TUBERCULOID CHANGES IN LEPROSY

III. THE PATHOLOGY OF A NERVE ABSCESS

By H. W. Waile, M.D.

From the Leonard Wood Memorial Laboratory
Calidn, Philippin Islands

Abscess of the nerve is a particularly interesting feature of leprosy in India, evidently being so much more frequent there than elsewhere as to constitute one of the regional peculiarities of the disease. The writer has never seen in the Philippines anything faintly resembling the lesions which, during a visit to the Dighapli Leprosy Hospital, Dr. Lowe kindly demonstrated to him as typical of the condition, and from which he supplied the specimens here described.

CLINICAL REPORTS

Muir, in 1924 (4), made what he believed was the first report of this condition from India. The case presented two enlargements in the median nerve above a skin area that showed sensory changes. One of them contained about 10 cc. of yellowish pus; the smaller one was emptied through it, the nerve between being hollow. The anesthesia immediately decreased and healing was uneventful. The pus contained no microorganisms and caused no infection in guinea-pigs. The author remarked that extreme swelling of the nerve often happens when no other sign of the disease can be found.

Lowe, in 1929 (4) and in a report concurrent with the present one (5) has summarized the condition as seen at Dighapli. Among some 5,000 cases of leprosy about 100, all males, had nerve abscesses. The rate, about 2 per cent, he believes would have been halved had potassium iodide not been used in treatment. The arm nerves are usually affected, commonly the ulnar, similarly lesions may be seen in the great auricular, the peroneals and elsewhere. Frequently the condition is multiple, this being more common in the cutaneous nerves than in the trunks. Once there were five small abscesses at two-inch intervals in a single nerve, and one patient over a period of years developed fourteen in various nerves. One type of abscess is within the nerve sheath, either localized or extending for two or three inches. This is firm, frequently very painful, the contents often under pressure. The other is produced by an internal abscess herniating through the sheath, connection with the nerve being maintained; it is usually well-encapsulated, not painful, sometimes quite large, occasionally adherent to the skin, and it may perforate. The contents is usually a turbid fluid and a white or slightly yellowish, semi-solid, cheesy substance, these containing leucocytes, lymphocytes and lepra cells. In about half of the cases bacilli were
found—few, usually short, perhaps "degenerated or dead." These lesions Lowe associates with high resistance and the milder forms of the disease, and often with lepra reaction. There is a local reaction in the nerve which does not entirely subside, and with repeated reactions an abscess is produced. In several cases the abscesses were the only symptoms; in many more there were evidences of skin leprosy but nerve lesions predominated.

These reports were made without referring to any other, but Henderson (2), who refers to the matter very briefly, mentions reports by Arning, Glück and Shiota. Klingmüller (3) pays the condition some attention—summarizing Lowe's clinical description, without any account of the pathology—and refers to several reports, the earliest being ascribed to Sellman, in 1869, though the first important one was by Arning, in 1898. The originals of these reports have not been seen by the writer.

MATERIAL EXAMINED

Several cases of this condition were seen during a visit at Dibpali. Clinically they corresponded to the descriptions summarized above. To demonstrate the material contained in them Lowe aspirated a fluctuating one. Smears of the thin turbid fluid showed no bacilli. There was considerable amorphous sediment with only moderately numerous leucocytes, chiefly polymorphonuclears.

Tissue for study was obtained from another case, an abscess of the internal cutaneous nerve. This was rather thick-walled and pale, ovoid, nearly an inch long in the direction of the nerve, adherent to the nerve but intimately related to it at only one point; it was in effect a pedunculated cyst continuous with an elongate cavitation in the nerve itself. These cavities contained some fluid material and a peculiar granulous, slightly yellowish substance which extended along the nerve trunk for a considerable distance in both directions. Smears were essentially like those from the other abscess.

The abscess wall was fixed in picric-formol, becoming curled in one direction. Dividing it across and embedding one piece on end gave a crescent section cut transversely to the axis (Fig. 1). The other piece, laid on the curled-down edge, gave longitudinal sections of these and transverse sections of the structures between them (Fig. 2). This was done in Zanzibar, where preliminary sections were obtained, including one stained for acid-fast bacilli which proved negative. Later, at Culion, numerous further sections were made and special stains employed.

MICROSCOPIC FINDINGS

Transverse sections (Fig. 1) might have been taken from the intestine, with its outer muscular and inner mucous layers each contributing about one-half. The longitudinal sections also (Fig. 2)

For this aid thanks are due Dr. H. C. Wiltshire of the public health laboratory in Zanzibar, and to the technical assistant of that laboratory.
seem so orderly as to suggest a functioning organ. Actually it is a tuberculoid granuloma, with no suggestion of nerve substance. Inside a laminated capsule (Fig. 3) is a narrow transitional zone, which in turn is the base for a predominantly epithelioid layer that is arranged in such relation to discrete, well-vascularized lymphoid foot as to appear as pseudo-villi (Fig. 4).

Capsular layer.—Inside a coarse layer of bland fibrous tissue the capsule is rather finely knitted. The strands are arranged horizontally to the surface in a crossed network that looks practically the same in all sections. It is well supplied with blood vessels from which arise large capillaries that cross abruptly to the inner layers (Figs. 5 and 6). Scattered lymphoid, plasma, and macrophage cells are present, and a few eosinophils. Occasionally are found sharply-localized because of epithelioid cells (Fig. 5), sometimes with a giant cell.

Intermediate zone.—In the narrow transition zone (Figs. 3 and 4) there is an increase in the leukocytic invasion, the fixed elements become less fibrous, and numerous capillaries push through to the lympho-epithelioid layer.

Lympho-epithelioid layer.—Most of the tissue here is in the form of papillate pseudo-villi, some cut vertically (Fig. 7), others transversely (Figs. 2 and 8). They are composed of (a) a central lymphoid focus, (b) an epithelioid zone that clothes the follicle and (c) upon this a layer of necrotic material.

The central follicles, usually showing shrinkage spaces, contain massed lymphoid cells and conspicuous straight capillaries streaming inward toward the cyst cavity (Fig. 9). No epithelioid or giant cells are found here and rarely any macrophages; plasma cells are found only at the periphery, where they are numerous (Fig. 11). Between the follicles the epithelioid layer dips down to the intermediate zone but is no wider than over the follicles because of necrosis.

The epithelioid layer (Fig. 10), strikingly uniform in width, is composed largely of epithelioid cells, sometimes collected in small whorls (Fig. 12); giant cells are present but rather scarce; mitotic figures (Fig. 11) are rare. Leuco- cytes are not numerous; the plasma cells are mostly confined to a narrow zone about the central follicle; macrophages occur throughout but are not abundant; and polymorphonuclears are mostly in the necrotic layer. Some of the spaces between the fixed elements appear as if they had contained droplets of lipid material. Occasionally is seen material suggestive of the cytoplasm of attenuated, finely-vacuolated lepra cells, and a few definite cells with such cytoplasm are found in the necrotic material.

Usually the necrotic layer is thin, evidently tending to diffuse into the fluid that had filled the abscess. However, between the villousities it is more abundant, often containing them, and it can be rather massive. In the process of necrosis, occurring at a fairly uniform distance from the capillaries, that produces the indentations or sulci that define the villousities.

Bacilli.—Sections stained for acid-fast bacilli have shown none.

DISCUSSION

This observation is apparently the first report of the pathology of the nerve abscess of India, which is seen there with a frequency...
that is strikingly in contrast with its apparent rarity elsewhere. If the present case is typical it would seem that the condition is predicated on tuberculoid changes, with which Klingmüller classes it. Further, it would seem to be another example of chronic lepra reaction in tuberculoid leprosy, a topic discussed in another paper of this series.

Comparatively little is known of the occurrence elsewhere than in India of tuberculoid changes in the nerves. From Henderson's finding of giant cells in cutaneous nerves (1) it would seem that these changes were not uncommon in his material. Muir and Chatterji (?) not only describe such changes—in non-technical terms and without specific designation—but put them forth as the typical lesion of the nerve in the cutis and subcutis. This, unacceptable as a general dictum for leprosy, indicates the frequency of such lesions in India.

Experience in the Philippines is in marked contrast. Except in tuberculoid lesions of the skin such changes in the nerve are rather a curiosity. In our own abundant autopsy material, including very many skin specimens with intradermal and often subdermal nerves, epithelioid foci in those structures have been found only very occasionally, and never in marked degree. This, of course, refers to cutaneous-type cases and secondary neural cases that had once been cutaneous, for bacteriologically negative cases are not isolated, but it demonstrates that such changes are not typical of the disease as a whole. Further, one is informed (1) that in primary neural cases in this country it is very seldom that palpation reveals enlarged cutaneous nerves leading even to tuberculoid macules.

This rarity of tuberculoid nerve changes is in line with experience with nerve abscess at Culion. The few cases that the writer has examined were of the ulnar at the elbow, very different clinically from the Indian nerve abscess and not tuberculoid. The material from them contained abundant bacilli; in it resembled that from the ordinary lepromata that break down as a result of lepra reaction, and differed from that found in the nerve abscesses of India as markedly as do the typical lepromata themselves from tuberculoid lesions. The contrasting experiences in India make it seem quite probable that tuberculoid changes constitute the basis of the abscesses that occur there. In view of the relation of the so-called tuberculoid variety of the disease to the neural type, there doubtless is significance in Lowe's statement that abscesses occur only in cases of the pure

*Dr. J. N. Rodriguez, in charge of the Cebu Skin Dispensary, personal communication.
nerve type, or of mixed type with neural signs predominating. From recent information one seriously questions whether these were really mixed cases; they may have been neural cases with active tuberculoid skin lesions taken to be lepromatous.

As for the genesis of the abscess condition, it seems evident that there is in operation some factor that is not a regular part of the leprosy process. Muir, in speculating as to the cause of the condition in his case, pointed out that if it were due either to special virulence of the organism (none of which could be found), or to low resistance of the host, more lesions would be expected; he wondered whether they could be caused by a non-acid-fast form of the bacillus. He had not then arrived at the highly hypothetical view (7) that the (tuberculoid) lesions of the nerve are due to a submicroscopic—"virus"—phase or form of the organism.

Lowe considers abscess formation associated with marked immunity, a method of localizing and overcoming the disease process, and explains it on the ground of incomplete subsidence and repetition of reaction. It would be difficult indeed to understand its occurrence in whatever form or phase of leprosy on any other basis, even if one were to accept the view of a submicroscopic agent as causative of the tuberculoid variety of lesion. Abscess formation can hardly be an ordinary, usual stage of the tuberculoid nerve lesion, for if that condition is as common as Muir and Chatterji indicate then abscesses would probably be even more frequent than they are, and there would be no reaction feature in their development. Why they seem to occur only in men is not evident.

Turning to the picture presented by the case described, the tuberculoid change is peculiar both in nature and degree. As for the latter, one may only speculate as to whether the active production of epithelioid tissue is evidence of a reaction condition, (8). Be that as it may, the lesion is organized to a degree unusual for a granuloma, and with its vascular lymphoid follicles and continuous maintenance of the epithelioid layer is quite different from anything heretofore seen in leprosy.

The necrotic process seems negative, or passive. It occurs only at a certain distance from the vascular centers of the villi, as if from simple lack of nutrition rather than from the effect of any positive or actively harmful factor. Also, the lesion enlarges by expansion and not by invasion of the surrounding tissues. Evidence
of exudation is definite but not marked; there is clearly a steady if moderate passing of polymorphonuclear leucocytes into the cavity.

The peculiar nature of the capsule—fine-fibered, crossed-structured and vascular—indicates its source to be the highly differentiated perineurium rather than the coarse, simple epineurium, which forms coarse cicatricial tissue. From this it follows that the original lesion itself is probably inside a single nerve cord or fascicle, as would be expected, and that the granulous material exposed at operation is inside a cord unless, and until, it has ruptured the perineurium and diffused into the epineurium.

The picture as a whole, as seen in our specimen, bespeaks a mild sustained stimulation or irritation by an infecting organism in some form or phase, but evidence is lacking as to what that is. In keeping with the pathology of this example, leprosy bacilli are not abundant in these abscesses when they are found at all, and in the present case, as stated, none were found in smears or sections. Muir sought for tubercle bacilli in his reported case by guinea-pig inoculation, with negative result. One would suggest on general principles that control procedures of this sort should be carried out in a series of cases. It may also be suggested that this material should be exceptionally useful for an attempt to demonstrate the existence of the hypothetical submicroscopic form or phase of the leprosy bacillus. On the whole it would seem that this feature of leprosy in India is worthy of further attention.

SUMMARY AND CONCLUSIONS

1. A description is given of the histopathology of a specimen of the peculiar chronic leprous nerve abscess of India, the frequency of which in that country—if not its occurrence at all—constitutes one of the regional peculiarities of the disease.

2. The tissue is a highly organized tuberculoid granuloma, with outer capsular and inner pseudo-villous layers. The latter consists of isolated, vascular lymphoid follicles clothed top and sides with a layer of proliferating tuberculoid tissue; necrosis of this occurring beyond a given distance produces villousities in a strikingly regular manner. The capsule is of comparatively finely-knit structure, well supplied with vessels; it apparently derived from the perineurium, indicating that the process arose within a nerve cord.

3. This finding, in view of the evident frequency of tuberculoid affection of the nerve in India, and on the other hand the non-
occurrence in the Philippines of abscess of this kind and the rarity and unimportance there of tuberculoid lesions of the nerve, indicates that the latter forms the basis of the former.

4. In view of the clinical features, and especially of Lowe's opinion that this abscess formation is a reaction condition and greatly increased in frequency by the use of potassium iodide, it is accepted as entirely probable that the condition is a manifestation of lepra reaction and, more specifically, of chronic, persistent lepra reaction in a tuberculoid lesion. The extensive epithelioid production is in keeping with findings in chronic reaction of tuberculoid skin lesions and is a further indication that that feature is characteristic of chronic reaction in lesions of that nature.

5. Leprosy bacilli were not found in this specimen, though Lowe found a few, apparently degenerated, in about half of his cases. However, though there is need of further control work, the causative agent is in all probability that of leprosy.

6. It is believed that these abscesses are worthy of further attention. It remains to be determined whether they are regularly tuberculoid and regularly associated with reaction. The fact that they are apparently limited to males involves an intriguing question. Finally, material from these lesions might prove of special value in an investigation of the hypothetical submicroscopic form or phase of the leprosy bacillus.

ACKNOWLEDGMENT

In indebtedness to Dr. John Lowe, formerly medical officer of the Diegpi Leprosy Hospital and now a leprosy research worker at the School of Tropical Medicine, Calcutta, for his courtesy in demonstrating this condition and for supplying the pathological material here described, is acknowledged with pleasure.

REFERENCES

FIG. 1. Section cut transversely to the axis of the curled, fixed specimen. Showing the differentiation of outer and inner portions, and the apparently folded or villus-like structure of the latter. X6.

FIG. 2. Section of tissue embedded on the curled-down edge, the capsule being cut longitudinally of the axis. The villi in the center are cut transversely, and those nearer the capsule obliquely; most of the former are cut beyond the lymphoid centers, which are evident in the others. X6.

FIG. 3. Low-magnification view of the capsule, showing the narrow outer cicatricial zone and the wide, loosely-knit vascular layer, evidently of perineural origin. Beyond it to the right is the cellular intermediate zone. (FIG. 4 is of the lower right-hand corner of this field. X40.

FIG. 4. Section of intermediate zone and the inner layer, with a lymphoid follicle of some size but without the usual shrinking effects. This villus is fairly well separated from the one above; it is less so from the one below (lower third of picture), but necrosis has occurred in a narrow zone there. X50.

FIG. 5. Detail of the outer portion of the capsular layer, showing both a large vessel and one of the lacunae of tuberculous tissue that occur here and there in this structure. X120.

FIG. 6. Detail of the inner portion of the capsular layer, showing its loose-knit, seemingly longitudinally-arranged structure and the conspicuous capillaries that cross it. (From the lower portion of field shown in Fig. 2.) X120.
An excellent example of the pseudovillus, with its vascular (and shrunken) central follicle, its uniformly wide epithelial nodal layer, and the necrosis that usually separates these structures. ×55.

Fig. 8. A transverse section of a villiity such as that shown in Fig. 7, cut well above the major part of the lymphoid center. (This structure can be identified in Fig. 5, central and quite separate from other elements.) ×40.

Fig. 9. One of the lymphoid centers, with its out-cursing capillaries, central focus of lymphoid cells, and zone of plasma cells between that and the epithelial layer. ×110.

Fig. 10. Outer portion of one of the smaller villiities, with the central lymphoid cells and long capillaries on the left, and the plasma-cell zone just beneath the epithelial layer. (Fig. 11 was taken from just below the point marked A.) Leucocyte accumulation in the necrotic material covering the villity is evident. ×110.

Fig. 11. Detail of the plasma-cell zone just beneath the epithelial layer. In the latter (at B) is to be seen a mitotic figure. (Taken from just below the point marked A in Fig. 10.) ×400.

Fig. 12. Detail of the epithelial layer showing one of the whorls seen occasionally, sometimes with a Langhans giant cell. ×220.