M. Leprae and its "Affinity" for Nerves

Ever since the publication of the "Atlas Colorié de Spedalskhed" by Danielssen and Boeck in 1847,[1] neural involvement in leprosy has been recognized as a striking characteristic of this disease. It is so remarkable that for many years the clinical classification of the disease was designated by the shadings of the degree of involvement of skin and nerve, as for example L_1N_2, L_4N_1, etc. As histopathologic study, correlated with lepromin-originating immunologic understanding of the disease manifestations advanced the immunopathologic basis for classification changed, but appreciation of the diagnositic significance of neural involvement was enhanced. Today demonstration of acid-fast infiltration of cutaneous, or other nerves is regarded as a significant diagnostic feature and no histopathologic description of presumptive leprous skin biopsy is complete if it does not note the status of the cutaneous nerves.

[1] Danielssen, D. C. and Boeck, C. W. Atlas Colorié de Spedalskhed. Bergen: Norwegian Government, 1847.

Khanolkar[2] reported studies on the basis of which he concluded that "All leprosy is neural in its inception, in-as-much as the spread of micro-organisms is either in or along nerve fibers in the initial stages. The bacilli are attracted toward the degenerating and regenerating nerve fibers in the cutaneous nerve plexuses. . . . The proneness of children to acquire the disease is explained on the basis of a continuous growth and change in the skin in childhood and the special liability of the cutaneous nerve plexuses to damage." In a subsequent paper[3] he postulated that "The leprosy bacilli multiply in the axoplasm of the nerve fibers, enter the bodies of the Schwann cells and often remain dormant in that sheltered location for long periods of time. Under the stimulus of certain supervening changes . . . the bacilli begin to proliferate in the nerve fibers and appear in large numbers in the intercalated zones, from which they burst out into the endo- and perineural tissues. There they are taken up by histiocytes which gradually become transformed either into lepra cells or into epithelioid cells depending upon the immunological response of the host to the presence of leprosy bacilli." As far as we know these concepts have not been championed by others. Weddell[4] and Lumsden[5] have each been intrigued by the mechanisms of the neural affinity of *M. leprae*. In many ways their interest in the pathogenic role of the Schwann cell have been complementary and in opposition to Khanolkar's concept of the extension of *M. leprae* within the neural axon. Lumsden thus concluded "that the bulk of the bacillary spread and multiplication occur along the columns of Schwann cells enveloping the individual nerve fibers. . . ." With this viewpoint we are at variance.

Despite these studies, the term "neural affinity" is unexplained and, in-so-far as it implies some selective prediliction of the leprosy bacillus for any or all elements of the peripheral neural structures, may be misleading. Nerves are essentially fixed sign posts in the tissue and their associated Schwann cells are more fixed in location than wandering macrophages moving about in the tissues. It requires a considerable concentration of acid-fast organisms in a tissue before they can be detected by either light or electron microscopy. With their established frequency in Schwann cells, which are favorable for their accumulation and probably also their multiplication, it is not unreasonable that they will be found more readily in this location than in wandering macrophages. The latter need not, therefore, be regarded as less involved in the phagocytosis of these organisms than are the Schwann cells. The situation is somewhat akin to a hound ranging a field—he may do this rapidly and only relatively rarely find something of interest to him, whereas the same hound will almost invariably find any tree which is present and find something about that tree that interests him.

Khanolkar suggested that "from the point or points of entry in the skin the bacilli find their way anywhere under the epidermis, through the intercommunicating superficial lymphatic network." This may well be true and it is possible that this movement may be either transport of free organisms or transport through spaces by engulfing macrophages. In our own observations[6] we have often, in lepromatous leprosy, seen dilated endothelium lined spaces lying about and within the perineural fibers of small dermal nerves. Within these one occasionally finds acid-fast organisms in small numbers. The fact that these organisms can be found in this manner under light microscopy suggests that there may be a considerable number actually passing in these channels. Our interpretation has been that these are lymphatic spaces though, admittedly, it

2 Khanolkar, V. R. Perspectives in pathology of leprosy. Indian Jour. Med. Sc. *9* (1955, Supplement) 1-44.

3 Khanolkar, V. R. Diagnosis of leprosy, Lep. Rev. *32* (1961) 158-166. Reprinted from Triangle, the Sandoz Jour. of Med. Sc.

4 Weddell, A. G. M., Jamison, D. C., and Palmer, Elisabeth. Recent investigations into the sensory and neurohistological changes in leprosy. *In*: Leprosy in Theory and Practice, Eds. Cochrane, R. S. and Davey, T. F. Bristol: John Wright and Sons, Ltd. 1964, pp 205-220.

5 Lumsden, C. E. Leprosy and the Schwann cell in vivo and in vitro. Ibid. pp 211-250.

6 Skinsnes, O. K. Presented at Fifth Annual Leprosy Research Conference U.S. Japan Cooperative Med. Sc. Program. Boston, Mass. Apr. 24-26, 1970. Presently in manuscript.

is often difficult or impossible in histopathologic sections to differentiate lymphatics from small venous capillaries. These same nerves also show a pattern of bacillary distribution within their structure. Both this internal distribution pattern and the perineural lymphatic pattern of the presence of organisms is morphologically similar to the pattern of distribution seen when neoplastic cells show neural infiltration, as seen in instances of prostatic carcinoma and of pancreatic carcinomatous cells invading a neural plexus of the abdominal cavity. Similarly striking in analogy has been the pattern of mammary carcinoma cells infiltrating the large nerves of the brachial plexus.

We recall that many anatomists, including Abel,[7] hold that the only true lymphatics of nerve trunks lie outside the perineurium. Others have, however, postulasted the presence of lymph-containing spaces between the nerve fibers themselves whether or not such spaces are morphologically delineated by endothelial or other lining. The pattern seen in extensive peripheral nerve infiltration by neoplastic cells is consonant with this possibility. In a considerable number of ulnar and sciatic nerves, which we have examined by serial sections,[6] we have found a remarkably similar pattern of foam cell infiltration throughout the length of several such nerves and acid-fast organisms were demonstrated in some of these cells.

In a previous editorial,[8] we ventured to compare first and second infection types of tuberculosis with lepromatous and tuberculoid leprosy and suggested that in many ways lepromatous leprosy is immunopathologically the equivalent of an ongoing first infection type of disease, whereas tuberculoid leprosy, once cellular immunity and hypersensitivity is established, is immunopathologically akin to a second infection type of tuberculosis. It will be recalled that in tuberculous infection, during the period before the development of cellular immunity and hypersensitivity, there is lymphatic drainage of tubercle bacilli from the infected focus to adjacent lymph nodes and that severe progressive first infection tuberculosis is, in many instances, largely a lymph node disease. Once cellular immunity and hypersensitivity are established, this lymphatic bacillary passage ceases. By analogy, therefore, it may be that there is similar lymphatic passage and continual seeding of peripheral nerves by *M. leprae* in lepromatous leprosy as seems to be the case also with lymph nodes. It matters not if the formed lymphatic channels lie only in the perineurium, for if there be connecting interfibullary spaces with circulation of fluid there is opportunity for deeper nerve invasion by the bacilli. Schwann cells, being phagocytic, phagocytose any bacilli within reach. In this analogy, similar seeding in the tuberculoid leprosy would primarily be in association with initial lesions and occur, in all probability, only during that period of time that exists between infection and the establishment of cellular immunity and hypersensitivity. Lumsden postulates years or decades as being necessary for such cell passage of bacilli up the length of a peripheral nerve. In many patients it seems much more rapid than this and more consonant with possible lymphatic distribution. In tuberculoid leprosy this seeding would result in the neural presence of potential liberated *M. leprae* antigen and potential violent hypersensitivity reactions within these nerves. It is, of course, recognized that even if this hypothesis be valid, this is not the only way in which nerves are seeded by *M. leprae*. Bacillemia is a frequent and often an almost continuous process in lepromatous leprosy and probably occurs also, to varying degrees, in other forms of leprosy. This may well provide opportunity for neural localization of bacilli, most particularly in areas of *locus minoris resistentiae*.

If there be validity to this hypothesis—and we suggest that there are enough morphologic indications to warrant its consideration—then the situation exists whereby anatomical channels in low resistance hosts may allow leprosy bacilli to pass to nerves. Such low resistance hosts might be immunologically suppressed animals as well as any experimental animal found to be highly susceptible to infection by this organism,

[7] Abel, J. J., Hampil, B., and Jonas, A. F., Researches on tetanus, III Johns Hopkins Hosp. Bull. 56 (1935) 317-336.

[8] Skinsnes, O. K., "First Infection Type" Leprosy. Internat. J. Leprosy 37: pp 310-313 (Editorial)

possibly even armadillo number eight.

This discussion is not intended to vitiate the significance of neural involvement as a helpful criteria in determining whether or not the acid-fast organism causing infection in a given experimental animal is indeed *M. leprae*. It does suggest caution, however, in regarding this as an absolute criterion until such a time as the nature of a specific affinity of *M. leprae* for nerves be elucidated and demonstrated as unique, or until such a time as it is shown that markedly susceptible hosts, in the virtual absence of cellular immunity and hypersensitivity, will not, if given a dermal infection, seed their nerves with products of the inoculum either through lymphatic drainage or hemic perfusion. (O. K. Skinsnes)