VISCERAL TUBERCULOID LEPROSY

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In a previous communication (5) one of us described the finding of histological lesions in the liver and abdominal lymph nodes in a case of tuberculoid leprosy in a state of reaction, from which biopsy specimens of those organs had been obtained by laparotomy. The lesions were regarded as of leprous etiology because of the presence of *M. leprae.*

In that report it was demonstrated that in the course of tuberculoid lepra reaction the viscera may contain histiocytic granulomas with peripheral lymphocytic reaction. It was not possible in that instance to demonstrate the existence of definitely formed tuberculoid follicles, and that fact was explained by the phase of reaction at the time of the intervention, when the tuberculoid follicles might have been temporarily effaced.

We have continued that study, and now present the histological findings of liver biopsies performed in eight more cases.

MATERIAL AND METHODS

Five of the patients here dealt with had tuberculoid leprosy —three in a state of reaction and two in the quiescent form— while two were of the undifferentiated form. All of them were first studied clinically, histologically and immunologically. None presented any sign or symptom of digestive disturbance. The criteria applied in the selection of the cases were the presence of lesions fully characteristic of the forms of the disease which they represented, the lack of history or present clinical evidence of complicating infection of tuberculous or other etiology, and the patients' acquiescense to the study to be undertaken.

Of the possible methods of obtaining tissue from the liver or other visceral organs we did not choose the most simple one, that of puncture. We prefer to open the abdomen surgically, because in that way we can explore the organs and, without undue risk, obtain liver specimens of larger size which permit better histological study. The harmlessness of this method, when proper technique is used, was demonstrated in our previous report.

The laparotomy incision is a paramedial one, made under local anesthesia, extending 5 to 7 cm. downward from the right costal border and involving all of the layers including the peritoneum. After exposure of the anterior border of the liver, a triangular prism of liver tissue is taken out with the aid of a scalpel. The abdominal wall is closed by layers. In no case was there hemorrhage of any importance during or after the removal of the specimen, and in all cases correct healing was obtained without any ill effect.

The biopsy specimens were fixed in 10 per cent formalin and embedded in paraffin. The sections were stained with hematoxylin-eosin and by the Ziehl-Neelsen method. Besides that, a part of each specimen was saved for frozen sections, for a study of its fat content.

OBSERVATIONS

In none of the cases studied was any macroscopic alteration of the liver observed during operation.

In all five specimens from the tuberculoid cases, tuberculoid follicles are present in the sections. These foci are always multiple, of small dimensions, and situated by preference under the peritoneal serosa and in the portal spaces (Figs. 1 and 2). Each follicle is made up of a group of 8 to 10 epithelioid cells; in only two instances are multinucleated giant cells to be found (Fig. 3). In the reactional cases these lesions are in larger numbers than in the others, with more of the nonspecific inflammatory component—lymphocytic halo and some polymorphonuclear leucocytes—and with vacuolization of the monocytes, congestion and interstitial edema.

The parenchymal liver tissue and the intrahepatic bile ducts appear to have suffered no anatomical changes of note. The focal nature of the lesions explains this fact, and constitutes a differential characteristic with respect to the lepromatous infiltration of the liver, which in contrast is of the diffuse type (11, 12, 19, 21).

In one of the two cases of undifferentiated leprosy studied the only abnormality found consists of small subcapsular and interstitial foci of lymphocytes and polymorphonuclear neutrophiles. Because no acid-fast bacilli could be found, we are unable to assert that these lesions are of leprous nature; in fact, their morphology may correspond to any chronic inflammatory process, hepatic or general.

The second case of undifferentiated leprosy showed, a few weeks prior to the biopsy, congestion and tumefaction of the old macules and at the same time the appearance of new ones. The lepromin reaction was weakly positive, and bacteriological examination of the skin lesions revealed scarce, isolated bacilli.

In this case the biopsy specimen reveals follicles of the type called "subtuberculoid" by Wade (22, 23)—meaning epithelioid foci "too small or too undifferentiated to be called definitely tuberculoid"—and "pretuberculoid" by Portugal (15). (Fig. 4.) This case would seem to be an "incharacteristic" one undergoing change to tuberculoid. We do not know if this differentiation or transformation is histologically apparent earliest in the skin or in the viscera, for no biopsies of the skin and of the liver have been made simultaneously. We are inclined to believe, however that the changes may occur in both tissues at the same time, on the assumption that they result from a general immunological factor and not from local causes in the individual tissues.

The findings here described are summarized in Table 1.

TABLE 1.—Summary of cases studied and findings of liver biopsies.

Case No.	Type of leprosy	Histological lesions of the liver
1	Tuberculoid, reactional	Tuberculoid follicles
2	Tuberculoid, reactional	Tuberculoid follicles
3	Tuberculoid, reactional	Tuberculoid follicles
4	Tuberculoid, quiescent	Tuberculoid follicles
5	Tuberculoid, quiescent	Tuberculoid follicles
6	Undifferentiated	"Pretuberculoid" follicles
7	Undifferentiated, reactional?	Tuberculoid follicles

DISCUSSION

The literature available to us reveals decided differences of opinion regarding the existence of tuberculoid leprous lesions in regions other than the skin, nerves and superficial lymph nodes. These differences are due, in our opinion, to the difference of prognosis between the two polar forms of leprosy. The lepromatous form is of bad prognosis, of itself and because of the frequent association of tuberculosis and other processes which lead to the death of the patients, thus making possible the postmortem study of such cases, whereas the tuberculoid form is usually of good prognosis and there is practically no opportunity to perform autopsies of such cases. It was for this reason that we undertook to make biopsies of the liver.

Since the time when Danielssen and Boeck, in their atlas (7), depicted miliary and larger lesions on serous surfaces which they assumed to be of leprotic nature but which generally have been

taken for tuberculous, so far as we know only Arning (1) has reported such lesions with the same belief as to their etiology. While studying leprosy in Hawaii, it seems, he performed 17 autopsies and in 11 of them found macroscopic, palpable, semiglobular masses which contained bacilli, singly and in groups, but which failed to infect rabbits. A picture of one of his spleen specimens, with relatively large nodules on or showing through the surface, and one of a uterus with adnexia showing "papillary excresences," were later published by Schaeffer (19). As in the earlier instance, these lesions have been generally believed to have been of tuberculous nature.

A few years later, at the German Dermatological Congress held in Strasbourg in 1898, Jadassohn (9) reported the first case of leprosy with tuberculoid skin lesions recognized and designated as such, and on the same occasion Arning (2) reported on a case of tuberculoid nerve abscess which had been operated on and reported by Cramer some years previously; and he also told of such lesions which he had observed in Hawaii. He held that the differences between lepromatous and tuberculoid leprosy are "solely dependent on the reciprocal state of the host and the invader." In connection with these two papers, Blaschko and Gluck presented sections of nerves with tuberculoid changes. Jadassohn had in mind the possibility that similar lesions might also occur in the viscera, and later (10) he wrote: "Such histological changes probably also occur in the inner organs." This uncertainty about this form of leprosy is in great contrast with the many reports—too numerous and too well known to require further reference here—which describe the visceral lesions of the lepromatous type.

Nearly forty years after the Strasbourg conference referred to, when the tuberculoid condition in leprosy had become more familiar, Arning (3) again raised the question of whether tuberculoid changes of leprotic nature may occur in the viscera, and suggested that an inquiry on the subject be made. In the symposium which ensued all of the participating leprologists manifested lack of knowledge of visceral manifestations of tuberculoid leprosy, and Lowe pointed out that such cases do not come to autopsy. Wade, although not convinced that visceral lesions occur in that form of the disease, agreed that "special efforts should be made in different regions to settle the question definitely"; and Lie also agreed with Arning's proposal that it should be reexamined.

The more recent literature which we have been able to con-

sult set forth the problem in different ways, and even with contradictions, which shows how little information there is about this matter.

Müller and Mertodidjojo (14) asserted that "tuberculoid structures found in the viscera are never caused by leprosy," and Müller (13) maintained that view in saying that "tuberculoid leprosy of the internal organs does not exist."

Other authors have been less positive, admitting the possibility that such lesions may exist and that with better means of study they may be demonstrated in the future.

Rabello Jr. (16) at first indicated a contrary point of view, saying: "We give the name tuberculoid leprosy to bacillogenous changes of leprotic nature in the skin, nerves and lymph nodes"; but in a later communication (17) he expressed an opinion more in harmony with our findings, saying that ". . . tuberculoid leprosy, like the leprosy of Virchow, is not limited to the skin, but rather is a syndrome which can be placed in parallel with the lepromatous syndrome; that is to say, it is a general disease."

More recently, Schujman and Carboni (20) have said that "tuberculoid leprosy may...even be accompanied...by visceral manifestations"; and Rotberg and Bechelli (18) maintained that future investigations "will permit the demonstration of these extracutaneous manifestations in tuberculoid cases."

The orthodox view nevertheless persists. For example, Büngeler, in the chapter on pathology of tropical diseases in the book of Hueck (8), states textually: "Tuberculoid leprosy is . . . exclusively a cutaneous disease. Only in the lepromatous form are internal lesions produced." Most recently, Cochrane (6) has asked why tuberculoid histological lesions in internal organs have not been described, and he answers himself with the supposition that in tuberculoid leprosy the bacilli are retained in the subcutaneous tissues and have no possibility of dissemination into the deeper organs.

This hypothesis is in conflict with the frequent observation of reactional cases in which there is blood-stream dissemination of *M. leprae* and consequent formation and development of new skin lesions by metastasis. If there is dissemination by that route, there is no reason to suppose that the bacilli cannot reach the viscera, and that, once settled there, they cannot produce anatomical lesions such as those which we have found. In keeping with this idea, Cochrane himself maintains that in cases in which there is resistance—and such is the case in the tuberculoid form of leprosy—"whatever the tissue which *M. leprae*

invades, it forms tuberculoid foci which fix the invading organism . . ."

What in our opinion may occur in tuberculoid leprosy—and in fact it evidently occurs in most cases—is that there are anatomical changes which have no manifest clinical expression because of their focal character and their small size. This may be the reason for the lack of clinical symptoms referable to the viscera in that form of the disease, in contrast to the lepromatous form in which they frequently occur (4).

We believe that the tuberculoid follicles which we have found in our cases are of leprous etiology, for the following reasons: (1) None of the patients presented signs or symptoms of tuberculous infection of the lungs or of any other organ. (2) If the follicles described were tuberculous they would belong to a process of hematogenous miliary dissemination; but the fact that the patients were in perfect physical condition and have remained well during the two years which have elapsed since we performed the biopsies permits us to discard that possibility. (3) None of these patients showed then, or show now, signs or symptoms of any other disease such as syphilis, leishmaniasis or sarcoid, which might possibly give rise to similar lesions. (4) On the other hand, if we consider what is known of the pathology of leprosy we are unable to acknowledge that such an infection can be limited exclusively to the integument, since in the course of its evolution there occur hematogenous disseminations and extensions, especially during the phases of reaction.

We must conclude, as stated, that the fact that other authors have been unable to find tuberculoid leprous lesions of the viscera, or have been unable to accept their existence, is due primarily to the technique employed, to the fact that these lesions do not cause manifest clinical symptoms, and, finally, to the fact that tuberculoid leprosy is a benign process which does not cause death of the persons in whom such lesions are produced.

SUMMARY

The histological lesions encountered in biopsies of the liver performed in five patients with tuberculoid leprosy and two patients with the undifferentiated form are described. In the first five cases and in one of the latter two, there were found characteristic tuberculoid follicles which we attribute, for reasons which have been given, to the action of the leprosy bacillus. In the other undifferentiated case there was found only infiltrations of chronic type the etiology of which cannot be determined.

The existence of such visceral granulomas in tuberculoid cases permits the conclusion that in this type of leprosy the infection is not confined solely to the skin, nerves and superficial lymph nodes, as has been maintained by almost all authors, but that it also produces lesions in deep organs, even though the condition is not made manifest by clinical symptoms.

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DESCRIPTION OF PLATE

PLATE 12.

FIG. 1. Low-power view of a liver section demonstrating the focal and perilobular localization of the granulomatous follicles described.

FIG. 2. Subcapsular tuberculoid focus of the liver. Note the polymorphonuclear and peripheral lymphocytic infiltration, characteristic of the reactional conditions.

FIG. 3. A Langhan's giant cell in a tuberculoid liver follicle.

FIG. 4. "Pretuberculoid" follicle, with abundant peripheral lymphocytic reaction. This lesion was found in Case 7.

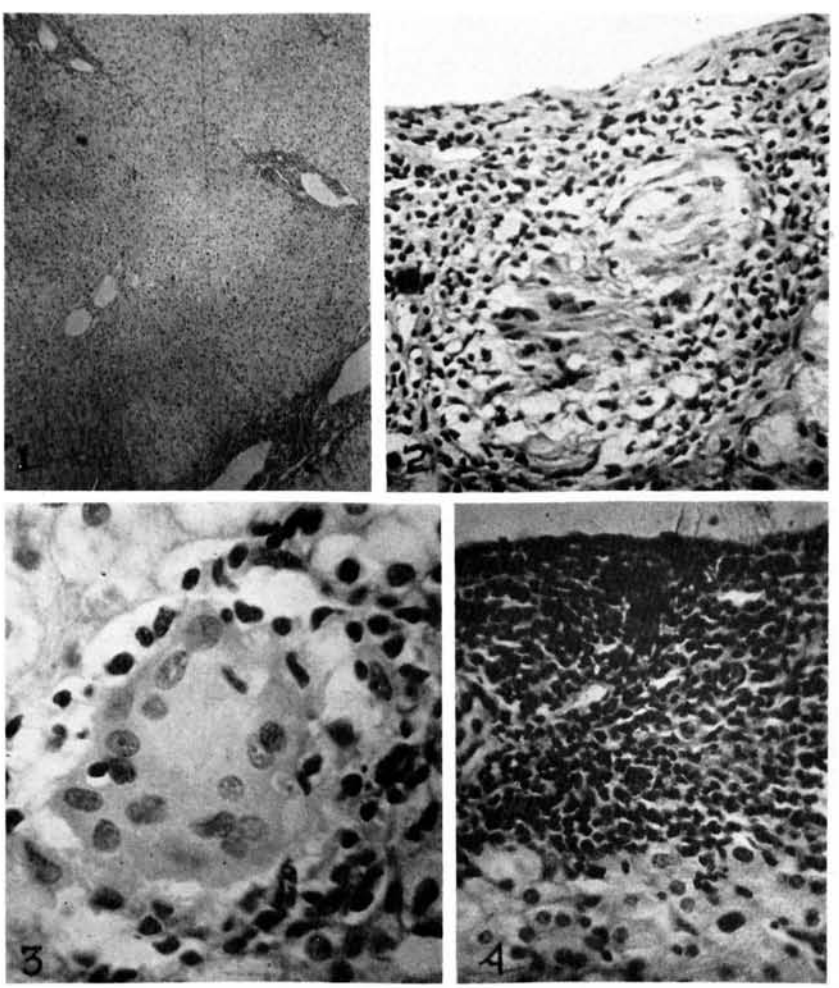

PLATE 12.