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ORIGINAL ARTICLES

LEPROUS NERVE LESIONS OF THE CUTIS AND SUBCUTIS

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SELECTION OF MATERIAL

Much of the study of the histopathology of leprosy in the past has been made from post-mortem material and from lesions of long duration. Hansen and Looft state in their monograph (2) "as a matter of fact we do not know the earliest symptoms of the disease", and this is evident from the descriptions given by them, though their account of the more advanced stages is most excellent.

For the present study all material was obtained by biopsy, patients being chosen with early advancing lesions. In the case of smaller macules we removed the whole of the clinically apparent lesion. When the macule was too large to remove entirely an elliptical piece of skin was excised from the margin along with surrounding, apparently normal skin. In each case as much subcutaneous tissue as possible was removed along with the skin. When thickened nerve branches were palpable in the subcutaneous tissue care was taken to excise these intact along with the skin.

The tissues were fixed in alcohol and sectioned from paraffin blocks. Some sections were stained with haematoxylin and eosin, and others by the Ziehl-Neelsen method to demonstrate *Mycobacterium leprae.*

Sections from a large number of cases were examined, but from these ten typical cases were chosen to illustrate the main points brought out by the study. In every case the history of the disease was inquired into carefully and a general and local examination was made, special care being taken to test and record the clinical features of the lesion chosen for histological examination.

NOTES ON SELECTED CASES

Case 1. Shek Nathni. The patient had noticed two macules on the front of his right forearm and one on his chin for one and one-half months. On examination the three macules were slightly and uniformly raised and erythematous. The one on the chin was not anesthetic when tested with a feather. Those on the forearm showed superficial anesthesia, deep analgesia and partial depilation. On the proximal side of each macule a thickened nerve could be palpated, dividing up into branches which apparently supplied the affected skin areas. No other lesions could be detected.

A piece of skin and nerve was removed from the more distal of the two arm macules in the following manner: A racket-shaped incision was made, the handle of the racket being over the thickened nerve and the loop taking in a portion of the anesthetic skin supplied by this nerve. The thickened nerve was first exposed and isolated from the surrounding fibrous tissue in a distal direction until it was seen to break up into branches (also thickened) which entered the skin. The top of the racket was then completed. It included an elliptic portion of the skin supplied by these branches, having its long axis continuous with that of the nerve. The skin and branching nerve were thus removed together.

Sections were made parallel to the long axis of the specimen. These stained with haematoxylin and eosin show in their deeper parts, lying in the subcutaneous tissue, two rows of circular or elliptical granular foci (Plate 1, fig. 1). These are the nerve branches in cross section, those in the deeper row being larger than those in the more superficial. These foci consist of large and small cells, more or less round, with sparsely interspersed fibers. Their margins are clearly defined from the surrounding subcutaneous tissue. They show large numbers of the bodies generally known as multinuclear or giant cells. The more superficial and smaller nerve branches are those which supply the skin nearer to the part sectioned; the deeper and larger branches after subdividing supply more distant skin.

Still more superficially, in the corium itself, are seen sections of thickened cords passing upwards perpendicularly or obliquely towards the surface. Their structure is similar to the horizontal nerve branches in the subcutaneous tissue. As they pass upwards they subdivide into smaller branches. Some of these surround the sweat glands and hair follicles and spread out horizontally a short distance from the surface, sending up finer but more numerous shoots, which run along parallel to the epithelium in the subpapillary layer of the corium. From these again finer branches pass into the papillae. In the intradermal cords giant cells are found similar to those in the subcutaneous nerve branches.

Sections stained by the ordinary Ziehl-Neelsen method fail to show acid-fast organisms. Using a modification of this method two bacilli were found.

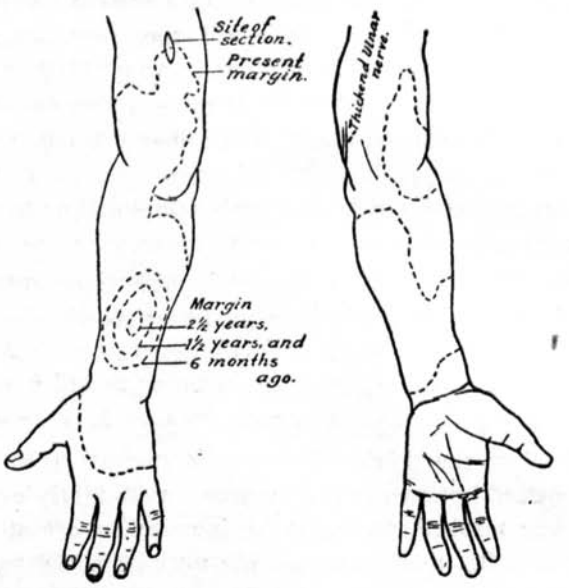
Case 2. Panchnan Mandal, aged 19. The only lesion found in this patient was a patch occupying the larger part of the front of the lower half of the thigh. This patch was not raised above the surrounding skin, but was hypopigmented and slightly erythematous. Depilation was marked, the hairs having broken off at the mouths of the hair follicles, the latter showing up as black dots. Keratosis and anhydrosis were marked, giving the skin a dry, rough feeling on passing the finger over it. Both superficial anesthesia and deep analgesia were present. No thickened nerve could be palpated. An elliptical piece of skin was removed from the upper margin of the lesion; it included a portion of apparently healthy skin beyond the lesion.

Sections show a thickened granular cord entering the corium from below and dividing into branches, some of which embrace a sweat gland. This cord is similar in appearance to those described under Case 1. Sections stained by the Ziehl-Neelsen method fail to show any acid-fast organisms.

Case 3. Montaz Halder, aged 55. This patient showed two lesions, one on each arm. The larger of the two occupied the greater part of his left arm, as shown in Text-fig. 1.

One of the important points of interest in this case was the history of the growth of this lesion, as elicited from the patient. Two and a half years previously he had noticed a small, anesthetic patch on the back of his forearm. During the subsequent two years this had increased slowly in size, as shown in the diagram. But during

the last six months the lesion had grown rapidly covering the greater part of both the front and back of the arm. The size when examined was as shown by the outer dotted line in the figure.



Text-fig. 1—*Case 3, showing lesion on left arm.*

The whole macule appeared to be slightly raised above the level of the surrounding skin, but the margin was still more raised, and was erythematous. Depilation and anhydrosis were marked over the whole lesion. The ulnar nerve was thickened and slightly tender on pressure. Superficial anesthesia and deep analgesia extended over the entire macule. An elliptical piece of skin was removed from the upper spreading margin, including apparently normal as well as affected skin.

Sections show thick granulomatous cords, occupying the deeper parts of the corium, similar to those described in Cases 1 and 2. Here, however, the whole of the papillary and subpapillary areas show a solid mass of granuloma. Both the deeper cords and the superficial granuloma show numerous large and small giant cells. Sections stained by the Ziehl-Neelsen method fail to show any acid-fast organisms.

Case 4. A. L. Nath, aged 67. This patient, a man of education and intelligence, had apparently had anesthetic patches over

his elbows for some considerable time but they had not particularly attracted his attention until, a month before he came for consultation, they had become raised and erythematous. At the same time numerous small circular red macules appeared all over the body, along with a red anesthetic patch extending over the big toe and inner side of the dorsum of the left foot. An elliptical piece of skin, including a small macule 5 mm. in diameter, was excised from the forearm. This macule had shown deep analgesia but not superficial anesthesia.

Preparations show sections of granulomatous cords, with clearly defined margins, but thinner than those described under the previous cases. These cords contain giant cells. Some of them are almost as superficial as the subpapillary layer (Plate 2, fig. 1).

Sections stained by the Ziehl-Neelsen method show acid-fast rods lying on the endothelial cells of the capillaries which pass between the cords (Plate 2, fig. 2). The rods are absent, however, from the cords themselves. As many as 10 or 12 of these organisms can be found in some fields; they occur singly, not in clumps.

Case 5. Samara Ram, aged 40. This patient showed numerous macules all over the body. He had attended the dispensary for treatment some 8 years ago, then, considering himself cured, he had stopped coming. It was only when there was a considerable exacerbation of the disease that he returned. The patches were hypopigmented and slightly erythematous; superficial anesthesia was absent but deep analgesia was present. Scrapings from the sides of deep incision in several of the lesions failed to show any acid-fast rods. An elliptical piece of skin was removed from the centre of one of the lesions on the back.

Sections show branching cords in the corium similar to those described in the first three cases, but no giant cells are found. Sections stained by the Ziehl-Neelsen method show no signs of *M. leprae* in the superficial parts of the skin. Inside the deeper cords, however, acid-fast rods are found, two or more in every field.

Case 6. Lohar, aged 25. This patient had noticed patches on his arm for two and one-half years. At the time of examination the whole of the back of the right forearm was ocupied by two macules separated from each other by a space of about 4 centimeters. They showed hypopigmentation, erythema, thickening and very marked keratosis. Both the macules and the intervening skin showed super-

ficial anesthesia and deep analgesia. An elliptical portion of skin and subcutaneous tissue was removed by biopsy from the area between the two macules. Sections show thickened cords, chiefly in the subcutis, but also to a less extent in the cutis. These cords contain abundant giant cells, and there is also necrosis in the centre of the thickest of them (Plates 3 and 4). No acid-fast rods are found in Ziehl-Neelsen sections.

Case 7. Naina, aged 26. This patient showed on his left buttock a round, superficially anesthetic area, hyper- rather than hypopigmented but surrounded by a much larger hypopigmented area without superficial anesthesia. The former dated from sixteen months before. The latter had appeared 12 months before, along with numerous small round patches in different parts of the surface of the body. These small patches were also hypopigmented but lacked superficial anesthesia. An elliptical piece of apparently healthy skin, including part of one of the small patches, was taken from the back.

Sections show no sign of disease in the deeper parts of the corium around the sweat-glands or hair follicles, but in the subpapillary layer granulomatous changes are noted around some of the capillaries of the vascular plexus. This granulomatous thickening extends to the vascular branches passing up from this plexus into the papillae.

Sections stained by the Ziehl-Neelsen method show acid-fast rods singly, in pairs and in small clumps in the papillary and subpapillary layers, lying on the endothelial cells of the capillaries.

Case 8. Dhiren, aged 22. This patient was treated as a case of ichthyosis for a considerable time in the skin clinic before an anesthetic area was noticed on his ankle and he was sent to the leprosy clinic. There was nothing in the outward appearance to suggest that the patient was suffering from leprosy, but a diagnosis was made on the ground of the anesthesia. However, routine examination showed large numbers of acid-fast rods in both the nose and the skin. Sections taken from the skin confirmed this and showed acid-fast rods, not only in the corium but also among the epithelial cells and even on the superficial scales of the epithelium. This case has been described in full by us elsewhere (Muir and Chatterji, 1932).

Sections show areas of granuloma around blood vessels. The main part of the section is occupied by normal dermal tissue, which is interspersed with small, diffuse, granulomatous areas which have

not the clear-cut margin of the cords described in the first six and last two cases of this series. There is nothing whatever resembling these cords in the deeper parts of the corium.

Sections stained by the Ziehl-Neelsen method show very clearly that the bacillary invasion is along the line of the blood vessels, some of which stand out as clearly as if they had been injected artificially with a suspension of acid-fast organisms.

Case 9. Mrinal, aged 14. A flat anesthetic patch had been noticed on the front of the patient's left forearm for six months, when it suddenly became raised and erythematous. On examination we palpated a thickened branch of the medial cutaneous nerve passing to the lesions. An elliptical piece of skin and subcutaneous tissue was removed from the centre of the macule. Sections show a nerve branch entering the cutis from below (Plate 1, fig. 2), and similar cord sections throughout the whole thickness of the cutis. The smaller and more superficial cord sections are shown better in Plate 1, fig. 3. No acid-fast rods were found.

Case 10. Abdur Rahaman, aged 32. The patient gave a history of having first noticed a thickening of the ulnar nerve 2 years ago. On examination a patch was found occupying the medial aspect of the forearm. This lesion was not at all conspicuous clinically, showing only slight hypopigmentation and slight depilation. There was no erythema and it was not raised above the surrounding skin. Superficial and deep anesthesia were marked. The fourth and fifth fingers were not affected. The medial cutaneous nerve of the forearm and the ulnar were both thickened.

Sections show thickened nerve cords with abundant giant cells both in the cutis and the subcutis (Plate 5, figs. 1 and 2). No acid-fast rods were found.

DISCUSSION

Eight of the ten cases, viz. Nos. 1 to 6, and 9 and 10, are described as showing neural lesions. Cases 7 and 8 have been included to show by contrast the features of non-neural, or what is commonly known as *cutaneous,* leprosy. Three main features of the lesions of intradermal and subcutaneous nerve leprosy have been brought out by this study: (1) The appearance of granulomatous cords in the subcutaneous tissue and corium, which divide into finer and finer branches as they approach the surface. (2) The presence in these cords and their branches of giant cell formation and occasionally

of necrosis, caseation and abscess formation. (3) The complete absence or comparative sparseness of acid-fast organisms in these granular cords.

MACULES OF NEURAL LEPROSY

In some parts of India one of the commonest forms of early leprosy is distinctly neural in type. Clinically the lesions are in the form of macules (and sometimes papules) which show certain distinct characteristics, such as superficial anesthesia (negative response to light touch), diminished sense of pain and heat and cold, keratosis, anhydrosis and depilation. The macule is sometimes flat and sometimes distinctly raised above the surrounding skin; but perhaps the commonest form is that with a raised margin and flat centre. Hypopigmentation is generally present, though the centre may show hyperpigmentation. Erythema, either of the margin or of the whole lesion, is a common accompaniment. The lesions vary in size from a small pin-head papule to a macule one or one and a half feet in diameter. The larger lesion is formed by the gradual radial extension of an originally small macule, or by the coalescense of two or more of such spreading macules. Only one lesion may be present, or they may be multiple, covering sometimes half the surface of the body. Not infrequently, a thickened nerve branch can be palpated passing to the macule; this sometimes, but not always, can be traced to a thickened main nerve.

Formerly this type of lesion was looked upon by us as comparatively rare. It gives little or no distress to the patient and, except when appearing on the face, is easily hidden from view. Many patients are unaware of its nature and do not seek medical advice; others hold back because of fear of the consequences of its recognition. But as the result of the popularization of anti-leprosy treatment, this type of lesion has been becoming more and more familiar at leprosy clinics. At the clinic of the Calcutta School of Tropical Medicine on a recent date, of 34 new cases of leprosy presenting themselves for diagnosis, 17, or 50 per cent, belonged to this type.

The granular cords.—On examination of sections stained with haematoxylin and eosin the corium is found to be made up chiefly of two elements: (a) normal areas consisting chiefly of the usual collagenous fibres, and (b) areas round or elongated in shape that are composed of large and small round cells, with a few capillary vessels and attenuated collagenous fibres interspersed. These gra-

nular areas vary in size; the larger ones are in the subcutaneous and deeper dermal layers, while towards the surface they become smaller. The proportion of the corium occupied by granular areas to that occupied by collagenous fibres varies in different lesions. In some only a few granular areas are found, while in others they form almost the whole of the corium, the collagenous fibres filling only the interstices between large granular masses. In various lesions the proportion varies between these extremes.

Previous writers have given different names to these granular areas, according to the theories that they have held regarding their origin. The commonest name given to them is *follicle* (Henderson, (1), under the supposition that they are rounded, separate foci similar to those found in tuberculosis. Serial sections, however, show that these areas are connected with one another, and that the appearance of isolated foci is a fallacious one. We have, in fact, a network of branching cords both in the subcutis and in the corium, which are thicker in the deeper layers and become finer as they proceed towards the surface. Hence the term *cord*, used by Unna (12) and by Hansen and Looft (2), is much more appropriate than *follicle*.

Serially cut sections also show that these cords are continuous with the thickened nerve branches which we have mentioned above. Therefore, little doubt can remain that in early neural leprosy we have a lesion of the peripheral nerves and their branches, the thinner bundles in the subcutis and cutis as far as the termination of the connective tissue sheath being affected in the same way as the main nerves.

A striking phenomenon is the clear-cut edge of the cords, beyond which the collagenous fibres are not invaded. These fibres, at least below the subpapillary layer of the corium, become gradually eliminated not by invasion but by pressure. As more and more of the nerve bundles become granulomatous, and as the affected bundles increase in diameter and exert pressure on the surrounding healthy tissue, the area occupied by the collagenous fibres gradually shrinks in size.

The relation of the cords to the epithelial appendages in the corium has also to be noted. It is well known that the cutaneous nerves, as they divide and pass upwards in the corium, give off branches to supply the oil glands and ducts, and the sebaceous glands and hair follicles; these branches form a fine network round these

various organs. When they become affected they form a granulomatous sheath around these organs, interfering with their function and often causing their destruction. Thus we have the appearance of more or less disintegrated sweat gland acini and hair follicles lying in the midst of, or in approximation to, many of the cords.

The condition in the papillae and subpapillary layer of the corium also requires special description. At first the round cell infiltration in the papillae is less clear-cut and more diffuse than in the larger cords, though the connection of this granuloma can be traced to the finer cords of the subpapillary stratum. As the condition advances, however, the granular units in these two layers coalesce and form a solid mass of round-cell infiltration, with only an interspersion of capillaries and finer collagenous fibres.

Giant cells.—The second phenomenon noticed in our study is the presence in the granulomatous cords of bodies similar to those described as giant cells in chronic tuberculous lesions. As we can find no difference in appearance between these bodies in leprosy and in tuberculosis we shall call them giant cells in this description. Along with the presence of these cells we have sometimes (as in Case 6), the formation of necrosis. This latter phenomenon occurs more commonly in the larger cords, especially in those of the subcutis. The centre of the cord is more likely to be affected than the periphery. Giant cells are similarly found in the larger thickened nerves; and in these the process goes on not only to necrosis, but also to caseation and cold abscess formation (8, 5).

We have thus in this type of leprous lesion a series of phenomena very similar to those found in chronic tuberculosis, viz., granuloma, giant-cell-formation, necrosis, caseation and cold abscess. It is on account of this that many writers term these lesions *tuberculoid* (3, 5, 11, 13). Apparently, however, we have this difference that whereas these pathological changes are found in many different forms of tissue in tuberculosis, in leprosy they are confined to nerves. So far we have failed to find the formation of typical giant cells except in leprous lesions of peripherial nerves and of their branches in the cutis and subcutis; nor are we aware of any description in the literature of leprosy which should lead us to change this view. We therefore prefer not to use the term tuberculoid.

Some of the older writers have denied the existence of giant cells and caseation in leprosy. Hansen and Looft (2) state:

"In the many, we can truthfully say thousands of preparations of leprous affections which we have had under the microscope, we have never seen either a typical giant cell with marginal nuclei or caseous degeneration. There are indeed multinucleated cells in the lepromata, but never giant cells like those of tubercle."

Obviously these writers, as they themselves state, did not know the earliest signs of the disease. Later in the same work they state:

"In connection with the presence of giant cells in leprous products, we may note that we have received from two foreign colleagues preparations in which they believed giant cells to be present. But we have found on careful examination of the preparations that they were cross and oblique sections of blood vessels, which with their endothelial nuclei gave the impression of giant cells. Without the use of a homogeneous immersion lens it was impossible to make a definite distinction."

We ourselves are familiar with this appearance, and in these lesions frequently have noticed what were obviously sections of vessels side by side with typical giant cells. We think it not at all unlikely that the apparent arrangement of the nuclei of the giant cells in leprosy is due to the endothelial cells of obliterated capillaries and that this obliteration is to a certain extent connected with the necrosis formation.

It may be a subject for discussion whether the giant cells of leprosy are formed in the same way as those of tuberculosis; but there can be no doubt of the existence of the more advanced stages of caseation and abscess-formation of the nerves in leprosy.

Generally speaking, it may be stated that the thicker the cords in the subcutaneous tissue and corium the more numerous and well formed are the giant cells, and the more likely is the process to go on to necrosis. In certain lesions of this type, however, giant cells either are not present in the cords or they are so few in number that they are not found on examination of a series of sections.

Giant cells are found in the subpapillary layer (Plate 4, fig. 2) but we have so far failed to find them actually inside the papillae. There is reason to believe that the presence of a giant cell in any leprous lesion shows that the part affected is a nerve origin.

So far we have used the word "nerve" in its general sense. There is no reason to believe, however, that the actual nerve fibres are primarily affected. It is the connective tissue sheath consisting of epineurium, perineurium and endoneurium which is actually attacked by the infection. The nerve fibres suffer secondarily, chiefly because of pressure.

The lesions of the skin found in neurofibroma resemble in some respects those of early nerve leprosy. In both we have a hyperplasia of the connective tissue of nerve branches in the cutis and subcutis, causing pressure atrophy of the normal cells and fibres. In both the epithelial projections into the cutis (hair follicles, sweat glands, etc.) are engulfed by the new growth. The difference is that neurofibroma is not inflammatory; the new fibrous tissue formed does not contract, and therefore does not destroy either the nerve fibres or the epithelial projections. In the neuro-granuloma of leprosy we have a chronic inflammatory process, followed by contraction of newly formed fibrous tissue, and both of these cause blocking and, to a large extent, destruction of the nerve fibres, and the epithelial projections. Thus we have changes in sensation, anhydrosis, depilation and keratosis in neuroleprosy but not in neurofibroma.

In this paper we have refrained from discussing the origin of the various types of cells found in the leprous granuloma, and the methods by which that granuloma resolves later on, either naturally or as the result of treatment. Observations on these matters were made in the course of our study, but we consider them beyond our present scope.

Bacilli.—The third observation brought out by our study is the complete absence or comparative sparseness of acid-fast organisms in the subcutaneous and intradermal cords described above. In Cases 2, 3, 6, 9 and 10 repeated examination of sections stained by the Ziehl-Neelsen method failed to show any acid-fast organism. In Case 1 repeated examination revealed only a few bacilli. In Case 4 no bacilli were found in the cords, but a considerable number were found in the walls of the vessels between the cords. Only in Case 5 were acid-fasts found in any number in the cords, and these only in the deeper cords. In fact, it may be stated that the greater the proportion of a section occupied by the nerve cords, and the larger and more numerous the giant cells, the less likelihood is there of finding acid-fast bacilli.

If we compare the first six and last two cases with the seventh and eighth, the contrast in this respect between nerve and skin leprosy is brought out. In Case 7 we find only slight granular thickening of the vessels in the papillary and sub-papillary layers; haematoxylin and eosin sections show us no other abnormality. Yet Ziehl-Neelsen sections show bacilli in abundance, both singly and in clumps, in the

superficial layers of the corium. In Case 8 bacilli are in such abundance that they are found in superficial scrapings of the epithelium; yet the clinical signs were far less, and the granulomatous change was less marked than in Case 2, which shows no bacilli.

Various theories have been put forward for explaining this incongruity:

(a). It has been suggested that the absence or sparseness of bacilli is due to the greater resistance of the tissues in cases like Number 3. It has been stated that bacilli are present to begin with, but are destroyed by the tissue reaction. It is difficult to fit this theory into the facts of Case 3. There we had a small lesion beginning two and one-half years ago. During the first two years it spread slowly; but during the last six months it had increased rapidly in size (Text-fig. 1) and was still spreading at the time of examination. According to this theory living organisms might have been destroyed in the centre, but they would surely have been found at the spreading margin or possibly just beyond the visible margin. The skin examined included the margin and beyond, yet bacilli were not found. Moreover, if the causal organisms had been destroyed in the centre, the clinical signs should have disappeared or begun to disappear from the centre; but we found the whole lesion swollen and erythematous, obviously still active.

(b). A second theory is that such lesions are caused not by bacilli present in the lesion itself but by toxins set free by bacilli in some distant focus in the body. Lesions of this nature, classified as tuberculides, are found in tuberculosis, and on this assumption it has been suggested by some writers that leprous lesions of this type should be called *leprides*. A tuberculide is described by MacKenna (6) as follows:

> "Some hold that they are due to the action of tubercular toxins; others that they are caused by a local tissue reaction, set up by the presence of dead or attenuated tubercle bacilli. Clinically the members of the group have certain common features. The lesions may occur symmetrically or asymmetrically; they tend to be disseminated and to come out in crops without any febrile accompaniment. They are prone to break down, but do not tend to spread progressively."

Obviously therefore this theory is not applicable to a gradually spreading lesion like that in Case 3.

(c). A third theory is that the disease is due to bacilli present in the larger nerves; that, though acid-fast organisms are not found

in the skin lesion, they are present in the corresponding main nerve, and that the changes in the skin are vasculo-trophic and due indirectly to the disease in the nerves. This theory is put forward without consideration of the proposition discussed above, that the granulomatous cords found in the corium are actually cross sections of thickened nerve branches. These intradermal branches are continuous with the subcutaneous branches, and through them with the main nerves themselves. Very frequently the subcutaneous branches are palpably far more thickened than the main nerves, and bacilli are as frequently absent from the main nerves as they are from the cords of the subcutis.

(d). A fourth explanation is that acid-fast bacilli are really present, though in small numbers, and that improved methods of staining and more care in examination would reveal them. This we are willing to admit may be so in many cases. Indeed, in Case 1 bacilli were not found at first, but two were found on special staining and repeated examination. We hold, however, that this does not explain the discrepancy between the much more marked granuloma with few or no bacilli found in Cases 1, 2, 3, 6, 9 and 10, compared with the many bacilli and less granuloma found in Cases 7 and 8. If it is suggested that bacilli are found in rapidly spreading lesions and are not found in slow-growing lesions, we would reply that in Case 3 the spread of the lesion was more rapid during the last six months than it is in many lesions where bacilli are found in abundance.

(e). Not being satisfied with the four explanations mentioned above, we propound another theory which, though at present impossible of direct proof, yet seems to us to be supported by indirect evidence. Since Hansen discovered the acid-fast rod which is associated with his name, it has been usually considered as the one and only causal organism of leprosy. Our hypothesis is that in early nerve leprosy the causal germ is one which so far has been microscopically invisible or unrecognized; that it is a living germ or virus which has a predilection for the connective tissue of peripheral nerves; that, under certain circumstances generally associated with lowering of the general health of the patient, it can become transformed into the well-known acid-fast rod of Hansen; that it is closely associated with the formation of giant cells, necrosis, caseation and cold abscesses.

According to our theory the granulomatous cords, present in all the cases except 7 and 8, were due to this form of *M. leprae.*

In Case 1 there probably had been for some considerable time a nerve lesion of the arm, which the patient had not noticed. Six weeks before he appeared for examination, there had been an exacerbation of the disease due to lowering of his health, and it was only then that the condition attracted his attention for the first time. This exacerbation was associated with the formation of a very few acid-fast bacilli.

Similarly, in Case 4 anesthetic patches over the elbows had been noticed for some considerable time. It was only when, one month before appearing for examination, his general health became bad and an acute exacerbation occurred, with the swelling up of old patches and the appearance of new ones, that he realised that anything serious was wrong. The exacerbation was accompanied by the appearance of acid-fast bacilli, not in the cords but in the capillaries running between the cords.

We may also suppose that in Case 5 bacilli appeared after a recent acute exacerbation in which new lesions had become visible. In this case the bacilli were found in the deeper cords.

In Cases 1, 4 and 5, according to our hypothesis, the granulomatous cords in the cutis and subcutis were the result of infection of the nerves with the unrecognized neurophilic form of *M. leprae,* and the acid-fast rods were formed from the virus at a later date.

The condition described above was well known to Unna (12), who has accurately described the thick cords in the cutis and subcutis. The presence of bacilli occurring in and between the cords was, however, explained by him as caused by re-embolism. The sites of old lesions were supposed to be less resistant to blood-borne infection than healthy skin, the former retaining and the latter destroying the embolised bacilli. Unna's theory was supported by the fact that fresh lesions often appear in other parts of the skin suddenly, and simultaneously with the appearance of acid-fast rods in old lesions of the cutaneous nerve cord type.

These new lesions may be due to bacillary embolism, but we have frequently noticed that flat, scarcely noticeable lesions will suddenly become raised and erythematous, and yet on careful microscopic examination of sections we have failed to find in them any trace of acid-fast rods. Therefore we are inclined to think that this

apparent exacerbation, though often accompanied by an increase of bacilli or by their first appearance in a lesion, is due not to re-embolism but possibly to an allergic condition dependent on the general condition of the patient.

As we have mentioned above, we can put forward no direct proof of this neurophilic virus. We can only speculate as to its nature. Obviously, it must be a small size or else it surely would have been demonstrated microscopically.

The difficulties connected with the cultivation of *M. leprae* in vitro and its successful inoculation in experimental animals make it very difficult to demonstrate whether there is a filtrable form of the organism. Markianos (7) claims to have obtained a living, active, filtrable form of *M. leprae muris* which has reproduced rat leprosy in rats.

Similar results were obtained at the Calcutta School of Tropical Medicine with first experiments; but we had reason to doubt the integrity of our filters; and a series of filtrations with L5 Chamberland filter candles gave uniformly negative results. Candles of this size have, however, a very fine bore; we are at present conducting careful experiments with candles of various sized bores with a view to finding out the size of the filtrable virus of rat leprosy, if such an organism actually exists. The demonstration of the existence of this virus in rat leprosy, while it would not prove that there is a similar virus in human leprosy, would at least be of considerable confirmatory value.

We have also the possible analogy of a filtrable virus in tuberculosis, the existence of which is claimed by some but still requires further confirmation. For references see the work of Sanarelli and Allessandrini (10).

There are two different types of granules found on examination of *M. leprae*: (a) Those formed by partial staining of the rods, and which are commonly associated with the name of Much, who first described them. These generally are held to be associated with degeneration or destruction of the rods. (b) Lutz particles, which are round, spore-like bodies, their diameter being two or three times the breadth of the rods. They take on a very dark stain in Ziehl-Neelsen preparations. They generally appear at the end or in the centre of a red-coloured rod, but they also appear with only the rudiments of a rod or entirely isolated. Lutz particles often are found in

as many as 50 per cent of bacilli in lesions (as in Cases 4 and 5) in which bacilli are few in number and in which clinical and microscopic evidence points to a recent exacerbation. The question occurs as to whether the Lutz particle is an intermediate form between the unknown neurophil virus and the acid-fast rod.

Another question of importance raised by our hypothesis is the path of entrance of the virus into the nerves. Are the main nerves invaded primarily and the cutaneous nerves secondarily, or does the infection first enter the nerve terminals in the skin and then spread collaterally through the cutaneous and subcutaneous communications, at the same time finding its way up into the main nerves? The results of our study favour the latter view. In the earliest lesions we frequently find considerable palpable thickening of small dermal branches, while the corresponding main nerve (such as the ulnar above the elbow) shows no sign of thickening. In one interesting case there was, on the back of the hand, thickening of branches of the ulnar and radial nerves and of a communication branch between the two. The patient had a clearly defined anesthetic patch on the back of the hand, but no other lesion was found in the body. It is more reasonable to suppose that the infection entered the nerves through their dermal endings and spread collaterally and proximally, than that it primarily entered two neighbouring main nerve branches and from them spread to their cutaneous branches. This question is also discussed by one of us elsewhere (9).

The question of how the infection first reaches the skin cannot be discussed here at length. The probabilities are that this takes place by vascular embolism, and in some cases by local inoculation through the epithelium.

We frequently have found thickening of the ulnar nerve above the elbow in cases in which there was apparently no other clinical sign of leprosy; but careful examination has revealed some small, limited area of anesthesia, sections of which have shown the presence of established local disease. We are inclined to consider, therefore, that nerve leprosy is generally, if not always, a dermal infection with collateral and proximal spread.

Around the margin of a spreading macule it is common to find papules surrounded by apparently healthy skin. Sections of skin and subcutaneous tissue including these papules show thickened granulomatous cords in the subcutis which send up branch cords to the

surface. The collateral spread of leprosy in these cases is therefore largely in the subcutaneous nerve plexus; it may be compared to the growth of certain plants like the sweet potato, which extend their corms at a certain level below the ground, sending up shoots at intervals to the surface.

If our theory concerning the neurophilic virus is correct, current views regarding the transmission of leprosy may have to be revised. But it does not seem likely that such a virus, if it is confined to the nerves, will easily find its way from one host to another. Moreover, the experience of most leprosy workers is that the cause of the spread of infection is the advanced cutaneous case with bacillus-laden nasal discharge and ulcerating nodules.

Lastly, our hypothesis, if adopted, possibly will call for some revision of the clinical classification and terminology adopted at the recent Leonard Wood Memorial Conference in the Philippines; as it is difficult to classify this type of case according to the definitions laid down there. It is difficult to speak of *leproma* in, say, Case 7, an obvious cutaneous case, and to exclude that term in Case 3, an obvious neural case. If the word *open* is used to define those cases in which acid-fast rods are found in the skin or nasal mucosa, is this term to be applied alike to Case 4 in which these rods were found only in the cutaneous nerve cords and in other cases in which bacilli can be found only in subcutaneous cords or in the main nerves? It is unfortunate that the term *cutaneous* should have to be used to the exclusion of cases like Nos. 2 and 3, in which such gross (albeit neural) lesions of the skin are present.

We may mention incidentally that we can find no fundamental difference between the cytology of the well-established nodule of skin leprosy and that of the cord in the neural macule. In a haematoxylin and eosin section, apart from the presence of giant cells in the dermal nerve cord, it is difficult to distinguish the one type of lesion from the other by means of the cells alone; though the presence of the cords with their clearly defined margins makes the difference clear. In both we have a chronic inflammatory granuloma.

SUMMARY

1. It is sought to demonstrate in this paper that the early leprous nerve lesions, common in India and other countries, are caused by thickened granulomatous nerve cords found in the cutis and subcutaneous tissue.

2. These cords are continuous with the thickened main nerves and branches often palpable in these cases.

3. Giant cells, and frequently necrosis, caseation and cold abscess-formation are found, probably exclusively, in these nerve lesions.

4. The acid-fast rods of Hansen, because of their absence or scarcity in many of these nerve lesions, cannot be regarded as the only, or even the principal, form of the causal organism.

5. A hypothesis is put forward that there is a minute form of *M. leprae,* which has not yet been recognized microscopically, and that that this germ is the usual cause of at least early nerve lesions.

6. The nature of this virus, and and the possibility of its being filtrable, are discussed, an analogy being drawn to filtrable forms of virus in rat leprosy and tuberculosis, which certain workers claim to have demonstrated.

7. The mode of entrance of this germ into the nerves is discussed. Intradermal infection of nerve endings, with collateral spread in the cutis and subcutis, and proximal spread to the main nerves, is considered the most probable.

8. Mention is made of the possible need of reconsideration of (a) the present theories regarding the spread of infection, and (b) the existing terminology used in defining cases of lesions of leprosy.

The investigation on which this paper is based has been carried on under the Governing Body of the Calcutta School of Tropical Medicine and Hygiene and the Indian Research Fund Association, to both of which we express our thanks. We wish also to acknowledge the excellent work of Mr. S. Ghosh, technician of this department, who was responsible for the preparation of sections.[1]

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[1] The drawings reproduced in the plates accompanying this article are signed Mullick in such a way that the signatures do not appear in the reproductions.—*Editor.*

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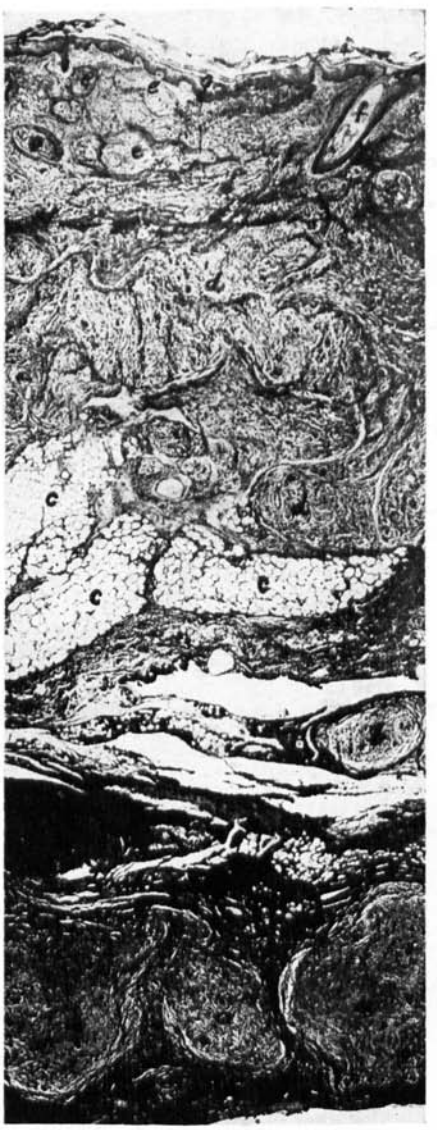
DESCRIPTION OF PLATES

Note—Both figures in Plate 2 and Fig. 1 in Plate 4 are reproductions of colored drawings.

PLATE 1

FIG. 1. Photomicrograph illustrating Case No. 1. Area marked *a*, large, and *b*, smaller thickened nerve cords in subcutis; *c*, fat cells; *d*, large thickened cords in cutis; *e*, smaller cords in subpapillary layer; *f*, hair follicle; *g*, flattened epithelium.

FIGS. 2 and 3. Photomicrographs illustrating Case No. 9, the latter showing the more superficial cords. Areas marked *a*, larger thickened nerve cords in cutis and subcutis; *b*, finer branches in cutis; *c*, fine granulomatous branch in papilla.



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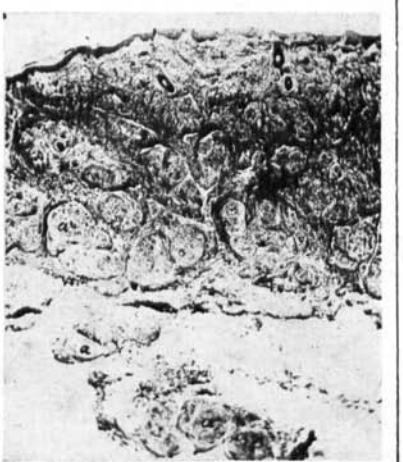

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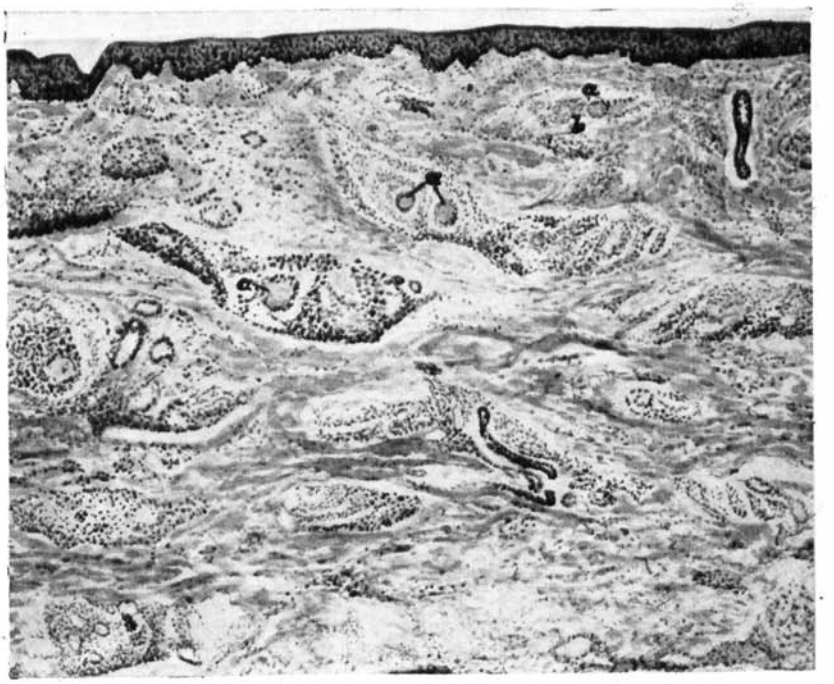
PLATE 1.

DESCRIPTION OF PLATE

PLATE 2

FIG. 1. Illustrating Case No. 4. Areas marked: *a*, giant cells inside granulomatous cords; *b*, approximate position of Fig. 2. Magnified about 27 diameters.

FIG. 2. Detail from Fig. 1, *b*, showing *M. leprae*. Areas marked: *a*, sections of old granulomatous cords; *b*, vessels containing *M. leprae*. Magnified 500 diameters.



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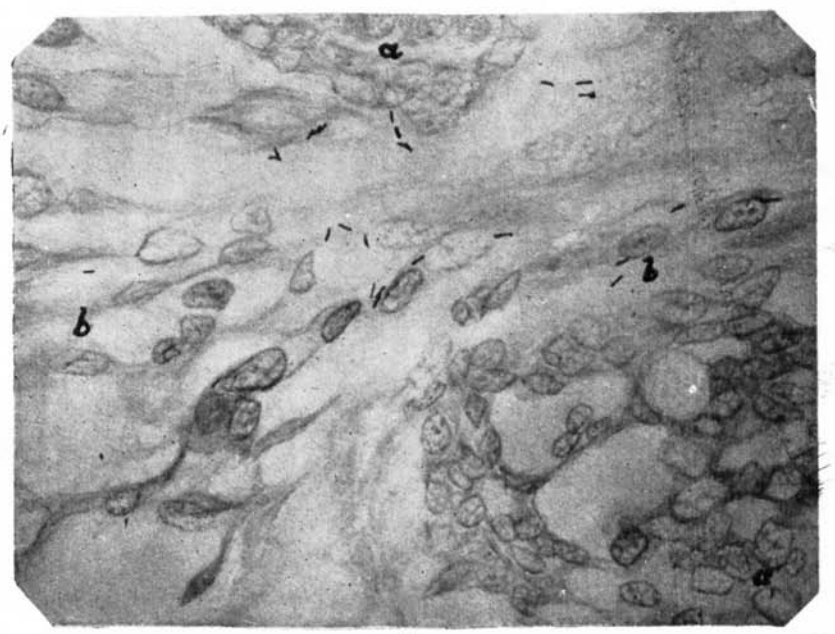

2

PLATE 2.

DESCRIPTION OF PLATE

PLATE 3

Illustrating Case No. 6. Areas marked: *a*, necrosis of center of nerve bundle in cutis; *b*, giant cells; *c*, smaller granulomatous cords in cutis. Magnified 20 diameters.

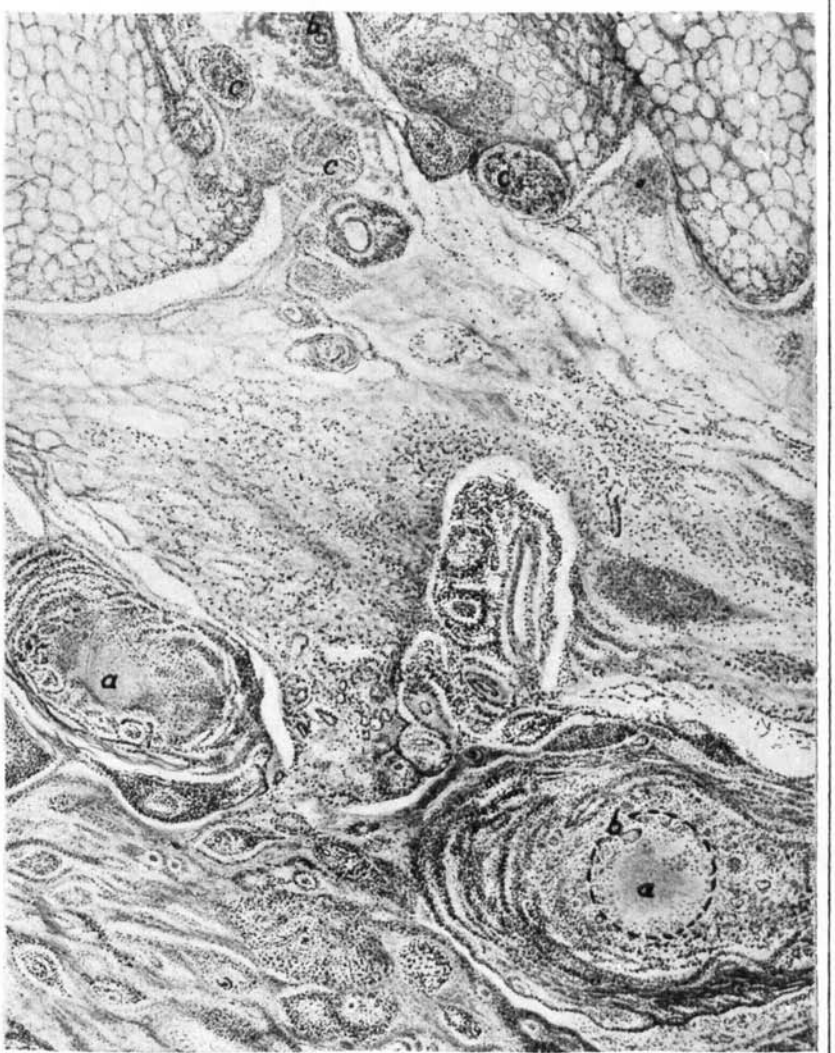

PLATE 3.

DESCRIPTION OF PLATE

PLATE 4

FIG. 1. Illustrating Case No. 6; higher magnification (120 x), of the area marked *a* in Plate 3. Note *a*, a giant cell, and *b*, necrotic area.

FIG. 2. Giant cells in subpapillary layers. Areas marked: *a*, sections of giant cells; *b*, outer surface of giant cell; *c*, flattened epithelium. Magnified 300 diameters.

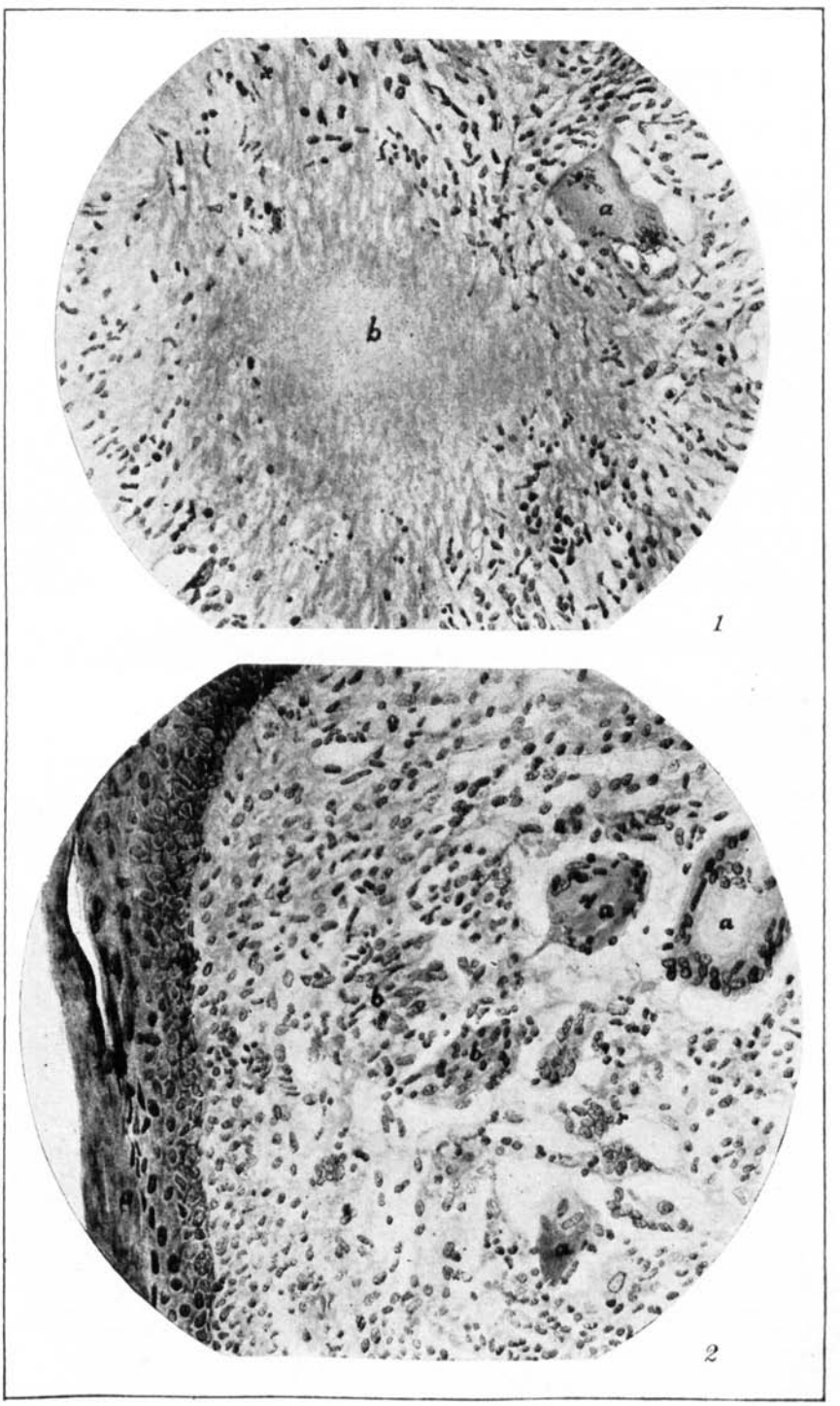

PLATE 4.

DESCRIPTION OF PLATE

PLATE 5

FIG. 1. Illustrating Case No. 10. Areas marked: *a*, sections of thickened nerve cords; *b*, sections of branches of nerve cord; *c*, hair follicle; *d*, sweat gland connected with nerve cord.

FIG. 2. Greater magnification of area of Fig. 1 enclosed by broken lines. Areas marked: *a*, giant cells; *b*, branch of thickened nerve cord.

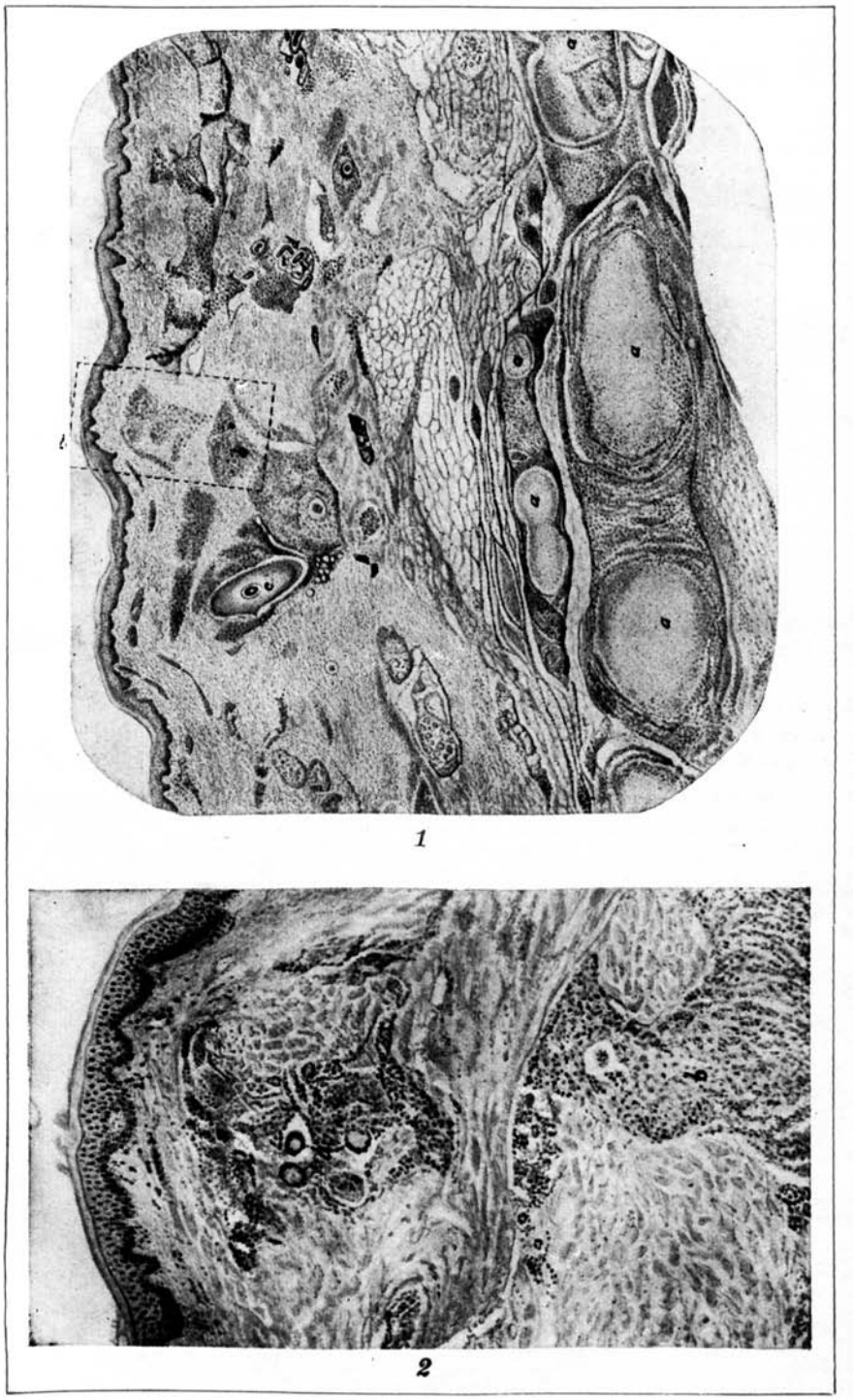

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PLATE 5.