Routine Hepatic Tests *

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At present, we have a variety of hepatic tests on hand. They are counted by scores or a hundred. There have been an increase not only in the variety but also in the accuracy of tests for these thirty years. Nevertheless, evaluation of the hepatic tests as diagnostic means has not been elevated so pronouncedly as expected on account of the recent advent of newer and excellent techniques such as needle biopsy of the liver,[1] laparoscopy,[2] radioisotope scanning of the liver,[3] and angiography of the portal system.[4] In spite of this situation, routine hepatic tests are still being used widely and frequently for the diagnosis of hepatobiliary diseases. They are retaining undiminished favour of clinicians, because they permit us to use repeatedly without causing any hazard to every patient. Safety and possibility of repetition are notable merit of the routine hepatic tests which enables us to pursue the clinical course of the patient. In the present lecture we should like to discuss the characteristic features of the routine hepatic tests together with their application to diagnosis.

(1) The present day hepatic tests are based on clinical observation.
Their diagnostic significance is independent of the morbid anatomy or pathological histology of the liver. The results of those tests are usually poorly correlated with hepatic histology.

Table I presents one of the examples of the studies made on the correlation between hepatic tests and the histology of hepatic tissue fragments obtained by needle biopsy. Scrutiny of the table will tell us the following facts:—

a) Cephalin cholesterol flocculation test, serum transaminase, cholinesterase, albumin to globulin ratio, and zinc sulfate turbidity test mirror hepatocellular damage to some extent.

b) Increase in serum alkaline phosphatase, cholesterol, phenol turbidity test and leucine aminopeptidase are suggestive of obstruction to biliary flow.

In any way, reasoning from the poor correlationship between hepatic tests and hepatic histology there is no room for doubt that a single or a few hepatic tests when applied to a patient are not so helpful for us in imagining the morbid anatomical picture of his hepatobiliary disorder, and it is feared that they may occasionally lead us to misdiagnosis.

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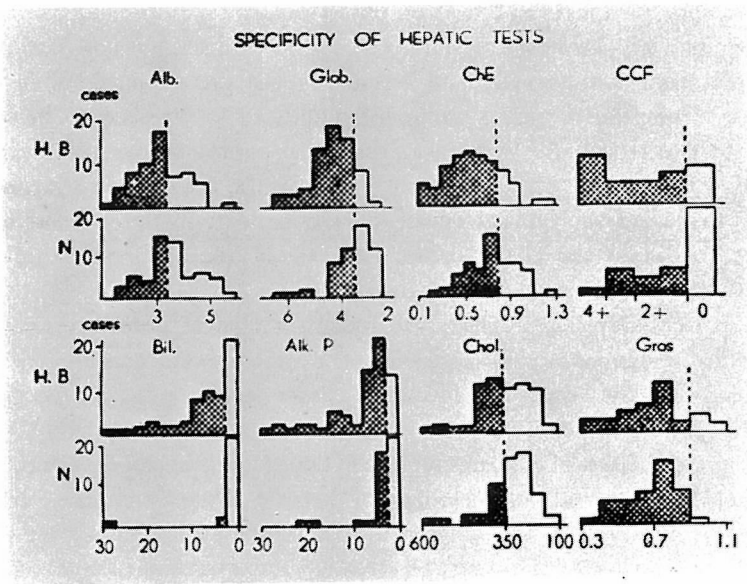
Routine hepatic tests of the present days are not always satisfactorily specific for hepatobiliary disorders, being frequently influenced by the general condition of the patient. Figure 1 depicts the distribution of the results of various hepatic tests in hepatobiliary and non-hepatobiliary disorders for the purpose of comparison. Histograms (HB) refer to hepatobiliary diseases, and histograms (N) to non-hepatobiliary disorders. With respect to a particular hepatic test the greater the difference in the shapes of the histograms is seen between the two groups of diseases, the more certain is the specificity of the relevant test to hepatobiliary disorders. Looking at this figure in this way, we can see that alkaline phosphatase, bilirubin, and transaminase are superior in specificity to albumin and globulin.



Figurre 1. Specificity of the hepatic tests.
Shaded area : abnormal values. White area : normal values.
HB : hepatobiliary disorders
N : non-hepatobiliary diseases.

Hepatic tests vary widely in sensitivity. Some are sensitive, while others are not. They are classified roughly as slown in Table II.

Since individual hepatic tests are not uniform in sensitivity and specificity, it is unwise to place overreliance upon the result of a single particular test for the correct diagnosis of hepatobiliary disorders. In this connection it must be emphasized that hepatic tests should be used in combination including several kinds, because a single hepatic test is often misleading and valueless.

Table I. Hepatic tests in relation to hepatic histology

	Cell damage	Inflammation	Scarring	Biliary stasis
Albumin			##	
Globulin	÷	÷	+	
CCFT	+÷	+÷	÷	
ChE	##	÷	##	
PTT	+		##	
BSP	+ ?		+ ?	
GPT	##	##		
Znt.t.	÷ ?			
Thymolt.t.	÷ ?			
Bilirubin				##
Alk Phos				##
LAP				+
Cholesterol				+
Phenol.t.t.				÷

Material : 88 hepatobiliary cases
: Highly significant, + : Significant, ÷ : Equivocal

Table II. Hepatic tests classified on the basis of sensitivity

Sensitive tests : —— BSP retention, CCFT, ChE, transaminase, urobilinogen
Relatively sensitive tests :——Alb., prothrombin, cholesterol ester ratio, blood lactic acid, blood pyruvic acid, hippuric acid test, glucose tolerance test
Insensitive tests : —— UreaN/NPN, blood NH_3, serum α-KG

The purpose of hepatic tests is (1) to reveal hepatobiliary disorders, either overt or latent, (2) to unravel the character of the disorders, discriminating the diseases which are to be subjected to internal treatment from those which are to be surgically treated, and (3) to predict the future outcome, pursuing the clinical course continuously.

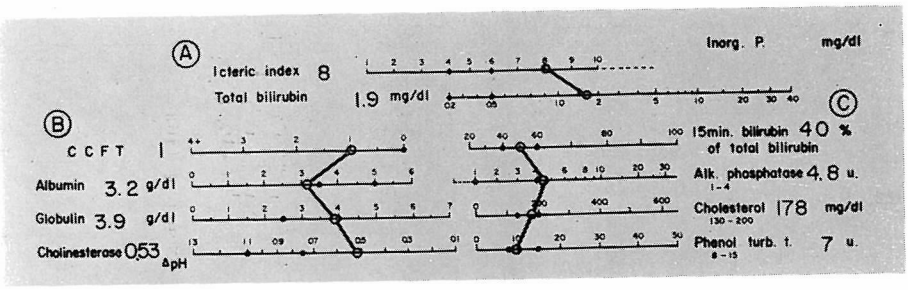
The cardinal principle of the application of hepatic tests consists in the following points : —

a) Sensitive tests should be chosen to maintain the sensitivity of the detection of hepatobiliary disorders as large as possible. However, extremely insensitive tests are also useful for the diagnosis of hepatic coma.

b) The tests ought to be used in an epuilibrated combination of detectors suitable for disclosing hepatocellular damage and those useful for revealing biliary

obstruction. In our experience, only the tests arranged by this principle can answer satisfactorily the purpose of hepatic tests which have been mentioned.

In the following we should like to present two illustrative examples of the application of hepatic tests to the diagnosis of hepatobiliary disorders.



Transaminase GPT, 8u., Serum iron, 100γ/dl,
Paper electrophoresis of serume protein : Total protein 7.0g/dl, Alb. 44.3,
α_1G 4.9, α_2G 10.2, βG 9.5, γG 31.0 %(↑)
BSP test : —— 15min. 46 ; 30 min. 30 ; 45min. 16%

Figure 2. Hepatic tests of the first case (male, aged 45).

Figure 2 concerning the first case, a male patient ages 45, is a graphical representation of the results of hepatic tests. The tests are arranged in 3 groups of parallel transverse lines, namely groups A, B and C. Group A which comprises icteric index and serum total bilirubin refers to the detection of jaundice and representation of its degree. Group B includes the detectors of hepatocellular damage, namely, the results of cephaline cholesterol flocculation test, albumin, globulin, serum cholinesterase and transaminase. Group C gathers those of biliary obstruction, namely the values of 15-minute bilirubin, alkaline phosphatase, cholesterol and phenol turbidity test.

The values of the tests are scaled on the relevant lines, and their normal ranges are indicated by the portions of the lines partitioned by two black nodules. The results of tests of this patient are plotted on the lines by hollow points which are connected by bending lines.

This graph signifies that the patient has a latent jaundice which is represented by the very slight degree of increase in icteric index and total serum bilirubin..

The jaundice is thought to be of hepatocellular type, because abnormality in the detectors for hepatocellular damage is distincter than in those indicating biliarry obstruction.

The hepatocellular damage will not be related to the acute phase of hepatitis, since serum transaminase and iron which show remarkable increase in hepatitis remain within normal range in this case. However, paper electrophoresis of serum protein revealed a considerable increase in γ globulin, and bromsulphalein test

disclosed a significant degree of dye retention. So, liver cirrhosis may be conceived for this case as a possibility. Then, questionable increase in serum alkaline phosphatase may be accounted for by the non-specific elevation of this enzyme activity in liver cirrhosis, although latent neoplastic process should also be taken into consideration. Occasionally, serum isozyme study answers whether cirrhosis is present or cancer is existing in the liver.

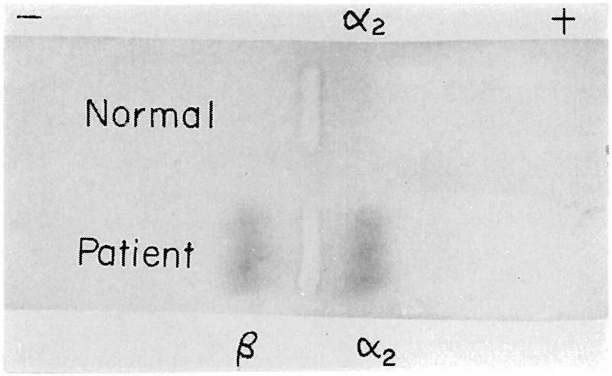


Figure 3. Alkaline phosphatase isozyme of the first case.

Figure 3 is the serum alkaline phosphatase zymogram of this patient. There are two isozymes : one possessing the electrophoretic migration corresponding to α_2 globin, and the other conforming to β globulin. The former one, namely α_2 isozyme is seen in normal subjects, but the latter, namely β isozyme is pathognomonic of liver cirrhosis. This isozyme is encountered in about 60 per cent of the cases of cirrhosis. Accordingly it is diagnosed from the results of hepatic test that the patient has liver cirrhosis.

The morbid history tells us that the patient had repeated episodes of jaundice about 20, 17, and 4 years ago, apporoximately two months ago he had hematemesis and tarry stool. The liver was enlarged two finger-breadths below the costal margin and it was firm.

The diagnosis was confirmed by needle biopsy of the liver, the result of which is presented in Figure 4.

Figure 5 shows the graph of the hepatic tests of the second case, a sixty-five year old male patient. The tests are interpreted as follows.

The patient may have very slight latent jaundice, since icteric index shows a questionable increase. There may be a slight degree of hepatocellular damage, but diminution of serum cholinesterase seems to be too pronounced for the hepatic dysfunction of this degree. There is a remarkable increase in serum lactic dehydrogenase activity in spite of approximately normal activity of serum trans-

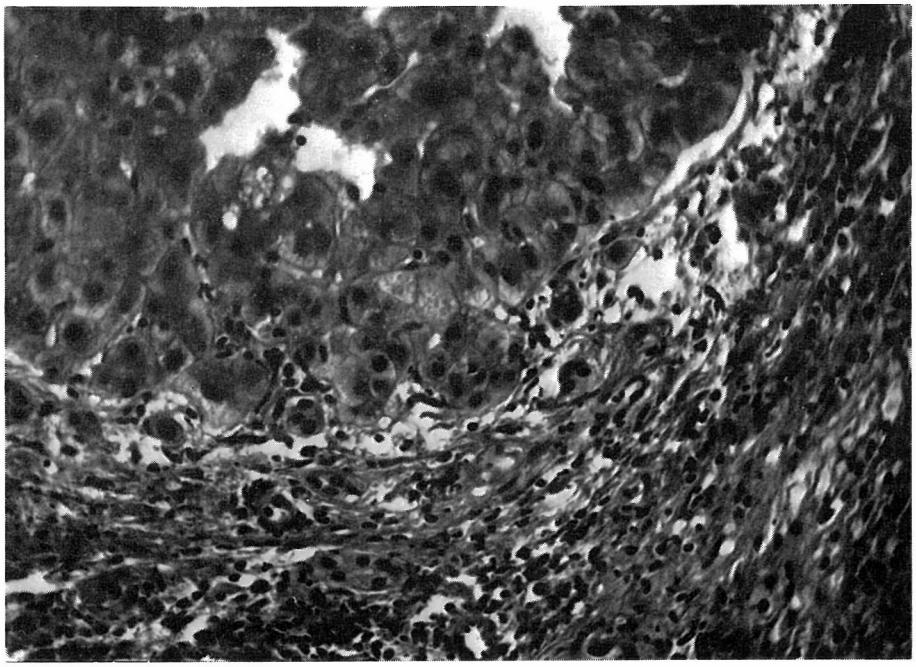
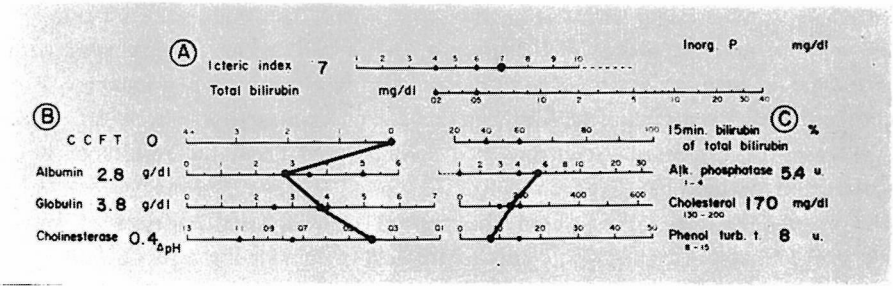


Figure 4. Histological picture of hepatic trssue fragment obtained by needle biopsy. (the first case).



Transaminase GPT 11u. Leucine aminopeptidase 37u. (↑)
LDH 145u. (↑↑)
BSP test : 15min. 49; 30min. 32; 45min. 25% (↑↑)

Figure 5. Hepatic tests of the second case (male, aged 65).

aminase. Neoplastic disease is therefore conceivable.

Slight increase in alkaline phosphatase without rise in serum cholesterol and in phenol turbidity test is suggestive of a latent biliary obstruction. Serum leucine aminopeptidase is increased, but the increase is not so distinct as secures the diagnosis of the obstruction to the extrahepatic biliary tract. Isolated elevation of the activity of serum alkaline phosphatase with or without minor sign

of hepatocellular damage is common in metastatic neoplasm to the liver. If bromsulphalein retention which is evident disproportionately to the minor degree of abnormality in the detectors of hepatocellular damage is observed for such a patient, the diagnosis of metastatic tumor to the liver becomes more likely. In this patient a remarkable retention of BSP was demonstrated as shown in figure 5, So, it is presumable that the patient may have metastatic neoplasm to the liver.

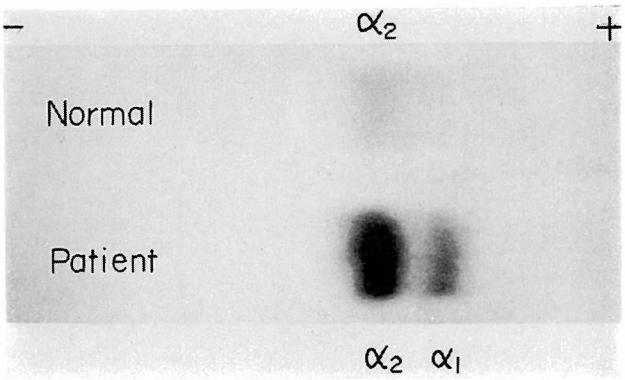


Figure 6. Alkaline phosphatase isozyme of the second case.

Figure 6 presents the results of our isozyme studey on the second case. There are two alkaline phosphatase isozymes. A pathologic one at the position of α_1 globulin and a normal one at α_2 globulin site. This pattern is seen in about 60 per cent of the hepatic neoplasm. It is accordingly very probable that the patient has neoplasm in the liver.

The diagnosis was confirmed by needle biopsy of the liver. The histological picture of the hepatic fragment obtained by this technique is presented in Figure 7.

The morbid history of the patient was not so specific. He had attacks of epigastralgia, nausea and rigidity of the shoulders and became anemic for the recent several months. The liver was palpable about 3 finger-breadths below the costal margin.

These two examples which have just been presented are helpful for us to understand how hepatic tests are used to establish the clinical diagnosis of hepatobiliary disorders.

The present day hepatic tests are useful also for pursuing the clinical course of the patients with hepatobiliary diseases.

Patients with jaundice can be chased by successive determination of serum bilirubin. Those with diseases of the hepatic parenchyma can be observed con-

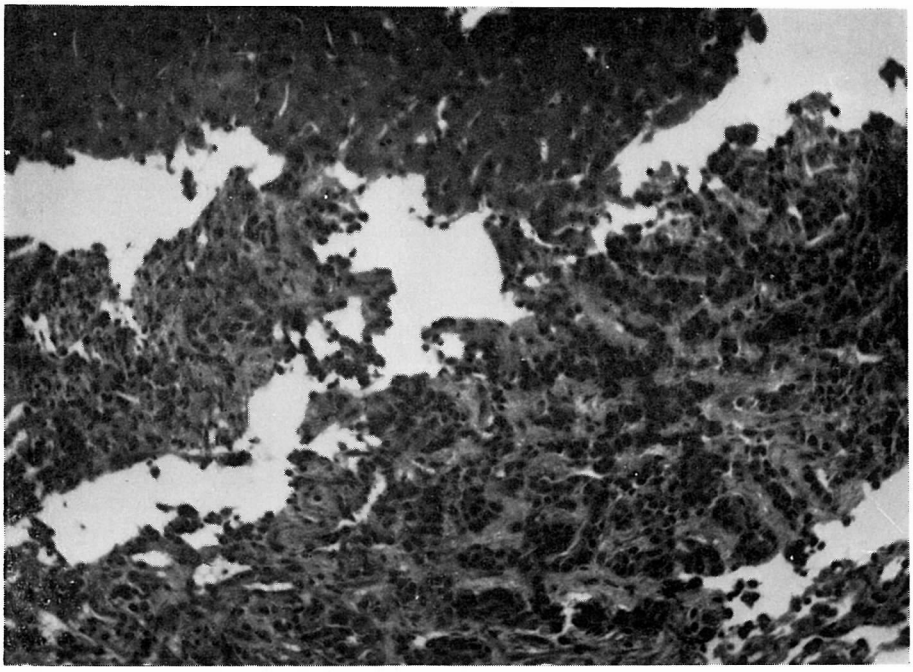


Figure 7. Histological picture of the hepatic tissue fragment of the second cose (obtainal by needle biopsy).

tinuously by repeated determinations of serum transaminase, cholinesterase, albumin or cholesterol ester ratio. Continuous increase in serum bilirubin is generally suggestive of aggravation of the hepatobiliary disease. It is especially so when serum transaminase which was elevated high together with serum bilirubin in the past is dropping rapidly with lapse of time. Remarkable increase in serum transaminase is almost pathognomonic of hepatitis. Relatively low transaminase activity in the presence of remarkable abnormality in other tests for hepatocellular damage is often an ominous sign of severe hepatitis.

Cosecutive decrease in serum albumin or serum cholinesterase is suggestive of that the hepatobiliary disease is becoming chronic. Restoration of normal values of albumin and cholinesterase implies amelioration of the disease. Continuous drop of serum cholesterol ester ratio is also indicative of the advance in the hepatic parenchymatous damage. Perpetual increase in γ globulin with concomitant absence of distinct increase in α and β globulin refers to chronicity of the hepatobiliary disease. Successive BSP tests may be helpful for chasing the clinical course of hepatic disease, but caution should be taken lest the patient should be endangered be allergic side effects of BSP injection. BSP test is not an almighty hepatic test. It is not rare that the test fails to detect liver cirrhosis.

In conclusion we should like to say that the routine hepatic tests of the present days are not satisfactorily sensitive and specific to the hepatobiliary diseases, failing to contribute to the formation of exact image of the morbid anatomical pictures. Nevertheless, they are fairly well helpful for the diagnosis of hepatobiliary disorders if they are used in an equilibrated combination of the detectors of parenchymatous damage and those of biliary obstruction.

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