PAPERS AND ORIGINALS

Liver in Leprosy: Histological and Biochemical Findings

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Summary

The histological findings and their correlation with biochemical functions of the liver in 240 leprosy patients are presented. In 21% with tuberculoid leprosy and in 62% with lepromatous leprosy leprosy granulomata were found in the liver. A significant prevalence of granulomatous lesions in the liver among patients with tuberculoid and borderline-tuberculoid leprosy of less than one year's duration suggests that bacillaemia occurs early in all forms of leprosy.

There was a direct correlation between bacterial index and the presence of acid-fast bacilli in the liver. Of 50 patients with negative skin smears seven had acid-fast bacilli at liver biopsy. From none of these liver homogenates were acid-fast bacilli grown on culture in Löwenstein-Jensen medium.

The alterations in liver functions were more consistently seen when acid-fast bacilli were associated with the presence of leprosy granulomatous lesions. The acid-fast bacilli were found to persist even after one to five years of specific antileprosy therapy and after the bacilli in the skin had cleared up. This may explain the relatively frequent recrudescence or relapse of the bacillated types of leprosy when specific antileprosy therapy is stopped soon after bacterial negativity is attained on skin smears.

Introduction

That leprosy is a systemic disease which results in involvement of internal viscera is no longer in doubt. Biochemical alterations of liver functions have been reported (Ludin and Ross, 1959; Verghese and Job, 1965; Shivde and Junnarkar, 1967) as well as good descriptions of histopathological findings in liver biopsies from leprosy patients (Job, Karat,

and Verghese, 1965; de Brito, Carvalho, Marques, Penna, and Azevedo, 1969; Sood and Grueber, 1969). The relatively frequent occurrence of lepromatous granulomata in the liver in lepromatous leprosy and the less common presence of granulomatous lesions in tuberculoid leprosy are fairly well documented, though few biopsy specimens from non-lepromatous leprosy patients have been studied. None of the studies to date has been able to correlate histological appearances with biochemical changes or with disease and treatment status. Further, there are no reports on studies of liver function in so-called purely neural forms of leprosy (presenting with neurological lesions of leprosy without the presence (past or present) of skin lesions of leprosy and with negative skin smears) in which a diagnosis of leprosy has been confirmed by appropriate nerve biopsy.

We have investigated the alterations in liver function in various types of leprosy in relation to length of history of disease, duration of treatment, bacillary load as judged by bacterial index in skin smears, and histological appearances on liver biopsy. This paper discusses the occurrence of granuloma and the presence of acid-fast bacilli in the liver and skin and their correlation with biochemical changes.

Patients and Methods

Two hundred and forty leprosy patients admitted to the Schieffelin Leprosy Research Sanatorium, Karigiri, South India, were studied after careful clinical examination and histological confirmation of classification of leprosy (Ridley and Jopling, 1966). A liver biopsy specimen was obtained with Menghini's (1958) liver biopsy needle. Half of the specimen was fixed in 10% formalin, and sections of 5-micron thickness were cut and stained with haematoxylin-eosin and Ziehl-Neelsen stain and examined under the light microscope. Half the liver biopsy specimen was homogenized and cultured in Löwenstein-Jensen medium for *Mycobacterium tuberculosis*.

Patients known or suspected to have tuberculosis and those with severe intercurrent infections were excluded from the study. Duration of disease and duration of treatment were noted. The distribution of patients according to sex and classification of leprosy is shown in Table I. None of those with indeterminate, tuberculoid, or purely neural leprosy had bacilli in skin smears.

Liver function tests were carried out with samples of blood

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TABLE I—Distribution of Cases According to Sex and Classification

Classification	Male	Female	Total
Indeterminate	15	3	18
Tuberculoid	22	2	24
Borderline-tuberculoid	24	10	34
Borderline-borderline	15	5	20
Borderline-leproma	17	3	20
Polar-lepromatous	99	16	115
Purely neural	9	—	9
Total	201	39	240

obtained by venepuncture. Total plasma protein was estimated by the biuret method (Kingsley, 1942) and individual protein fractions by cellulose acetate electrophoresis and subsequent elution of individual fractions (Smith, 1960). Thymol flocculation and zinc sulphate turbidity were estimated according to the method described by Varley (1962), serum alkaline phosphatase by the method of Wootton (1964), bromsulphthalein retention test according to the method described by Henry (1964), and prothrombin time by Quick's (1940) method. Skin smears for acid-fast bacilli were obtained from eight sites by Wade's (1964) slit-skin technique and the bacillary index was scored according to Ridley's (1964) scale. Bone marrow aspirate was obtained by sternal puncture according to the technique described earlier (Karat, 1966), spread on glass slides, and stained with Ziehl-Neelsen stain for acid-fast bacilli.

Findings

The histopathological changes in the liver found in these 240 biopsy specimens were similar to those described earlier on a smaller sample (Job *et al.*, 1965) except for the presence of tuberculoid granulomatous lesions in 2 out of 115 liver biopsy specimens from the polar-lepromatous type of leprosy. From none of these specimens was *M. tuberculosis* grown on culture of liver biopsy specimen homogenate. In the specimens examined there was no evidence of cirrhosis of the liver or of amyloidosis of the liver.

The prevalence of leprosy granulomata and acid-fast bacilli in the liver in the various types of leprosy is shown in Table II. In none of the 18 patients with indeterminate type and

TABLE II—Acid-fast Bacilli and Granuloma in Liver According to Classification of Leprosy

Classification	No. Studied	Granuloma		Acid-fast Bacilli (%)
		Lepromatous (%)	Tuberculoid (%)	
Indeterminate	18	0	0	0
Tuberculoid	24	0	21	0
Borderline-tuberculoid	34	0	47	3
Borderline-borderline	20	0	55	10
Borderline-leproma	20	0	40	25
Polar-lepromatous	115	62	3	55
Purely neural	9	0	0	0
Total	240	30	18	30

9 patients with purely neural type could we demonstrate leprosy granulomata, while in 5 of the 24 patients with tuberculoid leprosy tuberculoid granulomata were found on liver biopsy. From none of these specimens was *M. tuberculosis* grown in culture. In none of the patients with indeterminate, tuberculoid, or purely neural type of leprosy was acid-fast bacilli found in the liver. There was a steep rise in the number of patients with acid-fast bacilli in liver biopsy specimen as one moved from non-bacillated (tuberculoid and borderline-tuberculoid) to bacillated types of leprosy, the highest being 55% in lepromatous leprosy patients.

The relationship between bacterial index in skin smears and presence or absence of leprosy granulomata and acid-fast bacilli in the liver is shown in Table III. Among 101 patients who had no acid-fast bacilli in skin smears 22 had leprosy granulomata in the liver, 21 being of tuberculoid type, and 14% had easily demonstrable acid-fast bacilli in the liver biopsy specimens. With rising bacterial index a higher proportion had acid-fast bacilli in the liver.

TABLE III—Acid-fast Bacilli and Granuloma in Liver According to Bacterial Index in Patient

Bacterial Index	No. Studied	Granuloma		Acid-fast Bacilli (%)
		Lepromatous (%)	Tuberculoid (%)	
Negative	101	1	21	14
0.1—0.9	25	20	28	16
1.0—1.9	38	24	29	29
2.0—2.9	35	71	6	60
3.0 and over	41	76	5	68
Total	240	30	18	30

The correlation between the duration of disease, the duration of treatment, and the presence or absence of leprosy granulomata and acid-fast bacilli in the liver is shown in Table IV. The prevalence of leprosy granuloma in the liver among those who had had less than one year's treatment was not significantly different compared with those who had had

TABLE IV—Acid-fast Bacilli and Granuloma in Liver According to Duration of Disease and Duration of Treatment

Duration of Disease (in Years)	Duration of Treatment	No. Studied	Granuloma		Acid-fast Bacilli (%)
			Lepromatous (%)	Tuberculoid (%)	
<1 .. {	>1 Year	6	—	33	—
	<1 Year	40	7	25	5
1-5 .. {	>1 Year	33	24	18	39
	<1 Year	60	28	18	30
>5 .. {	>1 Year	29	38	7	41
	<1 Year	44	41	14	34

treatment for more than one year, in each category based on duration of the disease. There was a significant rise in the proportion of patients having acid-fast bacilli in the liver among those who had had the disease for more than a year. This percentage continued to remain high, despite specific treatment for more than a year. In 56% neither liver biopsy nor bone marrow examination showed any bacilli, while in 17% both liver and bone marrow contained acid-fast bacilli. Of patients who had acid-fast bacilli in the liver, 57% had such bacilli in bone marrow. At the same time, among those who had acid-fast bacilli in the marrow 45% did not have acid-fast bacilli on liver biopsy.

Further analysis of this correlation for the 50 patients whose bacterial index was zero in the polar lepromatous, borderline-leproma, borderline-borderline, and borderline-tuberculoid types of leprosy showed that one had acid-fast bacilli in both liver and bone marrow, six had acid-fast bacilli in the liver but not in the bone marrow, while in the remaining 43 acid-fast bacilli were not present in either the liver or the bone marrow. The one patient who had acid-fast bacilli in both liver and bone marrow had had the disease for more than a year and was treated for more than a year.

For purposes of this study those with serum albumin levels less than 3 g/100 ml, globulin greater than 5 g/100 ml, alkaline phosphatase greater than 13 units, zinc sulphate turbidity greater than 12 units, thymol flocculation greater than 2 units, difference in prothrombin time in control and patient greater than 2 seconds and bromsulphthalein retention in the

blood greater than 5% at 45 minutes were considered to be abnormal.

The proportion of patients with granuloma in the liver among those who showed normal levels in the various biochemical tests was compared with that of those who had abnormal levels (Table V). There were significantly more with

TABLE V—Granuloma in Liver Among Those with Normal and Abnormal Levels in the Various Biochemical Tests

Biochemical Test	No. Whose Test Levels Were:		Percentage with Lepromatous Granuloma Among Those Whose Levels Were:		Percentage with Granuloma Among Those Whose Levels Were:	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Albumin	207	33	26	55	19	9
Globulin	210	30	25	63	19	10
Alkaline phosphatase ..	168	30	32	30	20	3
Zinc sulphate turbidity ..	148	91	18	48	19	17
Thymol flocculation ..	209	30	23	77	19	10
Prothrombin time ..	185	46	30	33	17	17
Bromsulphthalein ..	126	11	31	36	22	9

lepromatous granuloma among those with abnormal values for serum albumin, serum globulin, zinc sulphate turbidity, and thymol flocculation. No such associations were noticed with regard to the abnormal levels in the other biochemical tests. In patients with tuberculoid granulomata in the liver there was no correlation between functions of the liver and the leprous lesions. Further, as compared with those with lepromatous lesions of the liver, in only a small number of patients were the results of biochemical tests abnormal.

The alteration in liver functions in relation to granulomatous lesions of the liver and the presence or absence of acid-fast bacilli in the liver were further studied, the findings being shown in Table VI. The presence of granulomatous lesions in the liver increases the percentage showing abnormal levels of

TABLE VI—Percentage Showing Abnormal Biochemical Test Results Among Lepromatous Leprosy Patients According to Presence of Granulomatous Lesions and Acid-fast Bacilli in Liver

Biochemical Test	Granuloma Absent		Granuloma Present	
	Acid-fast Bacilli			
	Yes (10)	No (31)	Yes (52)	No (19)
Albumin	20	13	25	26
Globulin	10	13	27	26
Zinc sulphate turbidity . .	40	47	65	53
Thymol flocculation . .	—	3	35	26
Alkaline phosphatase . .	22	25	17	7
Prothrombin time . .	30	10	20	26
Bromsulphthalein . .	29	21	9	10

Figures in parentheses indicate number done in each group.

liver function, regardless of the presence of acid-fast bacilli. The differences noticed in abnormal levels among those in whom acid-fast bacilli were present compared with those who did not show acid-fast bacilli were not significant. Culture of liver biopsy specimen homogenates in Löwenstein-Jensen medium did not produce any growth.

Discussion

In moving from polar tuberculoid to polar lepromatous leprosy one finds a sharp rise in the prevalence of leprous lesions in the liver. In three patients who were clinically, histologically, and immunologically classified as having lepromatous leprosy, granulomatous lesions characteristic of tuberculoid leprosy were found on liver biopsy. That 21% of patients with polar tuberculoid leprosy and 47% with borderline-tuberculoid leprosy have histological lesions of leprosy on liver biopsy suggests that even in these types of

relatively stable disease, in the so-called "immune" group, bacillaemia occurs commonly.

There is a direct correlation between the bacterial index and the frequency of histological involvement of the liver. Among 25 patients with a bacterial index on skin smear between 0.1 and 1.0+ (Ridley's scale), 12 (48%) had granulomatous lesions of the liver. Of those with a history of leprosy of less than one year who had been on specific treatment for less than one year 33% were found to have granulomatous lesions of the liver.

It is important to note that even though the bacilli had cleared from skin smears, as shown by negative bacterial index, 14% still had easily demonstrable acid-fast bacilli in sections of liver biopsy.

While there is no doubt that among patients in whom the disease is of longer duration there is a higher prevalence of visceral lesions, a significant proportion of those with histories of less than one year also have acid-fast bacilli or easily demonstrable leprous lesions in the liver, thus further substantiating the suggestion that the bacillaemic phase occurs early in the disease. This finding is at variance with the usual concept of leprosy (Binford, 1969). Furthermore the percentage of liver biopsy specimens with leprous granulomata does not show a significant rise after one to two years of disease, and among those with a history of one to five years is similar to that found in those with a longer history.

Alterations in liver functions become more obvious only after the presence of bacilli has resulted in the formation of granulomatous lesions (Table VI). The thymol flocculation and the serum albumin and globulin levels appear the most consistently sensitive indices of liver involvement in leprosy.

The degree of involvement of the liver and consequent derangement of its function is significantly greater in those with lepromatous granulomata in the liver than in those with tuberculoid granuloma. This could be due to the focal nature of tuberculoid lesions: for in those with lepromatous lesions in addition to the numerous lepromatous granulomata, foamy macrophages and bacilli-filled Kupffer cells are seen throughout the liver.

Since the presence of lepromatous granulomata is related to the bacterial load, the higher the bacterial load the higher is the globulin level in the blood (Karat, 1970); and since the rise in globulin levels results in alteration in thymol flocculation, thymol turbidity, and zinc sulphate turbidity, the changes noted in these measurements of liver function could be thought merely to reflect changes in globulin rather than to be due to appreciable parenchymal damage to the liver. This is borne out by the relatively small proportion of patients with granulomatous lesions in the liver who show abnormal bromsulphthalein retention tests.

The findings of granulomatous lesions and the persistence of bacilli in the liver after they have been cleared from the skin have an important bearing on therapeutics. So far, clinicians have recommended prolonged treatment with dapsone for bacillated types of leprosy because of the fear of relapse following premature cessation of therapy. The "relapse" could be due to proliferation of bacilli in the reticuloendothelial system, such as the liver and the bone marrow, on withdrawal of therapy, since they persist in these organs long after their disappearance from the skin. It has been demonstrated by using Shepard's foot pad technique that acid-fast bacilli in the liver and the bone marrow of lepromatous leprosy patients are viable even when bacilli obtained from skin biopsies of the same patients on treatment fail to multiply in mouse foot pad (Karat and Harmer, 1970). Thus the need for prolonged specific antileprosy therapy becomes rational rather than empirical.

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Effect of Psychiatric Intervention in Attempted Suicide: A Controlled Study

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Summary

All patients presenting at the casualty department of King's College Hospital during the first six months of 1968 with deliberate self-poisoning or self-injury were followed up. Of 211 patients 204 (97%) were traced after a mean interval of 18 months (range one to two years). Despite official hospital policy, 22% had not been seen by a psychiatrist before discharge; these 44 untreated patients were compared with the remaining 160 who had received either brief (one or two interviews) or more prolonged psychiatric and social help.

Subsequent suicidal attempts occurred significantly more often among untreated than among treated patients, prolonged treatment being associated with the best prognosis. The same trend was observed in respect of actual suicide, though the numbers were small and differences did not reach statistical significance. These findings held good when the untreated and treated groups were controlled for other variables which were found to be correlated with outcome. These results indicate that psychiatric intervention is associated with a significant reduction in subsequent suicidal behaviour.

Introduction

Each year at least 50,000 patients are admitted to hospital in Britain following deliberate self-poisoning or self-injury (Roberts and Hooper, 1969; Bagley, 1971). The rate of such

"parasuicide" (Kreitman *et al.*, 1969) is increasing each year, probably by as much as 10% per annum (Aitken *et al.*, 1969; Bagley, 1971). Many will repeat the attempt (Kessel and McCulloch, 1966), and the more often a patient attempts suicide the more likely it is that he will kill himself (Ettlinger, 1964).

In 1961 the Ministry of Health issued a circular to all hospitals recommending that any patient admitted to a casualty department should be seen by a psychiatrist before discharge. A more recent report of the Central Health Services Council (1968) again recommended that "all cases of deliberate self-poisoning should receive psychological and social evaluation and help." Despite these recommendations there is virtually no information on the efficacy of psychiatric treatment in preventing further suicidal attempts, though it is known that voluntary services (Bagley, 1968) and a community care service for old people (Walk, 1967) can have a beneficial effect on suicide rates. Hitherto, reported follow-up studies of attempted suicides—for example Schmidt *et al.* (1954), Rueggsegger (1963), Ettlinger (1964), Kessel and McCulloch (1966), Greer and Lee (1967)—have been confined to patients who received psychiatric treatment of some kind. The absence of any data about the progress of untreated patients is, of course, due to the ethical problems of conducting controlled studies in this area. In the present study an untreated group of patients was made available by an artefact of medical policy.

Patients and Methods

The records of all patients (about 25,000) who presented at King's College Hospital casualty department during the first six months of 1968 were examined. By this means 211 cases of parasuicide were obtained for study. It was discovered that 22% of these patients had not been seen by a psychiatrist at the time of their attempt, either because the attending doctor—withstanding official hospital policy—had discharged the patient without psychiatric referral or, in some cases, because the patient apparently refused such referral. The remaining patients were divided into two groups according to the

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