INTERNATIONAL JOURNAL OF LEPROSY Volume 57, Number 2
Printed in the U.S.A.

XIII LEPROSY CONGRESS STATE-OF-THE-ART LECTURES

We are pleased to have the opportunity of publishing the full texts of the state-of-the-art lectures presented at the XIII International Leprosy Congress at The Hague, The Netherlands, 11–17 September 1988. The first two of these appear in this issue. Remaining lectures will appear in subsequent issues—RCH

Nerve Damage in Leprosy*

Leprosy in humans is essentially a disease of the peripheral nerves. The clinical diagnosis of leprosy depends largely on the recognition of the results of nerve damage in the patient. The findings of thickened peripheral nerves, of anesthetic areas in the skin, and of paralyzed muscles in the hands, legs or face, lead to the diagnosis of leprosy. The histopathological demonstration of nerve invasion by *Mycobacterium leprae* or the presence of an inflammatory granuloma in and around a nerve is mandatory to confirm the diagnosis of leprosy.

Even in 1988, in spite of the many advances in the understanding of leprosy and its management, leprosy evokes fear in the common man and in professionals alike. In a recent survey in a western country it was surprising to find that, when asked, people preferred to contract AIDS rather than leprosy. There is no doubt that ignorance about leprosy is the major factor in this public reaction. However, it is important to note that it is the deformities brought about by nerve damage that are largely responsible for this horror and dread of the disease; a horror and dread which appear to be almost universal.

It is estimated that more than one fourth of all reported leprosy patients have disabilities, and of these nearly half are severely disabled. With over 12 million estimated leprosy patients in the world, the economic loss to the community caused by leprous neuritis must be enormous. The social and psychological effects of deformity cannot be measured.

In this presentation I shall briefly outline the pathology and pathogenesis of nerve damage, its clinical presentation and its management.

The structure of the nerve

The peripheral nerve consists of myelinated and nonmyelinated nerve fibers of various sizes. The myelinated axons are surrounded by a multilayered myelin sheath. The Schwann cells cover the nerve fibers, and each Schwann cell contains one myelinated fiber or several nonmyelinated fibers. The Schwann cells are surrounded by loose connective tissue called the endoneurium. The sensory and motor nerve fibers are intermingled and are structurally indistinguishable. Nerve fibers are grouped and held together to form nerve fascicles by dense connective tissue and blood vessels called the perineurium. The perineurium and the blood vessels offer a barrier between the nerve parenchyma and the circulating blood and tissue fluids, and this barrier is compromised during injury or infection. Several fascicles are bound together by the epineurium composed of loose connective tissue, blood vessels and lymphatics to form a nerve trunk.

The number of fascicles in a nerve, such as the ulnar nerve, varies as it courses down the arm. The bundles of nerve fibers that form the fascicles branch and rearrange. The fibers are so distributed in the fascicles that a third of a nerve trunk may be severed without causing demonstrable motor or sensory loss.[1]

* Based on state-of-the-art lecture presented at the XIII International Leprosy Congress, 15 September 1988, The Hague, The Netherlands.

[1] Sherren, J. *Injuries of Nerves and Their Treatment.* New York: William Wood and Co. As quoted by Sun-

Definition of neuritis

Neuritis or inflammation of the nerve is the most important feature of leprosy, and nerve invasion is a unique characteristic of *M. leprae.* However, the response of the tissue to intraneural invasion by *M. leprae* varies a great deal. It can be very minimal with a few intraneural acid-fast bacilli and an obvious proliferation of Schwann cells with no functional change in the nerve, or it may be very extensive with granulomatous infiltration of the entire nerve parenchyma resulting in total structural destruction and complete loss of function of the nerve. Clinically, neuritis can be silent with no noticeable signs or symptoms or it can be very obvious and acute, accompanied by severe pain, tenderness, swelling, loss of sensation and paralysis of the muscles. In the very early stage of the disease, leprous neuritis is present without demonstrable nerve damage. However, it usually becomes chronic and progresses on to show nerve damage, typically beginning with loss of sweating, then loss of sensations and, finally, muscle paralysis.

Neuritis and nerve damage are not synonymous. There can be neuritis with little or no evidence of nerve damage. Nerve damage can also occur due to some other causes. In common practice, the clinical diagnosis of neuritis is made only when there is pain or tenderness, or swelling of a nerve, or a sensation of pinprick and tingling localized to that part of the skin supplied by the nerve. It is important to remember that in leprosy, as we define the disease now, there is always neuritis. I would like to reemphasize this fact so that you will never forget it in your clinical practice. Most of the time it is silent, and the medical care personnel should look for evidence of nerve damage even though the patient may not complain about it.

Mode of entry of *M. leprae* into the nerve

M. leprae can enter the nerve by four different pathways. It was suggested that *M. leprae* enter the body through naked nerve filaments in the epidermis and spread centripetally along the axon. The upward movement of the bacilli along the axonal flow was compared to fish swimming against the stream.[2, 3] Intra-axonal bacilli have been shown by several workers in electron-microscopic studies, but it is a rare occurrence.

The second suggestion was that *M. leprae,* on entering the skin, are phagocytosed by Schwann cells in the upper dermis. Thus protected from the cells of the immune system, they multiply inside the Schwann cells and travel along the nerve from one Schwann cell to another by contiguity. Many workers consider that *M. leprae* has a special predilection for Schwann cells and it remains as an important host cell of *M. leprae.*[4]

The third possibility is that macrophages in the upper dermis initially take up the bacilli and these bacilli-laden cells aggregate around skin adnexal structures, including nerve bundles. Bacilli released from these macrophages are ingested by perineurial cells which pass them on to Schwann cells, or the macrophages containing the bacilli infiltrate the perineurium and invade the nerve. In thymectomized irradiated mice, or in athymic, nude mice infected with *M. leprae,* nerve involvement follows the formation of dermal lepromatous granulomas which grow to a fair size before there is evidence of nerve invasion by the bacilli. Bacilli-packed macrophages invade the perineurium and then enter the nerve parenchyma.[5]

The fourth possibility, and the one which is perhaps the most frequent route of entry into the nerve, is through the bloodstream via the intraneural capillaries. Evidence of bacillemia is seen in all forms of leprosy. Therefore, organisms could easily be transported into the nerve by the bloodstream. Minimal injury to a nerve may increase the

derland, S. Intraneural tomography of radial, median and ulnar nerves. Brain **68** (1945) 243–299.

[2] Khanolkar, V. R. Studies in the histology of early lesions in leprosy. New Delhi: Indian Council of Medical Research, 1951, p. 180. Special Report Series No. 19.

[3] Khanolkar, V. R. Perspectives in pathology of leprosy. Indian J. Med. Sci. **9** (1955) 1–44.

[4] Weddell, G., Jamison, D. and Palmer, E. Recent investigations into sensory and neurohistological changes in leprosy. In: *Leprosy in Theory and Practice.* R. G. Cochrane, ed. Bristol: John Wright & Sons, Ltd., 1959, pp. 96–113.

[5] Job, C. K. and Desikan, K. V. Pathologic changes and their distribution in peripheral nerves in lepromatous leprosy. Int. J. **Lepr. 36**: (1968) 257–270.

stickiness of the endothelial cells of intraneural capillaries and also may compromise the blood–nerve barrier. Schwann cells will actively phagocytose *M. leprae* brought into the nerve through the blood circulation. Perivascular intraneural granuloma is not an uncommon finding in tuberculoid neuritis (unpublished personal observation).

Site and extent of nerve involvement

The nerves involved in leprosy are of two types: first, the autonomic and sensory nerves in skin lesions which supply the structures in the dermis and subcutaneous tissue and, second, the portions of nerve trunks such as the ulnar, median, radial, common peroneal, posterior tibial and facial nerves which are subcutaneously placed and which supply specific areas of the skin and certain groups of muscles.

The extent and degree of the loss of sensation and paralysis varies considerably depending on the disease classification, its spread, its duration, and the reactional episodes. In tuberculoid groups the lesions are localized and patchy, and in the patches only the superficial sensations may be lost. When nerve trunks are involved it involves one or a few of them but then the deep sensations and muscle functions supplied by them are impaired. On the other hand, in lepromatous groups the disease is extensive. The involvement of the skin is generalized and can affect virtually the entire skin except that of the axillae, the groin, and the perineum. The scalp and the midline of the back are relatively spared. Many, if not all, of the nerve trunks are affected to a lesser or greater degree. There are borderline lepromatous patients who present with every nerve trunk of the extremities and face paralyzed.

It is important to know that in leprosy during the early stage of the disease only the nerves present in the skin lesions are affected, and there are losses of superficial sensations and autonomic functions of that localized part of the skin. In the more advanced stage, one or more nerve trunks with mixed nerve fibers can become infected and damaged, producing loss of all sensations in the distribution of the nerve trunk, superficial and deep, and muscle paralysis. Loss of muscle function alone is not reported in leprosy; paralysis of muscles always coexists with the loss of cutaneous sensation.

Pathology of neuritis

The tissue response to intraneural invasion by *M. leprae* depends largely on the immune status of the patient and the competency of the blood–nerve barrier.

Indeterminate leprosy. The indeterminate form of leprosy is considered the earliest manifestation of the disease. The histopathological appearance can be of two types. In one form the bacilli gain entrance into the nerve and the patient has not been sensitized to the antigens of *M. leprae*. It is possible that the bacilli entered the nerve before the patient had a chance to get sensitized to *M. leprae* or the patient failed to become sensitized for some reason we do not yet understand. The nerve looks almost normal, and there is little or no damage to the structure and function of the nerve. The earlier change is an apparent increase in Schwann cell nuclei,[6] and one or a few bacilli are present in Schwann cells. There is no noticeable increase in inflammatory cells. In the other form there is evidence of inflammation. The perineurium shows some reactive proliferation, and collections of mononuclear cells are present around neurovascular bundles. In some sections the perineurium is also infiltrated. This is evidence of damage to the blood–nerve barrier and leakage of antigen from the nerve. Rarely the nerve parenchyma is also infiltrated by mononuclear cells. The skin patch shows impairment of superficial sensation. There is loss of touch, loss of temperature sensation, loss of sweating, and loss of the triple response of Lewis. The nerve trunks are not affected in this type of disease.

Tuberculoid leprosy. In tuberculoid disease the patient has enough resistance to localize the disease but not enough resistance to be rid of it. Apparently, there is considerable delayed-type hypersensitivity to the antigens of *M. leprae*, and this hypersensitivity produces intense granulomatous reactions and, sometimes, necrosis at sites where antigens continue to appear. Almost every dermal nerve present in the localized tuberculoid skin lesion shows in-

[6] Shetty, V. S., Mehta, L. N., Irani, P. F. and Antia, N. H. Study of the evolution of nerve damage in leprosy. Part I—Lesions of the index branch of the radial cutaneous nerve in early leprosy. Lepr. India **52** (1980) 5–18.

flammation which destroys large portions of the nerve. In advanced lesions, even the perineurium is destroyed[7] and only the form of the nerve is left behind. There is total loss of sensation in these patches. The inflammation is composed of epithelioid cells, giant cells and lymphocytes. Acid-fast organisms are rare. Occasionally they can be found in Schwann cells and arrectores pilorum muscle cells.

In tuberculoid leprosy one or a few nerve trunks may be affected. The affected portion of the nerve shows localized enlargement. There may be abscess formation with fusiform or nodular swelling of the nerve. The nodules may even be multiple. Sections of nerve trunks in tuberculoid leprosy may show a perivascular granuloma affecting a small portion of one fascicle or the entire fascicle, or all the fascicles of a nerve trunk. Caseous necrosis with abscess formation is a common complication of tuberculoid neuritis. Healing takes place by fibrosis.

Lepromatous leprosy. In lepromatous disease the Schwann cells, perineurial cells, axons, and intraneural macrophages of dermal nerves contain acid-fast bacilli. There may or may not be a macrophage granuloma surrounding the infected nerve because, ordinarily, the spread of the bacilli to the nerve is by the blood stream and the perineurium is intact. Damage to the nerve parenchyma is minimal in the early stages although Schwann cells contain a large number of bacilli. The functions of the nerve are intact. In recent years we have seen an unusual presentation of lepromatous disease with a single localized nodule. In this lesion the nerve bundle is surrounded by large collections of macrophages packed with bacilli, but only a few bacilli are present within the nerve bundle.[8] In these instances the macrophage granuloma can be compared to that in the infected foot pads of T900R or athymic nude mice. The bacilli entered the nerve through the perineurium following the granuloma formation around the nerve.

The nerve trunk shows a similar histopathological appearance. Almost all of the subcutaneously placed nerve trunks are affected in this type of the disease. The nerve trunks are of normal size or may be slightly enlarged and may feel firm. The disease in the nerve is often silent, and the bacilli slowly and steadily multiply within the nerve. The nerve destruction which is produced is gradual, slow, insidious and unnoticed until it is very late. The nerve parenchyma is gradually replaced by fibrous tissue.

Borderline leprosy. In borderline disease there are varying degrees of hypersensitivity to *M. leprae* and its antigens and varying degrees of ability to limit the disease. In the skin lesions the dermal nerves show a marked perineurial cell proliferation and an onion-peel appearance. There is granulomatous inflammation composed of macrophages and lymphocytes in and around the nerve. Acid-fast organisms are present in Schwann cells, perineurial cells and macrophages.

Like lepromatous leprosy, the disease is so generalized that many nerve trunks are affected. The granulomatous inflammation characteristic of hypersensitivity is present in all of the involved nerves. There is extensive destruction of many nerves by the granuloma, and the nerves are finally replaced by fibrous tissue. Large portions of the subcutaneously placed nerve trunks show marked thickening. Deformities due to nerve damage are the worst in borderline leprosy.

Reaction

All diseases caused by infectious agents, including leprosy, are due to the response of the body or the reaction of the tissue to the invading organism. The word "reaction" in leprosy is used to describe only an episode in a major disease and is, therefore, not properly used. Leprosy is a silent disease most of the time. Early leprosy not only has very few symptoms to complain about, but it also makes the patient "silent" about the disease because he is afraid of being found out. Usually a leprosy patient does not identify himself until such time when he can no longer hide his disease. Reaction is the acute phase of the disease and the patient is "sick." During reaction in lepromatous leprosy there is erythema nodosum leprosum (ENL); in

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[7] Dastur, D. S. The nervous system in leprosy. In: *Scientific Approaches to Clinical Neurology*. Goldensohn, G. S. and Appel, S., eds. Philadelphia: Lea & Febiger, 1977, p. 1547.

[8] Job, C. K., Kahkonen, M. E., Jacobson, R. R. and Hastings, R. C. Single lesion subpolar lepromatous leprosy and its possible mode of origin. Int. J. Lepr. **57** (1989) (in press).

tuberculoid-borderline leprosy there is acute exacerbation of the disease.

ENL is a generalized acute manifestation and when it affects the nerve there is acute inflammation of the nerve. The neuritis is no longer silent. There is sudden swelling in addition to severe pain and exquisite tenderness localized to the subcutaneous portion of the nerve trunk. The site of the nerve affected may be diffusely infiltrated by collections of neutrophils or there may be microabscess formation. Neutrophilic infiltration can be confined to one or a few fascicles or may involve the entire nerve. There is extensive destruction of the nerve at this phase by proteolytic enzymes, and paralysis of the nerve at the time of ENL is very common.

During acute exacerbation in borderline leprosy there is erythema and edema of the skin lesions. The patient complains of pain and tenderness of the nerve which shows well-marked localized thickening. Occasionally, the disease process in the nerve may be too severe and too quick to produce any pain or tenderness. Sudden onset of paralysis may be the only symptom. The nerve is infiltrated by an epithelioid cell granuloma with numerous lymphocytes and is destroyed. Caseous necrosis and abscess formation are common features of the reactive phase. Acute neuritis and paralysis of nerve trunks are common complications of reaction in borderline leprosy.

End-stage neuritis

Whatever be the type of neuritis the nerve underwent, it finally gets fibrosed and hyalinized. There is perineurial fibrosis, and the nerve parenchyma is completely replaced by hyalinized fibrous tissue. Hardly any inflammatory cells are seen. Occasionally, one or a few acid-fast organisms are found incarcerated in the "fibrous coffin." These organisms are often solid-staining, viable-looking bacilli. It is possible that they may serve as a nucleus for relapse. At this point I would like to state that in leprous neuritis the axons, their myelin sheaths, and their Schwann cells are destroyed and replaced by fibrous tissue. There are no Schwann tubes left behind for regrowing nerve fibers, if any, to grow into and, therefore, nerves destroyed due to leprous granuloma are permanently destroyed.

End-stage neuritis can be compared to end-stage nephritis in most of its pathological characteristics. Often it is hard to tell whether the "end-stage neuritis" is due to leprosy or due to some other cause.

Mechanism of nerve destruction

There are four features of nerve damage which are common to all forms of leprosy.

1. Presence of *M. leprae* or its antigens at cooler sites. *M. leprae* has a special predilection for the cooler parts of the body.[9] Leprosy, therefore, is a surface disease affecting the skin, the anterior aspect of the eye, the mucosa of the nose and upper respiratory tract, the testes, and the subcutaneously placed portions of the nerves. The distribution of the lesions in the nerve trunks has been shown to be in areas where the temperature is lower.[10] Localization and preferential growth of the bacilli at these sites have also been demonstrated.[11]

2. Trauma. Most nerve trunks that are damaged are usually superficially placed and are liable to be traumatized, e.g., the ulnar nerve just above the medial epicondyle. Also, there are nerve bundles at positions where they have to negotiate a narrow tunnel. A slight edema to the nerve due to minimal inflammation will produce enough thickening of its size to cause trauma during its passage in and out of the narrow tunnel. A good example is the median nerve at the carpal tunnel.

3. Increased intraneural pressure. In all reactive states, there is edema of the nerve and infiltration of the nerve with numerous inflammatory cells causing marked swelling. The perineurium and epineurium are tight structures composed of large amounts of collagen and fibrous tissue. They do not lend themselves to quick expansion and, therefore, there is considerable buildup of intraneural pressure resulting in localized reduction or loss of blood supply. Although

[9] Binford, C. H. Comprehensive program for inoculation of human leprosy into laboratory animals. Pub. Health Rep. **71** (1956) 995–966.

[10] Job, C. K., Chacko, C. J. G., Verghese, R. and Padam Singh, S. Leproma of the mouse foot. Lepr. Rev. **46** (1975) 39–49.

[11] Hastings, R. C., Brand, P. W., Mansfield, R. E. and Ebner, J. D. Bacterial density in the skin in lepromatous leprosy as related to temperature. Lepr. Rev. **39** (1968) 71–74.

the destruction of nerve tissue due to inflammation may be limited to a small area, the increase in intraneural pressure due to inflammation produces ischemia of the nerve, and even the remaining normal axons lose their function. Temporarily the entire nerve is paralyzed. If the intraneural pressure can be relieved soon enough the nerve can recover very quickly. If the relief of compression is delayed the nerve may undergo segmental demyelination and may take a much longer time to recover. If there is much delay in relief of intraneural pressure, ischemic necrosis of the nerve can take place causing irreversible damage to the entire nerve.

4. Vascular changes. Electron-microscopic studies have described changes in the intraneural blood vessels. Disruption in endothelial continuity,[12] thickening, and reduplication of the basement membrane of capillaries and edema of vessel walls will result in occlusion of their lumina, potentially causing ischemia to nerves.

I believe that these four factors—cooler sites of the nerve helping bacterial localization and multiplication, trauma, increase in intraneural pressure, and occlusive changes of intraneural blood vessels—all play a significant role in nerve damage in all forms of leprosy.

In experimentally infected armadillos, cutaneous nerves are infiltrated and destroyed by *M. leprae* and the nerve trunks, such as the sciatic nerves, are much less frequently involved. Even when they show invasion by the organisms, lepromatous granuloma resulting in fibrosis of portions of the nerve has been seen in only one animal out of the several hundreds that have been studied. Paralyzed extremities and trophic ulcers have not been documented. The nerve trunks in these animals are deep seated, have no special sites of predilection, are not exposed to trauma, and are not subjected to significant increases in intraneural pressure. Therefore, signs of nerve paralysis are yet to be seen. The nerve paralysis in uncomplicated lepromatous leprosy is slow and takes many years to happen. Lepromatous armadillos do not develop ENL reaction, and perhaps they die of lepromatous disease, unlike humans, long before they can develop lepromatous nerve destruction.

5. Hypersensitivity granuloma in the nerve. Much work has been done to elucidate the hypersensitivity reaction in tuberculoid-borderline neuritis which is largely responsible for the damage to the nerves. Several hypotheses have been put forward. Since *M. leprae* are hardly seen in these lesions, experimental evidence has been presented to show that the hypersensitivity reaction may be initiated against: nonmyelin components of sensory nerves,[13] persisting bacterial antigens,[14] and the cytoplasmic antigens of *M. leprae* rather than the cell-wall components.[15] Since *M. leprae* are phagocytosed by Schwann cells, they may play an important role in processing and presenting the antigens of *M. leprae*.[16] The role of autoantibodies to some components of myelin and the axon has also been emphasized.[17] Needless to say this field is wide open for further investigation, particularly using monkey models which show nerve damage similar to that in human leprosy (W. M. Meyers, personal communication).

In lepromatous leprosy there is unrestricted multiplication of bacilli in Schwann cells, perineurial cells, and macrophages in and around nerves. So long as there is no swelling of nerves, no increase in intraneural pressure, and no trauma, the paralysis is very slow. Recently, we saw a newly diagnosed 72-year-old lepromatous patient with a 5+ bacterial index who had been on corticosteroid therapy for 8 years for rea-

[12] Boddingius, J., Rees, R. J. W. and Weddell, A. G. M. Defects in blood nerve barrier in mice with leprosy neuropathy. Nature (New Biol.) **237** (1972) 190–191.

[13] Crawford, C. L., Hardwicke, P. M., Evans, D. H. and Evans, E. M. Granulomatous hypersensitivity induced by sensory peripheral nerve. Nature **265** (1977) 457–459.

[14] Pearson, J. M. H. and Ross, W. F. Nerve involvement in leprosy—pathology, differential diagnosis and principles of management. Lepr. Rev. **46** (1975) 199–212.

[15] Bjune, G., Barnetson, R. St. C., Ridley, D. S. and Kronwall, G. Lymphocyte transformation test in leprosy: correlation of the response with inflammation in lesions. Clin. Exp. Immunol. **25** (1976) 85–94.

[16] Mshana, N. M., Humber, D. P., Harboe, M. and Belehu, A. Demonstration of mycobacterial antigens in nerve biopsies from leprosy patients using peroxidase, antiperoxidase immunoenzyme technique. Clin. Immunol. Immunopathol. **29** (1983) 359–368.

[17] Wright, D. J. M., Hirst, R. A. and Waters, M. F. R. Neural autoantibodies in leprosy. Lepr. Rev. **46** (1975) 157–169.

sons other than leprosy. She showed no loss of nerve function either motor or sensory. There is no doubt that the slow but steady growth of intracellular *M. leprae* would have ultimately brought about the insidious but certain destruction of her nerves, but it would have taken several more years.

It has been found that much of the nerve destruction takes place during the reactive phase of all types of leprosy because of the acute onset of the reaction accelerating the damaging effects of trauma, increased intraneural pressure, and extensive vascular changes. In addition, in ENL there is acute neutrophilic abscess formation, and in exacerbation in tuberculoid-borderline disease there is caseous necrosis and formation of a cold abscess. In these cases, irreversible nerve damage can happen very quickly even before sufficient preventive measures can be undertaken.

Management of neuritis

Silent neuritis. In all leprosy patients with active disease, neuritis is always present. Most of the time it is asymptomatic or "silent." Therefore, in the management of neuritis a careful documentation of sensory and motor functions should be done at regular intervals to assess the progress of the disease and the benefits of the treatment.[18] The most important step to prevent nerve damage or to arrest the damage that has already taken place is to see that the patient gets regular antileprosy chemotherapy. In the lepromatous group, where nerve destruction is mainly due to the presence and multiplication of *M. leprae,* the sooner the intraneural bacilli are killed the sooner further nerve damage is prevented. In patients of all leprosy types with thickened nerves, if there is evidence of progressive nerve paralysis despite administration of regular antileprosy drugs, a course of corticosteroid therapy is indicated, even if there are no symptoms such as nerve pain and tenderness.

Acute neuritis. During acute neuritis patients complain of pain and tenderness of nerve trunks localized to the sites of predilection. They may also experience hyperesthesia, feeling of pinpricks and tingling in the skin areas supplied by the nerve. The pain is caused by the sudden swelling of the nerve due to intraneural edema and cellular infiltration producing stretching of perineurium and epineurium. Acute neuritis can be seen during the ordinary course of the disease, but it is more often present during times of ENL and during exacerbation reactions in borderline-tuberculoid disease. In addition to treating the general symptoms that accompany neuritis, the nerve should be put at rest with an appropriate splint or a comfortable sling. Prevention of movement of the swollen nerve through narrow passages will frequently alleviate the pain. In addition, steroid therapy which suppresses edema and hypersensitivity reaction should be administered. Prednisone, up to a dose of 60 mg daily in divided doses, may be given to start with and it may be reduced weekly to less than 10 mg daily in 4 to 6 weeks. If successive documentation of the sensory and motor functions done weekly shows progressive loss in spite of corticosteroid treatment, it is necessary to relieve the intraneural pressure by surgery.[19] At the site of the swelling, the nerve is exposed and the epineurial sheath is incised longitudinally, taking care not to cut the blood vessels. In ulnar nerve swelling, the epicondyle may be excised or the nerve may be transposed in front of the epicondyle and buried in the muscles. In tuberculoid leprosy the nerve may have a localized cold abscess, containing caseous material, which should be excised. It is important to continue antileprosy therapy together with the antiinflammatory drugs during the reactive episodes.

In recent years, there have been several instances of neuritis due to dapsone (DDS) toxicity. Therefore neuritis caused by DDS should be carefully differentiated from leprous neuritis. DDS toxicity affects only motor nerve fibers. The drug should be discontinued in such patients.

Conclusion

Nerve damage is an ever-present serious complication of all forms of leprosy. We

[18] Pearson, J. M. H. The evaluation of nerve damage in leprosy. Lepr. Rev. **53** (1982) 119–130.

[19] Palande, D. D. Surgical management of acute neuritis in leprosy. Lepr. India **48** Suppl. (1976) 770–773.

now understand much of its pathology and some of its pathogenesis. Its pathogenesis is closely linked with the reactive phase of leprosy about which we know very little. We should explore the possibility of producing ENL in the now available animal models such as the nude mouse, the armadillo, and the mangabey monkey. In experimental armadillo leprosy there is no evidence of nerve damage; whereas in the primate model we see the nerve damage characteristic of leprosy. Studies using these three experimental animal models to probe the unanswered questions on nerve damage are long overdue. In closing, I would like to repeat that in leprosy there is always neuritis, in some instances even after pronouncement of medical cure.

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