

Quantitative liver imaging using ^{131}I Rose Bengal as an index of liver function and prognosis

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SUMMARY A technique for assessing quantitatively hepatic function by direct measurement of liver parenchymal cell uptake of ^{131}I Rose Bengal using a scintillation camera with a digital store and retrieval system is described. Ninety-four studies were performed on 84 patients with a variety of hepatic disorders over a two-year period, the diagnosis in each case being established by liver biopsy or laparotomy. The results were compared with the clinical, biochemical and histological assessment of the patients.

A good correlation was found between the half-time for hepatic uptake of ^{131}I Rose Bengal and the histological changes, as well as with clinical prognosis measured in terms of clinical improvement or deterioration to death. The rate of liver uptake was found to be a better index than the clearance of radioisotope from the blood and was superior to conventional biochemical investigations in both icteric and anicteric patients. The test was not shown to be of clinical value in discriminating between intra- and extrahepatic causes of jaundice.

It is suggested that this technique may provide a safe and sensitive method for assessing the severity of liver dysfunction and also for monitoring clinical progress, especially in situations where liver biopsy may be unreliable or hazardous.

There is no reliable method for evaluating hepatic function and assessing the prognosis of patients with liver disease (Tygstrup, 1973). Conventional measurements such as serum albumin and prothrombin are non-specific and insensitive (Schiff, 1969) and liver clearance of bromsulphalein (BSP) from the circulation, whilst sensitive for relatively minor hepatic damage (Mateer, Baltz, and Marion, 1943), is unreliable in advanced disease, particularly for jaundiced patients (Mendenhall and Leevy, 1961; Schoenfield, Onstad, and Goldstein, 1970; Grausz and Schmid, 1971). Isotope measurements using radio-labelled Rose Bengal were introduced as a test of liver cell function and biliary patency in 1955 (Taplin, Meredith, and Kade, 1955) but fell into disfavour because of the difficulty in interpreting the results obtained from probe detectors. Rose Bengal is a fluorescein dye similar to BSP which is bound to plasma albumin (Meurman, 1960), cleared from the

blood by hepatic parenchymal cells (Mendeloff, 1949) and excreted by the biliary system into the gut. More recent work has suggested that scintillation cameras may be useful in assessing hepatic function, although most studies have been confined to the problem of differentiating between extrahepatic and intrahepatic biliary obstruction (Taplin, 1970). We report here the direct assessment of liver function by measuring hepatic uptake of ^{131}I Rose Bengal using a scintillation camera with a digital store and retrieval system able to quantify activity in selected regions of interest.

The purpose of this study was to evaluate the technique as a means of assessing liver function and prognosis of adult patients with liver and biliary tract disorders and comparing it with conventional biochemical and histological tests. In all patients with hepatocellular disease the diagnosis has been supported by biopsy, whilst cases of obstructive jaundice were all confirmed by subsequent laparotomy.

Methods

The investigation was carried out after the patient had fasted overnight and the oral administration of 120 mg of potassium iodide to reduce the uptake of free ^{131}I by the thyroid gland. After the patient had rested supine for 15 minutes to stabilize hepatic blood flow (Rowell, Blackmon, and Bruce, 1964) a scintillation camera (Nuclear Enterprises improved mark III) with diverging field collimator was positioned with the heart, liver and gut in its field of view. One hundred microcuries of ^{131}I labelled Rose Bengal (containing 0.09 to 0.4 mg of Rose Bengal) was administered by injection into an antecubital vein, and serial images were taken of the changes in the distribution of activity with time. Concurrently, data were recorded as a digital 64×64 matrix at one-minute intervals on magnetic tape (Intertechnique cinescintigraphy system) for a period of one hour. At 40 minutes a glass of milk was given to promote biliary flow. At the end of the investigation the cardiac, liver (excluding the gallbladder region), gallbladder (if seen) and gut regions were selected by light pen from a playback of the integrated digital image, and activity in these regions was plotted against time, after statistical smoothing by a digital computer. Hepatobiliary function was defined by three indices: (1) the 20- to five-minute ratio of activity within the blood obtained from the curve of the cardiac region (fig 1); (2) the half-time of hepatic uptake ($T_{1/2}$). The uptake of isotope by the liver describes a curve consisting of an initial rise which flattens off to a broad peak or plateau value A (fig 1). The rise can be mathematically described as

$A(1 - e^{-0.693t/T_{1/2}})$ (Loewenstein, 1956). A straight line graph can be constructed by subtracting the values on the curve from A, and plotting the results against time (t) on log-linear graph paper. The hepatic half time ($T_{1/2}$) is the time at which the straight line thus obtained falls to half its initial value. (3) The 60- to 20-minute ratio of activity in the gut region, which was taken to indicate biliary patency.

$^{99\text{m}}\text{Tc}$ sulphur colloid rectilinear liver scans were performed using a Selo double-headed scanner. Anterior, posterior, right and left lateral images of the liver were assessed for position, size, distribution of activity, and hepatic, splenic and bone marrow uptake.

The hepatic radiation dose to the normally functioning liver from 100 μCi ^{131}I Rose Bengal is approximately 100 mrad, increasing to 8.7 rad when hepatic function is severely impaired. A typical $^{99\text{m}}\text{Tc}$ colloid investigation (3 mCi) gives about 1 rad to the liver (International Commission on Radiological Protection, 1971).

Patients Studied

Ninety-four studies were performed on 84 patients over a period of two years. The normal range was established on 16 controls. These included five healthy subjects (hospital staff) and 11 patients without clinical or histological evidence of liver disease in whom liver biopsy was performed in an attempt to diagnose systemic disease. In all patients conventional biochemical tests of liver function were performed within 48 hours of the Rose Bengal study and colloid scans were also carried out in 73 patients.

The patients with liver disease were divided into the following diagnostic categories:

OBSTRUCTIVE JAUNDICE

Fifteen patients (six carcinoma of pancreas, three intraduct carcinoma and six with cholelithiasis) were all studied preoperatively within one week of operation. Liver biopsies were not taken at the time of surgery but in no case was there macroscopic evidence of gross abnormality in the liver.

PRIMARY BILIARY CIRRHOSIS

Nine patients, all of whom had positive mitochondrial antibodies and histological changes consistent with the diagnosis of primary biliary cirrhosis. Most biopsies were surgical specimens obtained at laparotomy and were staged 1-4 in severity (Scheuer, 1973).

ACUTE HEPATITIS

Thirteen patients (six in both acute and convalescent

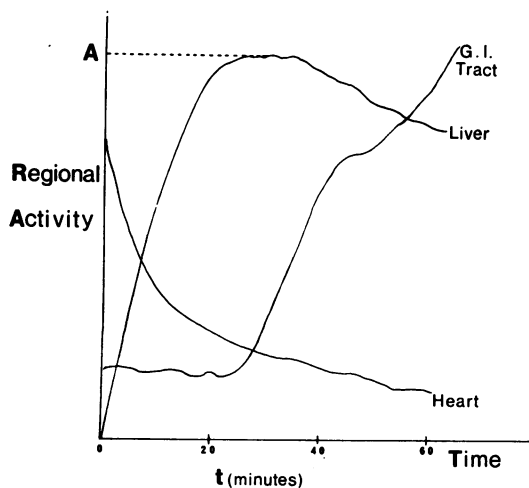


Fig 1 Normal ^{131}I Rose Bengal dynamics

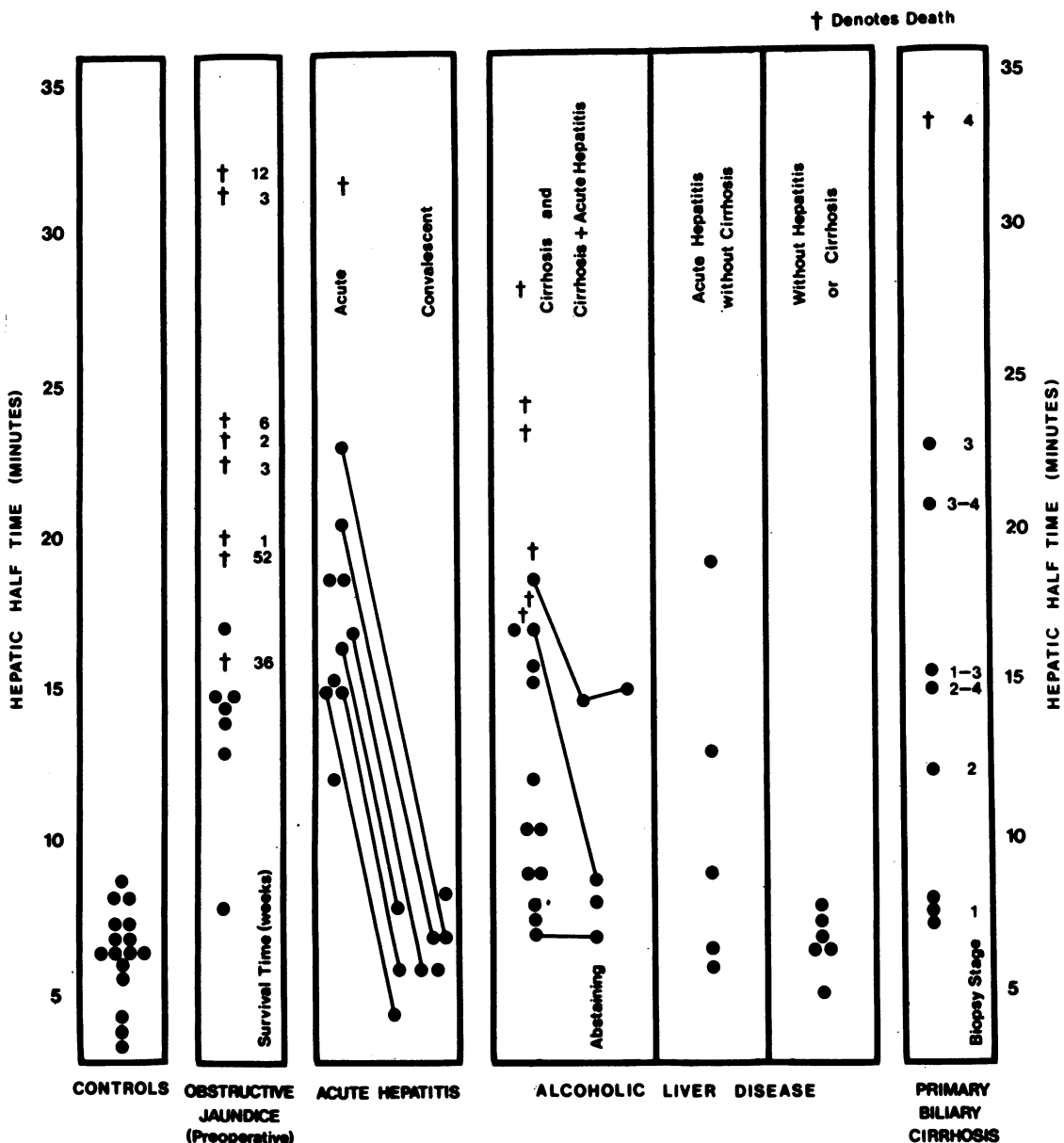


Fig 2 ¹³¹I Rose Bengal hepatic uptake in liver disease

stages) of whom seven had viral hepatitis and six were drug-induced.

ALCOHOLIC LIVER DISEASE

Thirty-one patients were divided into three groups on the basis of the liver histology (Scheuer, 1973) and clinical findings: (a) 20 patients with cirrhosis with or without hepatitis; (b) five patients with alcoholic hepatitis without cirrhosis; (c) six patients

with hepatomegaly and abnormal liver function tests in whom liver biopsy showed either fat or non-specific changes.

Repeat studies were performed on three patients following the withdrawal of alcohol.

Results

The clearance of Rose Bengal from the circulation

measured by the blood 20- to five-minute concentration ratio showed a wide range in normal subjects (0.51 to 0.73). The correlation with hepatic uptake in these subjects and in patients with histological evidence of liver damage was poor (correlation coefficient 0.69). Since hepatic uptake is a more direct measurement of liver function this was used as the principal index.

The results showing hepatic half-time in 94 studies are shown in figure 2. The studies in 16 control subjects showed the normal range to be between 3.5 and 8.8 minutes.

CORRELATION WITH HISTOLOGICAL AND CLINICAL FEATURES OF LIVER DISEASE

Obstructive jaundice

All patients with obstructive jaundice who had a hepatic half-time of 20 minutes or longer before operation died within a few weeks of surgery. The mortality in this group was unusually high, probably due to the inclusion of a number of patients with jaundice secondary to surgically unresectable tumours. Preoperative investigation of these patients did not suggest disseminated carcinoma, but the postoperative progress in each case followed a steady downhill course. By contrast two patients with carcinoma of the pancreas with half-times of 15 and 8 minutes before operation were still alive 52 and 96 weeks respectively after the study. Only one patient with jaundice secondary to gallstones had a hepatic half-time of more than 20 minutes (23.5 minutes), and she was the only patient to die in this group. Three days after surgery she suddenly collapsed and died with symptoms suggesting a Gram-negative septicaemia and at necropsy was found to have stones impacted in the left hepatic duct.

Primary biliary cirrhosis

The hepatic half-times for patients with primary biliary cirrhosis showed a wide range which correlated well with histological staging (see fig 2). Furthermore, in patients with stage 1 disease, activity was seen to pass into the gut, indicating a patent biliary tree.

Acute hepatitis

Hepatic half-times in patients with acute hepatitis were surprisingly prolonged in relation to the clinical severity of their illness. Only one patient in this group died, the hepatic half-time being one of the longest recorded in the series (31.5 minutes). No difference was found between the patients with hepatitis of viral origin compared with those secondary to drugs. The overlap in results between this group and those with obstructive jaundice was considerable. Six

patients were studied again after recovery and the results of the repeat tests correlated well with their clinical, biochemical and histological improvement. The complication of cholestasis in an otherwise recovering liver did not appear to affect the test. One patient with a persisting hyperbilirubinaemia of up to 12 mg per 100 ml had a normal hepatic half-time. In this patient liver biopsy showed a resolving hepatitis. Subsequent recovery was complete and uneventful.

Alcoholic liver disease

Twenty-four studies were performed on 20 patients with biopsy-proven alcoholic cirrhosis. All six patients who died of liver disease within nine months of the study had hepatic half-times greater than 17 minutes. Hepatic half-times showed a wide range but the figures correlated well with clinical assessment, eg, hepatic encephalopathy was found only in patients with a hepatic half-time greater than 15 minutes. Several patients had histological evidence of alcoholic hepatitis as well as cirrhosis, and the serial studies on two of these after several months of abstinence from alcohol showed clinical and histological progress which correlated closely with hepatic half-time. In a third patient, with established cirrhosis but no active alcoholic hepatitis and a normal hepatic half-time, a three-month follow-up Rose Bengal study showed a similar result.

Five patients with alcoholic hepatitis alone had half-times between 6.0 and 19.5 minutes. The histological severity of the hepatitis correlated well with the hepatic half-time although the number of patients studied was small.

All six patients with steatosis or mild non-specific changes had hepatic half-times within the normal range.

CORRELATION WITH BIOCHEMICAL TESTS

Bromsulphalein retention tests were available for 18 non-jaundiced patients (bilirubin less than 2.0 mg/100 ml). There was a fair correlation with the hepatic half-time with a coefficient of 0.72.

The correlation between the hepatic half-time and other conventional biochemical tests of liver function in the patients with hepatocellular disease (excluding patients with obstructive jaundice) was poor. The correlation coefficient for the height of the bilirubin was 0.66, for albumin 0.50 and for the prothrombin ratio after vitamin K 0.49. The hepatic half-time proved to be of better prognostic value than the serum albumin or prothrombin ratio. Of the 16 adults dying from liver disease, in all the hepatic half-time was grossly abnormal (17 minutes) whereas nine had a normal serum albumin and seven a prothrombin ratio within the normal range.

ASSESSMENT OF BILIARY PATENCY

The control group all showed a gut 60:20 minute activity ratio of greater than 1.5, while patients with known biliary obstruction showed a gut 60:20 minute ratio of 1.0. In patients known to have a patent biliary system a ratio of less than 1.5 was also seen, usually when hepatic function was impaired. There was no correlation between the gut 60:20 minute ratio and the serum bilirubin, ratios of 1.0 being recorded in several anicteric patients with advanced liver disease. Thus it was concluded that in the presence of significant hepatic function impairment the gut 60:20 minute ratio was not a reliable index of biliary patency.

CORRELATION WITH ^{99m}Tc COLLOID SCANS

Comparing the Rose Bengal scintillation camera image with the ^{99m}Tc colloid rectilinear image, similar information on the position and size of the liver was obtained. The relatively low administered radioactivity for the Rose Bengal study makes an exact comparison of the images for intrahepatic filling defects difficult; in most cases the Rose Bengal image was similar to the colloid. A good overall correlation was found between the Rose Bengal half-time and the semi-quantitative assessment of the colloid scans (table) implying some correlation between hepatic parenchymal and reticuloendothelial cell function. A few notable exceptions were found, mainly in patients with acute hepatitis in whom the Rose Bengal function was often disproportionately reduced compared with the colloid scan appearance. However, even if the scans of patients with alcoholic liver disease alone are compared the statistical correlation between colloid and Rose Bengal scans is no better.

Colloid Scan Report (Reticuloendothelial Cell Uptake)	Rose Bengal Half-time (Parenchymal Cell Uptake)	
	All Groups (73) (Mean \pm SD)	Alcoholic Liver Disease (Mean \pm SD)
Normal liver uptake	9.9 \pm 7.0 (20)	8.8 \pm 4.0 (8)
Patchy liver uptake	12.1 \pm 4.7 (28)	11.7 \pm 5.1 (11)
Reduced liver uptake and increased splenic uptake	13.7 \pm 6.8 (5)	None
Reduced liver uptake, increased splenic uptake and activity in bone marrow	16.9 \pm 5.9 (20)	17.3 \pm 6.7 (14)

Table Comparison of ^{99m}Tc colloid scan report and ^{131}I Rose Bengal hepatic uptake in liver disease

Discussion

The purpose of this study was to assess the value of

a ^{131}I Rose Bengal and scintillation camera technique as a measurement of function in different types of liver disease. Since histological examination of the liver provides the most accurate information for diagnosis and assessment of severity of liver dysfunction the data presented are confined to a small number of clearly defined clinical disorders in which histological evidence was available or in which a diagnosis of obstructive jaundice was confirmed at laparotomy. The results show that the hepatic half-time for ^{131}I Rose Bengal correlates well with the clinical state and histological changes in patients with hepatocellular disease and is superior to conventional liver function tests such as serum albumin or prothrombin ratio. In non-jaundiced patients the technique provides similar results to those obtained using the BSP retention test. In patients with advanced liver disease the correlation with BSP is poor. This may be because the administered doses of Rose Bengal are small (approximately 0.1% of a typical BSP dose) and are less likely to be affected by the variations such as serum dye and albumin concentration which affect hepatic uptake of BSP (Mendenhall and Leevy, 1961; Barber-Riley, Goetzee, Richards, and Thomson, 1961; Freston and Englert, 1967). An additional factor in favour of Rose Bengal is the absence of adverse reactions, whereas fatalities have been reported with intra-venous BSP (Astin, 1965).

In addition it was found that the hepatic half-time provided a good prognostic guide. Thus during a two-year period of follow up, all patients who died of liver disease had hepatic half-times greater than 16 minutes. The correlation between hepatic half-time and survival was particularly striking in patients with obstructive jaundice. None of these livers showed macroscopic evidence of advanced hepatic damage or of malignant infiltration at the time of surgery or subsequent necropsy. The explanation for this unexpected observation is uncertain, but the possibility that ultrastructural changes in the liver may be present in the obstructed liver of patients with grossly prolonged hepatic half-times has not been excluded.

Prolonged hepatic half-times of a similar value to that recorded in cases of obstructive jaundice were found in patients with acute viral hepatitis of relatively mild clinical and histological severity who recovered completely and uneventfully. The half-times recorded in patients with hepatocellular jaundice tended to be longer than those found in extrahepatic obstruction but in our experience the overlap in the results between the two conditions is too great to make the test of much clinical value as a method for distinguishing between intra- and extra-hepatic jaundice. In this respect our results do not

agree with those of Watson, Bone, Testa, and Torrance (1975) using a similar technique.

In certain liver diseases the information gained from liver biopsy may be unreliable due to sampling error. In the clinical disorders studied here this applies particularly to primary biliary cirrhosis (Scheuer, 1973), and for this reason the histological assessment was based on surgical biopsies which often showed different stages of disease in various areas of the biopsy (fig 2). Assessment of function using the hepatic half-time may overcome such errors of sampling. Furthermore, serial studies using ^{131}I Rose Bengal may be safely used in this and other liver disorders in order to assess clinical progress, thereby avoiding the risks of repeated liver biopsy and the inaccuracies of tissue sampling.

Comparison of ^{131}I Rose Bengal and $^{99\text{m}}\text{Tc}$ sulphur colloid images suggests broad correlation between parenchymal and reticuloendothelial cell function. Occasionally the Rose Bengal image can show concentration of activity in regions of poor colloid uptake (Gamlen, Ackery, Grant, Jacoby, Kenny, MacIver, and Triger, 1975).

We feel that the use of a scintillation camera and data handling system is necessary to analyse precisely the change of activity with time within the liver and other organs. Probe systems do not give this precision since they are subject to positioning errors. Determination of hepatic function from the blood clearance of Rose Bengal in our experience correlates poorly with the more direct measurement of hepatic uptake of radioisotope. Although the gamma camera with associated digital equipment is costly, such systems are now available in many large centres, and are used for a variety of non-hepatic radioisotope investigations.

In conclusion, we consider that quantitative ^{131}I Rose Bengal imaging is a simple, safe and useful method of assessing hepatic function which may be repeated frequently in conditions where liver biopsy is contraindicated. Although it does not provide a specific diagnosis for the type of liver disease for which one would have to rely on histology and clinical features, it may be a useful guide to prognosis. It may also be of value in specialist centres in the objective evaluation of therapeutic procedures in liver disease, although its use as a routine test of liver function is not yet established.

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