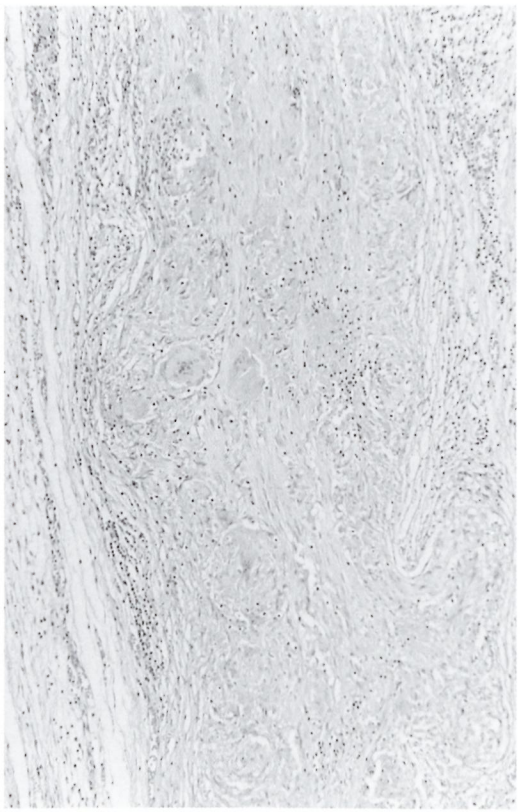

FIG. 4. Tuberculoid leprosy: Longitudinal sections of a fascicle of a radial cutaneous nerve. The peri- and endoneurium is infiltrated by epithelioid cells, lymphocytes and Langhans' giant cells (H&E ×100).

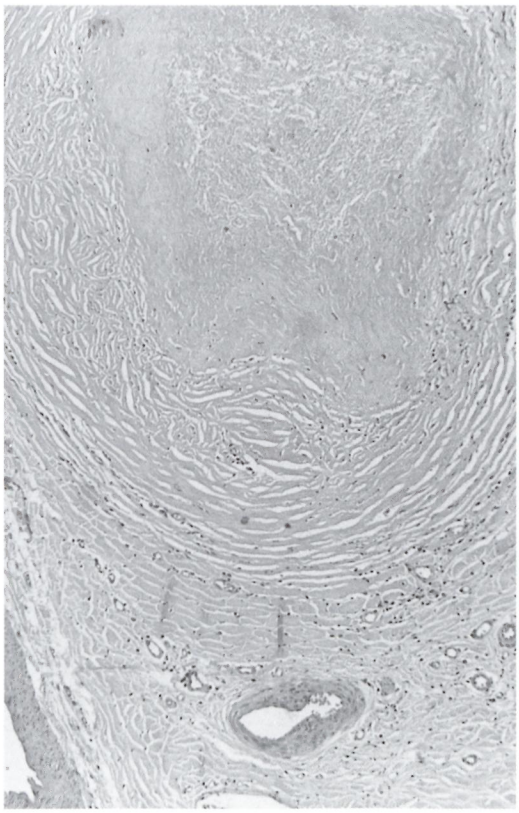

FIG. 5. Tuberculoid leprosy: A fascicle of a radial cutaneous nerve is replaced by caseous necrosis and hyalinized fibrous tissue (H&E ×200).

lumina and a consequent ischemia to the nerve. The progress of these inflammatory changes in the nerve is so slow and insiduous that it takes some years for nerve paralysis to develop.

Borderline neuritis. Neuritis in borderline disease can produce the worst form of deformity. Ordinarily multiple nerves are involved, and the disease can be generalized like lepromatous leprosy. It will also cause irreversible destructive lesions in a short period of time, as in tuberculoid leprosy. All or some of the fascicles in a nerve trunk may be affected (Fig. 10). The perineurium is thickened and laminated. The endoneurium is infiltrated by granuloma consisting of macrophages, dense collection of lymphocytes and occasional epithelioid cells (Fig. 11). The affected portions of the nerve tissue may be irreversibly destroyed by the granuloma. The loss of nerve function depends on how much of nerve tissue is irreversibly destroyed by the granuloma and how much is temporarily paralyzed by ischemia.

End-stage neuritis. In all types of leprosy the infected and destroyed nerve is finally replaced by hyalinized fibrous tissue. Ordinarily at this stage it is not possible to differentiate the various types of leprosy or even to find out whether it is the result of leprosy or due to other causes. Rarely, lurking AFB or small clumps of foam cells may persist and give a clue that it is due to leprosy.

Reaction and neuritis

Reversal (type 1) reaction is seen in tuberculoid and borderline neuritis. There is a marked and sudden increase in the size of the intraneural granuloma with fresh invasion by numerous lymphocytes and epithelioid cells. There is also much tissue edema. The destruction and consequent paralysis of

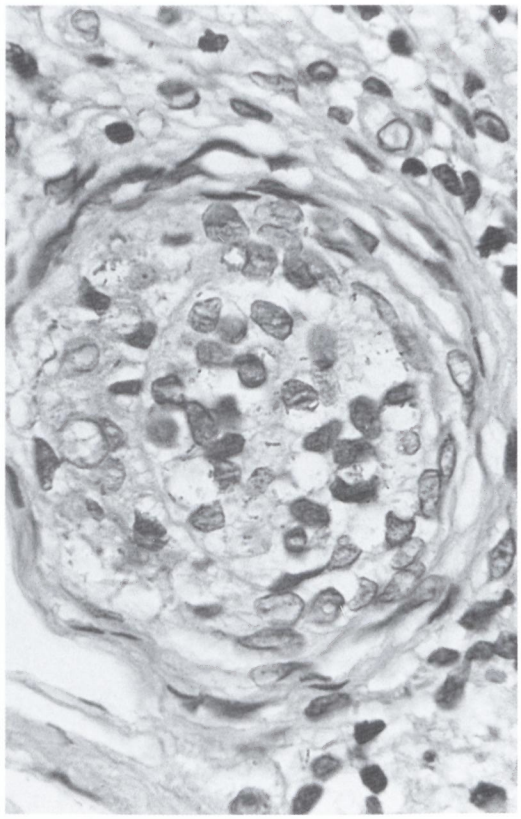

FIG. 6. Lepromatous leprosy: Cross section of a dermal nerve. AFB are present in Schwann cells, perineurial cells and macrophages. Perineurium is thickened (modified Fite ×800).

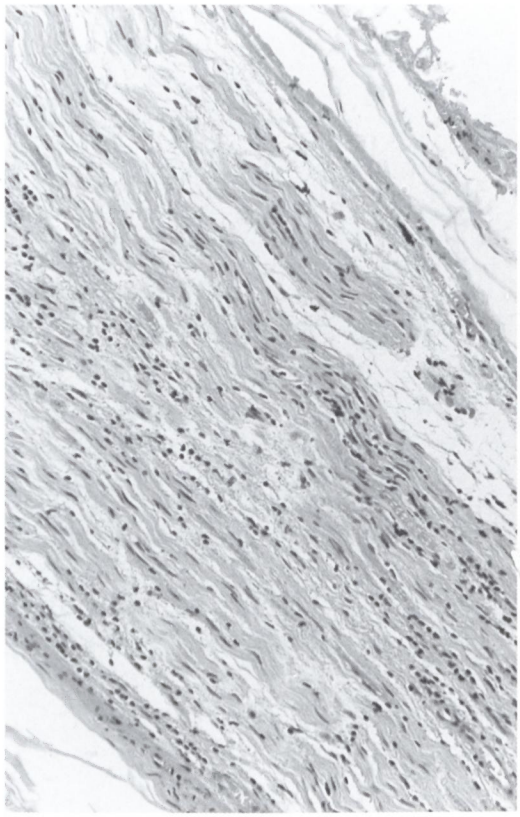

FIG. 7. Lepromatous leprosy: Longitudinal section of a fascicle of a radial cutaneous nerve infiltrated by a few scattered lymphocytes (H&E ×200).

the nerve is rather fast and may be due partly to irreversible granulomatous destruction of nerves and partly to reversible ischemic paralysis caused by increase in intraneural pressure. In some instances the granuloma may destroy the entire nerve or the nerve may undergo caseous necrosis, forming a nerve abscess (Fig. 12) resulting in permanent damage to the nerve.

In lepromatous leprosy the reactive phase is known as erythema nodosum leprosum (ENL). In this condition there is marked infiltration of the nerve by neutrophils (Fig. 13) and formation of intraneural microabscesses. The affected portions of the nerve trunk is usually irreversibly destroyed. The unaffected portions of the nerve may be temporarily paralyzed by ischemia. Lepromatous patients who develop ENL are prone to develop more paralyzed nerves than those who do not experience ENL. Some patients suffer from repeated ENL reactions and go into a chronic phase, resulting in more deformities. Fortunately, they are only a few.

Mechanism of nerve destruction

Invasion by *M. leprae*. It appears that it is very difficult for *M. leprae* to gain entry into nerves but once they enter, the havoc they produce cannot be easily prevented unless the invasion is detected before it enters a nerve trunk. Peripheral nerve fascicles, bound and protected by the perineurium, are safe places for *M. leprae*. They multiply inside Schwann cells and establish a strong foothold in the nerve. In lepromatous leprosy the unhindered multiplication of *M. leprae* gradually destroys the Schwann cells, and the fibrosis that follows prevents any attempted regeneration. In tuberculoid leprosy the antigens of *M. leprae* evoke a granulomatous reaction that irreversibly destroys the involved nerves which are re-

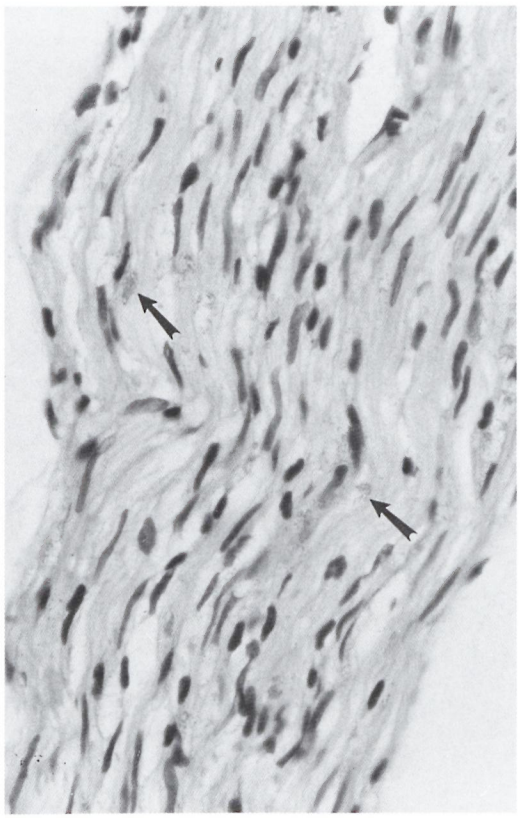

FIG. 8. Lepromatous leprosy: Longitudinal sections of a fascicle from a radial cutaneous nerve. Several Schwann cells are packed with AFB (modified Fite ×400).

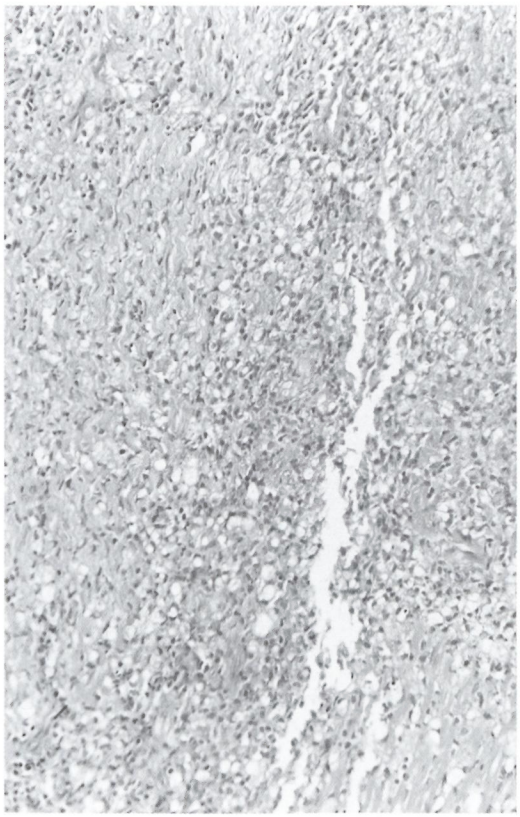

FIG. 9. Lepromatous leprosy: Longitudinal section of a fascicle from a radial cutaneous nerve. Much of the nerve tissue is replaced by macrophages, lymphocytes and fibrous tissue (H&E ×200).

placed by fibrous tissue. Antileprosy drugs are known to enter the nerve and kill the organisms. If there is fibrosis due to long-standing inflammation, *M. leprae* may conveniently hide in it and are not reached by the drugs ([16]). Therefore, in some patients long after cure, even after many years of complete skin-smear negativity, there may be progressive nerve paralysis ([10]). There is also the possibility of relapse of the disease from persistent *M. leprae* in the fibrosed nerves.

Trauma. The segments *M. leprae*-infected nerve trunks are very often proximal to certain specific fibrooseous canals and joints of the extremities. The inflamed nerve is usually enlarged and is, therefore, likely to be constantly traumatized at these sites during joint movements. Trauma itself will produce inflammation and affect the permeability of vessels. The size of the nerve is further increased which, in turn, enhances the risk of trauma. A vicious cycle is thus established. It is well known that nerve trunks of the extremities, except the radial nerve, are more often paralyzed than the facial nerve. It is also a fact that the facial nerve and radial nerve are exposed to much less trauma.

In experimental leprosy produced in animals, such as the nine-banded armadillo and immunologically deficient mice (T900r mice and nude mice), although nerves are infected, the destruction of nerves is not a serious event. In the armadillo the reticuloendothelial system, such as the liver, spleen and lymph nodes is infiltrated extensively by lepromatous granuloma. Even the lungs and adrenal glands are invaded by macrophage granuloma. The animal usually dies of lung complications before nerves of the extremities are sufficiently destroyed to cause muscle paralysis or plantar ulcers. Similarly, in immunologically suppressed

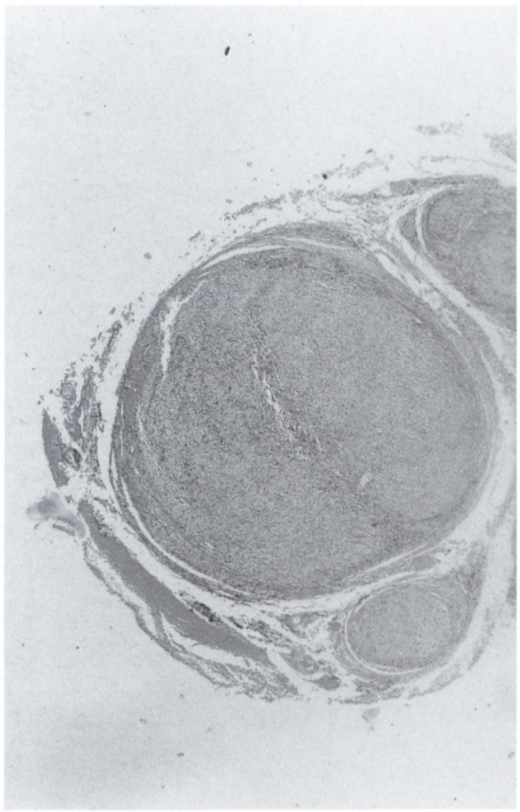

FIG. 10. Borderline lepromatous leprosy: Three fascicles from a radial cutaneous nerve are infiltrated by lymphocytes and macrophages. There is perineurial lamination (H&E ×40).

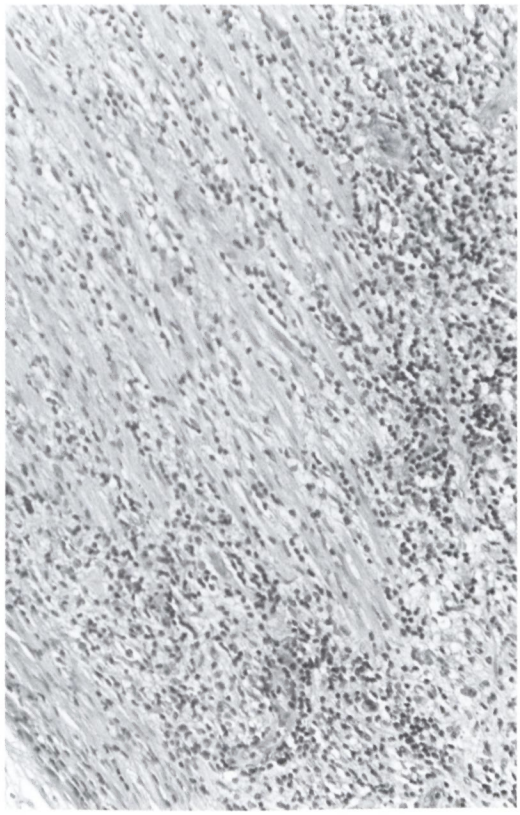

FIG. 11. Borderline lepromatous leprosy: Longitudinal section of a radial cutaneous nerve. Endoneurium is infiltrated by numerous lymphocytes and macrophages (H&E ×200).

mice infected by *M. leprae* in the foot the striated muscles are invaded by *M. leprae* and replaced by lepromatous granuloma and, finally, undergo fibrosis. The paralysis of the foot produced in them is mainly due to the destruction of the small muscles of the foot. Nerve invasion by *M. leprae* by itself in mice is not known to produce paralysis. Therefore, it is reasonable to infer that in human leprosy perhaps trauma which the nerve undergoes at the selected sites is largely responsible for aggravating nerve destruction. Of course, the nerves in those who develop ENL (type 2), and reversal (type 1) reactions obviously are destroyed by the acute inflammation, such as infiltration by polymorphs in ENL and by granulomatous reaction accompanied by caseous necrosis in reversal reaction.

Leprous vasculitis. In leprosy, especially in lepromatous disease, the small blood vessels including those present in nerves are involved ([3]). Very often endothelial cells of capillaries are parasitized by *M. leprae* (Fig. 14). Swelling of the endothelium of these small blood vessels causes narrowing of their lumina and ischemia to the nerve. Further, endothelial invasion of *M. leprae* may make the capillaries ore permeable and cause intraneural edema, resulting in increase of intraneural pressure.

Ischaemia. The perineurium is a very tight investment and does not yield and expand easily to increasing intraneural granuloma and edema. Therefore, there is an increase in intraneural pressure and a collapse of the veins and capillaries, resulting in ischemia. Prolonged ischemia results in necrosis of nerve parenchyma and fibrosis.

Management of leprous neuritis

Prescribe rest. A clear understanding of the pathogenesis of neuritis has helped greatly to manage and often restore func-

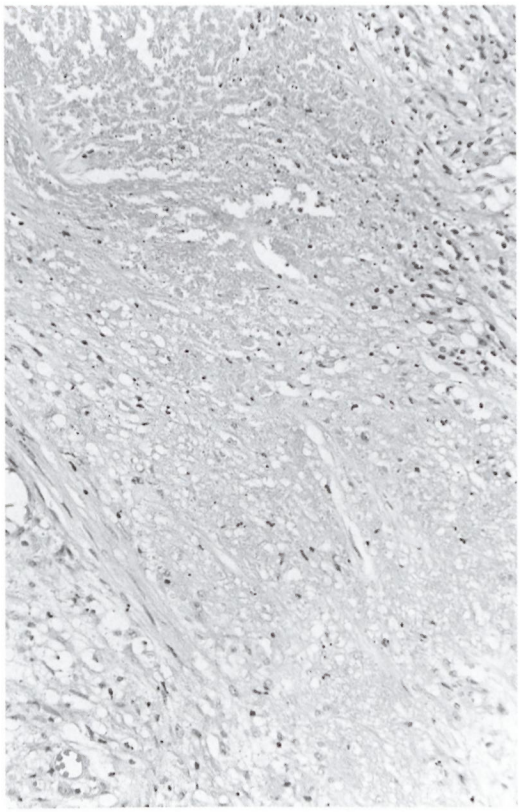

FIG. 12. Tuberculoid leprosy: Caseous necrosis is surrounded by fibrous tissue, epithelioid cells and lymphocytes to form a nerve abscess (H&E ×200).

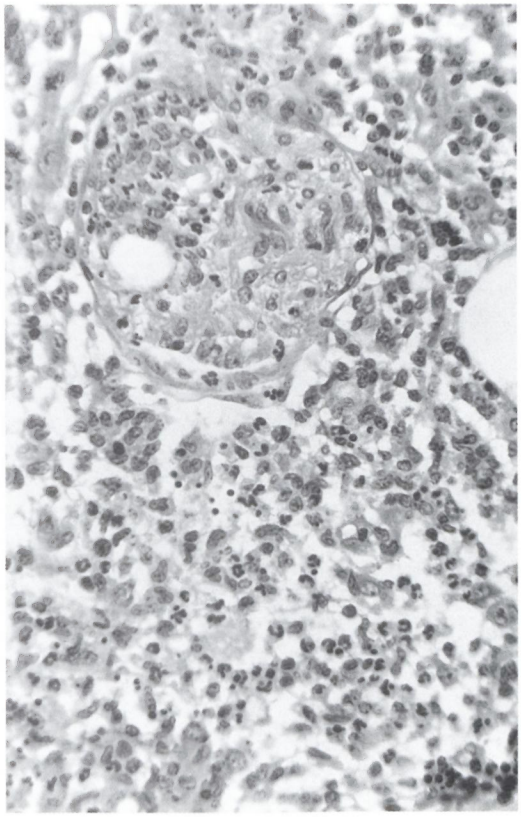

FIG. 13. ENL: Dermal nerve is surrounded and infiltrated by numerous polymorphs (H&E ×800).

tion and always relieve the pain in neuritis. Since trauma plays a significant role in aggravating the already inflamed nerve, the nerve should be put to rest as much as possible. Rest to the nerve is prescribed now only during the acute phase when the patients suffer pain. If the vasa nervorum is destroyed neuritis will not be accompanied by pain. As far as possible any nerve with signs or symptoms of infection with *M. leprae* should be given adequate rest until *M. leprae* are not only killed but cleared from the nerves. Rest will surely prevent edema and reduce considerably the reactive and replacement fibrosis of the inflamed nerve.

Decrease size of the inflamed nerve. The inflamed nerve is swollen with edema and the presence of inflammatory cells, such as lymphocytes, epithelioid cells and Langhans' giant cells in tuberculoid neuritis and macrophages and lymphocytes in lepromatous neuritis. During ENL (type 2) reaction, in addition to lepromatous granuloma large numbers of polymorphs migrate into the nerve, and in reversal reaction (type 1) there is marked increase in the existing granuloma. Administration of corticosteroids in adequate doses will quickly reduce edema and inflammatory cells and bring down the size of the nerve and intraneural pressure considerably. It is heartening to see that trials using various regimens of steroids have been very successful in arresting nerve damage, although it is not possible to have reversal of nerve damage in every case. Different regimens using steroids are under trial. Final results in multicentric studies in this area is awaited. However, if the nerve is extensively damaged by caseous necrosis in tuberculoid leprosy during reversal (type 1) reaction and by formation of microabscesses in ENL (type 2) reaction, reversal of nerve damage is not possible.

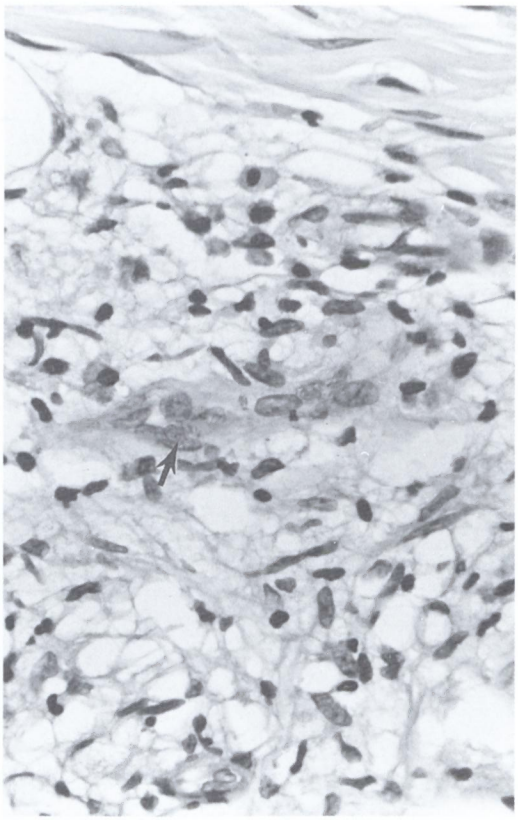

FIG. 14. Lepromatous granuloma: A capillary with swollen endothelial cells contains clumps of AFB (modified Fite ×800).

Prevention of nerve damage

Early diagnosis and treatment of leprosy. It should be realized that once a nerve trunk is infected with *M. leprae,* the organisms will have firmly laid the foundation of nerve damage. Early diagnosis of leprosy even before nerve trunks are infected is the only sure way to totally prevent nerve damage. It is not always possible to detect early infection with our present knowledge of the immunology of leprosy. Further studies to detect leprosy infection during its incubation period are imperative. The next best thing is to give adequate and effective antileprosy therapy to kill and clear the nerves of *M. leprae.* In this effort multidrug therapy instituted and implemented by the WHO (WHO/MDT) during the last two decades should be highly commended.

Prevention of reactions. Much of the nerve damage takes place during the reactive phase (ENL and reversal). The pathogenesis of the reactions is poorly understood. Much research has to be done to identify patients prone to develop reactions and to take such measures as would prevent the onset of reactions.

Treatment directed toward protection of infected nerve. Prevention of edema, cellular infiltration and progressive fibrosis of the *M. leprae*-infected nerves is attempted by giving steroids along with antileprosy drugs for a period, from the time of diagnosis of leprosy, even before the onset of any nerve injury. Follow-up studies of patients in this trial are now under way. The results of this study are eagerly awaited.

Rest the infected nerve. Prescribing adequate rest for even asymptomatic but infected nerves should be explored in preventing quiet nerve paralysis. It is comparable to prescribing rest and protective footwear for anesthetic feet. Anesthetic feet, with no pain sensation, were not properly cared for or protected until it was recognized that silent damage to feet causing plantar ulcers was mainly due to repeated trauma. Also, the patients did not complain. Quiet nerve paralysis seems to be neglected because the patients do not complain. Rest for the affected nerves to prevent trauma must be seriously considered in the prevention of quiet nerve paralysis.

SUMMARY

In conclusion, it may be said that many advances have been made in the diagnosis, treatment and prevention of nerve damage. It is now a well accepted fact that the affinity of *M. leprae* for Schwann cells and the property of *M. leprae* to grow in cooler sites of the body have made certain segments of nerve trunks vulnerable. Trauma that supervenes the inflammation and swelling severely aggravates the nerve damage. The reactive phase in all forms of leprosy, the etiology of which is not clearly understood, produces intraneural caseous necrosis in tuberculoid disease and microabscesses in lepromatous disease, causing much irreversible damage to nerves.

The steroid treatment that is administered during the reactive phase has helped greatly to stop further damage, although the damage already done to nerves is not always reversible. Preventive measures like detecting the disease before nerve trunks are infected

and offering prompt and adequate antileprosy therapy as early as possible have helped to reduce the prevalence of deformities. It is hoped that administering steroids along with antileprosy therapy to prevent active inflammation and or fibrosis of the nerve will reduce the prevalence of nerve damage significantly. Measures which provide rest for the infected nerve to prevent trauma should be explored.

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