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Research Article

THE PHOSPHATASE CONTENT OF THE BLOOD SERUM IN JAUNDICE[1]

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Enzymes which hydrolyze esters of phosphoric acid, *phosphatases,* are found in many mammalian tissues. Robison (9) has stressed the presence of these enzymes in growing bone and their importance in relation to the processes of calcification and bone development. Further evidence of the importance of this enzyme in the metabolism of bone (6) was adduced with the discovery that the phosphatase content of the blood serum was increased in various diseases such as rickets, Paget's disease or hyperparathyroidism in which osseous changes are marked. In these conditions the increase in the serum or plasma phosphatase apparently is secondary to the osseous lesions.

Phosphatases are present in many tissues and occur in greatest amount in the intestinal mucosa and the kidney. Smaller amounts have been reported in the liver and in the bile (4). Bodansky and Jaffe (2, 3) have found that in normal individuals the phosphatase content of the serum varies with digestive activity and so postulate that while some of the phosphatase in the serum may be osseous in origin some at least is non-osseous. This is also true in some pathological conditions for Roberts (7, 8) who was one of the first to study the changes in the phosphatase content of the serum in disease, reported that high values were present in cases of obstructive jaundice whereas in catarrhal jaundice the value was only slightly increased over the normal. Roberts (8) considered this difference to be sufficiently marked to be of diagnostic value in the differentiation of the several types of jaundice. Bodansky and Jaffe (2) confirmed the increase in the serum phosphatase in jaundice but their results cast doubt on the diagnostic value of the test for they reported a series of nine cases of catarrhal jaundice and hepatitis in which elevated readings were obtained.

METHODS AND MATERIALS

Using the method of Bodansky (1) we have studied the phosphatase content of the serum in a series of 40 cases of jaundice of various types.

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Determinations in a series of 73 miscellaneous cases, representative of the general run of hospital patients, and a series of 33 cases of chronic cholecystitis or cholelithiasis without jaundice were used as controls. The phosphatase content of the bile obtained by duodenal drainage was also determined in a series of 15 cases.

RESULTS IN CONTROL CASES

The determination of enzymatic activity is difficult and the results vary with the details of the particular method used so that often the data of different investigators cannot be compared directly. This is particularly true in the study of the phosphatase content of the serum. Roberts (8) considers 5.5 units as the upper limit of normal but in cases of jaundice does not think the results of clinical significance unless values of 10 units or over are obtained. Bodansky and Jaffe (3) consider the normal range for adults to vary from 1.5 to 4.0 units, while in children it is 5.0 to 13.0 units. Under the conditions of routine hospital use we have found much greater variations than these. The mean of the control cases was 6.3 units with a standard deviation of 2.2, while the mean of the series of cases of chronic cholecystitis without jaundice was 7.3 with a standard deviation of 2.9 units. The increase of the mean value for the serum phosphatase in the cases of cholecystitis when compared with the control series is suggestive but when subjected to statistical analysis is not sufficiently great to be conclusive. Under these conditions values between 2.0 and 11.0 may be considered as without definite pathological significance.

RESULTS IN CASES OF JAUNDICE

The results obtained in the different types of jaundice are shown in the accompanying tables. Table I comprises 8 cases of obstructive jaundice due to extrinsic pressure on the common duct, usually from carcinoma of the head of the pancreas. Jaundice was present in all, and the icterus index and serum bilirubin were elevated. The phosphatase was elevated in the majority of cases. Especial interest attaches to Case 8 in which the biliary obstruction was due to pressure from an echinoccus cyst for readings were obtained both before the onset of obstruction and after its surgical relief.

Ten cases of jaundice due to chronic cholecystitis with cholelithiasis or choledocholithiasis are given in Table II. The serum phosphatase was elevated in all though to a variable degree, the highest reading, 64.5 units, being obtained in Case 13 in which there was very little jaundice but in which there was a marked cholangitis. Cases 9, 11, 13, and 17 all show a reduction in the phosphatase reading following operation and relief of the obstruction but the changes in the serum phosphatase are not as marked as those in the serum bilirubin. There was a series of colics in Case 10

TABLE I

The phosphatase content of the serum in obstructive jaundice

Case number	Age	Sex	Date	Serum phosphatase	Icterus index	Serum bilirubin	Van den Bergh reaction*	Diagnosis
	years			*units per 100 cc.*		*mgm. per 100 cc.*		
1	66	M.	March 2, 1933	63.2	200	23.5	+	Carcinoma pancreas?
			March 20, 1933	55.9	200	18.8	+	Clinical diagnosis
2	57	M.	September 30, 1933	22.6	41	6.0	+	Carcinoma stomach and pancreas.
			October 4, 1933	14.5	45	6.2	+	Operation September 29, 1933
3	32	M.	December 19, 1932	20.9	150	18.7	+	Carcinoma pancreas
4	61	M.	February 9, 1933	2.3	100	14.0	+	Carcinoma pancreas
			February 14, 1933	6.4	111	13.6	+	Hepatic metastasis
5	63	M.	February 13, 1934	29.5	94	10.6	+	Carcinoma of liver
			February 23, 1934	29.5	75	9.5	+	
6	65	M.	September 26, 1933	36.4	12	2.9	+	Carcinoma gallbladder; metastasis to liver; ascites
7	44	M.	October 14, 1933	11.0	94	7.3	+	Pancreatitis or carcinoma
			October 23, 1933	11.2	39	3.2	+	Operation October 18, 1933
			October 27, 1933	10.5	33	2.9	+	
8	56	M.	July 22, 1933	14.2	9	Trace	0	Echinococcus cysts of liver
			January 5, 1934	34.6	83	12.9	+	Operation January 6, 1934
			January 16, 1934	24.5	53	7.2	+	
			January 25, 1934	11.4	19	2.6	+	

* + Direct Van den Bergh reaction.
0 Indirect Van den Bergh reaction.

with intermittent obstruction and consequent marked fluctuation in the serum bilirubin level. The phosphatase showed similar fluctuations but the changes were much less striking than those in the bilirubin.

Twelve cases of hepatitis of one type or another were studied (Table III). Seven of these were of the type ordinarily referred to as catarrhal jaundice. Two were cases of syphilitic hepatitis and there was one case of toxic hepatitis following arsphenamine. The phosphatase was elevated in eight of these cases. The highest reading was obtained in Case 23 in which the serum bilirubin was most markedly increased. In general, how-

TABLE II

The phosphatase content of the serum in obstructive jaundice

Case number	Age	Sex	Date	Serum phosphatase	Icterus index	Serum bilirubin	Van den Bergh reaction	Diagnosis
	years			*units per 100 cc.*		*mgm. per 100 cc.*		
9	62	F.	November 22, 1933	57.7	44	7.2	+	Common duct stone
			November 29, 1933	46.4	47	6.0	+	Obstructive cirrhosis
			January 17, 1934	39.2	23	2.3	+	
			January 31, 1934	36.1	33	2.2	+	
			February 28, 1934	47.9	136	17.9	+	
			March 7, 1934	53.0	120	16.0	+	
10	65	M.	March 18, 1933	64.5	37	2.8	+	Chronic cholecystitis with stones
			April 7, 1933	35.3	15	1.0	+	Cholangitis. Cholecystectomy March 12, 1933
11	25	M.	February 14, 1933	42.0	23	2.8	+	Common duct stone
			February 16, 1933	26.4		Less than 2	0	
12	60	F.	April 12, 1933	31.6	120	19.5	+	Chronic cholecystitis with stones
			April 24, 1933	19.3	75	4.0	+	
			May 22, 1933	20.8	250	15.8	+	Following colic
			May 23, 1933	18.6	40	9.0	+	After duodenal drainage
13	48	M.	November 5, 1933	21.7	125	15.7	+	Chronic cholecystitis with stones
			November 10, 1933	14.0	71	5.5	+	Cholecystectomy November 3, 1933
14	70	F.	October 10, 1933	17.5	100	11.3	+	Chronic cholecystitis with stones
			November 2, 1933	11.6	21	2.0	+	Cholecystectomy October 9, 1933
15	46	M.	October 17, 1933	12.6	108	10.7	+	Common duct obstruction—stone
			October 23, 1933	14.0	65	6.0	+	Acute subsiding cholecystitis
			November 20, 1933	13.4	20	2.0	+	Choledochostomy. Cholecystectomy
16	50	M.	October 31, 1933	12.7	40	5.8	+	Chronic cholecystitis. Postoperative biliary fistula
17	49	F.	December 21, 1932	20.6	35	4.5	+	Common duct stone
18	59	M.	December 14, 1933	22.3	125	15.7	+	Postoperative stricture
			December 18, 1933	21.0	150	20.8	+	Common duct
			December 21, 1933	14.1	158	21.1	+	Operation December 18, 1933
			December 26, 1933	14.6	100	15.3	+	

TABLE III

The phosphatase content of the serum in hepatic jaundice

Case number	Age	Sex	Date	Serum phosphatase	Icterus index	Serum bilirubin	Van den Bergh reaction	Diagnosis
	years			*units per 100 cc.*		*mgm. per 100 cc.*		
19	27	M.	February 23, 1934	44.8	300	46.8	+	Acute hepatitis
			February 25, 1934	72.2	375	47.3	+	
			March 2, 1934	35.6	273	42.4	+	
			March 6, 1934	52.2	204	25.0	+	
			March 10, 1934	68.4	167	14.0	+	
			March 28, 1934	53.9	136	12.2	+	
20	26	M.	March 7, 1933	54.5	166	17.3	+	Acute hepatitis
			March 22, 1933	14.5	64	7.8	+	
			April 7, 1933	50.7	38	2.5	+	
21	34	M.	April 24, 1933	20.4	55	18.0	+	Acute hepatitis
			May 3, 1933	8.2	21	3.7	+	
			May 24, 1933	8.6	13	3.2	+	
22	38	M.	September 16, 1933	10.4	125	11.7	+	Subacute hepatitis
			October 2, 1933	10.2	125	22.5	+	
			October 12, 1933	11.5	100	13.1	+	
			October 17, 1933	8.4	75	7.4	+	
23	10	M.	May 4, 1933	28.8	200	5.0	+	Acute hepatitis
24	51	M.	April 25, 1932	12.4		10.7	+	Acute hepatitis
25	27	M.	December 26, 1933	10.6	38	3.1	+	Acute hepatitis
26	29	F.	April 25, 1932	9.5		6.8	+	Acute hepatitis
27	42	M.	March 27, 1933	18.4	105	7.3	+	Subacute hepatitis, syphilitic
			March 31, 1933	13.9	150	6.8	+	
			April 7, 1933	12.1	86	5.4	+	
			April 19, 1933	13.3	47	3.4	+	
			April 27, 1933	11.7	30	2.7	+	
28	48	M.	April 19, 1933	20.6	176	17.4	+	Acute hepatitis, syphilitic
			May 12, 1933	12.2	150	18.8	+	
			May 18, 1933	12.4	100	10.7	+	
			May 24, 1933	11.8	30	4.0	+	
29	63	M.	May 15, 1933	10.4	37	5.0	+	Syphilis, post-arsphenamine jaundice
30	22	F.	October 12, 1933	58.1	71	4.4	+	Acute septic hepatitis

ever, there was no definite correlation between the changes in the phosphatase and the bilirubin content of the serum.

Eight cases of hepatic cirrhosis were studied (Table IV) and the phosphatase was elevated in five. Normal readings were obtained in two cases of congenital hemolytic jaundice.

TABLE IV

The phosphatase content of the serum in hepatic cirrhosis and hemolytic jaundice

Case number	Age	Sex	Date	Serum phosphatase	Icterus index	Serum bilirubin	Van den Bergh reaction	Diagnosis
	years			*units per 100 cc.*		*mgm. per 100 cc.*		
31	37	M.	April 26, 1933	11.7	7	1.4	0	Portal cirrhosis. Ascites
			February 27, 1934	12.4	136	17.5	+	Toxic hepatitis with jaundice
			March 5, 1934	8.2	107	14.6	+	
			March 6, 1934	13.5	115	14.2	+	
			March 10, 1934	15.7	97	7.9	+	
			March 14, 1934	13.9	136 (hem.)	11.3	+	
32	33	M.	February 25, 1933	1.3	122	30.5	+	Portal cirrhosis—No ascites. Toxic hepatitis with jaundice
33	46	M.	December 28, 1933	21.8	19	3.0	+	Portal cirrhosis of the liver due to CCL_4 poisoning. Ascites
34	57	M.	May 22, 1933	19.9	5		0	Portal cirrhosis
35	40	M.	July 19, 1933	11.8	17	3.5	+	Portal cirrhosis. Ascites
36	59	M.	October 18, 1933	15.4	11	2.0	0	Portal cirrhosis. Ascites
37	29	M.	January 31, 1933	8.6	15	2.0	+	Portal cirrhosis. No ascites. Wilson's disease
38	68	M.	May 16, 1934	9.2	14	1.3	±	Obstructive biliary cirrhosis
39	14	F.	April 20, 1934	9.9	167	24.4	0	Congenital hemolytic jaundice
40	24	M.	June 13, 1933	3.2	88	5.8	0	Congenital hemolytic jaundice

The phosphatase was determined in bile obtained by duodenal drainage in a series of 15 cases of chronic cholecystitis without jaundice of one type or another (Table V). Phosphatase was present in all, but the amount varied widely, the lowest reading being 5 units per 100 cc. and the highest

224. In those cases in which the duodenal and concentrated specimens were both studied the activity was increased in the latter. This would suggest that the phosphatase activity was increased with the concentration of bile in the gallbladder. The phosphatase activity was also determined in a few specimens of bile removed from the gallbladder at operation. These readings are not included in the table but were similar in magnitude to those reported there. Case 16 in Table V shows the phosphatase con-

TABLE V

The phosphatase content of bile obtained by duodenal intubation

Case number	Age	Sex	Date	Phosphatase		Bile acids	
				Duodenal bile	Concentrated bile	Duodenal bile	Concentrated bile
	years			*units per 100 cc.*	*units per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*
1	27	F.	November 22, 1933		8		465
2	32	F.	November 15, 1932	0	5	180	484
3	24	F.	November 15, 1932	44	224	240	265
4	47	F.	January 18, 1933	5	102	74	182
5	43	F.	January 8, 1933	51	61	99	93
6	42	F.	November 15, 1933	25	97	80	91
7	32	F.	November 18, 1933	5	199	82	488
8	56	F.	October 25, 1933	51	53	0	484
9	32	F.	October 25, 1933	69	86	143	545
10	24	F.	December 6, 1933	5	130	0	408
11	55	F.	November 29, 1933	13	85	0	164
12	36	F.	November 19, 1933	0	5	23	438
13	34	F.	November 22, 1933	22	28	50	188
14	62	F.	November 22, 1933	28	30	59	96
15	35	M.	November 29, 1933	16	29	83	182
16	55	F.	July 27, 1933	59		335	

tent of bile obtained by surgical drainage of the gallbladder in a patient with acute pancreatitis and total destruction of the pancreas.

DISCUSSION

The finding of phosphatase in bile obtained by duodenal drainage is not conclusive evidence for the hepatic origin of the enzyme. Bile obtained from the gallbladder at operation frequently contains amylase and it is usually assumed that the presence of amylase indicates the back flow of a small amount of pancreatic juice into the gallbladder. We have found phosphatase in bile obtained from the gallbladder at operation and this too may be extra-hepatic in origin. On the other hand the constant finding of phosphatase in specimens of bile, whether obtained at operation or by duodenal drainage, and the greater concentration in specimens from the gallbladder speaks for the hepatic origin of a considerable part of the en-

zyme. Certainly the constancy of these observations would be difficult to explain on the assumption that the whole of the phosphatase came from pancreatic or duodenal juice which was present as a contaminant. The complete destruction of the pancreas in the case cited would further serve to exclude this organ as the source of the phosphatase found in the bile.

The present results confirm the earlier studies of Roberts (8) in demonstrating an increase in the phosphatase content of the serum in obstructive jaundice. This increase is further evidence for the hepatic origin of the phosphatase. The phosphatase content of the serum, however, contrary to the findings of Roberts (8) and in accord with those of Bodansky and Jaffe (2), is increased in cases of hepatitis as well as in obstructive jaundice. In our experience the test has been valueless in the differential diagnosis of the two types of jaundice. Hartman (5) has found that the serum phosphatase is increased in animals with experimentally produced cirrhosis of the liver. These observations are in agreement with our findings of an increase in the serum phosphatase in cases of hepatic cirrhosis without jaundice. These findings, together with the lack of correlation between the increase in the phosphatase and the elevation of the serum bilirubin, further suggest that in cirrhosis the serum phosphatase is a measure of hepatic disturbance rather than a consequence of the jaundice per se.

The finding of normal values in the two cases of congenital hemolytic icterus further emphasizes both the independence between the phosphatase and bilirubin and the difference in the pathogenesis of hemolytic icterus and of the obstructive and hepatic types of jaundice.

SUMMARY

Phosphatase was present in samples of bile obtained from the gallbladder at operation or by duodenal intubation.

The phosphatase content of the serum was increased in cases of jaundice due to hepatitis or to obstruction of the biliary passages. This test was of no value in the differential diagnosis of these two conditions. The phosphatase content of the serum was not increased in cases of hemolytic jaundice.

The phosphatase content of the serum was increased in cases of portal cirrhosis.

These findings suggest that the phosphatase in the bile probably is hepatic in origin and that some of the phosphatase normally present in serum is non-osseous and possibly hepatic in origin.

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