EXTENDED ABSTRACTS

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STUDIES OF MURINE LEPROSY [1]

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I. MURINE LEPROSY: A STUDY OF ITS PATHOGENESIS AND EVOLUTION IN RATS INOCULATED BY THE PERITONEAL ROUTE

Since the early descriptions of murine leprosy by Stefansky (81), Dean (20), and Rabinowitsch (75), many investigators have concerned themselves with its pathology, in both naturally infected and experimentally inoculated rats; but most of the work has been on the more advanced stages of the infection. With reference to the earlier stages, and the analysis of the pathogenic-evolutive picture of the disease, there is relatively little information. In this connection we can cite only Fite (26) and Henderson (35), who inoculated rats subcutaneously and studied in detail the lesions produced at the sites of inoculation, and also described the pathological processes observed in the internal organs; but they did not study the various stages of the infection at different intervals, as is necessary for an elucidation of the progression of the lesions.

To attempt a systematic analysis of the data recorded by the various investigators, who for the most part worked under dissimilar conditions, is practically impossible. One of the difficulties of summarization is the diversity of the routes of inocula-

[1] The present material derives from two separate articles which appeared in the *Revista brasileira de Leprologia* **16** (1948) 139-163 and 191-200, under the titles which here are used as section headings. Both articles in the original are provided with extensive summaries in English which, revised and approved by the authors, form the bulk of this presentation; but a translation of the introductory section of the first of them has been introduced. Each article has a bibliography of about 50 items, here consolidated as one. The 24 photomicrographs reproduced are a selection, provided by the authors, from the 52 which illustrated the first of these articles.—EDITOR.

tion which have been employed for the study of the pathogenesis of the disease. The results obtained when different routes are used cannot be correlated, at least in the first stages of the evolution of the infection.

Subcutaneous inoculation, used by the majority of workers (e. g., 21, 26, 28, 35, 39, 44, 51, 54, 55, 69, 90), causes, besides the local lesion, involvement of the regional lymphatics and, later, generalization of the disease which begins four to six months after the inoculation (26). Similar results are obtained by the intramuscular route (39). Dissemination occurs most quickly when the injections are made intravenously (1, 8, 30, 50, 90), or into the heart (50). Employing the peritoneal route (2, 21, 28, 39, 51, 54, 55, 66, 67, 68, 69, 90), generalization occurs after periods which are intermediate in length, shorter than when the subcutaneous route is used.

Besides these routes the following have also been employed: oral (69, 90), gastric (46), conjunctival (59), ocular (anterior chamber) (31), subdural (90), nasal (91), percutaneous (44, 56, 69), intradermal (51), and testicular, cerebral splenic, vaginal, etc.; also subcutaneous grafting of leprous tissue (54, 90).

Analysis of the data described by these various authors leads to the conclusion that transmission of murine leprosy, as the final objective, can be satisfactorily accomplished whatever the route employed. It is observed, however, that both the dissemination as the pathogenic-evolutive aspect of the condition, and the localization of the principal lesions, vary in accordance with the route of inoculation employed. From this fact come the great difficulties which confront us in the attempt of arranging systematically, comparison of these findings.

For this reason, and in the absence of systematic data on the evolution of the disease, we decided to undertake such a study by peritoneal inoculation, as we believe it to be a route by which dissemination occurs with some rapidity and the technique of which is simple and certain.

In this work we used 265 young rats between 30 and 50 days in age and 40 to 70 gm. in weight. Most of them were of the McCollum and Wistar breeds; a smaller number was of a strain cross bred with *Rattus norvergicus* in this laboratory for this purpose.

The material used for the inoculations derived from experimentally infected rats after several passages. Animals in an optimal stage of the infection were sacrificed, and the subcutaneous nodules and such internal organs as were rich in bacilli

were triturated to make a homogeneous paste and suspended in physiological saline with 40% glycerine in the proportion of 1 to 20. This suspension was filtered through gauze and kept in the refrigerator at 4°C., the inoculations being made within, at most, 45 days. Before use this suspension was diluted until it corresponded in turbidity approximately to the No. 5 tube of the MacFarland scale. The concentration of the bacillary suspension was checked microscopically before inoculation. The inoculations were made intraperitoneally, usually in single doses of 0.5 cc. although the dosage was varied with some groups. Animals were sacrificed daily from the 1st to the 20th days, every five days from then to the 180th day, and after that every fifteen days.

We enumerate briefly here the findings of most interest, considering separately the changes found in the peritoneal cavity, the lymph nodes, and the liver, spleen, kidneys, lungs and bone marrow.

When invading the organism from the peritoneal cavity the bacilli follow three routes: (*a*) the lymphatic one, which brings them to the ganglia; (*b*) the hematic one, evidenced by detection of bacillemia, most common between the 3rd and 10th days, in which manner they are disseminated throughout the entire system; and (*c*) by contact, spreading in the abdominal and mediastinal organs and elsewhere. In general the lesions have this genesis: proliferation of the reticuloendothelial elements, followed by their differentiation to lepra cells; these cells increase in number and give place to a diffuse infiltrate which grows in size and then becomes delimited to constitute a leprous nodule.

In the peritoneum the alterations can be divided into two phases. The first occurs in the peritoneal cavity. Here come cellular elements from the blood—neutrophiles, lymphocytes, and some monocytes—to be followed later by reticuloendothelial elements—endothelial and reticular macrophages. The influx of blood-cell elements precedes that of reticuloendothelial elements, and decreases in proportion to the increase of the latter, so that on the 4th and 5th days after inoculation the neutrophiles and lymphocytes are rather few in number. Bacilli are encountered predominantly in the neutrophiles at first, and then almost exclusively in the elements of the reticuloendothelial system. The second phase takes place within the peritoneum, where subserous lepra cells become manifest. Constantly increasing, these cells give rise to leprous nodules, which are visible microscopically by the 8th day. Around the 120th day there are to be found actual

tumors of variable size, which show necrosis and central dissolution.

In the lymph nodes, 24 hours after the inoculation there are to be seen, in the cortical sinuses of the mediastinal and retroperitoneal nodes, areas in which endothelial sinus cells are mobilized. These cells contain variable numbers of bacilli in their cytoplasm. The lepra cells increase in number, involving steadily increasing areas of the cortex and invading the radial lymphatic sinuses in irregular fashion. From the 5th and 6th days on, the leprous infiltration takes a rounded form, creating nodular lesions which contain great numbers of bacilli. Until the 45th or 50th day there is no noticeable change of aspect of the lesion, but there is observed a decrease in the number of bacilli after the 15th day, reaching a minimum between the 30th and 40th days. After about the 45th day the nodular lesions increase in size progressively, fusing one with another (aspect of the 60th and 70th days), and the numbers of bacilli have again increased. Around the 150th day necrosis and autolytic processes are manifest in the large nodules. After the 180th day the capsule of the lymph node and the neighboring tissues may be involved.

In the liver, from the 10th day, intumescence of the Kupffer cells is apparent, and bacilli are to be found in their cytoplasm. Around the 20th day there is found infiltration of lymphoid cells, without bacilli, surrounding the blood vessels in the interlobular areas and centrally in the lobules. Between then and the 25th day histiocytes containing bacilli are to be found in these infiltrations. These cells increase in number until, after the 25th day, they constitute leprous nodules. For some time thereafter, until the 80th to the 100th days, no change in this picture is seen; but later on the nodules grow and exhibit necrosis and autolytic processes. The peritoneal investment of the liver and spleen may present lesions common to this membrane.

In the spleen, from 1 to 3 days after the inoculation, the endothelium of the venous sinuses and the reticular cells of the pulp present bacilli, without any alteration of the structure of the organ. After the 20th day the first groups of lepra cells are found, and they increase so that around the 30th day leprous nodules are to be found in the white and red pulp. Arrived at this stage, the lesions become stationary. The number of bacilli in these nodules is not great.

Within the kidneys it was not possible to find any lesion, only leprous infiltration of the capsule and in the fat tissue around the organ. In the advanced stages (about the 150th day) there

may be degenerative changes of the parenchyma. This lesion has the character of "punctate hyaline" degeneration.

In the lungs, from the 1st day, there are bacilli in the interstitial cells. After the 30th day proliferation of the adventitial cells of the blood vessels and of the small lymphatic follicles of the bronchi are to be seen. The first perivascular infiltrations of lepra cells are found after the 60th day. Nearing the 100th day there are leprous infiltrations without relation to the blood vessels.

In the bone marrow, from the first day, reticular cells containing bacilli can be found. Nearing the 30th day infiltrates and nodules appear; in some cases the bone marrow lesions are very large and deep, and they may affect the bone itself. Other organs may present infiltrations or nodules, and some may be compressed by growing lesions in neighboring infected tissues.

Peritoneal inoculation gives rise to a generalized infection, with progressive evolution which presents constant and regular lesions, which show no tendency to spontaneous retrogression.

EXPERIMENTAL CHEMOTHERAPY OF LEPROSY; THE USE OF MURINE LEPROSY FOR THE EXPERIMENTAL TESTING OF CHEMOTHERAPEUTIC COMPOUNDS; DESCRIPTION OF A TECHNIQUE

The want of a culture of *M. leprae,* and the lack of an animal susceptible to infection by it, make difficult the experimental evaluation of antileprosy drugs. This difficulty may be overcome by utilizing *M. leprae muris,* submitting it to the action of these drugs. Several authors have reported studies of this nature in which different methods have been employed. They have treated animals in the early stages of the infection or in advanced phases of its evolution, or have determined the action of the drugs *in vitro* by inoculating rats with bacilli treated with them. The therapeutic effect was adjudged by the reduction in size of the lepromas or their ulcers, or by the behavior of the malady in evolution when the animal or the bacilli have been subject to the action of the drugs.

The experimental testing of drugs responsible for antileprosy effects is of great moment, especially in view of the increasing number of new medicaments which are being produced. It has been recommended by Wade that there should be established a program of work "whereby the new drugs now in use may be evaluated scientifically," and "to make preliminary tests of new

drugs which appear to be of promise but which have not yet been used in the treatment of leprosy." There is no established model method which allows a sure checking of therapeutic action against leprosy in the laboratory. Based on the findings presented in our previous work, a method of study has been designed.

Peritoneal inoculation of *M. leprae muris* gives rise to a generalized infection in rats, with progressive evolution which presents constant and regular lesions, with no tendency to spontaneous retrogression. It is on this basis that our work in the testing of antileprosy drugs has been established. The evolution of the lesions initiated in that way is observed under the action of the treatment.

The plan involves the use of young rats, of ages varying between 30 and 50 days, belonging preferably to the McCollum and Wistar breeds. The material used for the inoculations is that which has been described in the preceding report. Single inoculations of 0.5 cc. of the final dilution are used. The animals are separated into lots of 36, of which 24 receive treatment and 12 are saved for controls. They receive one or two doses of the drug daily, preferably by the peritoneal route. When given by mouth, it is added to the food in 0.5 per cent concentration. The doses are increased as the animals gain in weight. In any case they always have to be several times larger proportionately than the doses used in man.

From the 5th or 6th day on, the leprous infiltration takes a rounded form, creating nodular lesions which contain great numbers of bacilli. These lesions are evident, after intraperitoneal inoculation, in the retroperitoneal and mediastinal lymph nodes.

Treatment is begun when the first leprous nodules in the lymph nodes are manifest (i. e., on the 5th or 6th day after inoculation), while the animals still have a reserve of bodily defense and the lesions are recent and well vascularized. Observation of the treated animals has to be continued during the evolution of the malady, in some cases until the natural death of the animal. From the 90th day after the beginning of the treatment some of the treated animals and of the controls are sacrificed, and this is continued every 30 days.

The resemblance between *M. leprae hominis* and *M. leprae muris* is the justification for employing murine leprosy in the experimental testing of antileprosy drugs. It is realized that the results observed pertain to the therapy of murine leprosy; for

lack of more objective features no attempt is made to draw a parallel between murine and human leprosy, and the results obtained in the former may perhaps be applicable only in part to the latter. Nevertheless, the usefulness of this method of testing new antileprosy drugs is not confuted by these facts.

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DESCRIPTION OF PLATES

PLATE 7.

FIG. 1. Omentum. General aspect of the leprous lesions.

FIG. 2. Peritoneal nodule with area of necrosis.

FIG. 3. Liver. A small, early focus of cells with reticular nuclei and histiocytes near a portal vein.

FIG. 4. Liver. An early lesion, composed of lymphoid cells and histocytes, in the interlobular area.

FIG. 5. Liver. A leprous nodule near a portal vein.

FIG. 6. Liver. A nodule of advanced stage, with necrosis.

FIG. 7. Spleen. Leprous nodules at the periphery of a Malpighian corpuscle.

FIG. 8. Spleen. A leprous nodule in the capsule.

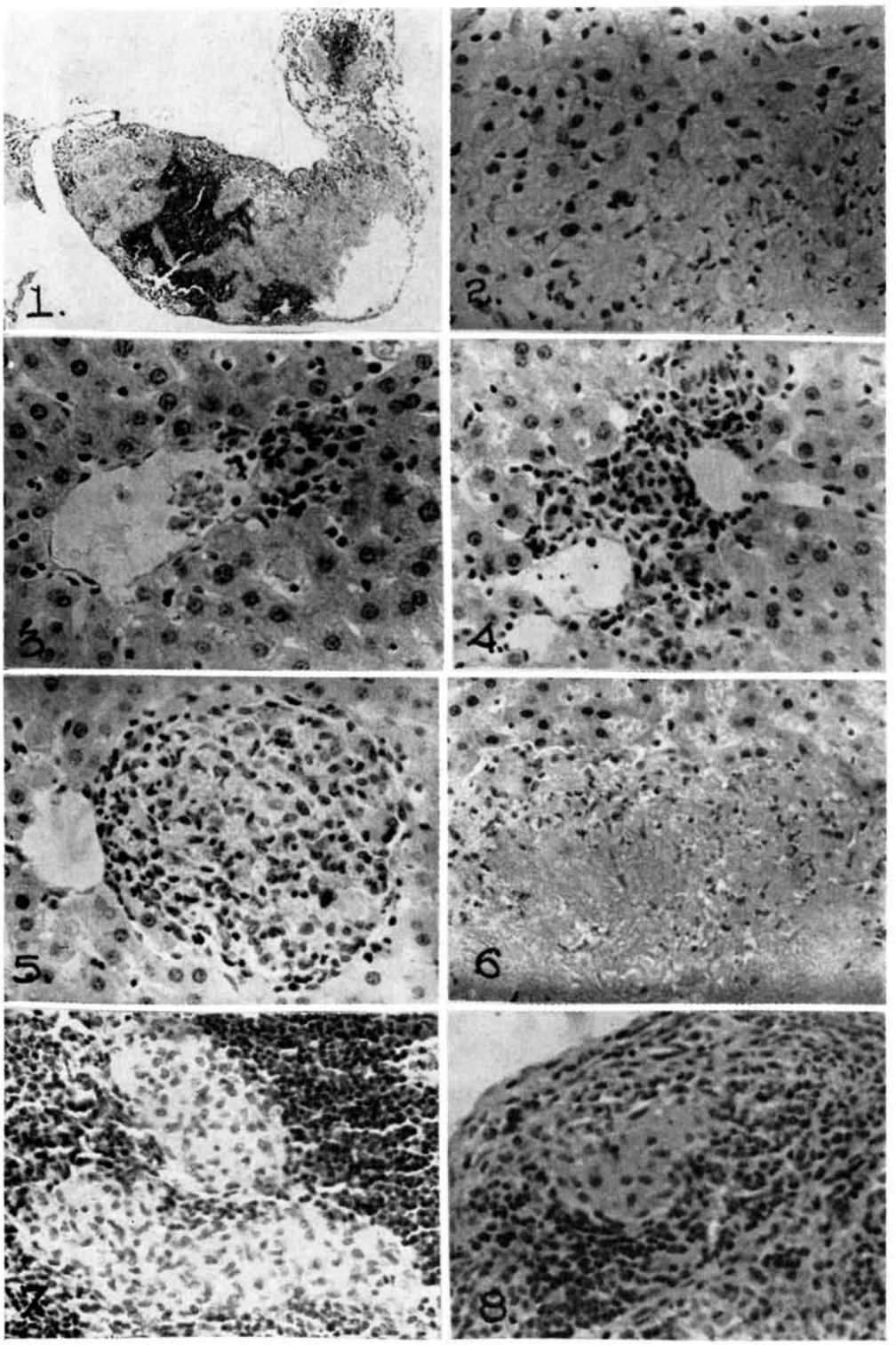

PLATE 7.

PLATE 8.

FIG. 9. Spleen. Leprous nodules in the white pulp.

FIG. 10. Lymph node. Early lesion near the marginal sinus.

FIG. 11. Lymph node. Impression smear, showing large numbers of bacilli, Ziehl-Neelsen stain.

FIG. 12. Lymph node. Bacilli in a lesion near the marginal sinus, Ziehl-Neelsen stain.

FIG. 13. Lymph node. Leprous infiltration of the cortex, showing reticular hyperplasia and the formation of macrophages.

FIG. 14. Lymph node. Showing the nodular arrangement of the lesions.

FIG. 15. Lymph node. Nodular lesions six days after intraperitoneal inoculation.

FIG. 16. Lymph node. Leprous nodules with giant cells.

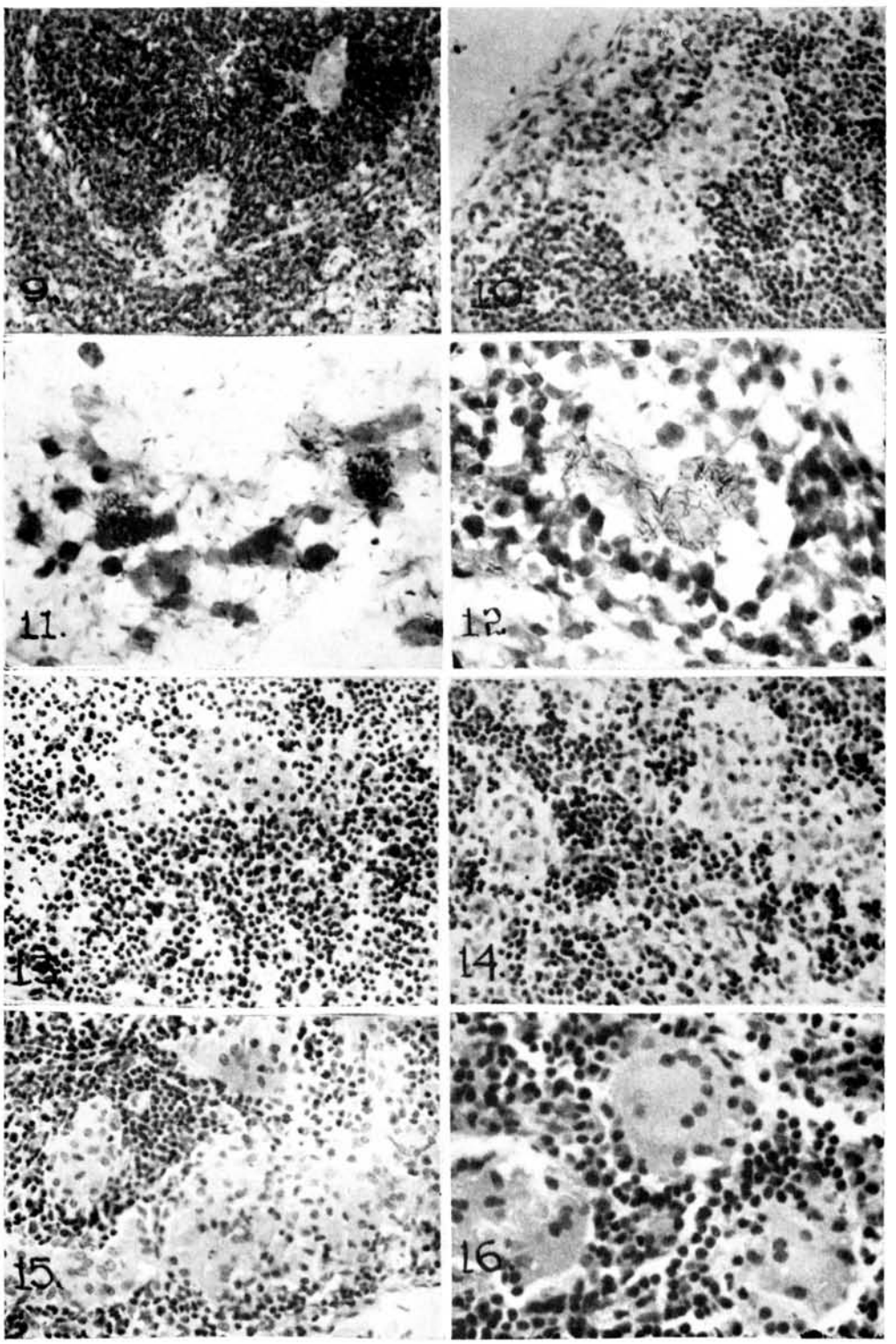

PLATE 8.

PLATE 9.

FIG. 17. Lymph node. Lesions of a moderately advanced stage.

FIG. 18. Lymph node. Leprous lesions.

FIG. 19. Lymph node. Leprous lesions.

FIG. 20. Lymph node. General view, low magnification, of lesions of a middle stage of advancement.

FIG. 21. Lymph node. Lesions of moderately advanced stage, with involvement of the capsule.

FIG. 22. Lymph node. Advanced stage, with destruction of the normal structure.

FIG. 23. Lymph node. Advanced stage, with a large central necrotic area.

FIG. 24. Lung. Small leprotic nodules in the alveolar septa.

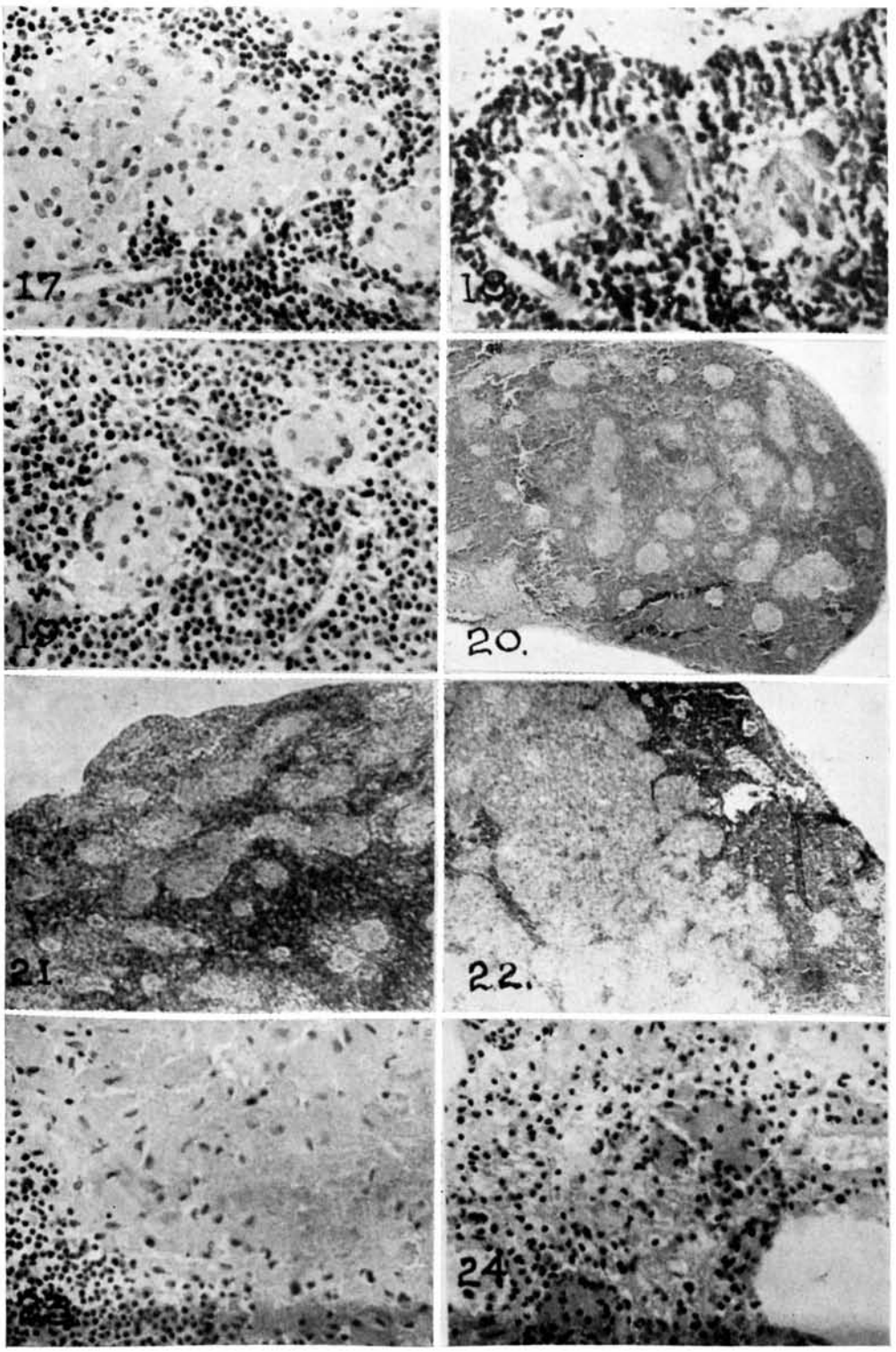

PLATE 9.