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CORRELATION OF LIVER FUNCTION WITH THE PATHOLOGY OF THE LIVER IN LEPROSY[1]

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Since the first detailed descriptions of the pathology of leprosy by Danielssen and Boeck in 1848 (4) and Hansen and Looft in 1895 (7), various workers have described lesions in the liver of patients suffering from lepromatous leprosy. The reports by Mitsuda and Ogawa in 1937 (11), Kean and Childress in 1942 (9), Black and Denny in 1938 (2), Fite in 1943 (5), and Powell and Swan in 1955 (13) are well documented, but they report lesions in lepromatous leprosy patients only. Arning's (1) description in 1936 of tuberculoid lesions in the liver of leprosy patients called forth much expression of disbelief, for several others workers did not find such lesions. However, Campos and Molina in 1950 (3) and Okada in 1954 (12) showed conclusively that granulomata do occur in the liver in patients suffering from the tuberculoid form of leprosy.

Liver function was studied extensively by Kinnear and Davison in 1957 (10) in an attempt to correlate it with hormonal status in patients with and without gynecomastia. They found poor function in the lepromatous group as compared with the tuberculoid group or normal controls. There was no relationship between hormonal levels and liver function, and the former did not appear to have much bearing on the presence of gynecomastia.

The present study was undertaken to determine the nature of liver pathology and liver function in patients suffering from the different forms of leprosy, and to find out if there was any correlation between leprotic lesions in the liver and liver function.

MATERIALS AND METHODS

Nineteen patients were studied. They were chosen from the outpatient clinic and the selection was purely random, depending on their willingness to undergo investigation and biopsy. In the group there were 11 lepromatous, 5 borderline and 3 tuberculoid types of leprosy patients. This represents a representative proportion of the various types of patients attending the clinic. The classification was made on the basis of a detailed clinical examination, skin smears for acid-fast bacilli by Wade's method (14), a lepromin skin test by Mitsuda's method, and a skin biopsy. The skin biopsy tissue was fixed in formol-Zenker's solution, embedded in paraffin, and sectioned. Routine hematoxylin-eosin stains, and acid-fast stains for *M. leprae*, made by Fite's method (6), were studied.

Besides the routine investigations for blood, urine and stool, the following tests were carried out: Prothrombin time by Quick's one-stage method, total serum protein by the

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copper sulfate method, serum albumin by the precipitation method and serum globulin by deduction, serum bilirubin, and the bromsulfalein test (B.S.P.) using 5 mgm. of dye per kilogram body weight. In the B.S.P. test a sample of blood was drawn 45 minutes after the dye was administered intravenously, and the percentage of dye retained was estimated by a photoelectric method using as a standard a graph prepared from some of the same solution that was used on the patient. Liver biopsy specimens were secured by the puncture method, using a No. 13 Menghini needle, usually in the eighth interspace. The tissue obtained was approximately 1 to 2 cm. long and about 1 mm. wide. It was fixed in formol-Zenker solution, embedded in paraffin and cut in sections 5μ thick which were stained with the routine hematoxylin-eosin stain and Fite's acid-fast stain for leprosy bacilli.

RESULTS

The bacteriologic index (B.I.) in 8 out of 11 lepromatous cases was above 2. In only 1 case was it below 1; the patient in this case had had the disease for less than 1 year. The average duration of the disease for the 11 cases was 6 years. The lepromin test was negative in all cases.

In the borderline group all 5 patients had a B.I. less than 1. The average duration of the disease was 5 years. The lepromin test was negative in all cases.

In the tuberculoid type of case one of the patients had a B.I. of 0.75. This patient had exacerbated lesions during the period of study. His lepromin test, however, was positive (15 mm.), and his skin biopsy

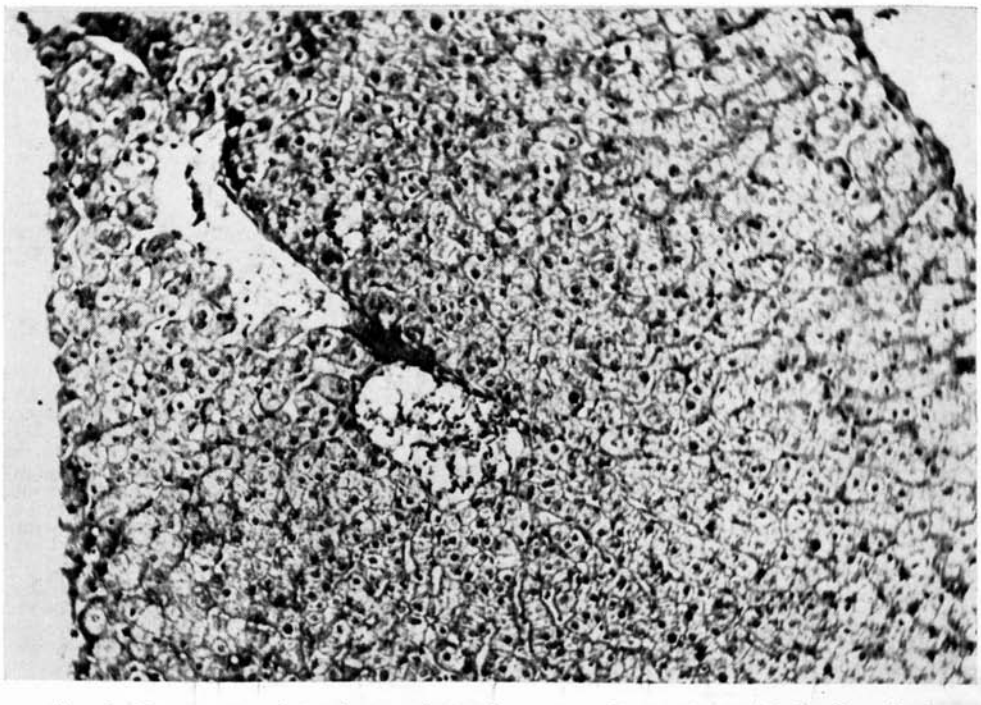

FIG. 1. Low power photomicrograph to show a small granuloma of the liver in lepromatous leprosy, situated adjacent to a portal vein.

showed a typical tuberculoid picture. The other 2 patients had a negative B.I. and their lepromin tests measured 6 mm. and 10 mm. The average duration of the disease was 3 years.

Of the various tests performed, the serum albumin, prothrombin time, and B.S.P. were used to assess liver function. A serum albumin content of 3 gm. per cent has been taken as the lower limit of normal as seen in our patients. Only 2 patients in the lepromatous group and 1 in the borderline group had a level below 3 gm. per cent. These had 2.5, 2.6, and 2.9 gm. per cent respectively.

Only 3 patients had a raised prothrombin time. Of these, 2 were of the lepromatous type and 1 of the borderline type of leprosy. As none of the patients had any other obvious cause for a hemorrhagic diathesis, it was believed that prolonged prothrombin time may have been due to defective synthesis in the liver of some coagulation factors.

The B.S.P. test as carried out in our laboratory showed 5 per cent retention as the upper limit of normal. Three lepromatous patients, and 2 borderline and 1 tuberculoid patient had a raised retention.

In the histopathologic study the liver showed a normal pattern. There was no increase in fibrous tissue or evidence of fatty change. The liver cells appeared normal. Eight out of 11 lepromatous patients showed numerous granulomata in a section from a small slice of liver

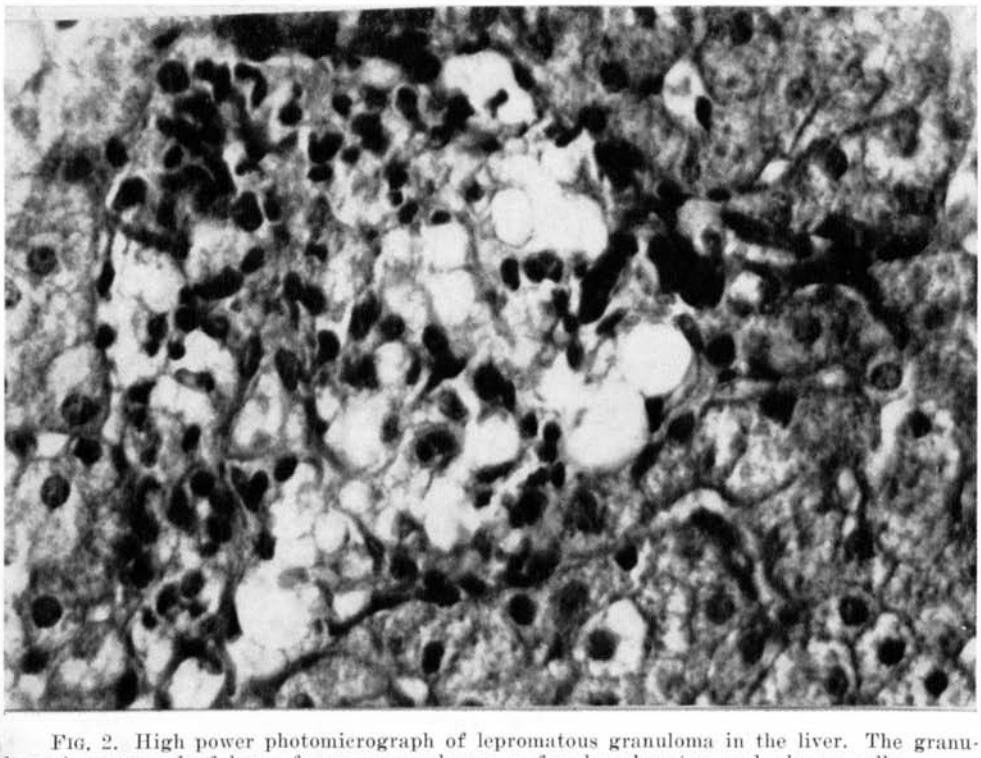

FIG. 2. High power photomicrograph of lepromatous granuloma in the liver. The granuloma is composed of large foamy macrophages, a few lymphocytes, and plasma cells..

FIG. 3. Photomicrograph of a tuberculoid granuloma consisting of a clump of epithelioid cells surrounded by lymphocytes in the liver of a patient with borderline leprosy.

tissue. The nature of the granulomata was identical with that seen in the skin. The granulomata consisted of collections of foamy macrophages and lymphocytes. The macrophages had significantly vacuolated cytoplasm and small vesicular nuclei pushed to the periphery. The granulomata were usually paraportal in position (Figs. 1 and 2). The Kupffer cells in the sinusoids were prominent. Acid-fast bacilli in varying numbers were found inside the macrophages, the Kupffer cells, and the endothelial cells lining the sinusoids.

In the borderline group, 4 out of 5 cases showed multiple granulomata in the liver tissue. They were very small, and composed of epithelioid cells and lymphocytes. There was no evidence of caseation (Fig. 3). The lesions were focal in their distribution. The Kupffer cells were not prominent. No acid-fast bacilli were present.

In the tuberculoid type of cases the lesions resembled very much the granuloma described in the borderline group (Figs. 4 and 5).

DISCUSSION

All the patients who had granulomata in the liver, had had the disease for 4 years or more. The longer the duration of the disease the greater the possibility for the infection to spread to the liver and cause specific lesions. Lepromatous patients who had had the infection for a shorter duration showed bacillus-filled Kupffer cells, but no definite granulomata. We suggest that the bacilli in the Kupffer cells

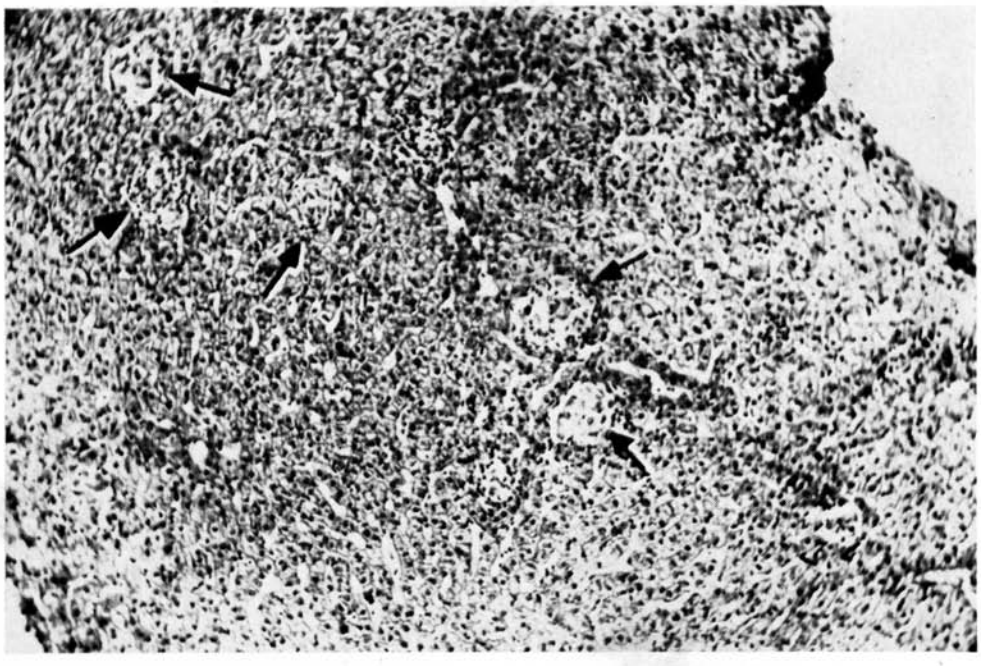

FIG. 4. Liver biopsy specimen from a tuberculoid case. Note numerous small tuberculoid foci.

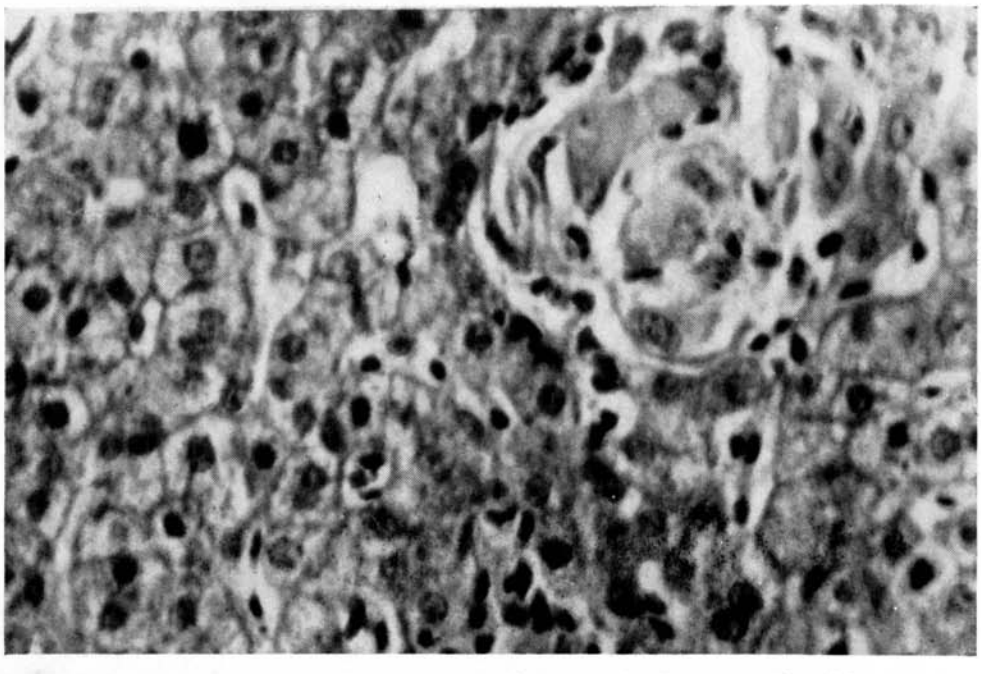

FIG. 5. High power photomicrograph showing a small clump of epithelioid cells.

are those that had been circulating in the blood stream and filtered out by these cells. In the course of time some of the bacilli in the Kupffer cells adapt to the new environment and proliferate to produce a granuloma consisting of small collections of bacillus-filled macrophages.

In the borderline and in the tuberculoid type patients the lesions were tubercles consisting mostly of epithelioid cells, Langhans type giant cells and lymphocytes. These lesions were focal in their distribution, very small in size, and almost always formed during exacerbation of the disease following a generalized spread. In these cases it may be presumed that the tissues of the body were sensitized to leprosy bacilli and their constituents. When there was exacerbation of the disease, the bacilli or their products were released in the blood circulation. Wherever these bacilli or their products were localized, a tuberculoid granuloma was formed.

The presence of tuberculoid lesions in other internal organs in leprosy has been well documented. Job and Macaden (8) have described tuberculoid lesions in the testes. A paper describing tuberculoid granulomata in lymph nodes is under preparation. It is reasonable to state that the tuberculoid type of leprosy is not necessarily a localized disease confined to the skin and peripheral nerves.

Liver function was diminished in 3 lepromatous, 2 borderline and 1 tuberculoid patient but the disturbance in liver function seems to have had no significant correlation with bacterial index, duration of the disease or presence of leprotic granulomata in the liver. Moreover, we did not detect any other factor directly related to leprosy to account for the diminished liver formation.

SUMMARY

Histopathology and liver function were studied in 19 cases of different forms of leprosy. In lepromatous leprosy the miliary granulomata consisted of collections of many bacillus-filled foamy macrophages and a few lymphocytes. Leprosy bacilli appear capable of proliferating inside the liver to produce granulomata. In tuberculoid and borderline cases the granulomata showed epithelioid cells, giant cells and lymphocytes; leprosy bacilli were not detected. There was diminished liver function, as estimated by the Bromsulfalein test, in 6 cases. This was not related, however, with the bacteriologic index, duration of disease, or presence of leprotic granulomata.

RESUMEN

Fueron estudiados en 19 casos de diferentes formas de lepra, la histopatología y la función hepática. En la lepra lepromatosa los granulomas miliares consistieron en colecciones de macrofagos vacuolados llenos de bacilos y unos pocos linfocitos. Los bacilos leprosos parecen capaces de proliferar dentro del tejido hepático y producir granulomas. En los casos tuberculoides y limites (borderline) los granulomas mostraron celulas

epitelioides, celulas gigantes y linfocitos; no fueron detectados bacilos leprosos. Hubo disminución de la función hepática, estimada por el test de la bromosulfaleina en 6 casos. Esto no fué relacionado, de cualquier manera, con el indice bacteriológico, duración de la enfermedad o presencia de granuloma leprótico.

RÉSUMÉ

L'histopathologie de foie et la fonction hépatique ont été étudiées chez 19 malades atteints de diverses formes de lèpre. Dans la lèpre lépromateuse, les granulomes miliares étaient constitués par l'aggrégation de nombreux macrophages spumeux remplis de bacilles et de quelques lymphocytes. Les bacilles de la lèpre paraissent capables de former un granulome en proliférant à l'intérieur du tissu hépatique. Dans les cas tuberculoïdes et dimorphes, le granulome révèle des cellules épithélioïdes, des cellules géantes et des lymphocytes. On n'y a pas détécté de bacilles de la lèpre. La fonction hépatique était diminuée, ainsi que l'épreuve à la bromesulfaléine l'a montré dans 6 cas. Cette diminution, toutefois, n'était associée ni à l'index bactériologique, ni à la durée de la maladie, et pas davantage à la présence d'un granulome léprotique.

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