
**Histology of the Skin Lesions.**

Leprosy is generally classified among the infective granulomata.

(1) The examination of the earliest and mildest skin lesions shows an increase of the cellular elements in the most superficial, i.e. the papillary, layer of the corium, which underlies the basal layer of the epithelium. The epithelial ingrowths, viz., the hair follicles with their appendages the sebaceous glands, and the sudoriferous glands and ducts, are also coated by this increased cellular element, the disease thus being carried down deep into the corium. This cellular increase consists of the following elements: connective tissue cells; star-shaped mast cells containing in their cytoplasm granules which are to a great extent acid-fast when stained by the Ziehl-Neelsen method; large epithelioid cells apparently of endothelial origin, which, when they have ingested B. leprae, are known as "lepra cells"; and small cells similar in appearance to lymphocytes.

It is often impossible in such early lesions to discover any acid-fast bacilli. Whether this is due to their scarcity or to the infecting organisms not being acid-fast, though present, it is difficult to say. It is not likely that these cellular changes are due to the toxins of distant organisms and they must, therefore, be due to B. leprae present locally. Nor are the changes caused by germs which were formerly present and have now died out, as the changes described occur in the active, extending margin of the lesions also. The presence of B. leprae is also proved by the fact that, when the resistance of the patient is suddenly lowered by any intercurrent cause, such lesions often change into lesions of the type next to be described; and in the latter type organisms of various degrees of acid-fastness may be found, some retaining the stain dark red, others staining only slightly, and others appearing as "ghost forms," only their outline appearing in the counterstain.

In this earliest lesion there is a slight amount of flattening of the papillae and in consequence of the interpapillary spaces of the epithelium. The infection does not appear to invade
the epithelial elements, but it is accompanied by trophic changes in the epithelium, such as parakeratosis and hyperkeratosis. The hairs become affected and break off at the mouth of the follicle, the part inside the follicle becoming softened and swollen with a bulbous end. There is a loss of the sweat function. Granulation appears to be perivascular and to follow and surround the vascular plexus which immediately underlies the epithelium, but there is often at first no vascular engorgement. Such lesions may remain stationary or may advance slowly, the infection probably being spread by mobile cells which ingest the organisms and carry them forward in the intercellular lymph spaces surrounding the superficial vascular plexus.

The nerve-branches supplying such a cutaneous lesion seem invariably to be affected, infection with cellular changes similar to those described in the skin gradually spreading upwards and affecting the larger branches and then the nerve-trunks. In the nerves, the various connective tissue layers surrounding the axis-cylinders (endo-, peri-, and epineurium) become the site of a granulation process similar to that described in the corium. The fibres themselves are, to start with, affected by the pressure of the cells. Apparently the non-medullated, sympathetic nerve-fibres are the first to suffer, and this, together with the cells proliferation causes the changes in the epithelium—keratosis, loss of sweat function and changes in the hair follicles; while at the same time there is a loss of epicritic sensation and of pigmentation. If the pressure is prolonged, the fibres are destroyed; but, if resolution takes place in time, the fibres are preserved and function is restored. In other lesions the nerves appear to be affected first, and it is possible (though proof is wanting) that there may be a descending infection of the skin from the nerves.

(2) The lesion described above is of the most mild and chronic nature. When the resistance of the patient, either local or general, is less, the lesion is subacute, its margin spreads more rapidly and shows engorgement of blood-vessels. In this type a few acid-fast organisms can be found in sections; they lie chiefly inside the large epithelioid (lepra) cells, and there are also a few lying apparently in the intercellular spaces. In this lesion there are often multinuclear giant cells as described by Kedrowsky (1914), Bayon (1916), and Henderson (1928), very similar in appearance to the typical giant cells of Langhans found in tuberculosis. Here the granuloma tends to become more thickened and to spread to the deeper vascular plexus. The centre
of the lesion does not show engorgement of the vessels, but only the periphery.

(3) A third type of lesion rather more acute than the last may arise from either of the types described above or may belong to this type from the beginning. There is engorgement of the superficial capillary plexus throughout, but the invasion of the nerve-branches is less certain, being sometimes present and sometimes absent. Giant cells are not found as a rule, and epicritic anesthesia, keratosis, anhydrosis and depilation may or may not occur. Acid-fast organisms are present in larger numbers and granulation of the corium, though it does not yet invade the lowest layers, is more widespread. The epithelium is raised above the level of the surrounding skin surface by the pressure of the granulomatous corium and is flattened out and thinned, the interpapillary spaces disappearing.

(4) In the fourth type there is a further progression from the last. The lower layers of the corium are invaded; lepra cells are large, some containing large numbers of acid-fast bacilli and others few, while some organisms are to be seen in the intercellular spaces, possibly set free from broken-down cells. Pressure on the hair follicles and sweat organs causes their gradual destruction. The epithelium is forced outwards between the rows of hair follicles and the natural folds of the skin are exaggerated, giving the surface a tesselated or mosaic appearance. The most superficial layer of the corium is edematous and comparatively free from acid-fast organisms, lepra cells and cellular infiltration. This is in marked contrast to the first type in which the superficial layer alone is affected. Such a lesion may originate either by a more superficial infection spreading to the deeper layers of the corium or by the extension of a focus deep in the corium which has been produced by a mycobacterial embolus in a vessel of the deep vascular plexus.

(5) The fifth type is the cutaneous nodule, starting round a deep embolus, but unlike the last it does not spread through the skin but forms a round circumscribed mass. In the centre there are aggregations of lepra cells, intermixed with small, round cells, while at the margin the proportion of the latter is greater. As a nodule becomes old the granular formation is often replaced to a large extent by fibrous tissue making it firm and hard. During severe reactions a nodule frequently shows degenerative changes and this may go on to pus formation, the pus being absorbed and discharged through a small perforation in the epithelium, or resulting in destruction of epithelium and the production
of an ulcer of which the remains of the nodule forms the hard base. At other times nodules are resolved, leaving only a small quantity of fibrous tissue under the thin epithelium.

These various types of skin and subcutaneous lesions have been described, but one type often merges into another, and lowering of resistance generally tends to change a less into a more severe type.

**Lesions of the Nerves.**

Equally important with lesions of the skin are those of the nerves. As has been mentioned, the central nervous system is seldom or never affected, but any of the peripheral nerves and their branches may become involved. Disease is found most frequently in subcutaneous nerves, especially in those most liable to injury, torsion, bending or pressure; thus the commonest nerve-trunks to be affected are the ulnar, peroneal and great auricular.

The histo-pathology of nerve-lesions corresponds more or less closely with that of the first three types of skin lesions described above. The nerve-fibres are destroyed by pressure of the granuloma, which infiltrates the connective tissue elements of the nerve, and later by the contraction of the new fibrous tissue which replaces the granular formation.

Nerve-trunks are invaded either by ascending lesions from the skin or by metastatic embolism. Proof of ascending invasion is exemplified when from a cutaneous lesion of the forearm thickening of branches of the radial and ulnar nerves gradually proceeds upwards to the respective trunks; proof of metastatic infection is shown when nerve-trunks are found affected but their branches and the skin supplied by them remain free.

One of the most important phenomena in leprosy has been referred to above, namely that the milder the type of lesion and the greater the resistance of the patient the more are the nerves involved; and inversely, the grosser the lesion and the lower the resistance the less is the disease found in the nerves. This cannot be explained by any essential difference either in the patient or in the strain of organism, for in the majority of patients the disease begins with the nerve type, passing on later into the skin type, and patients in whom the former has been maintained for years will pass on rapidly into the latter if their resistance is markedly lowered by an intercurrent disease or by any other cause; and patients who are suffering from the grosser skin types will show a marked increase of nerve involvement as the skin lesions diminish either naturally or under treatment. Many theories have been put forward
to explain this phenomenon. Perhaps the most likely hypothesis is that B. leprae, when the resistance is low, quickly multiplies inside the ingesting cells and immobilisation takes place; whereas when the resistance is high the bacilli are able to travel up the nerve-branches from the skin, by direct spread, possibly of a non-acid-fast or less acid-fast form.

While in early leprosy the small cutaneous branches are most affected, in the last stage of the disease the trunks show most signs. In that stage therefore, whether the disease has been chronic throughout and never developed the grosser skin type, or whether in the intermediate stage there may have been gross skin lesions, we have the well-known acroteric (glove and stocking) trophic lesions due to pressure exerted on the axis-cylinders, first by the cell proliferation and later by the contraction of fibrous tissue. Seeing that the longer the nerve-trunk is the greater is the length of nerve-fibre over which pressure is applied, the distal parts of the limbs, i.e. the hands and feet, show the first and most marked signs of trophic involvement. Thus there is anaesthesia, both epicritic and protopathic gradually spreading up the limbs from the fingers and toes; thermal and pain sensations are lost; loss of sensation is often preceded by hyperaesthesia and paraesthesia. Side by side with these there are anhidrosis, depilation and changes in the nails; wasting and fibrosis first of the small muscles of the hands and feet and later of the forearms and legs. As the peroneal and ulnar nerves are most apt to be involved, the muscles supplied by these nerves are most markedly affected. Fibrosis of the small muscles of the hands and feet is followed by the typical claw hand (main en griffe) and the club-shaped foot; while drop-foot is a common result of wasting of the peroneal muscles. The bones are decalcified and slowly absorbed. Secondary infection often leads to abscesses and ulcers, while, apart from secondary infection, blisters, blebs and perforating ulcers occur generally as the result of a reaction in the affected nerve-trunk.

The Reaction in Leprosy.

B. leprae differs from most ordinary bacillary and coccal infections in its low toxicity, the lipoid material in its composition, its intracellular growth and the presence of a mucoid substance which accumulates round about it even after the cell has been destroyed. In the typical leproma, such as we find in B^i and B^s cases, we have, therefore, a threefold protective mechanism consisting of the composition of the bacilli, the lipoid material tending to prevent its destruction; its intracellular position, the lepra cell
acting more as a host than as a phagocyte; and the mucoid material, called by the earlier writers the "gloea." This protective mechanism enables the organism to multiply enormously, forming masses within separate cells, which, as the cells become further expanded and destroyed, coalesce, the bacilli embedded in the gloea being moulded in the intercellular spaces by the pressure of the surrounding cells.

The process of multiplication of bacilli may go on for months, or years, quietly without producing any marked local or constitutional disturbance. This period we may call the quiescent phase. When, however, due to any cause, there is a sudden breaking up of the lepra cells or liquefaction of the gloea, the bacilli are brought into contact with the surrounding tissues and a reaction takes place, there is engorgement of the blood-vessels, dilatation of the perivascular lymph spaces and marked local diapedesis of leucocytes, especially polymorphs, which phagocytose the organisms. Clinically there is sudden swelling and erythema of the affected lesions, and the appearance of rose-coloured cutaneous nodules in different parts of the body. As systemic changes we find a rise of temperature, bacillremia and alterations in the blood-serum indicated by acceleration of erythrocyte sedimentation (Muir, 1928). Only the lepra cells which are ripe and the gloea masses take part in the reaction, and thus lesions which do not contain ripe cells do not react. For this reason, reactions are comparatively uncommon in cases of the A types, though even in them reactions do occur in the nerve-trunks. Sections of a reacting lesion may show in the deeper layers of the corium vascular engorgement, perivascular oedema, marked polymorph leucocytosis with disappearance of acid-fast organisms; while the more superficial layers are still quiescent, with the bacilli chiefly intracellular but contained in the cells only in small numbers; in other words the deep parts having ripe cells have reacted in contrast to the superficial parts which remained quiescent, the lepra cells being immature.

Causes of Reaction.

The causes which bring about the reactionary phase spontaneously appear to be many; among them may be mentioned febrile intercurrent diseases, gastro-intestinal disturbances and unaccustomed physical exertion. It may also be caused therapeutically by the injection of certain drugs such as hydnocarpus oil and its preparations, and it has been noted after vaccination for smallpox. Potassium iodide has a specific effect in this direction; in certain cases in which ripe lepra cells or gloea masses are abundant as little as 1 or 2 grains given orally will produce a very marked reaction.
Effects of Reaction.

There are four well-marked effects resulting from reaction:—

(a) Resolution is brought about in the area which has reacted.

(b) Bacilli are set free in the blood-stream with resulting metastasis.

(c) There is a temporary depressant action on the general resistance of the body.

(d) When wisely induced with therapeutic intent by drugs in suitable doses, and at proper intervals, immunity results; contrariwise, when reactions occur, accidentally or are induced without safe precautions, an allergic condition is liable to result which is detrimental to the patient. This allergic condition is what is commonly known as lepra fever; the febrile condition may last for several weeks or even months, repeated reactions being induced and maintained by the high temperature and by the weak condition of the patient. One of the signs of immunity is the disappearance after two or three days of the rose-coloured, cutaneous nodules of embolic origin; in progressive cases, in which immunity has not yet become sufficient, these nodules form the nuclei of new, spreading lesions.

The term phase has been used because of the repeated recurrence of reactions. We have thus three phases; the quiescent, the reactionary and the resolutionary. The signs of resolution are indicated histologically by the appearance of resistant forms, spore-like swellings in the mycobacteria, granulation or loss of acid-fast staining, disappearance of acid-fasts and lepra cells, the cellular granuloma being replaced by fibrous tissue.

Treatment.

As may be gathered from the previous sections of this chapter, the chief emphasis in the treatment of leprosy must be laid on the improvement of the general health of the patient, and no line of treatment which neglects this factor is likely to give permanently good results. Syphilis, which is present in India and other places in a proportion varying from 25 to 50 per cent. of cases must be examined for and treated when present. Other predisposing diseases must be sought out and remedied when found. The diet must be carefully enquired into and regulated according to the ordinary rules of dietetics, remembering that leprosy is
a disease of over-eating as well as one of starvation. As in tuberculosis, exercise is very important; leprosy is a disease of the lymphatic system and flourishes best in patients with a stagnant lymph-stream and soft, flabby muscles. The hardening up of the muscles is often sufficient of itself to cause a gradual clearing up of the disease. Suitable climatic conditions, general hygienic surroundings and a healthy, cheerful, hopeful and purposeful mental attitude are essentials for successful treatment.

The special treatment of leprosy consists in the application of drugs which break down the defensive mechanism of the leprosy organism and at the same time increase the immunity of the patient. The former of these objects is secured by the injection of such drugs as chaulmoogra (or hydnocarpus) oil and its preparations, and by the administration of potassium iodide orally. It is also promoted by any drugs which cause either local or general polymorphonuclear leucocytosis. The external application of local counter-irritants, for example, by painting lesions with trichloracetic acid, which produces leucocytosis in the granuloma, has a beneficial effect. The injection of such irritants as turpentine or the induction of protein shock by the injection intramuscularly or intravenously of milk, bacillary suspensions, and other forms of protein have the same effect. This accounts largely for the innumerable forms of treatment that have been recommended in recent years. Attempts at the production of immunity have been made by the injection of suspensions of ground-up leprous nodules and of supposed cultures of the leprosy organism, such as Deycke's nasin (Deycke and Reschad, 1907) and Rost's leprolin. Similar endeavours have been made to produce group-specific immunity by the injection of other acid-fast cultures, such as tuberculin, used by many workers and autolyzed tubercle bacilli as proposed by Row (1926). Immunity can, however, be induced (in the opinion of the author, much more effectively and conveniently) by the internal autovaccination caused by the breaking up of the leproma which is produced by the injection of hydnocarpus oil and the oral administration of iodide.

An important point which must be remembered is that in the earlier stages, and especially in B4 cases, attempts to press this treatment excessively are apt to result in depressing the general resistance of the patient, and thus to lead not to amelioration of the disease but to its aggravation. In B4 cases this danger, though it exists, is not so great, as patients, because of the higher degree of immunity
induced, may continue to improve rapidly under vigorous treatment even when the general resistance is lowered. In all cases, however, there is the danger of the patient reaching an allergic condition with continuous fever, which is one of grave danger and not infrequently ends fatally. In the earliest cases of the \( A_1 \) and \( B_1 \) types, treatment may be pressed, provided the patient's general condition is favourable seeing that reactions do not occur to an extent likely to depress his vitality.

**Prevention.**

**General Measures.**

As has been mentioned above, leprosy is spread by contact with infectious (chiefly \( B_2 \) and \( B_3 \) types) lepers, the longer and the closer contact the greater being the danger of transmission. This being so an infectious patient should have a separate room into which no one but himself enters, except those in attendance on him. His linen, eating utensils, furniture and other things used or touched by him should not be touched by others without due precaution. It is specially important that children should not come into contact with infectious lepers. New-born infants should be separated from their mothers at birth. Those whose occupation entails touching lepers should do so with care; they should discriminate between different cases regarding the degree of infectiousness, should realise the danger of drop infection while standing near \( B_1 \) cases, and should take precautions in dressing ulcerating nodules or in touching or using furniture, utensils, etc., that have been in contact with such patients. Rubber gloves should be worn or the hands should be washed carefully after all possible contacts. At the same time, the most important preventive measures are perhaps those which ensure a high measure of physical health.

Children and others who show early signs of leprosy should not be allowed to live in contact with highly infectious cases, as there is good reason to believe that, as in tuberculosis, repeated massive reinfections of those who have only a slight degree of leprosy are apt to lead to a graver type of disease.

Marriage should be forbidden, especially in women, even in the earlier types, as child-bearing frequently leads to a rapid development of the disease. In patients recovering from leprosy, marriage or sexual connection should be interdicted for at least three or four years after all signs of leprosy have disappeared.

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