## Cellular Reaction to Bacillus Leprae\*

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THE cellular reaction is of importance in all diseases caused by infective organisms. It is of peculiar interest in leprosy because of the low toxicity of the causal organism, *Bacillus leprae*. Due to this low toxicity the organisms can multiply to extraordinary numbers without causing very marked clinical signs, and without apparently interfering to any great extent with the general health of the patient.

If we compare leprosy with the sister disease, tuberculosis, the contrast is very striking. In the latter disease even a small infection sensitizes the patient so that an inoculation of tuberculin causes an immediate focal and general reaction. In leprosy the inoculation of leprosy bacilli causes no immediate focal and general reaction. Indeed the condition in leprosy may be compared with that in an advanced case of tuberculosis, in which the tuberculin reaction is negative; only, while such a tubercular patient is in a highly toxic condition and appears extremely ill, the leprosy patient shows few or no signs of toxicity, can go about his work in good health, and may even show but few clinical signs.

The disease of leprosy is not caused then by the toxins of the causal organisms, nor, except in the complication known as "lepra reaction" or lepra fever, is it due to sensitisation to the bacillus. The clinical signs and symptoms are caused by local cellular reaction to the bacillus, and it is the nature of this cellular reaction which I shall attempt to study in this paper.

Leprosy may affect most of the organs of the body, but it is the skin and the peripheral nerves that are most markedly involved, and we shall confine our attention to these structures.

Under certain circumstances such as in lepra fever, and when a severe temporary reaction takes place, the blood cells invade leprous lesions and phagocytose the bacilli. But under ordinary conditions the cell responding to the presence of *B. leprae*, in both skin and nerves, is the endothelial cell of

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the capillary. It is difficult to say whether all endothelial cells respond, or whether, as some writers state, only certain specialised endothelial cells belonging to the reticuloendothelial system are involved.

The multiplication of lepra bacilli which have entered the skin or nerves takes place in the intercellular lymph spaces and inside the cells. The degree of this multiplication, and the subsequent spread of the organisms throughout the tissues, are largely dependent on the degree of cellular response.

The reaction of the cells to the bacilli in their neighbourhood is threefold, *viz.*, increase of cells by division, ingestion of bacilli, and destruction of ingested bacilli. The more the bacilli multiply, and, therefore, the more bacilli there are in the neighbourhood of a cell, the more is that cell stimulated to respond. But apart from the number of bacilli surrounding it, the degree of response varies greatly in degree, and this variation is dependent on certain factors to be mentioned later.

Comparison of weak and strong response.— If the response is weak then cell-division is sluggish, and ingestion feeble, so that numbers of bacilli remain outside the cells and spread in the lymph stream; while the ingested bacilli, instead of being destroyed, multiply in the cytoplasm. These cells gradually become distended with bacilli, vacuolated and destroyed. The distended, vacuolated cell is the well-known "foamy" or "lepra" cell. In the nodules and other gross lesions groups of these cells are pressed together and may form a more or less uniform bacillary mass, cemented together by mucoid material called by the early leprologists "gloea." Between the typical lepra cells is a varying number of small round, lymphocyte-like cells, called by UNNA "daughter cells," suggesting that they constitute the young form of lepra cells.

If the cell-response to the bacilli is *strong*, then both celldivision and bacillary ingestion are active (Fig. 1). The cells are formed into compact cords round the capillaries (see Fig. 2), from the endothelial cells of which they take origin. These are the well-known "epithelioid cells" (see Figs. 3 and 4) of the so-called "tuberculoid" type of leprosy. The bacilli, instead of multiplying and distending the cells, are phagocytosed and destroyed; they are, therefore, few in number and difficult to find in such lesions. So active is the response in some cases that the cells, instead of dividing in the usual manner, form multi-nucleated giant cells, similar to the Langhan's cells in tuberculosis. This may be carried one step further and, as in tuberculosis lesions, result in caseation, which, when extensive, may lead to abscesses in the nerves and ulceration of the skin.

We have described shortly the contrasting pathological results in weak and strong cell response to *B. leprae*. Between these two extremes we have all grades of cellular activity. Moreover the degree of reacting power may vary in any case from time to time. Hence the protean forms of leprous lesions.

The principal factors influencing the degree of cellular reaction are four in number, viz., (1) the age factor, (2) general health, (3) small infections with *B. leprae*, and (4) gross infection with *B. leprae*.

(1) Age factor.—It has long been recognised that young children are more susceptible to leprosy than adults. It is only recently that this important fact has been given due prominence, and its cause studied. The incidence among children in infectious contact is given as over 40 per cent., and conjugal infections as less than 5 per cent. It is generally recognised that a similar susceptibility of children also exists in tuberculosis. In the latter disease, the cause of this susceptibility is supposed to be that the child in a home infected with tuberculosis is liable to receive a greater degree of infection than the adult similarly placed. While increased liability to infection may partly explain the greater susceptibility of children (as compared with adults) to leprous infection, there is strong evidence that this is not the only cause.

When a suspension of killed *B. leprae* is injected intradermally in very young non-leprous children (leprolin test), it produces but little local cellular reaction as compa

a similar inoculation in older children or in adults. This suggests that the defensive mechanism against B. leprae, viz., strong cellular reaction resulting in phagocytosis and destruction of bacilli, is weaker in young children than in adults.

The typical form of leprosy found in children who have been in close contact with highly infectious cases during their first years of life is of a peculiar nature. The skin lesions take the form of hyperpigmented macules with slight parakeratosis but without any clearly defined margin. Clinically these lesions are difficult to recognise, while histologically they show only a mild degree of cellular reaction, and but few bacilli. These lesions may appear and disappear from time to time, and they are often widespread over the body. It has been shown that these macules often red with into





FIG. 1.—Macule of back in patient with high resistance  $(N_2)$ . The white mark denotes material removed by biopsy, a section of which is shown in Fig. 2. The resistance of this patient had been temporarily lowered, but had been restored shortly before the biopsy was made.

F16. 2.—Section from macule in Fig 1 showing skin and subcutaneous tissue. Note the sections of dense granulomatous cords round the vessels of the papillae, subpapillary plexus and hair follicle, which show white in the photograph; also the two thickened and granulomatous nerve branches in the subcutaneous tissue. The squares "a' and "b" in the latter indicate the areas shown enlarged in Figs. 3 and 4. o bacilli were found in the subcutaneous nerve at "a".



FIG. 2.



FIG. 3.



Fig. 4.

F16. 3.—Section of subcutaneous nerve enlarged from "a" in Fig. 2. Note the few bacilli showing singly and in bunches; and the large, densely packed epithelioid cells.

F16. 4.—Section of subcutaneous nerve enlarged from "b" in Fig. 2. No bacilli were found in this nerve. Note the giant cell and the dense cellular reaction.



## Fig. 6.

F16. 5.—Section of nerve—low power—in case with low resistance (C<sub>2</sub>). The section was stained by a combined Beilchowsky and Ziehl-Neelsen method. The dark dots are masses of bacilli lying between the nerve fibres. Cellular reaction is absent.

FIG. 6.—The nerve shown in Fig 5, further enlarged. Note the masses of bacilli between the nerve fibres and the absence of cellular reaction.







FIG. 8.

FIG. 7.-Section of superficial part of skin in a new lesion in a patient

with low resist papillary vessel with numerous bacilli, intra- and extra-cellular, but no signs of tissue reaction; "b" = epithelium, "c" = hair follicle.

FIG. 8.—Teased nerve fibres in a resistant  $(N_1)$  case. Bacilli are seen lying on the nerve fibres. The cells are those of Schwann's sheath. There is no sign of tissue reaction as the fibres were from the superficial part of the nerve bundle.

frank lesions in later life. "Juvenile leprosy" is a convenient term to apply to this type. In adults the early lesions tend as a rule to be more marked clinically and histologically, and they show a greater degree of cellular reaction.

We propound the hypothesis that effective cellular reaction to *B. leprae*, resulting not only in their ingestion but in their destruction, is the main protection of the body against the invasion and spread of these organisms. If this hypothesis is accepted there is considerable evidence that the greater susceptibility of children to leprosy is connected with weaker cellular reponse to *B. leprae* during the first few years of life, as shown by the weak cellular reaction to inoculated *B. leprae*, and by the type of lesions found in these cases.

(2) General health.—A similar weakening of cell activity occurs when the general health is depressed by predisposing or intercurrent diseases, or by any other cause. This, as in juvenile leprosy, is shown by the leprolin test, which shows a milder local reaction to injected bacillary suspension. It is also shown by the clinical and histological examination of lesions. The onset of diseases like malaria, kala-azar, dysentery and enteric is often followed by the flattening out or even disappearance of prominent leprous lesions, due largely to the diminution or cessation of cellular reaction to B. leprae present in the skin. The patient may appear to improve as far as his leprous lesions are concerned, while all the time the infection is increasing, uncontrolled by phagocytosis. When convalescence sets in and the general health again improves, cellular reaction is restored and the lesions appear considerably enlarged and more numerous as compared with their condition before the temporary lowering of general health.

(3) Small infections.—There is considerable evidence that, as in tuberculosis, small infections with leprosy in otherwise healthy subjects increase the resistance to the disease. This resistance shows itself in enhanced cellular reaction of the endothelial cells to bacilli in their neighbourhood. In such cases the tuberculoid lesion, with epithelioid and giant cells and but few bacilli, is common. In these cases the leprolin test gives a strong reaction, a large nodule, often with central necrosis, forming at the site of inoculation as the result of heightened cellular response to the injected If this nodule is removed by biopsy and sectioned, bacilli. an intense cellular reaction is found with giant cells present; in fact, a lesion similar in appearance to the leprous lesions present in the skin. In my experience in Northern India the majority of all cases of leprosy are of this type. This

is shown to be the case when a careful house to house survey is carried out in endemic areas, though the proportion may be much smaller if those attending a clinic or segregated in an institution be examined.

(4) Gross infection.—In contrast to the above, massive infection with B. leprae, or the presence of large numbers of these bacilli due to multiplication in the body (see Fig. 7), results in lowered cellular reactivity. When more than a certain number of bacilli have accumulated in the body a state of symbiosis is established between the endothelial cells and the bacilli, the latter being ingested and multiplying in the cells, which gradually become enlarged, vacuolated and destroyed. When the leprolin test is performed in patients with massive infection the result is generally negative, or only very slightly positive. In performing the test a piece of skin may be chosen where the infection is absent or only slight, and into this skin is injected an emulsion rich in B. leprae which has been heated to 120° C. for half an hour. If 2 or 3 weeks later the skin at the point of inoculation is removed by biopsy and sectioned, few bacilli are found present in the tissues, and only a mild degree of cellular reaction is seen. The bacilli, not having been ingested by the cells, pass up the lymphatics. In this case, too, the appearance of the leprolin nodule is similar to the lesions of short duration present in the skin.

We have thus four factors, three of which (viz., tender age, debility and massive infection) diminish cellular reactivity to *B. leprae*, and one of which (viz., slight infections) increases their reactivity. These factors may counteract, supplement or succeed each other. Thus temporary depression of general health may counteract for the time-being the increased resistance which has been acquired through small infections; but the state of increased resistance may be restored if the depression of health be not too severe or prolonged. The susceptibility of the first few years of life may be accompanied or succeeded by the low resistance attendant on a high degree of infection, and both of these may be supplemented by weak general health.

The ebb and flow and the interplay of these various factors and their effect on cellular reaction in the skin and nerves, account to a large extent for the multiformity of leprous lesions, so difficult to describe and explain.

So far we have referred chiefly to skin lesions, but the same laws and the same factors hold good in the peripheral nerves. When the skin is infected the infection not only spreads in the skin, but also passes up the supplying nerve branches. In fact, there is reason to believe that under certain circumstances the nerves form a more fertile medium than the skin for the multiplication of bacilli. This is apparently due, at least in part, to the comparative paucity of endothelial phagocytic cells in the nerves as compared to the skin. The bacilli enter a nerve bundle and pass up it in the spaces between the nerve fibres (see Figs. 5 and 6), and are thus not in close contact with the endothelial cells of the vascular capillary in the centre of the bundle. Sections of nerve bundles often show cellular multiplication and destruction of the central nerve fibres; while at the periphery of the bundle cellular proliferation is absent, the bacilli are present in large numbers and the nerve fibres remain intact.

It is questionable if the skin is ever infected to any marked extent without the supplying nerves becoming infected too. We speak of skin leprosy and nerve leprosy, and in the former it may be impossible to find clinical evidence of nerve affection. But in skin leprosy microscopic examination of the nerves shows the presence of large numbers of In this type of the disease the absence of clinical bacilli. signs connected with the nerves is not due to the absence of bacilli in their bundles, but to the comparative weakness of cellular response to the bacilli which are lying between the nerve fibres. The swelling and tenderness of nerves and the sensory and trophic changes in their distribution are due not to toxins set free from the bacilli, nor to pressure of the bacilli on the nerve fibres; they are due to the mechanical pressure of the cellular granuloma, i.e., of the cells proliferating in response to the bacilli lying between the nerve fibres. Thus, though in the low resistant case there is massive infection of the nerve, the absence of mark response accounts for the fact that neural signs are comparatively slight.

In the more resistant case, however, bacilli may be few or absent in the skin, having been destroyed by the strong phagocytic cellular response; at the same time the nerves are swollen and tender, the degree of resistance being sufficient to stimulate the endothelial cells of the central capillary of the nerve bundle to high activity against the bacilli present between the nerve fibres (see Figs. 2, 3, 4, 8). This can be demonstrated by making simultaneous clinical and histological studies.

Many theories have been advanced for the curious fact that neural signs and symptoms are so slight in cases in which bacilli are numerous in the skin, and so marked in cases in which the bacilli are comparatively few in the skin. The above, if confirmed by other workers, would seem to offer a satisfactory explanation of this phenomenon.

Effects of varying resistance.—We have mentioned above that not only do the resistance of patients and consequent cellular activity vary in different individuals, but they vary from time to time in the same individual. During the periods of low resistance the bacilli multiply, spreading along the subcutaneous and/or subpapillary plexuses, and from these along the hair follicles, and the sweat glands and ducts; from the sub-papillary plexus they invade the papillae, and from the subcutaneous plexus they pass up the nerve branches.

In the nerves, during periods of lowered resistance, the bacilli tend to accumulate at points of obstruction, such as bends, constrictions or where branches are given off. In this respect they resemble the leaves and other debris carried along in the current of a river and massed together whereever they meet with impediments. When a period of low resistance is succeeded by a period of higher activity, the cellular response is most marked at these points of obstruction and bacillary accumulation. Thus we find the ulnar nerve most thickened in the lower half of the arm between the obstruction caused at the elbow, and that caused as it passes through the intermuscular septum. Similarly the great auricular nerve is commonly thickened between its bifurcation at the angle of the jaw and its bend round the sterno-mastoid.

Bacillary reservoir in nerves.—Because of their lower or more tardy resistance to *B. leprae*, the nerves tend to form a reservoir for these organisms when the skin by its greater cellular activity has purged out the infection. Thus the infection may remain bottled up inside a single nerve for a long period, unable to escape through its branches in the skin, or through its connective tissue covering, the cells of which also, like those of the skin, react to and destroy bacilli.

It is well known that in a resistant case a single lesion of the skin may exist for years. Bacteriological examination may fail to show any bacilli in such a lesion, and yet it continues as a clinical lesion. A possible explanation of this phenomenon is that from the supplying nerves bacilli are from time to time entering the skin, the cellular elements of which react to and destroy the bacilli as they enter. Thus the skin lesion is maintained. But if the skin is re-infected from the nerve branches during a temporary depression of general resistance, the cellular seal is temporarily opened, and the infection may be broadcast through the body and enter other nerves in which it may again find sanctuary when resistance is restored.

It is probably largely on account of this neural reservoir that it is so difficult to eradicate leprosy from the body, and that relapses are apt to occur in cases whose skin and mucous membrane have become and have remained for some time, bacteriologically negative. On this account it is important in leprosy. as in tuberculosis, that in arrested cases the general health should always be maintained at a high level.