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Hepatic Lesions in Lepromatous Patients[1, 2]

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In spite of the increase in knowledge derived from hepatic biopsy in recent years, studies on hepatic morphopathology in leprosy are not numerous. Some investigations, however, ([1, 3, 6, 8, 9, 12, 14, 15, 16, 17, 18, 19, 20]) have dealt with the description of hepatic lesions in leprosy and the frequency with which they occur. Others ([2, 4, 5, 7, 11] etc.) have attempted to establish more concrete anatomicoclinical relationships and to obtain results that are of practical importance in understanding hepatic lesions.

A review of these studies indicates (1) that hepatic involvement is frequent in lepromatous leprosy and deserves attention by leprologists, (2) that hepatic involvement in tuberculoid, dimorphous and indeterminate forms is inconstant, of little or no specificity, and therefore doubtful, and finally (3) that a knowledge of hepatic morphopathology can be useful for understanding the evolution of disease in leprosy patients. These possibilities have stimulated us to review our autopsy material with a view to bringing our experience to bear on the problem of hepatic morphopathology in leprosy.

MATERIALS AND METHODS

We have reviewed the morphopathology of the livers of 29 lepromatous patients, utilizing the following stains: hematoxylin-eosin; the Perl test for iron; Ziehl-Neelsen, for the demonstration of acid-fast bacilli; Congo red for amyloid; Masson's trichrome; and Laidlaw's silver impregnation method. The 29 clinical histories were reviewed and an effort was made to correlate clinical data with histologic findings.

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RESULTS

The 29 patients studied had all been classified as lepromatous on the basis of clinical, bacteriologic, immunologic and anatomopathologic characteristics. On the basis of common hepatic findings the cases were classified into seven groups, as follows:

I. Five cases (17.2%). All of these showed "lepromatous hepatitis," characterized by the presence of small, well limited portal and centrolobular lepromas, made up of Virchow cells with or without lymphocytes. Fibrosis was minimal and limited to the small lepromas. The lobular structure appeared perfectly preserved, and there were no other changes worthy of mention. Bacilli or acid-fast granular material, or both, were demonstrated in all cases, though sometimes with difficulty.

II. Two cases (6.8%). In these the picture was identical with that of Group I, except that in two patients there was cardiac disease, so that the lepromatous hepatitis was associated with changes due to congestion. Neither state modified the character of the other. In each case isolated bacilli, acid-fast granular material, or both together, were demonstrable, although visualization was quite difficult. The low grade of fibrosis encountered seemed more closely related to the congestion than to the lepromatous hepatitis.

III. Four cases (13.7%). In all these, in addition to lepromatous hepatitis, there was amyloidosis, minimal in one case, moderate in another, and intense in the other two. In the small lepromas seen in all cases, it was possible, although with difficulty, to demonstrate the same bacillary elements. The quantity and topography of amyloid bore no relation to the lepromatous lesions. The impression was gained that the two processes, although coexistent, were morphologically independent in origin and unrelated.

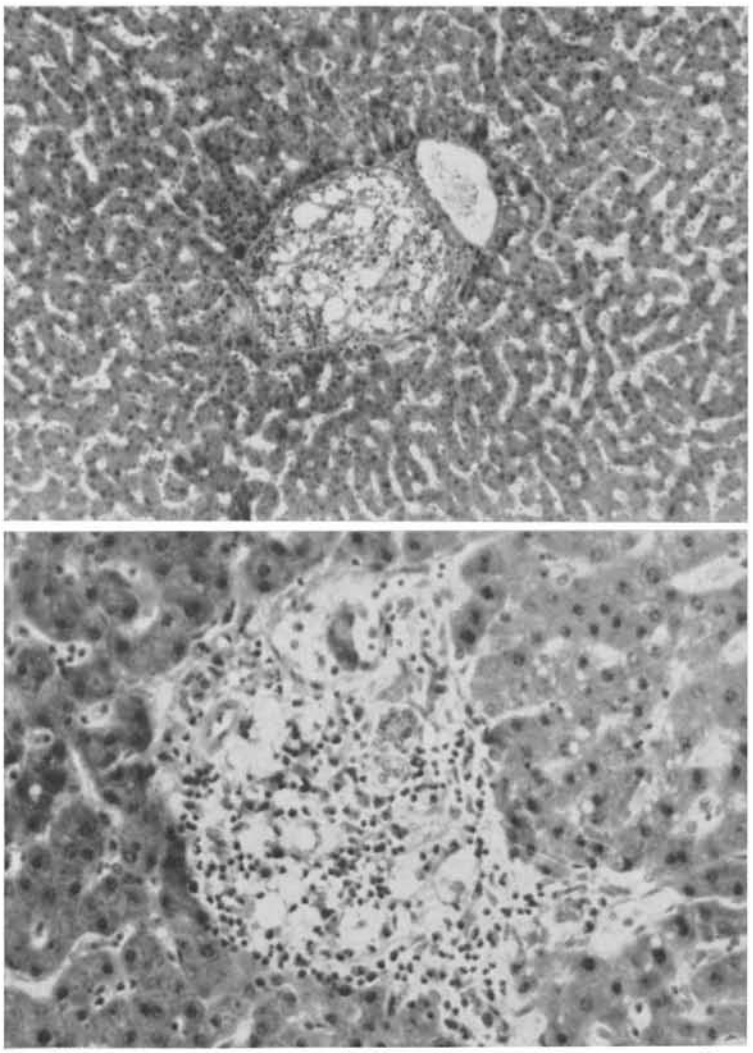

FIG. 1. Small leproma, well circumscribed, in the immediate vicinity of a centrolobular vein. Hematoxylin and eosin stain. Magnification: 40×.

FIG. 2. Leproma occupying a portal space. Hematoxylin and eosin stain. Magnification: 100×.

IV. Three cases (10.3%). Together with the lepromatous hepatitis, there was a true septal cirrhosis in one case (Group IVa) and postnecrotic cirrhosis in two cases (Group IVb). Except for the single case of septal cirrhosis, isolated bacilli, acid-fast granules, or both, were demonstrable in the small lepromas. The latter were clearly apparent in the fibrous bands, but in relation with pre-existent portal spaces or centrolobular veins. In no respect did these small lepromas modify the usual appearance of the fibrosis, and morphologically there was no indication that they were responsible for the cirrhosis. In one of the two cases of postnecrotic cirrhosis a certain amount of iron pigment was evident in relation to the hepatocytes and Kupffer cells, but not the Virchow cells.

When Groups I, II, III and IV are considered together, with the common denominator of lepromatous hepatitis, the frequency of this abnormality reaches 48.2 per cent in our material. Bacilli were found in all cases but one. Although the search was laborious, acid-fast granules, many of them of anomalous forms, were numerous. The small lepromas were always portal or cen-

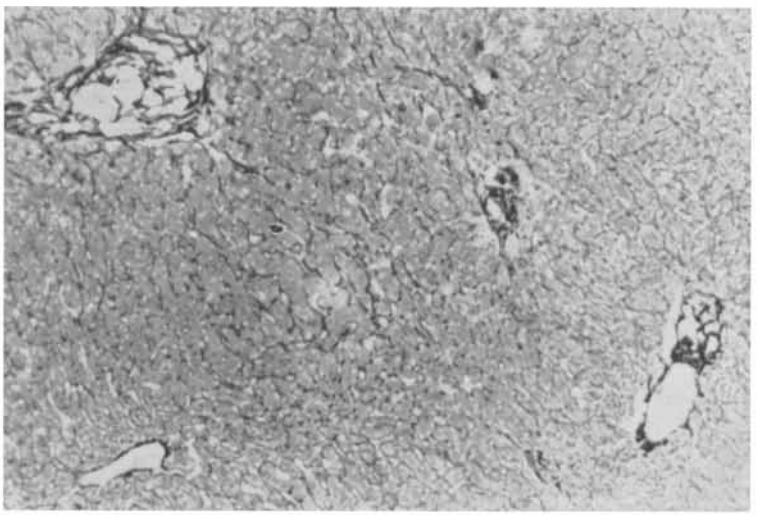

FIG. 3. The small portal or centrolobular lepromas seem well delimited, and there are no bands of collagen or reticulin going out from them to disturb the lobular structure. Laidlaw stain. Magnification: 40×.

trolobular, and even though Kupffer cells loaded with bacilli could be found in early stages, these tended to disappear, so that in advanced forms only small portal (Fig. 1) or centrolobular (Fig. 2) lepromas persisted. In one case only we could demonstrate an occasional vacuolated Kupffer cell, but without visible bacilli under the light microscope. In no case could we trace the presence of fibrosis to the small lepromas (Fig. 3), in spite of the fact that in some cases the evolution of the disease had taken place over many years. Thus we have not found any relation between lepromatous hepatitis and cirrhosis, nor between the latter and the amyloidosis.

V. Three cases (10.3%), in which the only hepatic lesion was amyloidosis. In all three the deposit was intense, and related both to the blood vessels and the sinusoids, with resultant atrophy of the hepatocytes. Staining with Congo red gave variable results; occasionally it gave negative results. With polarized light, however, it was possible to demonstrate the phenomenon of dichroism. This birefringence of amyloid stained with Congo red proved of great utility, for it was induced even in tissues having less apparent affinity for the stain and permitted differentiation from other pathologic substances. The amyloid, even in cases with heavy deposition, did not break down the reticular texture, nor lead to collapse, or induce cirrhosis.

When Groups III and V, with amyloidosis in common, were considered jointly, the frequency of the latter in this material was 24.1 per cent. The amyloidosis was not always coincidental with lepromatous hepatitis, nor related in quantity or topography to the latter. The deposit of amyloid seemed to begin in the portal vessels, and in the most intense cases extended to the sinusoids, with atrophy of the hepatocytes (Fig. 4). Deposits of surprisingly great intensity were compatible with survival. Study of preparations stained with Congo red, under polarized light, facilitated the finding of amyloid and its differentiation from other pathologic substances (Fig. 5, 6). In no case was there morphologic evidence that amyloidosis can cause cirrhosis (Fig. 7).

VI. Five cases (17.2%). In two cases the only lesion was septal cirrhosis (Fig. 8, Group VIa); in three there was postnecrotic cirrhosis (Group VIb). No morphologic data differentiated these forms of cirrhosis from those ordinarily found in nonleprotic patients. The morphology, therefore, suggested that the etiology was not to be attributed specifically to leprosy, but perhaps to toxic, viral, nutritional or other causes, as in the case of other types of cirrhosis.

When Groups IV and VI are considered

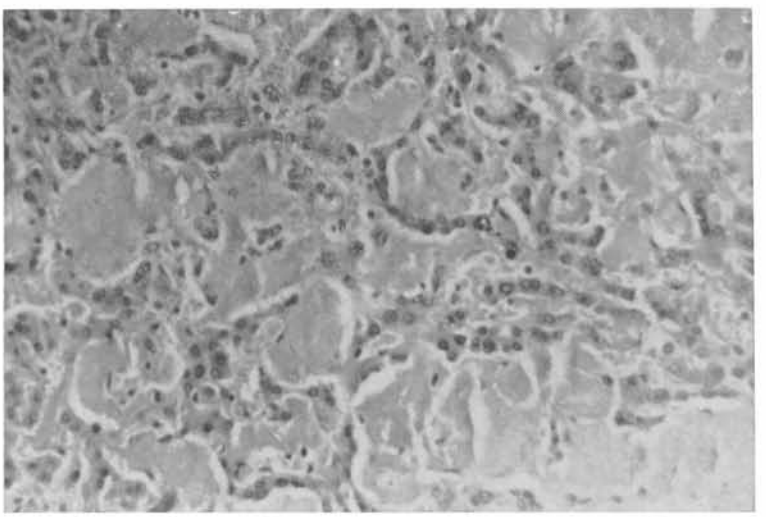

FIG. 4. The deposit of amyloid compromises and occasions atrophy of the cords of hepatocytes. Hematoxylin and eosin stain. Magnification: 100×.

on the basis of the common denominator of cirrhosis, the frequency of the latter in this material is 27.5 per cent. This figure (in spite of the small amount of material in this study) might seem to indicate a greater frequency of cirrhosis among leprosy patients than in the general population. As possible causes for this, the various injections and transfusions such patients receive which might lead to viral hepatitis, as well as alimentary defects, and the toxic action of alcohol, or the specific or nonspecific treatment given to leprosy patients, have to be considered.

VII. Seven cases. This group of seven cases lacks interest for this study, for it is made up of cases whose hepatic morphopathology corresponds with some well defined entities quite apart from leprosy. There were three cases of hepatic congestion in cardiac patients. There was one case of lymphomatous infiltration of the liver, in a patient with lymphoid leukemia. One case was diagnosed as cholangiolytic hepatitis; it was difficult to determine if this might be of viral or drug origin. One case showed an essentially normal hepatic picture. In the final case there was chronic hepatitis, with lymphohistiocyte and plasma cell infiltration of portal areas with slight fibrosis. The complete lack of specificity in the picture in these cases did not permit any suggestion of relation with leprosy.

The comparison of these morphologic findings with the clinical data is presented in Table 1. From the diagnosis of leprosy to the time of death there elapsed a minimum of five and maximum of 54 years. In 85.7 per cent of the patients in Groups I, II, III and IV there were symptoms of hepatic disease marked by insidious hepatic insufficiency, which was not intense except in cases in which severe amyloidosis or cirrhosis also occurred. The duration of this symptomatology varied from one to 15 years. Eight cases were treated specifically up to the time of death. In two cases treatment was suspended a year before death, and in the rest it was discontinued two to four years prior to death. Possibly the data observed might be indicative of poor response to the treatment of lepromatous hepatitis.

In 92.8 per cent of these patients the disease had progressed with leprosy reactions, almost always intense and repeated, probably indicating that "effective" hematogenous disseminations, giving rise to visceral lesions, are most frequent during leprosy reactions.

In 42.8 per cent there were no active cutaneous lesions at the time of death. They were burned-out cases, and 14.2 per cent did not have any cutaneous lesions; bacteriology was negative for skin, ear lobe and nasal mucosa. In these cases bacilli were found in the liver, long after the skin became negative. The concept, therefore,

TABLE. 1. *Comparison of morphologic findings with clinical data for Groups I–VII.*

Groups		Age of patient	Leprosy reaction	Yrs. neg. at time of death	Years with hepatic signs	Active leprosy of skin	Years without specific treatment	Corticoids
	H.L. 10	36	+++	0	4	−	1	+
	H.L. 13	21	+++	2	4	−	1	−
I	H.L. 19	20	+++	0	0	+	0	+
	H.L. 28	6	++	½	1	+	0	+
	H.L. 30	15	+++	0	2	−	0	−
II	H.L. 07	5	++	0	2	−	0	−
	H.L. 27	8	++	0	2	+	0	+
	H.L. 08	40	+++	0	5	+	0	+
III	H.L. 17	13	+	4	0	+	2	−
	H.L. 18	10	+++	0	2½	+	3	+
	H.L. 22	21	++	0	4	+	4	+
	H.L. 04	54	−	6	1	−	0	+
IV	H.L. 03	25	++	0	15	−	2	+
	H.L. 31	42	++	10	2	−	1	+
	H.L. 05	25	++	0	3	−	0	+
V	H.L. 09	16	+++	0	4	+	0	−
	H.L. 14	35	−	22	3	−	3	−
	H.L. 15	27	−	1	4	−	1	+
	H.L. 24	11	+++	2	5	+	0	+
VI	H.L. 16	19	−	6	0	−	2	−
	H.L. 20	18	−	13	5	−	1	+
	H.L. 26	34	−	14	10	−	0	+
	H.L. 11	20	−	10	3	−	0	−
	H.L. 12	27	−	8	3	−	0	−
	H.L. 25	45	+	13	0	−	0	−
VII	H.L. 01	15	−	2	0	−	0	−
	H.L. 02	2	−	0	0	−	0	−
	H.L. 21	50	−	20	3	−	3	+
	H.L. 23	24	++	5	0	−	0	−

that the liver can serve as a reservoir for bacilli should be kept in mind in accounting for otherwise unexplainable relapses.

In the cases with amyloidosis (Groups III and V), at the time of death 10 to 35 years had elapsed since the diagnosis of leprosy was made. It seems, therefore, that a long period of evolution takes place before amyloidosis appears. In 85.7 per cent of these patients, the cases evolved with frequent and intense leprosy reactions, a fact speaking for their importance in the etiopathogenesis of amyloidosis. Two patients in this group were bacteriologically negative at death, four to 22 years after recognition of the disease, and the deposit of amyloid was conspicuous, a fact suggesting that resorption of amyloid is difficult if not impossible, even though the fundamental cause of its origin has disappeared. In one case (14.2%), in spite of a noteworthy deposition of amyloid, there were no symptoms of hepatic involvement. This might be an example indicating the possible existence of subclinical cases of amyloidosis.

Fifty-seven point one per cent of the patients with amyloidosis had considerable quantities of corticoids repeatedly. In these cases (except for one) the deposit was intense and diffuse. Looked at in another way, among the 29 patients considered in this study 13 had received corticoids, and 30 per cent of these had amyloidosis. When these figures are considered jointly, it appears highly probable that corticoids have an unfavorable influence with respect to the onset and evolution of amyloidosis. In three of the cases treated with corticoids in which amyloidosis occurred, there was a diffuse and intense deposit that was with difficulty stained by Congo red, a fact suggesting the possibility that certain modifications occur in the chemical composition of amyloid, making its clinical (Benhold test) or histologic demonstration difficult.

When the cases of hepatic cirrhosis (Groups IV and VI) are considered jointly, it should be emphasized that only 25 per cent of them developed in association with leprosy reactions, and 63 per cent were bacteriologically negative from one to 14 years before death. These figures indicated to us that hepatic cirrhosis has no direct

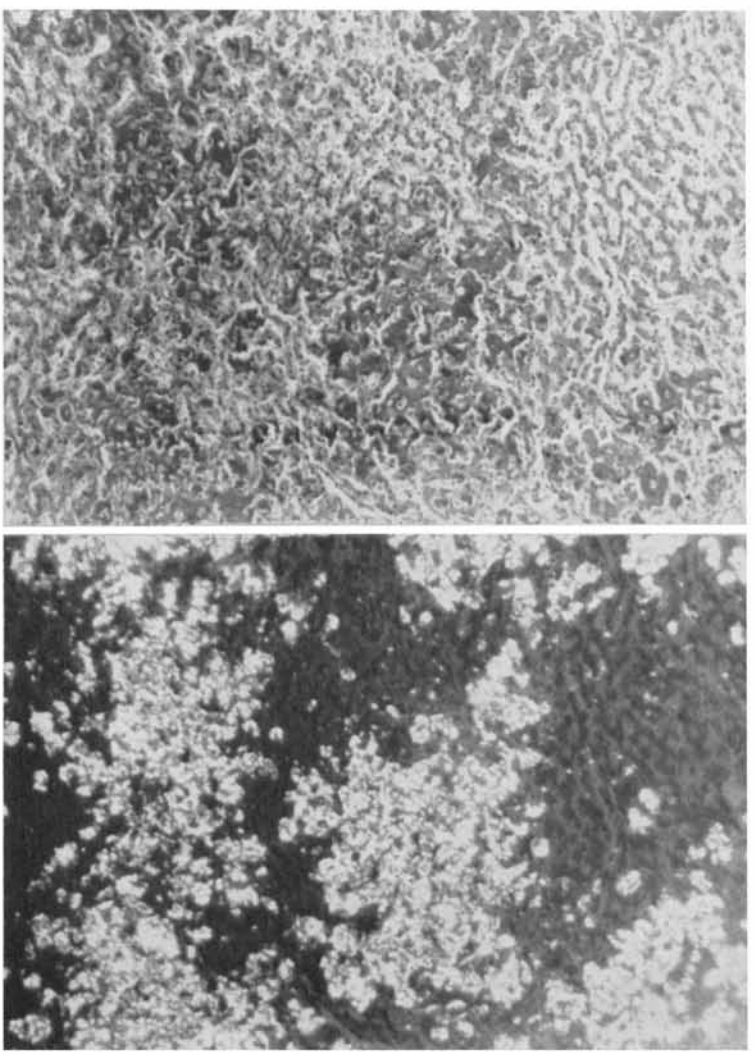

FIG. 5. Congo red stain is not definitive in this case. Congo red. Magnification: 40×.

FIG. 6. Same field as the previous illustration, examined with polarized light; it shows the deposit of amyloid clearly. Congo red; polarized light. Magnification: 40×.

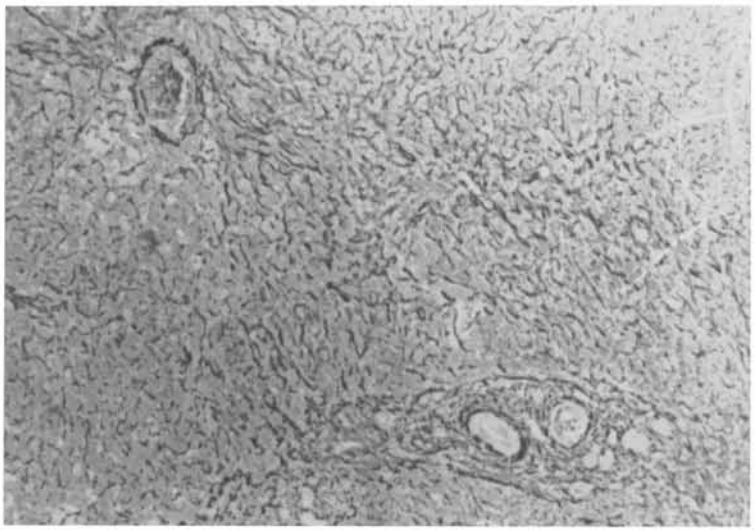

FIG. 7. In spite of an intense deposit of amyloid, distortion of the reticular texture is minimal, without evident tendency to the development of cirrhosis. Laidlaw stain. Magnification: 40×.

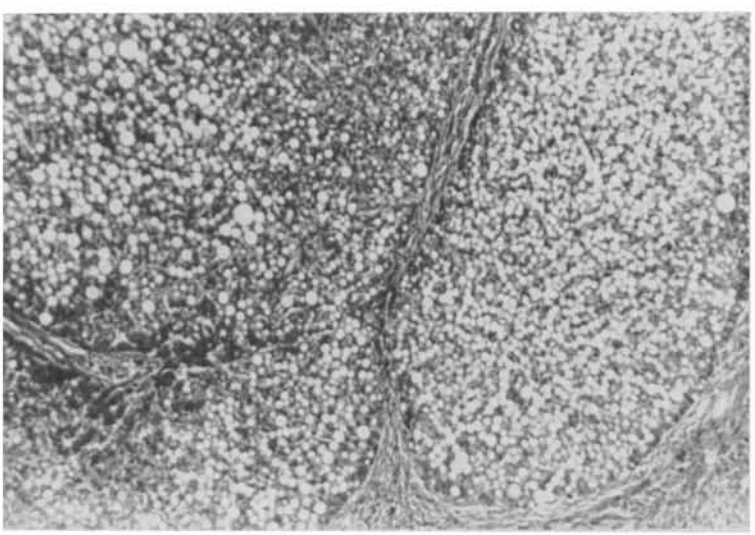

FIG. 8. Illustration of cirrhosis of septal type, differing in no way from that encountered in nonlepromatous patients. Hematoxylin and eosin stain. Magnification: 40×.

relation with leprosy, and that its etiology is to be sought in viral hepatitis, toxic phenomena, alimentary changes, etc.

The anatomoclinical correlation in Groups II and IV offers no problems worthy of comment, for they lack interest from the point of view of leprology.

SUMMARY AND CONCLUSIONS

From an anatomic-pathologic and clinical study of 29 lepromatous patients coming to attention because of hepatic lesions, the following conclusions have been reached.

Lepromatous hepatitis appeared in 48.2 per cent of leprosy patients autopsied. The finding of bacilli or bacillary granulations, although difficult, is for practical purposes constant. No data exist indicating that lepromatous hepatitis evolves toward cirrhosis or that it has some relation to the deposit of amyloid.

A long evolution of the disease and fre-