Functional Hepatic Impairment in Pulmonary Tuberculosis

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Introduction

The work presented in this paper has been prompted by the dearth of material on the subject. In a preliminary report of 18 cases by Hurst, Maier and Lough¹ the following observations have been made: That in a study of far advanced pulmonary tuberculosis using Hanger's cephalin cholesterol flocculation test, the Hippuric acid synthesis and the 5 mg. serial Bromsulphalein test as tests of hepatic function, where the NPN, Serum Protein, Cholesterol and Esters, Prothrombin Time, Bilirubin and Urobilinogen were within normal limits, hepatic dysfunction was demonstrated in a large percentage of cases. Bromsulphalein showed the greatest number of positive results—47 per cent.

It will be our object to limit study to what we believe to be two of the most reliable tests of liver function and critically examine the values obtained in the light of the stage of the disease, the chronicity, the amount of inanition present and the character of the pulmonary lesion, always considering other etiological factors which might tend to distort results.

The fact has long been established that hepatic parenchymal damage is a frequent finding at necropsy in the tuberculous. Conflicting opinions have been voiced as to the pathogenesis and the micropathology of the process. Florentin, et al,² reviewed 35 cases of chronic pulmonary tuberculosis that came to autopsy and only reported three cases with fatty livers. However, two-thirds of his cases gave evidence of typical inflammatory process without evidence of fatty degeneration. Periportal sclerosis was observed only rarely, but massive proliferation of Kupfer's cells was an almost constant feature. He points out that fat deposition in the liver cells usually starts at the periphery of the hepatic lobule. In order that fat may be deposited, the body must have sufficient reserves in lipids and glucosides, and the endocrine system must be intact. He further reasons that since fatty livers

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may occur in aviators flying at high altitudes or may be induced experimentally in animals by subjecting them to low concentrations of O₂. ever present anoxemia is a possible factor in the development of fatty liver in the individual having sufficient lipoid reserves.

Anoxemia alone however cannot solve this riddle if one recalls the infrequent occurrence of fatty livers in cases of pulmonary emphysema with long standing anoxia. General toxemia and inanition may play an important role. Parini³ who examined at post-mortem the livers of 50 patients with chronic ulcerative intestinal tuberculosis and those of a control series of 50 patients with active tuberculosis without intestinal disease, concluded that in ulcerative intestinal tuberculosis there are always fairly severe fatty changes in the hepatic parenchyma. Characteristically he found these changes involved the peripheral part of the hepatic lobule. Jones and Peck⁴ also discussed the extensive fatty infiltration of the liver often associated with extensive tuberculous enteritis. Both these conditions were more apt to occur jointly when mixed or exudative types of pulmonary disease existed. Extreme emaciation appeared to be a constant accompaniment of fatty liver even when enteritis was not present. This finding suggested an underlying metabolic factor such as poor absorption of food from the gastro-intestinal tract due to damage to the intestinal mucosa and increased peristalsis. Vomiting and anorexia similarly might be aggravated by the concomitant exudative disease and the toxemia thereof.

**Clinical Material**

Fifty-three cases of pulmonary tuberculosis in males were picked at random for this study. With the exception of No. 48 who had a draining empyema of one year's duration, there were no demonstrable tuberculous complications or extrapulmonary lesions. A classification of each case was made at the time of testing according to National Tuberculosis Association standards and a thorough history was taken to rule out other causes of liver damage. Special effort was made to elicit a history of: jaundice, starvation (many patients were refugees from concentration camps), alcoholism, prolonged anesthesia, occupational exposure, and intravenous plasma or whole blood within six months prior to testing. Both the cephalin-cholesterol flocculation test and the bromsulphalein tests were done during the same morning while the patients were in a fasting state. Positive and negative tests were checked periodically by the laboratory against both positive and negative known controls. All negative cephalin-cholesterol flocculation tests where the bromsulphalein retention was over 5 per
cent, were repeated independently. Results were gratifyingly confirmatory in almost every case.

The Studies

It has been shown at necropsy that a pathological diagnosis cannot be predicted on the basis of hepatic function studies alone. One can only interpret positive test findings in terms of the degree of damage to the functional capacity of the organ. F. Mann has emphasized that the various functions of the liver are not injured equally, and thus there is a dissociation of impairment of different liver functions and a corresponding dissociation of the results of the liver function tests. Our choice of two tests, one of which would reflect the active phase of liver damage and the other the residual damage to the parenchyma was made after a review of the recent literature.

The cephalin-cholesterol flocculation test which was chosen as an index of active liver disease has been found to be an extremely valuable test in routine clinical work because of its simplicity and small number of false positive reactions. Sensitivity studies according to Truscott placed cephalin-flocculation first in degree of sensitivity, colloidal gold second, and thymol turbidity third. Moore, Hanger, et al have postulated that a positive flocculation test may be due to an increase in the gamma globulin fraction, a decrease in serum albumin, or a decrease in the flocculation inhibiting property of the albumin.

Following the advice of Hanger a fresh unripened cephalin solution which had remained in the ice box protected from light was used. This emulsion was prepared from the commercial product supplied by Difco Laboratories, Inc. Preparation and laboratory testing was run exactly as described except that the centrifuge tubes were kept in the dark as directed by Neefe and Reinhold. Mateer has shown in a comparison of tests on normal individuals using unripened and ripened cephalin emulsions that if a one plus test with the former is regarded as within normal limits, and positive diagnostic importance is attached only to two, three and four plus tests, that studies with the latter reagent yielded numerous two and three plus false positive results. The unripened cephalin on the other hand, yielded 12.5 per cent of false positives, all of which were only of a one plus magnitude when tested against normal controls. Fresh unripened cephalin has been shown to lack sensitivity and may give negative results where impaired function actually exists. Additional laboratory precautions must and were taken in handling cephalin reagent since exposure to light or air for a protracted period of time will yield numerous two an dthree plus false positives.
A 48 hour reading was employed exclusively despite Saifer's admonition that 48 hour readings yielded a 10 per cent error in the plus one and two range. Our laboratory reactions appeared to be better defined after this period of time and allowance for slight error was made by disregarding all plus one reactions.

Delor and Rheinhart, Lichtman, and Mateer concur that the bromsulphalein test is the most sensitive test of the excretory function of the liver in the non-jaundiced individual. Marginal impairment of function is demonstrated by throwing a large excretory load on the liver.

Mateer, et al studied the bromsulphalein test using the new 5 mg. per kilo dosage. In a study of thirty normal individuals who were subjected to serial sampling of blood following intravenous injection of the dye, the dye had completely disappeared from the blood stream in 73 per cent in 30 minutes, in 86 per cent in 35 minutes, in 96 per cent in 40 minutes, and in 100 per cent in 45 minutes. The normal standard for complete disappearance of the dye after injection has thus been established as 45 minutes when 5 mg. per kilo of dye is used. From the standpoint of economy

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Cases Positive to Both Tests</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>C.P.</td>
</tr>
<tr>
<td>J.C.</td>
<td>4 plus 12</td>
</tr>
<tr>
<td></td>
<td>lesion: Unilateral Cavitation.</td>
</tr>
<tr>
<td>W.E.</td>
<td>2 plus 6</td>
</tr>
<tr>
<td></td>
<td>lesion: Millary.</td>
</tr>
<tr>
<td>L.G.</td>
<td>2 plus 7</td>
</tr>
<tr>
<td></td>
<td>lesion: Extensive Bilateral Cavitation.</td>
</tr>
<tr>
<td>T.G.</td>
<td>4 plus 5</td>
</tr>
<tr>
<td></td>
<td>lesion: Bilateral small cavitation.</td>
</tr>
<tr>
<td>H.M.</td>
<td>2 plus 16</td>
</tr>
<tr>
<td></td>
<td>lesion: Bilateral pneumothorax for cavitation.</td>
</tr>
<tr>
<td>J.M.</td>
<td>4 plus 6</td>
</tr>
<tr>
<td></td>
<td>lesion: Bilateral cavitation; healed one side, pneumothorax other.</td>
</tr>
<tr>
<td>A.P.</td>
<td>3 plus 12</td>
</tr>
<tr>
<td></td>
<td>lesion: Endobronchial disease and bilateral cavitation.</td>
</tr>
<tr>
<td>W.S.</td>
<td>2 plus 5</td>
</tr>
<tr>
<td></td>
<td>lesion: Pneumothorax left; thoracoplasty right. Other, Alcoholic. No palpable liver.</td>
</tr>
</tbody>
</table>
of time and effort, a single 45 minute specimen is satisfactory and was used in this study. The test was performed and evaluated according to the technique and standard laboratory procedure described by Lichtman. Blood bilirubin determinations were done whenever there was a suspicion of bilirubinemia. Precautions were also taken to withdraw the blood sample from the opposite arm from which the dye had been injected. Results were reported in per cent of dye retention, assuming 100 cc. of plasma contained 4 mg. of dye immediately after injection.

Results

A total of 53 cases were studied. Thirty-nine yielded positive cephalin-flocculation reactions, 16 of which were three plus or four plus reactions. Twenty-one cases showed retention of bromsulphalein after 45 minutes and 10 had retention of 6 per cent or more of the dye. Eight cases were positive to both tests of which only three met the three to four plus and 6 per cent more stringent requirements. See Table 1. Thus 43.4 per cent of all cases studied were positive to the cephalin reagent, 39.6 per cent to the bromsulphalein test and 15.1 per cent to both tests. In other words 34.8 per cent of the patients with positive cephalin-flocculation tests showed bromsulphalein retention and 38.1 per cent positive with bromsulphalein were positive to the cephalin reagent. (Where one of the two tests was highly positive, i.e. 5 per cent bromsulphalein retention or three to four plus cephalin-flocculation and the other was negative, a repeat test was always made).

An attempt to correlate the stage of pulmonary tuberculosis with progressive liver damage yielded these comparable but inconclusive findings. With the cephalin-flocculation test 33.3 per cent of the minimal cases, 44.1 per cent of the moderately advanced cases and 46.2 per cent of the far advanced were positive, while dye retention was evident in 33.3 per cent of the minimal, 38.2 per cent of the moderately advanced, 46.2 per cent of the far advanced cases. Of the cases studied six were classified as stage I, 34 as stage II, and 13 as stage III. The most interesting findings occurred in the group which was positive to both tests; it was unfortunately however, quite small. Here none of the minimal cases furnished positive results while 11.8 per cent (four cases) of moderately advanced disease and 30.8 per cent (four cases) of the far advanced cases were positive to both tests.

It was hoped that a reciprocal relationship might be found between the chronicity of the pulmonary lesion and hepatic parenchymal damage. Our findings definitely ruled out such a relationship. Patients with positive cephalin-flocculation tests
averaged 4.8 years, positive bromsulphaleins 5.3 years, with both tests positive 5.5 years, and with neither test positive 5.2 years.

All patients with inanition in this series were classified as mild, moderate, or severe according to past or present loss of body substance over a protracted period of time. Five of the eight patients who had positive bromsulphalein and cephalin-flocculation tests also had moderate to severe depletion of body substance. Six patients with mild to severe wasting had positive cephalin-floculation tests. In contrast 10 patients, the majority of whom suffered severe inanition had negative liver function studies. Thus of a group of 31 cases with varying amounts of cachexia, 51.7 per cent had a single positive liver function test, 32.3 per cent were negative to both tests and 16.0 per cent were positive to both tests.

*Interpretation of Results*

No didactic conclusions can be drawn from these data; certain trends may however be examined and added to the literature on the subject. There appears to be a relatively high incidence of liver disease in patients suffering from tuberculosis. Because of the low incidence of combined positive tests one must assume the presence of more than one type of parenchymal damage and of both active and quiescent disease.

There does not seem to be any correlation between the stage of the pulmonary process and the individual test. In fact the only near conclusion that can be drawn is in the small group of eight cases which were positive to both tests, where there was a definite correlation between stage of disease and liver damage as reflected by the function tests.

We may also assume that inanition per se has little influence over the individual's liver function. But where liver function is found to be impaired using both tests, the chance that cachexia is a factor is better than equal.

Presumption of liver damage was of necessity limited to the liver function tests employed; none of the 53 patients studied had jaundice, hepatomegaly, or other clinical evidence of liver damage. Many had been subjected to surgical procedures without developing complications. Since in our opinion a discrepancy seemed to exist frequently between the test findings and the individual case, an unbiased physician familiar with each case was asked to predict the individual test results basing his opinion upon the extent of the pulmonary lesion, the length of illness with tuberculosis, and the activity of the disease, the latter being defined in terms of symptomatology, interference with nutrition, and toxicity. He was able to prognosticate five cases or 63 per cent of the cases, where both tests were positive, but only 13 or 38 per cent of the
total number of cases for which we had found positive results in one or both of the tests. His predictions thus were no more accurate than a random selection of cases.

SUMMARY

1) Fifty-three cases of pulmonary tuberculosis varying in severity from minimal to far advanced were studied for functional hepatic impairment.
2) Studies were limited to cephalin-flocculation and bromsulphalein tests.
3) Although hepatic dysfunction was demonstrated in a large percentage of cases with a single test, only in a small percentage were both tests positive.
4) In the doubly positive group, correlation with the extent of disease seemed to exist.
5) Inanition per se had little influence over the individual cephalin-flocculation and bromsulphalein tests.
6) It is impossible to predict hepatic damage based upon history and clinical picture in pulmonary tuberculosis.
7) No relationship exists between the chronicity of tuberculosis and hepatic damage.

RESUMEN

1) Se estudiaron cincuenta y tres casos de tuberculosis pulmonar que variaban desde mínima hasta muy avanzada, para determinar la insuficiencia hepática funcional.
2) Los estudios se limitaron al uso de la reacción de la floculación de la cefalina y de la bromosulfaléina.
3) Aunque la disfunción hepática se encontró en gran porcentaje de casos con una sola de las reacciones solo en pequeño porcentaje, fueron ambas reacciones positivas.
4) En el grupo en que fueron ambas positivas pareció existir correlación con el grado de la enfermedad.
5) La inanición por sí sola tuvo poca influencia sobre ambas reacciones.
6) Es imposible predecir el daño hepático basándose en la historia clínica en tuberculosis pulmonar.
7) No hay relación entre la chronicidad de la tuberculosis y el daño hepático.

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