SOME LESS COMMON NEUROLOGICAL FINDINGS IN LEPROSY[1]

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INTRODUCTION

The peripheral neuritis occurring in leprosy is characterized by certain features that serve to distinguish it from other neuropathies. At sites of predilection, certain of the peripheral nerve trunks are enlarged, hard and tender, and cutaneous nerve filaments normally impalpable may become grossly hypertrophic. These changes are due essentially to a reaction provoked by the presence of *Mycobacterium leprae* in the nerves. The commonest sites affected are, in order of frequency, as follows: the ulnar just above the elbow, the lateral popliteal at the neck of the fibula, the posterior tibial midway between the internal malleolus and the point of the heel, and the great auricular as it passes over the sternocleido-mastoid muscle. Other peripheral nerves are less often affected.

The enlargement may be extreme, the ulnar being 3 cm. or more in diameter. The degree of hardness depends on the relative importance of edema and cellular infiltration in the nerve itself and of fibrosis in the sheath or in the nerve. Tenderness may be localized and minimal, or the nerve throughout its superficial course may be exquisitely tender. Pain in the nerve trunks themselves, unremarkable in neuritis due to other causes, is of frequent occurrence in leprosy.

While the precise pathogenesis of nerve involvement in leprosy is obscure, it may be recalled that the nerves in the situations named share certain common features: they pursue a superficial, subcutaneous course; they are exposed to repeated traumata, especially in the neighborhood of joints or as they pass over bones; they are subject to lower temperatures and to a greater temperature range than nerves situated more deeply (Brand, 1959). Nerve leprosy is commoner and more severe among Japanese living in the northern islands, and nerve symptoms are noticeably worse during colder weather in India and the East. Distal constriction may also determine the localization of the pathologic changes in the nerve; for instance, in the ulnar the enlargement begins abruptly either just above the internal epicondyle or above the two heads of origin of the flexor carpi radialis.

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The reactivity of the tissues generally to leprosy ranges from the completely anergic (lepromatous leprosy) to the hyperergic types (major tuberculoid leprosy). In the former, extremely numerous *M. leprae* are found between the nerve fibers like shoals of fish in a stream, but cellular infiltration is minimal and clinical evidence of damage (in the absence of acute reaction) is generally late, i.e., from the third year onwards. In tuberculoid leprosy, on the other hand, cellular reaction to paucibacillary infection in nerves and skin alike is both vigorous and early. The cellular reaction within the nerve, and hence the localized signs, run roughly *pari passu* with the intensity of the Mitsuda reaction.

LESS COMMON NEUROLOGICAL FINDINGS

This paper records diverse neurologic observations accumulated personally over the past 28 years in the study of about 20,000 patients with leprosy, mainly in Central and West Africa but also in India and the East and in the Americas. These findings are either novel or have received but scant notice in standard text-books and the literature, and emphasize that the essential pathology of leprosy concerns the peripheral nerves (W.H.O., 1961).

Precocious neurological symptoms.—Many of the nonnervous and systemic prodromal symptons of leprosy copied uncritically from one text-book to another, are of doubtful authenticity, but it is undeniable that, particularly in India and the Far East, neurological symptoms may antedate by many months any demonstrable pigmentary changes in the skin. The commonest symptom is localized paresthesia—spontaneous or provoked by minimal stimuli— especially when persistent or recurrent. While such symptoms are by no means pathognomonic of leprosy, they occur so often in patients who later develop signs of leprosy, as to be of diagnostic importance. Intense neuralgia and episodes of tabetic-like shooting pains in the limbs, trunk or face may precede demonstrable impairment of sensation in the same area. Spontaneous and short-lived painful sensations, often localized, and sometimes accompanied by painful muscular subsaltus, may also occur. Occasionally, severe causalgia provoked by a negligible stimulus, or a radiculitis, or a lumbar disc syndrome arising spontaneously, may herald the disease. Localized hyperalgesia of the skin may foreshadow the subsequent appearance there of a tuberculoid lesion of leprosy.

In lepromatous leprosy, the common widespread macular eruption may be preceded by a generalized formication or pruritus. As noted also by Dastur (1955), localized hyperalgesia and hyperesthesia of the skin may be early signs of leprosy.

Peripheral nerves less commonly involved.—In addition to the nerves commonly enlarged at the usual sites, other mixed nerve-trunks may occasionally be affected, e.g., the median nerve in the antecubital fossa or above the anterior annular ligament of the wrist,

and the musculo-spiral (radial) nerve in its groove. The popliteal nerve deep in its fossa may be enlarged continuously with the external (lateral) popliteal at the neck of the fibula. The dorsalis pedis is sometimes affected. The posterior tibial nerve may be tender for a variable length of its course above the ankle: severe pain and tenderness in the nerve internal to the Achilles tendon may be produced by the act of walking.

Gross enlargement of small cutaneous nerves close to leprous lesions of the skin has long been recognized as a diagnostic sign equal in value to the focal enlargement of the corresponding nerve trunk in the neighborhood of a tuberculoid lesion anywhere in the body. A leprous lesion near the knee or the elbow may be the center of a Medusa's head of radially disposed nerves. Though the axillary skin is generally spared in leprosy, a leash of enormously enlarged subcutaneous nerve twigs may be seen crossing the axilla from a pectoral tuberculoid lesion.

Sudden paresis of one arm, accompanied by enlargement and tenderness of all the nerves of the brachial plexus, and by wasting of the forearm muscles, is sometimes seen. (Different in pathology, though similar in clinical impairment, are the rare instances of extensive leprous myositis, in which the entire musculature of the arm is eventually replaced by fibrous tissue.)

Branches of the facial nerve may be enlarged as they pass over the zygoma and also occasionally at or near the stylo-mastoid foramen. The three divisions of the trigeminal nerve as they emerge from their bony foramina may all be abnormally tender on pressure when leprous lesions are present in the vicinity. Rarely, trigeminal neuralgia may for many months be the sole manifestation of leprosy; *M. leprae* may be demonstrated in the nerve. Sensory loss in the distribution of one trigeminal nerve may coexist with contralateral facial palsy. Loss of taste over half the tongue has been observed.

Of special interest is involvement of the brachial plexus, which may occur (though not exclusively) when extensive major tuberculoid lesions are present in the skin of the forearm, arm or the deltoid region. Any part of the plexus—roots or trunks or branches—may be enlarged, hard and exquisitely tender. The plexus may be involved in its entirety, or the lesions may be confined to the fibers supplying the skin that is the seat of a leprosy lesion. When one plexus is affected, and more especially if the involvement is extensive, the corresponding nerves of the contralateral plexus may be tender, even when there is no leprous lesion on that side.

Small unnamed nerve-fibrils, greatly enlarged, may form intricate subcutaneous patterns: on the dorsum of the hand, for instance, branches of the ulnar nerve may be seen joining and ramifying with branches of the median, and anomalous innervation and nerve shunting (Price, 1958) are relatively common. The great auricular nerve may be present as a leash of enlarged nerves when the skin over the

sternocleido-mastoid muscle is tensed. In parts of India, a visibly enlarged great auricular nerve is regarded as a stigma of active leprosy, and patients may request the surgical removal of an obvious nerve persisting after the disease has been cured. Enlargement and tenderness of the cutaneous twigs of the radial and ulnar nerves as they pass over the bony prominences at the wrist are valuable diagnostic signs of leprosy. The lateral digital nerves are enlarged in the presence of leprous lesions in the skin of the corresponding fingers. Trauma may precipitate a localized neuritis in leprosy, or reactivate a quiescent neuritis. A motor accident in which no specific injury is sustained may be followed by focal polyneuritis in a patient under treatment for leprosy.

Certain peripheral nerves may be affected in leprosy in one country but not in another. Thus, the posterior tibial nerve is rarely enlarged in Malaya, commonly in Africa. Some nerves (e.g., the sural and the anterior tibial) are not infrequently enlarged in India, very rarely in Africa. The musculo-spiral nerve is commonly affected in Japan and in southeast India, and sometimes in Ethiopia; elsewhere wrist-drop due to leprosy is quite rare.

Less common neurological symptoms.—While the symptomatology of established neuropathy in leprosy usually conforms to classical descriptions in which glove-and-stocking sensory impairment and peripheral muscular paresis figure prominently, from time to time less common symptoms arise.

Mention may be made of delayed pain and causalgia, which may occur in the localized neuritis of early tuberculoid disease, or in the generalized polyneuritis of late lepromatous leprosy. It may follow removal of a portion of a nerve for histologic examination. In the presence of a leprous lesion in the vicinity, percussion of a nerve as it passes over a bony prominence may evoke paresthesia or delayed pain in the area of distribution, even though the nerve trunk may not be demonstrably enlarged (cf. Kerandel's sign in trypanosomiasis).

Loss of nail pain in the ring and little fingers may be the first indication of involvement by leprosy of the ulnar nerve.

Absence of tenderness of the nerve trunks of the limbs at the sites of predilection is one of the accepted criteria of nonactivity of leprosy after effective therapy, but not infrequently local tenderness persists in the enlarged and hard nerve for several years after clinical and bacteriologic arrest of the disease and in the absence of progressive sensory or motor impairment. Similarly, tenderness may persist in lepromatous leprosy, and normal (i.e., viable) *M. leprae* may be found in nerve trunks occasioning no cellular reaction, some years after clinical cure and after the disappearance of all bacilli (normal and degenerate) from the skin and nasal mucosa.

"Primary" or "pure" polyneuritic leprosy.—Polyneuritis may persist for years with no demonstrable pigmentary changes in the skin. Cases of primary polyneuritis in which no skin lesion of leprosy ever

develops are not infrequently seen in India and the East. While this form of leprosy cannot be excluded *a priori* in Africa it must be excessively rare, and in Africa leprous infections of the nerves are invariably accompanied by hypopigmentary changes in the skin. The etiological role of *M. leprae* in such cases is demonstrated conclusively by finding the bacilli (usually scanty) between the nerve fibers, accompanied by intense round-cell infiltration.

Leprosy may sometimes be heralded by sudden and severe peripheral neuritis affecting all four limbs. The paresis in cases studied in Africa was partial from shoulder and hip downwards, and almost complete from elbow and knee. In each case, the first cutaneous lesions appeared some months after the onset of the paralysis, and the skin and nasal mucosa eventually become bacteriologically positive.

Spontaneous autolysis of nerves.—Some degree of softening of nerve trunks may be found when the sheath of an acutely inflamed nerve is incised longitudinally during the operative relief of tension due to edema and hyperemia within the unyielding fibrous sheath. Localized spontaneous autolysis of a peripheral nerve, typically at the sites of maximum enlargement, and commonly referred to as "abscess" formation, is usually a late complication of a major tuberculoid leprosy lesion in the vicinity, but it may be a presenting sign when a healed tuberculoid lesion has long since been forgotten by the patient. The commonest nerves subject to abcedation are the great auricular, the ulnar, and the external popliteal (*Internat. J. Leprosy* 1955; Browne, 1957). This condition is much more often met with in India than Africa, though it is not uncommon in northern Uganda.

Less common sensory disturbances.—There is great variability in the order in which the sensory modalities are affected and in the degree of impairment (Fritschi, 1956). The main brunt may be borne—fortuitously, and depending on the precise fibers damaged—by the motor and sensory paths in almost any proportion. Thus, while on palpation the ulnar nerves in an individual patient may be enlarged and hard apparently to the same degree, one hand may show complete atrophy of the intrinsic muscles with minimal impairment of sensation, while the other may have virtually intact musculature and maximal sensory loss. In another patient one hand may be crippled by reason of paralytic contractures, while the other may be functionally useless because of anesthesia and neuropathic ulceration. Sensory impairment and contractures from intrinsic paresis are usually accompanied by ulceration of the digits, but not invariably so, even in manual workers. In such cases, it is tempting to posit intact nerves subserving "trophic" functions. Paradoxical findings in neuritis due to leprosy have also been recorded by Carayon and Languillon (1959).

Reversible nerve blocking due to local edema or ischemia in the nerve may persist for 6–12 months. After such a lapse of time, footdrop may recover completely, and sudden paresis accompanied by complete electrical nonexcitability may clear up in cases of reactional tuberculoid leprosy.

Over the skin lesions themselves, light touch may be lost before or after thermal sensitivity, and when a tuberculoid lesion heals, sensation may return in any order. With the gross clinical methods of testing available, it may not be possible to detect any impairment of sensation at the site of a healed minor tuberculoid or indeterminate lesion. Gross destruction of skin appendages leads to permanent sensory loss.

Tactile localization and discrimination may be affected not only in the obvious cutaneous leprosy lesions, but also in the surrounding skin, and in the area immediately distal to the lesion. Mis-reference of tactile and of thermal stimuli may be present in the lesion itself and in the adjacent skin.

Symmetry of neurological findings.—Sensory impairment may sometimes be demonstrable in apparently normal skin in an area exactly corresponding to a localized tuberculoid lesion on the opposite side. Such an observation may provide confirmation that a suspicious skin lesion or an uncharacteristic residual scar is in fact due to leprosy. This phenomenon of contralateral sensory impairment is observed especially when a leprous lesion is present in the neighborhood of a superfical nerve trunk, e.g., near the head of the fibula, or near the internal epicondyle. Weddell (1963) has advanced neurohistological evidence to support this clinical finding.

The symmetry of leprosy lesions may become evident only after the lapse of some months or years. A lesion on the ear lobe, face, chest wall or limbs, may appear as the mirror image of a similar lesion that has existed for some time.

Hyperesthesia and hyperalgesia.—Hyperesthesia may be present in a skin lesion, or in the area surrounding a lesion, or in the neurologically distal skin, or in the corresponding contralateral region. It may occur during episodes of acute exacerbation in both lepromatous and tuberculoid leprosy.

Plantar hyperalgesia may be an early sign of leprosy, preceding by some months demonstrable changes in the nerves of the leg. Hyperalgesia of the skin may occur long before the appearance of typical tuberculoid lesions in any area.

A minimal stimulus directed to the wasted hypothenar eminence in a patient with ulnar neuritis may produce painful sensations not only locally but also proximally along the course of the ulnar nerve, and felt most intensely just above the elbow.

Bony tenderness is not common in leprosy, but percussion over the small bones of the hands or feet in the course of dactylitis occurring in acute exacerbation of lepromatous leprosy, is painful: the marrow is replaced by chronic granulomatous tissue. Percussion over the tibial crest is likewise painful in patients in whom the periosteum is radiographically separated from the shaft by diffuse granulomatous infiltration.

Localization of skin lesions.—The observed distribution of skin lesions in some forms of leprosy may suggest neurologically de-

termined patterns, e.g., the respect for the midline and for embryological cleavage lines, the limitation of skin lesions to the cutaneous areas of distribution of certain nerves, the disposition of lesions with their long axes parallel to the intercostal spaces, and also the initial accurate symmetry of some lesions. A zoster-like eruption may precede a leprous lesion in the same areas. On the trunk, a series of oval lesions, each with its long axis in line with an intercostal space, is not infrequently seen. (The symmetry of presumably hematogenous lesions is, of course, not relevant in this connection.)

Less common neuropathic anomalies.—The ulcers of the extremities in leprosy, often called "trophic" or "perforating" (but better termed "neuropathic") are due to repeated unappreciated traumata to the anesthetic part, followed by secondary infection of soft tissues and bone. Bizarre distortion of the fingers due to soft tissue contracture resulting from progressive lepra reaction may augment neuropathic contractures of the fingers.

When severe peripheral neuritis occurs in children, the rate of growth of the corresponding part may be seriously impaired, as in poliomyelitis. This is well seen when one ulnar nerve is damaged: the growth of bones and soft tissues of the corresponding fingers fails to keep pace with that of the unaffected fingers. Long-standing ulnar neuritis in adults as well as in children results in such changes as wasting of the finger-pulps, tapering fingers, shiny nail-beds; the nails are brittle, curved both from side to side and from above downwards, and are susceptible to infection and damage from slight trauma.

Changes precisely similar to Charcot's arthropathies can be seen in the feet and hands in leprosy. Walking on an anesthetic foot may result in damage to any joint from the ankle to the phalanges. Occasionally, the larger proximal joints may suffer while the more distal and smaller joints are radiographically intact.

Rarely, a thickening of the integument may be noted immediately proximal to a tuberculoid lesion of the skin, together with a similar thickening on the opposite side where there is no leprous lesion. The cause of this hypertrophy and fibrosis of the dermis may be an indolent type of tuberculoid leprosy that causes no pathological changes in the epidermis or in the melanocytes of the Malpighian layer.

Disturbances of the caliber of blood vessels may occur within the territory of a nerve that is the seat of changes due to leprosy. This is best seen in the lability of the caliber of vessels in the nail-bed and the finger-pulp, particularly of the fourth and fifth fingers when the ulnar nerve is affected. Persistent vasodilation of the blood vessels in the nail-bed, or even of the whole finger, may occur. When the two hands are held dependent, the hand in which nerves are affected by leprosy becomes cyanotic and congested. Completely anesthetic tissues, which tend to become ischemic, atrophic and fibrotic, are colder than unaffected tissues.

Disturbances of pigmentation may occur in association with nerve lesions in leprosy. Hypopigmented tuberculoid lesions may become hyperpigmented spontaneously (which is rare), or as the result of treatment. Of greater pathologic interest is the hyperpigmented lanceolate area that may be seen on the distal aspect of a tuberculoid lesion, for example on the chest wall. This area is immediately adjacent to the leprous lesion, and is usually smaller than the lesion itself. The hyperpigmentation may represent a melanocytic-stimulating activity of the disease process occurring before pigment formation has been temporarily or permanently impaired by some melanocytotoxic mechanism still obscure.

Disturbances of sweating. Partial loss of sweating as well as complete anhidrosis due to a localized leprous lesion of the skin may be of diagnostic value in the active as well as in the quiescent or residual scarred lesions of tuberculoid leprosy. Compensatory hyperhidrosis, particularly of the paravertebral areas, the palms, the perinasal skin and the axillae, is a well-recognized feature of widespread tuberculoid or lepromatous leprosy where sweat-glands in extensive areas of skin have been invaded by the granulomatous process. Less common is an anhidrosis or a hyperhidrosis confined to the area of innervation of a nerve that is the seat of gross changes due to leprosy. This may be seen in the hypothenar eminence and adjacent ulnar-innervated skin when the ulnar nerve is affected. It may be accompanied by the usual evidence of motor and sensory impairment and also by pigmentary disturbances, shown by hyperpigmented mottling in the same area.

Disturbance of the hair. Disturbances of hair growth associated with localized (nonlepromatous) and diffuse (lepromatous) leprosy are well known. The madarosis of lepromatous leprosy, especially when confined to the outer halves or outer thirds of the eyebrows, seems to have a neurological basis: the innervation of the affected skin has been shown to follow Sölder's lines (Polemann and Peltzer, 1952). Less well-recognized is the loss of hair and shininess of the skin of the forearms that may be an early manifestation of lepromatous leprosy.

It is noteworthy that while leprous lesions in the hyperpigmented skin always show some degree of pigment-loss (which, however, in the absence of true scarring never proceeds to complete achromia), the hair within the cutaneous lesions usually retains its pigment; and, in contradistinction to idiopathic vitiligo in the dark-skinned, leucotrichia is not seen.

DISCUSSION

The pathogenesis of nerve lesions in leprosy has many points of contact with other neuropathies and with immunological processes in other tissues. It has parallels with recent findings in experimental mycobacterial infection with unclassified or anonymous

mycobacteria, certain of which may show, after a varying number of animal passages, a predilection for peripheral nerve tissue (Ranadive *et al.*, 1962).

The pathology of the transient and reversible interruption of peripheral nerve pathways and of actual destruction of nerve fibers may be complex and multifactorial. Various suggestions have been put forward. Thus, it may be the result of a compression ischemia (Chatterjee, 1955) or a degeneration of the vasa nervorum (as in diabetes), (Hawthorn *et al.*, 1961), or an allergic neuropathy, similar to the experimental allergic neuritis reported by Waksman and Adams (1955) in a series of carefully documented papers. It has resemblances to the peripheral neuropathy of such collagen disease as rheumatoid arthritis (Hart and Golding, 1960; Steinberg, 1960; Kipler and Rose, 1960). Familial hereditary polyneuritis or hereditary sensory neuropathy (Thévenard's syndrome, Dejerine-Sottas' disease) (Heller and Robb, 1955) and primary amyloidosis of nerves (Chambers *et al.*, 1958; Gafni *et al.*, 1964) are the two diseases that most closely resemble polyneuritic leprosy, while Morvan's disease may be closely mimiced by leprosy where the brunt of the disease is borne by the sensory fibers of the mixed nerves.

Recently, attention has been drawn by several workers to certain features in the peripheral neuritis of leprosy that have their counterparts in autoimmune disease, and Illis (1962) stated that some of the features of nonleprous polyneuritis may be explicable on the assumption that it is an antigen-antibody disorder localized to nerve tissue. These features, again, run parallel to the vigorous tissue reaction seen in paucibacillary leprosy, which could be explained by a local concentration of autoimmune bodies. The studies of Melnick (1963) who has adduced evidence of the importance of antibodies to nerve tissue in the Guillain-Barré syndrome, may have a bearing on the peripheral neuritis of leprosy. Degenerating *M. leprae* may act as an adjuvant factor in accelerating the degeneration of nerve tissue (Weddell, 1963) that takes place normally. It may be that any agent, traumatic or toxic, acting on nerve tissue may be a precipitating factor in determining nerve damage in leprosy.

The role of constriction of nerve trunks has been demonstrated at operation in the case of patients suffering from the carpal tunnel syndrome. Enlargement of the nerve proximal to the constriction is seen not only in this condition, but in the similar tarsal tunnel syndrome (Lam, 1962) and in constriction of the ulnar nerve by fibrous or cicatricial bands.

The localization of changes in the nerve trunks at the sites of predilection is correlated only partly with the actual presence of *M. leprae* in those situations. Bacilli are also found elsewhere in the nerves, and particularly distally. Thus, while the optimum temperature for multiplication of *M. leprae* in the foot pads of mice (Shepard,

1962) and in the ear lobes and testicles of golden hamsters (Binford, 1958) is probably about 32°C, the lower temperature of subcutaneous nerves may favor a local antibody response in the nerve rather than local multiplication of *M. leprae*.

SUMMARY

In addition to the well-known characteristics of the peripheral neuritis occurring in leprosy (viz., enlargement, hardness and tenderness of certain peripheral nerve trunks at sites of predilection), less common neurological findings indicate the importance of peripheral nerve damage in the symptomatology of leprosy.

Prodromal symptons of leprosy and precocious manifestations of the disease are frequenly of neurological origin. Cutaneous nerve twigs in various situations may be enormously enlarged. Superficial nerves other than those classically affected by leprosy, may occasionally be involved. Sensory and motor impairment of widely differing combinations, may be transient or permanent. Diverse anomalies associated with neurological manifestations concern the calibre of blood vessels, and include disturbances of cutaneous pigmentation and of hair growth.

The predilection of *M. leprae* for peripheral nerve tissue is considered in relation to neuropathies occurring in collagen diseases, autoimune disease, and the Guillain-Barré syndrome.

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