

THE HISTOPATHOLOGY OF THE REACTIVE PHASE OF LEPROMATOUS LEPROSY

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The chronic course of leprosy is often interrupted by "exacerbations," which are accompanied by high or subfebrile temperature, eruption of fresh erythematous papules and nodules, and inflammation of old, preexisting lepromas. The eruption lesions, which appear on the skin and mucous membranes, differ from the ordinary lepromas by the acuteness of their onset, their considerable degree of erythema, and their painfulness. In some instances these lesions disappear after a few days leaving no traces, though in other instances they leave hyperchromic or bluish areas.

In cases in which the exacerbation is accompanied by high temperature, there may appear on the nodules a suppurative type of vesicle, the content of which dries up and forms a scab. Sometimes the rapidly developing vesicle is filled with hemorrhagic or purulent matter, and in some instances the purulent degeneration of the lesion becomes more marked, the pus being discharged and the wound healing by cicatrization. Severe lepra fever may be associated with swelling of the lymph nodes and testes. Neuritis and inflammatory affections of the eyes are also met with quite often. Such attacks may occur repeatedly, one following another and keeping the patient in bed.

The mechanism of these manifestations remained for a long time obscure and only with the development of the allergy concept did the nature of the reactive phase become clearer. Jadassohn was the first to express the view that lepra fever is a manifestation of an allergic condition. At the present time this concept is accepted by a number of leprologists (Stein, Wade, Lowe, Muir, Green).

Green carried out the following experiment during the period of exacerbation: He injected *M. leprae* intracutaneously and observed the appearance of vesicles, hyperemia and infiltration. These

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manifestations disappeared only after the end of the reactive phase. Vesicles also appear in the course of the usual quiet phase of the process, but they do not increase in size, there is no hyperemia, and they usually disappear after three or four days. Green's experiment demonstrates that there exists a heightened sensitivity to the causative organism during the reaction. He attributes the erythematous skin eruptions more to manifestations of a serous inflammation than to cellular lesions.

In the available literature I have found only a few reports dealing with the histopathology of the leprous process in exacerbations. Philippon (1893) studied the acute erythematous elements and observed a vascular reaction and numerous bacillary emboli in the skin capillaries. Siebert (1905) noted dilatation of the blood vessels and inflammatory changes, but found nothing particular that varied from the ordinary leproma. Brault (1923) described the appearance of fresh leprous infiltrations of young epithelioid cells around the blood vessels. Barrera and Chavarria (1924) observed the formation of new blood vessels and inflammatory changes. According to Hopkins (1926) the reactive nodules contain only a few bacilli and are the result of the action of a toxin on the tissue. Lowe observed that small hemorrhages and polymorphonuclear leucocytic infiltration is to be met with in the reactive elements.

These data cover all the information on the question available to me, and I have therefore considered it worth while to report the results of my study of the matter. The material involved consisted of one autopsy case, the patient having died during the course of severe lepra fever, and of 10 biopsy specimens of reacting nodules of various characteristics and ages.

AUTOPSIED CASE

The material obtained from the autopsied case is here reported separately.

PATIENT G. Clinical diagnosis: lepra tuberosa. Duration 8 years. During the last two years the patient often suffered from exacerbations of the process, with eruption of reactive nodules and inflammation of old lepromas. Two months prior to exitus lepra fever occurred, with a temperature of 39°-40° C. Fresh erythematous nodules developed and the inguinal, femoral and axillary lymph nodes became enlarged and painful. These manifestations were accompanied by severe neuritis of the large nerve trunks, and also by symptoms of stenosis of the larynx, because of which tracheotomy was performed. Following the operation there was some improvement, which continued for a month. Thereafter the temperature rose again, there was a relapse of the lepra fever, and the patient became very weak and died of cardiac failure.

Postmortem findings: Marked degenerative changes in the internal organs, dilatation of the heart, massive congestion and edema of the lungs, acute hyperplasia of the spleen. Leprous lesions of the skin, the mucous membranes, the upper respiratory tract (especially of the larynx and trachea), the large nerve trunks and the lymph nodes, the last being increased to the size of a dove's egg and larger.

Skin lesions.—On section of the cutaneous lesions there were observed hemorrhages which spread in the subcutaneous tissue. For microscopic examination several nodules with hemorrhages were taken. The histological picture was unusual, due to changes in the structure of the leprous granuloma. Against the hemorrhages as a background were found separate groups of foamy cells containing bacilli. The cellular picture of the granuloma was variegated, and together with the foamy and epithelioid cells large accumulations of lymphoid cells were observed (Plate 9, fig. 1). The picture was completed by a large number of plasma cells, concentrated around the capillaries or forming separate foci independent of the course of the blood vessels. Foci of necrosis of various sizes were often encountered (Plate 9, fig. 2). One of the nodules examined presented an entire coagulation necrosis, a condition not characteristic of the leprous granuloma.

The histological picture of the nodules would be incomplete without the bacteriological investigation. Preparations stained by the Ziehl-Neelsen method contained numerous bacilli in the lepra cells and the endothelium of the capillaries. The endothelial cells were packed with the organisms to such an extent that the contours of vessels and their courses could easily be observed by the accumulations of brightly stained bacilli. Furthermore, a small number of bacilli were found among the erythrocytes in the lumens of the vessels. In the necrotic nodule on the other hand the bacilli had undergone marked changes; they were faintly stained with fuchsin and had acquired a granular appearance or presented isolated granules and fragments, and in the central part of the nodule they did not stain at all. The large nerve trunks were also involved in the process of reactive changes. Here, as in the skin, there were thick accumulations of lymphoid cells (Plate 9, fig. 3) and numerous plasma cells scattered along the length of the nerve.

Lymph nodes.—The markedly enlarged lymphatic nodes were found on microscopic examination to consist almost entirely of lepra cells, their proper tissue remaining only as small islets. The endothelial cells of the sinuses appeared hyperplastic and

were exfoliated and filled the lumens, where they were intermixed with numerous erythrocytes. Everywhere among the lepra cells accumulations of plasma cells were met.

Spleen.—In the spleen was noted a considerable hyperplasia of the cellular elements. The plasma cells were arranged around the small vessels and capillaries. Infiltrations consisting of lepra cells followed the course of the large vessels and trabeculae.

Bone marrow.—Macroscopically the bone marrow of the diaphysis of the femur appeared grayish red. The histological picture revealed hyperplasia of the cells, among which numerous plasma cells were observed.

Liver.—In the liver, besides infiltrations consisting of lepra cells, there were thick accumulations of lymphoid cells and small groups of plasma cells.

Throat.—The mucous membrane of the larynx and trachea was markedly thickened by leprous infiltration and accumulations of round and plasma cells.

Other findings.—No special changes could be found in the other organs except that bacillary emboli were found in the capillaries of the lungs. On examining the lymph nodes, spleen, liver and bone marrow for bacilli, large numbers of them were found in the endothelium of the capillaries.

BIOPSY SPECIMENS

The second part of this investigation consisted of the study of the reactive elements obtained by biopsy of lepromatous cases in the course of lepra fever. Those taken for investigation comprised: (a) newly appeared erythematous elements, (b) erythematous nodules of several days duration (up to 5 days) without signs of suppuration, (c) nodules that had undergone superficial purulent vesiculation, and (d) reactive nodules that had undergone purulent liquefaction.

New and recent lesions.—In the fresh nodules and those of several days duration there were found hyperemia, edema and loosening of the cutaneous tissue, and at the border of the subcutaneous tissue there were, as a rule, foci of fibrinoid necrosis. The walls of some of the blood vessels had also undergone fibrinoid swelling. In the specific granulomatous tissue located along the course of the vessels, activation of the cellular elements was noted. Here and there were scattered groups of round cells and sometimes groups of plasma cells. In some erythematous lesions

there was an added element, namely, slight infiltration of polymorphonuclear leucocytes.

Lesions with superficial suppuration.—Study of the nodules with purulent vesicles revealed the same changes as in the previous specimens, but the foci of fibrinoid necrosis were larger and more frequent (Plate 9, fig. 4). The walls of some blood vessels were thickened and had a fine granular or netted appearance.

Conspicuous here were large numbers of polymorphonuclear leucocytes, scattered mainly in the specific leprous tissue. They were scattered generally or formed accumulations among the granuloma cells, compressing them and pushing them to the periphery. Because of that fact, the foci of polymorphonuclear cells appeared as lighter formations among the specific leprous tissue (Plate 9, figs. 5 and 6). In places, the formation of real microabscesses could be observed (Plate 10, fig. 7). The perineural sheaths of the small cutaneous nerve branches were thickly infiltrated with leucocytes, which at times separated them from the nerve-fiber bundles (Plate 10, fig. 8.)

The presence of large numbers of these leucocytes in the tissues had, evidently, exercised an influence on the condition of the bacilli. They presented a granular appearance or were found as separated granules and fragments. Especially noticeable was the destruction of the bacilli in the infiltrations that consisted of lepra cells thickly invaded by leucocytes. In the foci where there was the greatest accumulation of leucocytes no bacilli whatever could be found. The bacillary globi which were observed in some instances were included in giant cells, or large or smaller numbers of leucocytes were arranged around them (Plate 10, fig. 9). Sometimes small globi—or, rather, remnants of them—could be observed lying among the numerous polymorphonuclears.

Nodules with purulent liquefaction.—The histological picture of these elements is very similar to that of ordinary abscesses (Plate 10, fig. 10). Thick accumulations of leucocytes involved the skin throughout its entire depth and partly extended into the subcutaneous tissue. Among the mass of purulent cells could be observed degenerated, poorly staining lepra cells. The foci of fibrinoid necrosis in the connective tissue reached considerable size, and fibrinoid swelling of the vascular walls became more pronounced (Plate 10, fig. 11).

The bacilli in the lepra cells had a granular appearance

and hardly retained the fuchsin stain. The main mass of bacilli consisted of large globules situated among the purulent cells. Some of these bacilli stained by fuchsin while others were decolorized and took on the counterstain. Frequently in studying the bacteriology of this reactive phase of the disease, smears of pus from reactive nodules were made; in them the bacilli showed the same degeneration and loss of acid-fastness.

It cannot be said whether or not the other organs and systems undergo changes similar to those described, since only biopsied material could be examined, but careful study of the patients gave convincing evidence that these changes are not limited solely to the skin lesions. A similar picture was observed in one case of leprous orchitis, in which bacillary globi were seen in the purulent liquefied leprous tissue among accumulations of polymorphonuclears. These globi consisted mainly of nonacid-fast bacilli. Fibrinoid necrosis of the vessels and the collagenous fibers of skin was also present.

DISCUSSION

The results of this investigation show that during the period of lepra fever there exists a heightened sensitivity to the causative agent in the organism of the patient. Jadassohn's conception of lepra fever as an allergic state receives confirmation in the histologic picture, as background of which there occur alterative changes in the form of fibrinoid necrosis of the collagenous substances and of the vascular walls. These changes, according to the more recent investigations (Gerlach, Klinge, Rössle, Abrikossov), present the morphologic expression of allergy. Leprologists know well that lepra fever can be induced by the most varied causes; i.e., the organism may respond by an allergic reaction under the influence of nonspecific factors.

In the case that was autopsied the hypersensitization had evidently reached its highest degree, since there were extensive hemorrhages and necrosis, which closely resembles the Schwarzman phenomenon. Owing to the severe necrobiotic process that developed in the leprous lesions, dissemination of the bacilli through the blood circulation took place. In this instance the endothelium of the skin capillaries and organs of the reticulo-endothelial system were loaded with the bacilli to the maximum degree.

The disturbances in the reactive property of the organism were reflected in the cellular picture of the leprous lesions. In

the autopsy case there were observed larger and smaller accumulations of lymphoid and plasma cells. In quiet lepromas plasma cells are always present, but usually they appear singly. The change of reactive capacity becomes especially prominent in cases in which suppuration of nodules occurs. In that condition the polymorphonuclear leucocytes begin to play a prominent role, which evidently exercises a considerable fermentative action upon the lepra cells and the bacilli. The latter, if they are not disintegrated completely by the leucocytes, suffer considerable degenerative changes, including the loss of acid-fastness.

There arises the question if in all instances the changes in the reactive capacity of the organism of the leper aggravates the pathological process. My investigation lends support to the conclusion that this is not always true. Clinical experience with the exacerbation state leads to the same conclusion. In some instances after frequently recurrent exacerbation the disease process changes for the worse. In others, when the reaction is accompanied by high temperature and suppuration of the nodules, there is often seen an arrest of the process for a considerable period of time, or definite improvement. However, further investigation in this field is necessary.

CONCLUSIONS

1. The histopathology of the leprous process in the reactive stage warrants the conclusion that lepra fever represents an allergic state.
2. The degenerative and necrotic changes of the collagenous element and of the smooth muscles (fibrinoid swelling), noted in the reactive nodules are the morphologic expression of the hyperergic reaction of tissue sensitization.
3. In some instances of lepra fever the hyperergic reaction passes with hemorrhages and necrosis analogously to the Schwarzman phenomenon.
4. The changes in the reactive capacity of the organism are reflected in the cellular picture of the specific leprous tissue. There appear numerous lymphoid, plasma and polymorphonuclear cells.
5. In the reactive nodules in which suppuration develops there occurs considerable degeneration of the bacilli, even to the loss of acid-fastness.

6. The polymorphonuclear leucocytes which invade the leprous infiltrations exercise a fermentative action upon the cells of the specific granuloma and the bacilli.

DESCRIPTION OF PLATES

PLATE 9

FIG. 1. A thick accumulation of lymphoid cells in a reactive nodule.

FIG. 2. Necrosis in a reactive nodule.

FIG. 3. An accumulation of lymphoid cells in the ulnar nerve.

FIG. 4. Fibrinoid necrosis of connective tissue of the skin in a reactive element with suppuration.

FIGS. 5 and 6. Focal and diffuse accumulations of polymorphonuclear leucocytes in a reactive nodule with suppuration (low and high magnifications).

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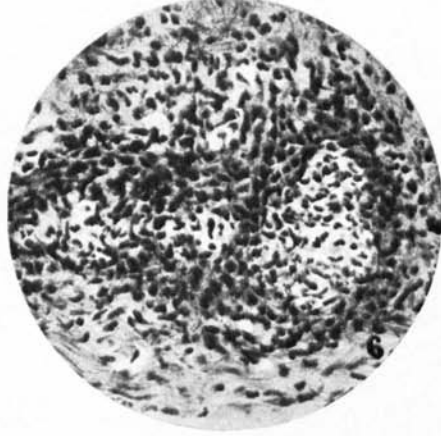
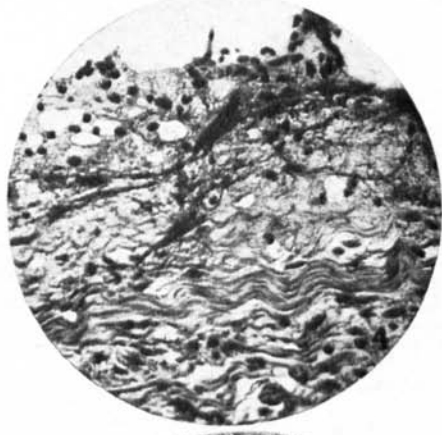
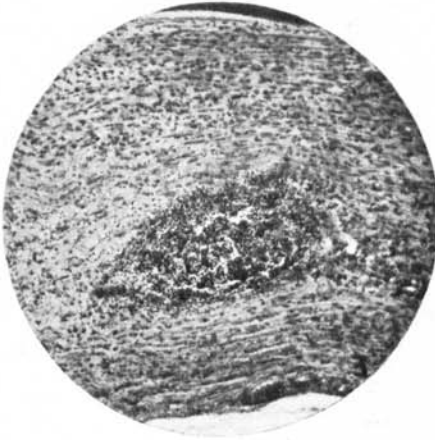
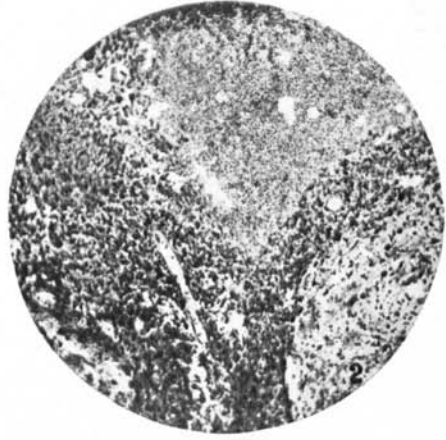
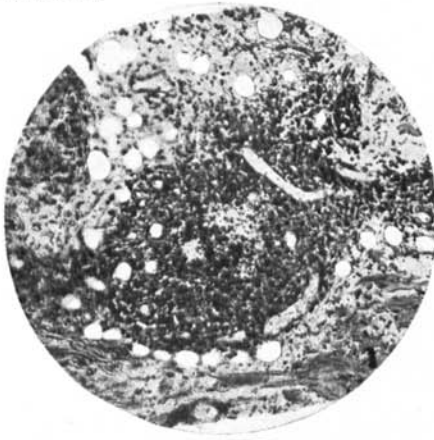


PLATE 9

PLATE 10

FIG. 7. Microabscess in a reactive nodule.

FIG. 8. Small cutaneous nerve branches with their perineural sheaths thickly infiltrated by leucocytes and in places detached. From a reactive nodule with suppuration.

FIG. 9. A bacillary globus surrounded by polymorphonuclear leucocytes.

FIG. 10. Purulent liquefaction of a reactive nodule.

FIG. 11. Fibrinoid necrosis of a blood vessel in a reactive nodule.

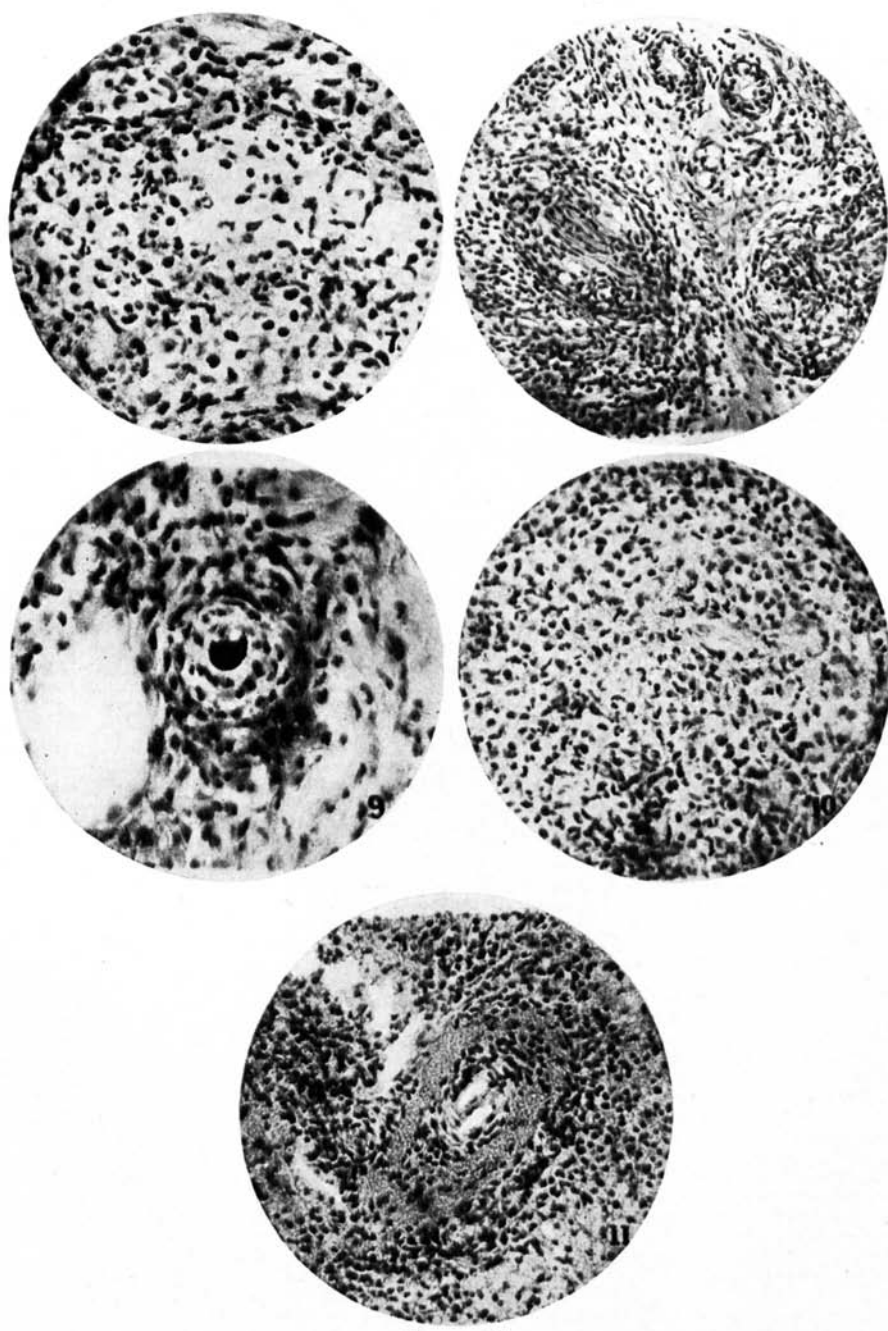


PLATE 10