The Immunopathology of Nerve Damage in Leprosy[1]

Over 10 million people in the world today have a chronic infection, leprosy. How many more uncounted millions have successfully fought off the disease? Unravelling the complicated immunopathology of leprosy could be the key to its management.

The bite of the disease lies in the disability it causes, and this is mainly a result of damage to nerves. After a brief summary of the general immunopathology of leprosy, the possible mechanisms of nerve damage are listed and then examined in the light of experimental evidence.

[1] This review was written in 1979 by Ian Hill-Smith, M.B., B.S., B.Sc., while he was a medical student at University College, London. It was written in response to the annual competition set up by the British Leprosy Relief Association (LEPRA) for essays on various aspects of leprosy and was one of the prize winning essays for 1979. We take pleasure in publishing this excellent review. Dr. Hill-Smith's present address is Stoke Mandeville Hospital, Aylesbury, Buckinghamshire, U.K.—RCH

GENERAL IMMUNOPATHOLOGY

Leprosy is a spectrum of disease; it ranges from tuberculoid, with granulomata heavily infiltrated with lymphocytes and a cell-mediated immune response, to lepromatous, in which there are numerous lesions containing a high concentration of acid-fast bacilli and causing a humoral response. There are two possible reasons for this spectrum: either the precise nature of the infecting organism is inconstant or the reaction of the host varies.

The experiments of Rees[2] support the latter; inoculation of the mouse foot pad with bacilli isolated from patients with different types of the disease resulted in apparently identical infections. However, as he points out, this is not conclusive evidence. Further support is gained from experiments

[2] Rees, R. J. W. New prospects for the study of leprosy in the laboratory. Bull. WHO **40** (1969) 785–800.

TABLE 1. *The immunological range of leprosy.*

	Tuberculoid pole (TT)	Lepromatous pole (LLp)
Lymphocyte infiltration	+	−
Histiocytes/foamy macrophages	−	+
Acid-fast bacilli in granulomata	−	+
Acid-fast bacilli in nose	−	+
Fernandez and Mitsuda reactions	+	−
Impaired CMI, using lymphocyte transformation test, % transformation	15	0.2
Allograft rejection, days tolerated beyond average	+2	+4
Antimycobacterial precipitins	−	+
Anti-*M. leprae* antibodies	−/+	+
T-cell lymphokine production	+	−
M. leprae-reactive lymphocytes	+	−
Dermal nerve max. diameter, μm	1000	80

using immunofluorescence, which indicated that the antigen specific to *M. leprae* can cause both a cell-mediated and a humoral response[3].

Table 1 shows the range of immunological response between the tuberculoid and lepromatous poles[4,5,6,7,8,9]. Epidemiological evidence that the type of leprosy is not related to contacts confirms that it is not the pathogen which determines the disease type[10]. Twin studies clearly show a genetic factor influences not only susceptibility to leprosy but to a particular type of the disease[11,12,13] whereas members other than twins show no such coincidence of types of disease. This argument is particularly potent in the case of leprosy in which infection involves a long period of contact, and spread within families is a major route of transmission.

THEORY

The nature of the damage to nerves in leprosy depends on the type of immune response. If we accept that the host response is variable and the mycobacterium otherwise consistent in its behavior and effects, nerve damage, being also variable, must be influenced by the immune response. Theoretically, as the Figure shows, damage to nerves could be a direct result of the immune response itself (A) or be indirectly linked via the influence of the response on the behavior of the pathogen (B). One example of the behavior of the pathogen is multiplication, which is known to be affected by the immune response. Similarly, its entry into nerves or the subsequent damage caused might be influenced by the host's response.

Is it possible to exclude pathways A or B?

Excluding B would mean that nerve damage could be entirely accounted for by the

[3] Abe, M. Anti-*M. leprae* antibodies in leprosy patients as demonstrated by indirect immunofluorescence. Int. J. Lepr. **41** (1973) 549.

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[11] Ali, P. M. and Ramanujam, K. Leprosy in twins. Int. J. Lepr. **34** (1966) 404–407.

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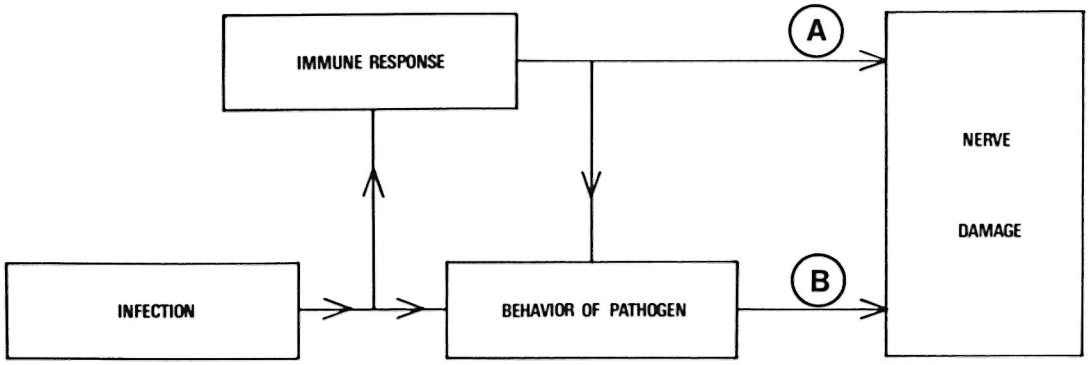

THE FIGURE. Pathways to nerve damage.

immune response and that the pathogen itself had no effect. On the other hand, if the immune response caused no nerve damage, A would be excluded.

Clinical observations cannot answer this question. It appears that no specific study has been made of the relative importance of these two pathways. The critical experiment would be to observe nerve damage in the guinea pig or mouse resulting from the injection of killed *M. leprae* into nerves and from the inoculation with live bacilli following irradiation or thymectomy. This experiment eliminates either the activity of the pathogen or the host's immune response.

It is tempting to suggest, bearing in mind that leprosy in immunodeficient animals resembles the lepromatous type, that B is more prominent in lepromatous and A in tuberculoid leprosy, resulting in the different characteristics of nerve damage associated with the range of the disease. Continuing on theoretical grounds, possible mechanisms which could cause injury to nerves are listed in Table 2.

What evidence is there to support or exclude any of these possibilities?

EVIDENCE

Appearance of nerve lesions. Within nerves leprosy bacilli are seen mainly in the Schwann cells and also in the perineural cells; few are actually within the axons[14]. Macroscopically the nerve may be irregularly swollen. The microscopic appearance depends on the stage of evolution of the intraneural infection and the immune response. In tuberculoid leprosy the nerve is replaced by epithelioid cell granulomata following the invasion of inflammatory cells through the perineural layers. The infection, however, is not limited by this because the mycobacteria released from destroyed Schwann cells can infect healthy tissue further along the nerve.

In borderline leprosy a higher concentration of bacilli is seen in the nerve before any inflammatory response is apparent. Foci of swollen cells tend to form next to, and within, the perineurium, leaving a central area of well-preserved though infected Schwann cells[15].

The greatest numbers of bacilli are seen in lepromatous leprosy, and they are particularly concentrated in the perineural

[14] Boddingius, J. The occurrence of *Mycobacterium leprae* within axons of peripheral nerves. Acta Neuropathol. **27** (1974) 257–270.

[15] Pearson, J. M. H. and Weddell, A. G. M. Perineural changes in untreated leprosy. Lepr. Rev. **46** (1975) 51–67.

TABLE 2. *Theoretical mechanisms of nerve damage.*

1. Intraneuronal *M. leprae*
2. Extraneuronal *M. leprae* damaging Schwann cells/epineurium
3. Host's immune response: CMI directly destroying nerve tissue; CMI + antibody destroying nerve tissue
4. Ischemia caused by granulomata or cold
5. Pressure from granulomata or intrasheath swelling and cellular infiltration
6. Biochemical disruption caused by intracellular *M. leprae*
7. Toxin produced by *M. leprae*

cells. These infected cells form thick layers surrounding the nerve; such multilayering is characteristic of leprotic nerve lesions as a whole, but the layers are thinner and more fibrotic towards the tuberculoid pole. The amount of layering is proportional to the maturity of the lesion and correlates with the degree of sensory loss.

The distribution of mycobacteria within the nerve and the fact that axons remain intact until after degenerative changes can be seen in Schwann cells make it improbable that intraneuronal bacilli are directly responsible for the loss of nerve function. Further indication to exclude this possibility comes from the observation that in large diameter nerves, central axons continue to function when outer axons, Schwann cells, and perineurium have been engulfed by fibrosis[16].

TIMING

Infection of nerve tissue does not coincide with loss of function; in lepromatous leprosy bacilli can be present in large numbers within a nerve which shows little functional loss. In contrast, sensory impairment is a common early symptom of tuberculoid leprosy. It is highly likely therefore that the cellular response at least partly accounts for nerve damage.

Pressure, ischemia, and temperature. The contained structure of a nerve is such that inflammation could destroy the tissue by pressure, possibly with associated ischemia. The subsequent replacement of necrotic tissue with granulomata would give the appearance of a single, direct inflammatory destruction of infected cells. Ischemic changes have been reported in nerves damaged by leprosy[17, 18].

Could the predilection of nerve lesions for superficial small nerves and large subcutaneous nerves which are immediately proximal to a joint be because they are more liable to ischemia? Such sites have been shown to be colder than the rest of the nerve length[19], but even though cold can injure small cutaneous vessels[20], such localized temperature differences would not give rise to persistent vasoconstriction.

M. leprae can multiply only in a relatively cold environment: the foot pad of the mouse is 27–30°C, and the nine-banded armadillo (*Dasypus novemcinctus* Linn.) has a core temperature of only 32–35°C. It appears that temperature affects the multiplication of the bacillus, either directly or by suppressing immunity[21]. Tissue damage is more likely to occur therefore in cold areas[22].

There is no evidence to support the theory which accounts for the preferred sites of nerve damage on the grounds of liability to repeated trauma. Pressure necrosis is also unlikely because of the sparing of central axons in some large diameter nerves.

Humoral response. The natural history and microscopic appearance of nerve damage varies according to the type of leprosy. Could the damage at the lepromatous pole be due to the host's humoral response which is more prominent at this end of the spectrum?

During Type 2 reactions, immune complexes have been demonstrated in erythema nodosum leprosum (ENL) lesions[23, 24],

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[16] 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.

[17] Carayon, A., Languillon, J., Camain, R. and Robin, P. A propos d'un type de lesion nerveuse non spécifique chez les lépreux. Bull. Soc. Med. Afr. Noire Lang. Fran. **15** (1970) 186–191.

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in renal glomeruli[25,26], and in the circulation[27,28]. ENL foci occur within nerves, and this reaction to bacillary antigens, which is similar to the Arthus phenomenon where immune complexes are deposited in and around blood vessel walls, undoubtedly can lead to tissue damage. ENL lesions tend to affect nerves which are already severely impaired by perineural layering and inflammation so the deposition of immune complexes seems unlikely to be the primary mechanism of nerve damage in lepromatous leprosy.

Another possibility with regard to the humoral response is that nerves are injured by autoantibodies formed as a result of leprosy infection. Autoantibodies have been found against testis[29], thyroid nuclear material[30], cardiolipin[31], as well as rheumatoid factors and cryoglobulins[32], but no autoantibodies have been demonstrated to react with nerve tissue specifically in leprosy patients[33].

ENTRY

Three ways of entry have been postulated:

1) By phagocytosis by Schwann cells in the upper layers of the dermis
2) By penetration of the perineurium
3) Via the endoneural blood vessels

Theory 1 is unlikely in view of the fact that the middle and deep layers of the dermis show consistently more nerve involvement than the superficial dermis. Neither is it likely that the mycobacterium could easily migrate down the nerve from this entry site since bacilli are so rarely seen in axons, the only continuous intracellular pathway[14]. Furthermore, free bacilli are not found in high concentration in the dermis. So theory 1 is unsatisfactory.

The problem with theory 2 is that the perineurium presents a formidable barrier; if mycobacteria were able to penetrate it, they could only cross by slow invasion, and there should be histological evidence of a peripheral invasion but there is none.

The only rapid way to cross the perineurium is via the endoneural blood vessels, and theory 3 is supported not only by the systemic nature of leprosy[34,35] but also by the high concentration of bacilli seen around these vessels in early nerve involvement. Certainly, bacteremia is known to be part of the natural history of the disease[36].

CONCLUSION

A review of Table 2 in the light of the evidence presently available excludes possibility 1 that nerve damage is caused by intraneuronal *M. leprae,* confirms 3 that the host's immune response must be involved to some extent, leaves 2, 4, and 5 as possibilities, and 6 and 7 as speculations.

What needs to be established is the relative importance of the types of immune response and the pathogen itself in causing the damage to nerves, especially since treatment can affect the immune response and hence the final, overall neurological impairment. —Ian Hill-Smith

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