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A Comparison of the Bromsulphthalein and Galactose Elimination Test in Patients with either Chronic Bowel Inflammation or Alcoholic Liver Disease

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Simultaneously infused bromsulphthalein (BSP) and galactose were used as a test of liver function in two groups of patients. One group consisted of all patients hospitalized over a period of two years for chronic inflammatory bowel disease. The other group comprised patients with clinical signs of liver damage due to chronic alcohol abuse; these patients were treated as inpatients during the same period of time. In patients with alcoholic cirrhosis, both substances showed a decreased elimination from the blood. Patients in the alcohol abuse group, with histologically verified steatosis of the liver but without reactive changes in the portal fields, were characterized by a prolonged galactose elimination time but a normal retention of BSP. A normal galactose elimination capacity was typical for the patients with chronic inflammatory bowel disease, whereas the BSP retention was increased in 47 per cent of patients admitted to hospital. This data suggests that the excretory function of the liver is frequently disturbed in chronic inflammatory bowel disease, whereas the parenchymal metabolic function is preserved. This is well in accordance with the modern concept that pericholangitis is the most common type of liver damage in cases of ulcerative colitis or Crohn's disease.

Key-words: Bromsulphthalein; colitis, ulcerative; enteritis, regional; fatty liver; galactose; hepatic cirrhosis; liver disease; liver function test

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Bromsulphthalein (BSP) and galactose are eliminated from the liver by different mechanisms. BSP is concentrated in the parenchymal liver cells, where it is conjugated with sulphhydryl-containing amino acids and thereafter excreted via the bile. The disappearance of BSP from the blood during the first 15-20 min is mainly a function of liver blood flow and uptake in the parenchymal cells. After this time the bile excretory capacity normally is the limiting factor (7).

Galactose enters the system of glucose metabolism via a series of enzymatic reactions after uptake in the liver parenchymal cells. No interference in the elimination of BSP or ga-

lactose has been observed when they are given simultaneously (13).

In the present study an attempt has been made to discriminate between different types of liver damage by studying the elimination pattern of the two substances given simultaneously. Two groups of patients were selected for examination - patients with chronic inflammatory bowel disease and patients with alcohol-induced liver damage. It is well known that in patients with chronic inflammatory bowel disease pericholangitis can occur with laboratory signs of cholestasis. In patients with alcohol abuse, histological signs of liver damage can either be absent or found in the form of

Table I. The patients in the two groups presented in Fig. 1 a & b grouped according to the results of the BSP retention test after 45 min and the galactose elimination test. The frequency of pathological alkaline phosphatase (ALP) and alanine aminotransferase (GPT) values in each group is given

	Bowel disease			Alcohol abuse		
	Pathological		n	Pathological		n
	n	ALP		GPT	ALP	
Normal BSP/normal gal.	46	3	2	16	3	5
Normal BSP/pathol. gal.	1	0	0	18	0	3
Pathol. BSP/normal gal.	27	5	7	7	2	6
Pathol. BSP/pathol. gal.	15	3	7	47	19	28

different degrees of fatty infiltration and/or cirrhosis.

MATERIAL

I. Bowel disease group (Table I, Fig. 1a)

This group included all patients with chronic inflammatory bowel disease hospitalized over a 2-year period; 89 patients (37 men and 52 women) with a mean age of 31 years. Ulcerative colitis was the diagnosis in 52 patients, of whom 11 had undergone panproctocolectomy more than 1 year before examination. Thirty-seven patients had Crohn's disease, 7 having undergone ileocecal resection but with recurrence observed on radiological examination. Routine laboratory tests were performed on all patients and percutaneous liver biopsy made on 18 of the 89 patients. All those who underwent liver biopsy showed clinical signs of liver injury. Nine had a typical chronic or subacute pericholangitis according to the histological description by Mistilis (10). These cases were characterized by fibrosis and inflammatory exudate in the enlarged portal tracts, but the liver lobules were without significant pathological changes. The remaining 9 patients showed non-specific changes in the liver biopsy specimen and therefore are not included in Table II.

II. Alcohol abuse group (Table I, Fig. 1b)

This group was collected over the same 2-year period and consisted of 88 patients (78 men and 10 women) with a mean age of 55 years and with long-standing alcohol abuse. All the patients had either an increase in

serum transaminase and/or a liver enlargement as signs of liver damage when admitted to the ward. Alcohol abuse patients without signs of liver damage were not hospitalized, and thus not included in this group. A few patients with increased bilirubin level were excluded. None of the alcoholic patients had significant signs of under-nutrition. No strict rules were followed in selecting patients for the liver biopsy. However, according to the routine of the hospital, biopsy was performed only in those cases where one or both of the elimination tests showed a pathological value. These patients have been arranged in the following 3 subgroups according to their diagnosis (Table II).

1. The biopsy specimens in 14 showed only fatty infiltration without other pathological alterations.

2. The histological picture in 6 showed reactive changes in the portal tracts with a light to moderate increase in the amount of connective tissue and round cells, and in addition fatty infiltration of the parenchymal cells.

3. A typical histological pattern of Laennec's cirrhosis was observed in 18. Another 5 patients included in this group had clinical signs of portal hypertension, for which reason no biopsy was made.

METHODS

The elimination tests were performed when the patients were afebrile and had been in the ward for at least one week without access to alcohol. The test was started after an overnight fast with an intravenous infusion of 350 mg of

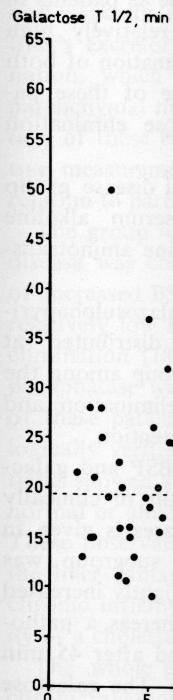
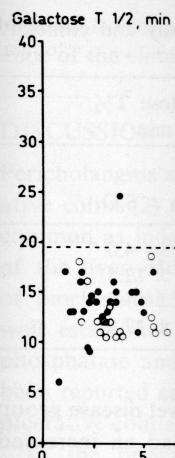


Fig. 1 a & b. The
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Alcohol abuse		
Pathological		
n	ALP	GPT
16	3	5
18	0	3
7	2	6
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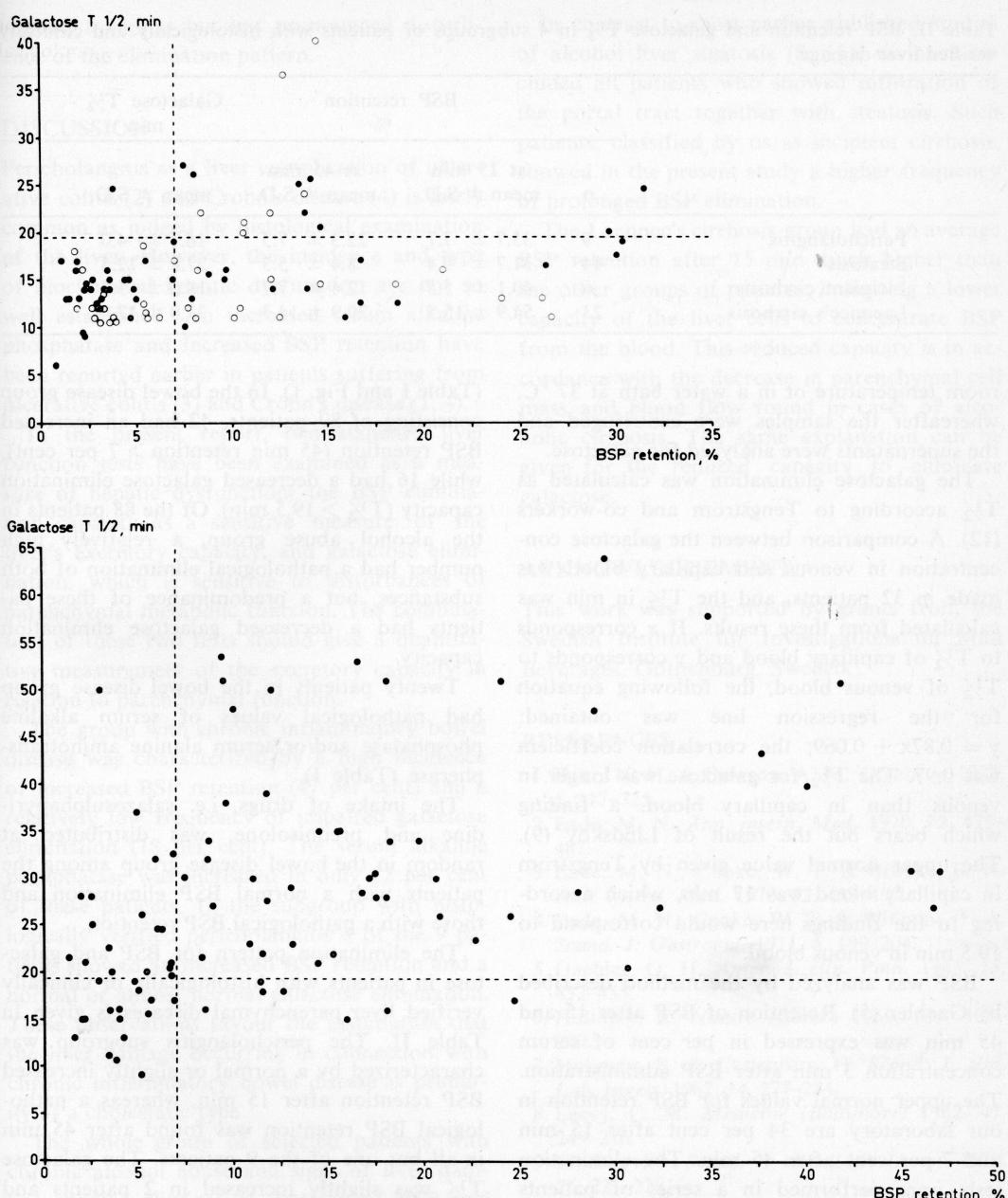


Fig. 1 a & b. The relation between BSP retention after 45 min and galactose elimination ($T_{1/2}$) in a. 89 patients with chronic inflammatory bowel disease. ● = 52 patients with ulcerative colitis. ○ = 37 patients with Crohn's disease. b. 88 patients with alcohol-induced liver damage.

galactose per kg body-weight, followed by infusion of the BSP dye, 5 mg per kg body-weight. Venous blood samples from a cubital vein were obtained 3, 15, 30, and 45 min after the BSP infusion.

Galactose was determined by the orthotoluidine method (6) modified as follows: 0.1 ml of whole blood was pipetted directly into 1 ml of 0.1 mol phosphate buffer (pH 7.0) containing glucose oxidase and left for at least 45 min at

Table II. BSP retention and galactose $T_{1/2}$ in 4 subgroups of patients with histologically and clinically verified liver damage

	n	BSP retention %		Galactose $T_{1/2}$ min
		at 15 min mean \pm S.D.	at 45 min mean \pm S.D.	mean \pm S.D.
Pericholangitis	9	35.7 \pm 7.7	22.3 \pm 7.5	16.7 \pm 4.0
Steatosis	14	31.7 \pm 9.4	8.4 \pm 5.3	27.8 \pm 12.5
Incipient cirrhosis	6	40.1 \pm 5.5	12.4 \pm 7.7	18.0 \pm 5.5
Laennec's cirrhosis	23	54.9 \pm 15.5	29.9 \pm 14.3	37.0 \pm 17.5

room temperature or in a water bath at 37 °C, whereafter the samples were centrifuged and the supernatants were analyzed for galactose.

The galactose elimination was calculated as $T_{1/2}$ according to Tengström and co-workers (12). A comparison between the galactose concentration in venous and capillary blood was made in 32 patients, and the $T_{1/2}$ in min was calculated from these results. If x corresponds to $T_{1/2}$ of capillary blood and y corresponds to $T_{1/2}$ of venous blood, the following equation for the regression line was obtained: $y = 0.87x + 0.069$; the correlation coefficient was 0.97. The $T_{1/2}$ for galactose was longer in venous than in capillary blood, a finding which bears out the result of Lindskov (9). The upper normal value given by Tengström in capillary blood was 17 min, which according to the findings here would correspond to 19.5 min in venous blood.

BSP was analyzed by the method described by Gaebler (5). Retention of BSP after 15 and 45 min was expressed in per cent of serum concentration 3 min after BSP administration. The upper normal values for BSP retention in our laboratory are 34 per cent after 15 min and 7 per cent after 45 min. The elimination tests were performed in a series of patients with chronic inflammatory bowel disease before and during treatment with salazosulphapyridine. There was no change in the elimination pattern of the two substances attributable to the medication.

RESULTS

The elimination of the two test substances showed different patterns in the two groups

(Table I and Fig. 1). In the bowel disease group consisting of 89 patients, 42 had an increased BSP retention (45 min retention $>$ 7 per cent), while 16 had a decreased galactose elimination capacity ($T_{1/2} > 19.5$ min). Of the 88 patients in the alcohol abuse group, a relatively high number had a pathological elimination of both substances, but a predominance of these patients had a decreased galactose elimination capacity.

Twenty patients in the bowel disease group had pathological values of serum alkaline phosphatase and/or serum alanine aminotransferase (Table I).

The intake of drugs, i.e. salazosulphapyridine and prednisolone, was distributed at random in the bowel disease group among the patients with a normal BSP elimination and those with a pathological BSP retention.

The elimination pattern for BSP and galactose in patients with histologically or clinically verified liver parenchymal diseases is given in Table II. The pericholangitis subgroup was characterized by a normal or slightly increased BSP retention after 15 min, whereas a pathological BSP retention was found after 45 min in all but one of the 9 patients. The galactose $T_{1/2}$ was slightly increased in 2 patients and normal in the other 7. Most of the patients in the subgroup with alcohol-induced steatosis had normal or only marginally increased BSP retention after 15 and 45 min, but 11 out of the 14 patients had a prolonged galactose $T_{1/2}$.

In the Laennec's cirrhosis subgroup the mean values of BSP retention after 15 and 45 min and the galactose $T_{1/2}$ were higher than in the other groups. The subgroup with incipient cirrhosis

showed a similar but less pronounced of the elimination pattern.

DISCUSSION

Pericholangitis as a liver comparative colitis (2) and Crohn's disease common as judged by histology of the liver. However, the incidence of biochemical hepatic dysfunction well established. An increased alkaline phosphatase and increased BSP been reported earlier in patients with ulcerative colitis (3) and Crohn's disease.

In the present report, two function tests have been examined to measure of hepatic dysfunction, namely BSP retention capacity as a sensitive test of the liver's excretory capacity, and galactose elimination, which is sensitive to parenchymal metabolic function. The function of these two tests should be compared with the relative measurement of the excretion of BSP in relation to parenchymal function.

The group with chronic intestinal disease was characterized by a high frequency of increased BSP retention (42 per cent) and a relatively low frequency of increased galactose elimination (18 per cent). The alkaline phosphatase was increased in 20 per cent of these patients. In the subgroup with histologically verified pericholangitis patients showed an increased BSP retention, but normal or almost normal galactose elimination. These observations favour the hypothesis that the liver damage occurring in pericholangitis is of a cholestatic type.

The whole group of selected patients with chronic alcohol abuse and steatosis showed elimination patterns of BSP and galactose less distinct than the bowel disease group. The patients with histologically verified steatosis, however, had an elimination pattern characterized by little or no BSP retention and a prolonged galactose $T_{1/2}$.

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Galactose T _{1/2} min	
5 min	mean \pm S.D.
\pm 7.5	16.7 \pm 4.0
\pm 5.3	27.8 \pm 12.5
\pm 7.7	18.0 \pm 5.5
\pm 14.3	37.0 \pm 17.5

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showed a similar but less pronounced disturbance of the elimination pattern.

DISCUSSION

Pericholangitis as a liver complication of ulcerative colitis (2) and Crohn's disease (4) is fairly common as judged by histological examination of the liver. However, the incidence and type of biochemical hepatic dysfunction are not so well established. An increased serum alkaline phosphatase and increased BSP retention have been reported earlier in patients suffering from ulcerative colitis (3) and Crohn's disease (1, 4).

In the present report, two standard liver function tests have been examined as a measure of hepatic dysfunction; the BSP elimination capacity as a sensitive measure of the liver's excretory capacity, and galactose elimination, which is sensitive to disturbances of parenchymal metabolic function. The combination of these two tests should give a quantitative measurement of the excretory capacity in relation to parenchymal function.

The group with chronic inflammatory bowel disease was characterized by a high incidence of increased BSP retention (47 per cent) and a relatively low frequency of impaired galactose elimination (18 per cent). The serum alkaline phosphatase was increased in only 12 per cent of these patients. In the subgroup with histologically verified pericholangitis 8 of the 9 patients showed an increased BSP retention and a normal or almost normal galactose elimination. These observations favour the assumption that the liver damage occurring in connection with chronic inflammatory bowel disease is primarily of a cholestatic type.

The whole group of selected patients with chronic alcohol abuse and signs of liver damage showed elimination patterns of BSP and galactose less distinct than the bowel disease group. The patients with histologically verified steatosis, however, had an elimination pattern characterized by little or no increase of BSP retention and a prolonged galactose elimination.

In contrast to most earlier published studies of alcohol liver steatosis (8, 11), we have excluded all patients who showed infiltration of the portal tract together with steatosis. Such patients, classified by us as incipient cirrhosis, showed in the present study a higher frequency of prolonged BSP elimination.

The Laennec's cirrhosis group had an average BSP retention after 15 min much higher than the other groups of patients, indicating a lower capacity of the liver cells to concentrate BSP from the blood. This reduced capacity is in accordance with the decrease in parenchymal cell mass and blood flow found in cases of alcoholic cirrhosis. The same explanation can be given for the reduced capacity to eliminate galactose.

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