EFFECT OF DISEASE OF THE LIVER AND BILIARY TRACT UPON THE PHOSPHATASE ACTIVITY OF THE SERUM

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The present study deals with the influence of common affections of the liver and biliary tract upon the level of serum phosphatase activity in the adult. It is an analysis of our observations during the period 1933 to 1939 on those patients with involvement of the liver or biliary tract in whom the diagnosis could be proven by exploration or necropsy, or when insusceptible of proof (as in the hepatitides), could be established with reasonable certainty by clinical methods. Some 350 cases satisfied these criteria: 79 adults with proven obstruction of the common bile duct; 75 cases of hepatitis of indeterminate etiology ("catarrhal" jaundice); 39 cases of jaundice following exposure to known hepatotoxic drugs; 15 cases of hemolytic jaundice; 45 patients with proven cirrhosis of the liver, exclusive of biliary cirrhosis; 46 patients with proven neoplastic involvement of the liver; 10 patients with proven liver abscess; 10 cases of proven chronic passive congestion of the liver, without significant "cardiac" cirrhosis; and 29 cases of miscellaneous disorders of the liver or biliary tract. The data in 123 of these patients have been reported elsewhere (1). We record here observations made subsequent to that report, together with a study of the distribution of values in our total experience.

On the basis of these empirical clinical data, we have attempted to define the clinical usefulness and limitations of the determination of serum phosphatase activity as applied to diseases of the liver and biliary tract. Three such applications of the method appear to be of promise: (*1*) as a supplementary aid to the clinical differential diagnosis of the several types of jaundice; (*2*) as an index to certain complications following surgical procedures on the biliary tract; (*3*) as a relatively early indicator of metastases in patients known to have malignant tumors.

It may be stated at the outset that our data do not wholly support Roberts' disputed claim that by determining the phosphatase activity of the serum "toxic, infective and catarrhal jaundice may be readily distinguished from jaundice of the obstructive type" (2). We find, as have most previous investigators (3), that while patients with obstructive jaundice show appreciable elevations in serum phosphatase activity with reasonable consistency, increased serum phosphatase levels of the same order may be observed also in some patients with hepatitis. Whether or not the overlapping of values in the several types of jaundice is sufficient to invalidate the serum phosphatase determination as a practical aid in differential diagnosis is the crux of the problem under consideration and the chief impetus for our studies. These studies have led us to believe that, in general, the determination of serum phosphatase activity affords evidence of limited but definite value in the major practical problem presented by patients with jaundice: the decision between surgical intervention ("surgical jaundice") and conservative management ("medical jaundice"). This usefulness is, of course, contingent upon the recognition of specific deficiencies in the method, to be pointed out later, and upon a general appreciation of the limitations of any one means of investigation in so complex a phenomenon as jaundice. Reproducibility in technique of the serum phosphatase determination is another essential, since application of the method depends upon a comparison of levels of phosphatase activity.

We have attempted, further, to derive such generalizations regarding possible mechanisms regulating the serum phosphatase level in hepatic disease as would seem to be justified by the consistency of our data. Obviously, uncontrollable

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variables encountered in any such clinical study necessitate cautious interpretation. However, it may be said that, with certain unexplained exceptions, the level of phosphatase activity of the serum in the adult appears to be peculiarly sensitive to any significant compromise of the patency of the extra- or intrahepatic biliary system, but is relatively unaffected by even extensive liver parenchymal injury *per se*. The determination of serum phosphatase activity in this sense complements the so-called "liver function" tests, which afford a measure of injury to the liver parenchyma, and the dye retention tests, which are inapplicable in the presence of jaundice.

The absolute values reported in our tables and the empirical levels derived in our statistical analysis refer to the Bodansky method for the determination of serum phosphatase activity (4). In our hands, as in those of Bodansky, this method gives a range of 1 to 4 Bodansky units per 100 cc. serum for normal adults (1). Serum bilirubin was estimated by the method of Thannhauser and Andersen (5). The results of various other determinations are not recorded, with a few exceptions that bear directly upon the interpretation of serum phosphatase values.

RESULTS IN CASES 124 TO 358 [2]

1. Jaundice due to obstruction of the extrahepatic biliary tract

A. Pre-operative values in 27 proven cases of common duct stone (Table IA); 19 proven cases of carcinoma of the head of the pancreas or of the extrahepatic biliary tract (Table IB); and 8 proven cases of obstruction of miscellaneous origin (Table IC). The phosphatase activity of the serum was definitely increased in every one of these 54 cases of obstructive jaundice. Initial values in 49 cases ranged from 113.1 to 10.9 Bodansky units per 100 cc. serum. Values of less than 10 Bodansky units were obtained in 5 patients, of whom 3 were found to have calculi in the common duct with incomplete obstruction; 1 was a typical case of carcinoma of the head of the pancreas with complete obstruction of the common bile duct; and 1 was a curious case of carcinoma arising from the proximal end of the common bile duct, with complete obstruction. The serum phosphatase values subsequently rose in this instance as the serum bilirubin level fell, for reasons that were never explained. The patient was not studied in the last months of life when jaundice recurred.

The total cholesterol content of these sera is recorded for comparison with the serum bilirubin and phosphatase levels. The significance of this comparison will be considered in the discussion.

B. Post-operative serum phosphatase values, with special reference to persisting external biliary fistulae. Serum phosphatase activity was determined post-operatively in 11 patients of the present series, at intervals varying from 3 days to 9 months after surgical intervention. Usually a roughly parallel trend in serum phosphatase and bilirubin was observed post-operatively. But sometimes there was a dissociation in serum phosphatase and serum biliriubin levels as illustrated particularly by the following 3 patients who developed persistent external biliary fistulae after cholecystectomy. It will be noted that, when such a dissociation in serum phosphatase and serum bilirubin levels occurred, the increased level of serum phosphatase activity paralleled the course of clinical complications, whereas the serum bilirubin showed little or no rise.

T. G., aged 45, developed bile peritonitis following cholecystectomy without drainage. Subsequent exploration disclosed disruption of the ligated cystic duct stump. The serum bilirubin rose to 5.2 mgm. per cent, perhaps due to resorption of intraperitoneal bile, but the serum phosphatase level remained within essentially normal limits (4.7 Bodansky units) so long as bile drained freely into the abdominal cavity. After correction of the leak and establishment of temporary external biliary drainage, the jaundice eventually cleared, the biliary fistula gradually closed, the stools showed bile and the patient became afebrile. He returned later with chills, fever and malaise suggesting cholangeitis, the symptoms subsiding after several weeks. Similar episodes recurred for the next 6 months. Throughout this period, he never developed jaundice, but the serum phosphatase activity was persistently elevated, ranging from 22.5 to 36.0 Bodansky units per 100 cc. As the febrile attacks gradually subsided, the serum phosphatase values began to fall.

A. P. (Case 6), following cholecystectomy, developed a stricture of the common bile duct with serum bilirubin of 10.7 mgm. per cent and serum phosphatase activity of 25.2 Bodansky units per 100 cc. Plastic repair of the common duct and establishment of a biliary fistula re-

[2] To avoid confusion with the 123 cases previously reported (1), the patients in the present series are numbered beginning with 124.

sulted in subsidence of jaundice but convalescence was stormy until, a month later, a perihepatic abscess was drained. After several uneventful months, jaundice recurred (serum bilirubin 7.2 mgm. per cent) with a serum phosphatase level of 34.9 Bodansky units per 100 cc. Exploration disclosed cicatrization of the repaired common bile duct. External drainage of bile again resulted in subsidence of jaundice but with cessation of drainage, fever, chills and jaundice returned. For the next 2 years, intermittent closure of the biliary fistula was associated with similar episodes suggesting cholangeitis; the serum bilirubin fluctuating between 8.8 and 3.0 mgm. per cent, the serum phosphatase level remaining in the region of 30 Bodansky units. Finally, choledochoduodenostomy was performed (at which time biliary cirrhosis was noted) and this apparently effected adequate internal drainage of bile. The patient has been virtually asymptomatic for 1 year and the serum phosphatase has fallen to 18.3 Bodansky units per 100 cc. with a trace of icterus.

The last patient, R. R., aged 28, survived an even more complex sequence of post-cholecystectomy complications with an accompanying dissociation of serum phosphatase and bilirubin trends. In this instance, post-operative recurrence of severe jaundice suggested possible stricture

TABLE I

Summary of analyses of the blood in fifty-four cases of jaundice due to common bile duct obstruction

(Diagnosis established at operation or autopsy in each instance)

Number	Sex	Age	Cause of obstruction	Approximate duration of jaundice before initial blood analysis	Bile in stool	Date	Serum			Remarks
							Phosphatase	Bilirubin	Cholesterol	
		years					*Bodansky units per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	
A. CALCULI IN COMMON BILE DUCT										
124	♂	53	Choledocholithiasis; carcinoma of body of pancreas; liver metastases	2 weeks	+	December 30, 1937	42.0	11.2	231	Operation January 8, 1939.
125	♀	63	Choledocholithiasis; sub-acute pancreatitis	1 week	±	February 20, 1939	27.1	2.4		Choledochostomy February 27, 1939; profuse biliary drainage.
					+	April 18, 1939	3.8	Trace	276	
126	♂	65	Choledocholithiasis; biliary cirrhosis?	6 months	+	December 23, 1938	24.7	2.0	189	Cholecystectomy, choledochostomy July 20, 1939; free biliary drainage.
					+	January 24, 1939	19.8	2.2	211	
					+	July 15, 1939	17.3	8.0	240	
						July 24, 1939	14.3	5.0	216	
						August 8, 1939	15.0	2.5	140	
127	♀	63	Choledocholithiasis	1 day	+	May 23, 1939	24.2	2.0		Operation May 30, 1939.
128	♂	80	Choledocholithiasis; biliary cirrhosis	3 weeks	+	July 8, 1938	21.8	5.3	191	Cholecystectomy, choledochostomy July 18, 1938; free biliary drainage. Transient abdominal pain, chills, fever 2 months after operation.
					+	July 15, 1938	23.7	4.7	147	
						September 12, 1938	5.9	Trace		
						December 8, 1938	7.4	Trace	134	
						April 13, 1939	4.0	0	163	
129	♀	65	Choledocholithiasis	1 week	0	October 10, 1938	20.9	10.0		Operation October 17, 1938.
130	♀	55	Choledocholithiasis; carcinoma of head of pancreas; liver metastases	15 months	0	March 9, 1937	19.9	13.6	227	Operation March 18, 1937.
131	♂	75	Choledocholithiasis	6 weeks	±	June 19, 1939	18.8	8.8	247	Operation June 26, 1939.
132	♂	55	Choledocholithiasis	1 week	0	January 26, 1938	18.7	12.5	250	Operation February 14, 1938.
133	♀	53	Choledocholithiasis	4 days	+	February 24, 1939	18.4	9.4		Cholecystectomy, choledochostomy February 27, 1939; febrile course, subhepatic abscess.
						March 13, 1939	6.8	2.6		
						March 20, 1939	16.2	Trace		
134	♂	56	Choledocholithiasis; carcinoma of head of pancreas; biliary cirrhosis	6 weeks	0	February 18, 1938	16.7	4.2	340	Cholecystostomy March 24, 1938; slight biliary drainage.
						March 17, 1938	20.1	11.0	418	
135	♂	37	Choledocholithiasis	2 weeks	+	July 26, 1938	16.6	2.0	262	Operation July 29, 1938.
136	♂	52	Choledocholithiasis	5 months	0	May 26, 1939	16.5	5.3	323	Operation June 3, 1939.
137	♀	37	Choledocholithiasis	4 days	+	June 15, 1939	16.3	1.0	175	Operation June 23, 1939.
138	♀	59	Choledocholithiasis	4 days	+	July 24, 1939	16.1	4.0	167	Choledochostomy August 1, 1939; intermittent biliary drainage, spiking fever (cholangeitis?)
						August 3, 1939	8.5	6.0	119	
						August 10, 1939	13.3	3.7	118	
139	♀	52	Choledocholithiasis	2 weeks	0	January 28, 1938	13.5	5.5	350	Cholecystectomy, choledochostomy January 29, 1938, free bile drainage. Autopsy February 13, 1938: terminal hepatitis.
						February 11, 1938	7.0	10.3	88	
140	♂	54	Stones in cystic duct and ampulla, intermittent common duct obstruction	2 days	+	February 8, 1938	13.2	2.0	115	Operation February 9, 1938; liver cirrhotic (biliary?).
141	♀	55	Choledocholithiasis	3 days	+	August 11, 1939	13.0	2.6	129	Operation August 16, 1939.
142	♀	31	Choledocholithiasis	5 months	+	April 21, 1937	12.8	4.7	174	Operation May 1, 1937.
143	♀	53	Choledocholithiasis	2 days	+	April 5, 1937	11.6	9.6		Operation April 12, 1937.
						April 8, 1937	14.7	8.0		
144	♂	50	Choledocholithiasis	2 weeks	0	January 24, 1938	11.6	8.3	286	Operation January 24, 1938.
145	♂	52	Choledocholithiasis	4 days	+	May 28, 1938	11.6	4.7		Operation December 13, 1938.
						December 5, 1938	10.4	8.0		
146	♀	32	Choledocholithiasis	4 days	±	April 28, 1939	11.3	10.7	324	Operation May 4, 1939.
147	♀	54	Choledocholithiasis	1 day	+	May 29, 1939	11.3	2.5	169	Operation May 30, 1939.
148	♂	84	Choledocholithiasis; suppurative pylephlebitis	4 days	+	June 28, 1937	6.8	2.0		Autopsy June 29, 1937.
149	♀	39	Ball-valve stone in cystic duct, intermittent common duct obstruction	6 days	+	May 28, 1939	5.9	6.0		Operation June 2, 1937.
150	♂	38	Choledocholithiasis, pancreatitis	3 months	+	January 14, 1938	5.3	2.0	223	Operation January 9, 1938.

TABLE I—*Continued*

Number	Sex	Age	Cause of obstruction	Approximate duration of jaundice before initial blood analysis	Bile in stool	Date	Serum			Remarks
							Phosphatase	Bilirubin	Cholesterol	
		years					*Bodansky units per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	
B. CARCINOMA OF HEAD OF PANCREAS OR OF EXTRAHEPATIC BILIARY TRACT										
151	♀	36	Carcinoma of head of pancreas, liver metastases	5 months	0	April 9, 1937	113.1	9.4		Cholecystogastrostomy April 19, 1937.
					0	April 13, 1937	101.5	11.0	1,515	
					+	April 28, 1937	29.4	3.7	707	
152	♂	49	Carcinoma of head of pancreas	1 year	±	July 18, 1938	63.8	15.0	417	Operation July 22, 1938.
153	♂	52	Carcinoma of head of pancreas? chronic pancreatitis obstructing common duct?	9 weeks	0	April 15, 1939	48.8	11.5	347	Operation April 20, 1939.
154	♂	70	Carcinoma at junction of main hepatic ducts	7 weeks	0	June 28, 1939	41.5	15.8	387	Autopsy July 5, 1939.
155	♂	65	Carcinoma of head of pancreas	4 weeks	0	February 24, 1938	33.7	19.0	248	Cholecystojejunostomy March 3, 1938.
					+	March 8, 1938	18.5	13.6	290	
156	♀	67	Carcinoma at junction of main hepatic ducts	2 months	0	June 15, 1937	27.6	15.0	675	Autopsy June 30, 1937.
157	♂	64	Carcinoma of head of pancreas	1 week	+	December 7, 1938	19.7	5.4	275	Operation December 23, 1938.
						December 13, 1938	20.2	8.1	278	
						December 15, 1938	20.7	9.0		
158	♂	48	Carcinoma of head of pancreas	6 weeks	0	October 8, 1937	17.8	12.5	291	Operation October 15, 1937.
159	♂	49	Carcinoma of head of pancreas, liver metastases	6 weeks	0	March 4, 1938	16.9	7.4	208	Operation March 11, 1938.
160	♀	72	Carcinoma of gall bladder or bile duct	2 weeks	+	July 13, 1939	16.2	17.6	308	Operation July 26, 1939.
						July 20, 1939	19.2	18.0		
161	♂	70	Carcinoma of head of pancreas? chronic pancreatitis obstructing common duct?	2 months	±	July 10, 1939	15.8	4.7	94	Operation July 18, 1939.
162	♀	75	Carcinoma of head of pancreas	2 weeks	0	January 28, 1939	15.4	21.4		Choledochoduodenostomy February 4, 1939. Enlarged liver, soon obviously metastatic.
					0	February 3, 1939	13.0	17.4		
					±	February 7, 1939	13.4	13.6	242	
163	♂	62	Carcinoma of head of pancreas	6 weeks	0	July 7, 1938	13.8	18.8	525	Operation July 14, 1938.
164	♀	62	Carcinoma of gall bladder, liver metastases	4 weeks	0	July 31, 1939	12.8	21.0	234	Operation August 11, 1939.
					0	August 5, 1939	13.7	18.8		
165	♂	48	Carcinoma of common bile duct	1 week	+	June 19, 1935	12.1	2.0	250	Autopsy August 22, 1935.
166	♂	55	Carcinoma of ampulla of Vater	2 weeks	0	December 29, 1938	12.0	6.5	270	Operation March 6, 1939.
					±	January 3, 1939	10.7	6.0		
					±	January 30, 1939	15.7	6.9		
					±	February 14, 1939	15.5	9.4	255	
					±	March 1, 1939	12.4	11.7		
167	♂	64	Carcinoma of head of pancreas	5 weeks	0	September 22, 1937	10.9	12.1	625	Operation October 6, 1937.
					±	September 27, 1937	11.8	16.6	586	
168	♂	58	Carcinoma of body and head of pancreas	6 weeks	±	December 21, 1938	9.6	20.0	242	Cholecystojejunostomy December 30, 1938.
					±	December 23, 1938	8.6	21.2		
					0	January 4, 1939	7.7	20.0	172	
169	♀	60	Carcinoma of main hepatic ducts	10 weeks	0	March 9, 1937	8.7	20.6	288	Exploration March 23, 1937.
					0	March 17, 1937	13.3	28.0		Autopsy April 4, 1938.
						October 13, 1937	28.2	2.0	191	
						October 26, 1937	26.6	2.0		
C. OBSTRUCTION OF COMMON BILE DUCT DUE TO MISCELLANEOUS CAUSES										
170	♂	61	Carcinoma of esophagus with extension to and occlusion of common duct	4 weeks	0	September 1, 1938	41.0	18.8		Autopsy September 13, 1938.
171	♀	29	Post-operative benign stricture of common bile duct	3 months	+	December 14, 1937	36.4	3.2	340	Operation December 20, 1937.
172	♀	50	Carcinoma, origin unknown; obstruction of common bile duct	4 weeks	+	October 14, 1938	17.8	3.1		Operation October 22, 1938.
173	♂	4 mths.	Congenital atresia of bile ducts	4 months	0	August 3, 1939	17.1	9.0	167	Operation August 10, 1939.
174	♀	32	Benign stricture of common bile duct	3 years	+	June 30, 1937	16.8	6.8		Operation August 16, 1937.
						July 6, 1937	11.8	3.0		
175	♂	38	Carcinoma, origin unknown; obstruction of common bile duct	3 weeks	±	July 27, 1939	15.5	4.8	223	Operation August 11, 1939.
					±	August 5, 1939	16.3	9.2		
176	♂	60	Carcinoma of stomach, extension to and occlusion of common bile duct	5 weeks	+	February 21, 1938	14.5	10.8	278	Operation March 12, 1938.
177	♀	65	Chronic pancreatitis, obstruction of common bile duct	1 month	+	May 3, 1939	10.9	1.5	197	Operation May 18, 1939.
						May 17, 1939	19.3	1.4		

of the common bile duct, although the serum phosphatase was only 7.8 Bodansky units with a serum bilirubin of 9.2 mgm. per cent. Exploration disclosed a patent common duct of normal caliber but free of bile. The operative findings suggested that the jaundice was of intrahepatic origin, probably hepatitis. During this procedure, the duodenum was entered inadvertently and in the course of her stormy convalescence, a duodenal fistula developed. Through this bile drained freely, with subsidence of jaundice and return of the serum phosphatase to 4.8 Bodansky units per 100 cc. The fistula closed eventually but transient episodes of chills, fever and malaise have recurred at frequent intervals since. Significant clinical jaundice has not developed, yet the serum phosphatase level rose and has remained at about 18 Bodansky units per 100 cc.

2. *Jaundice due to hepatitis*

Tables II and III together summarize our results in 67 cases of jaundice classified on clinical grounds as due to hepatitis. The distribution of serum phosphatase values in this group is not as sharply defined in relation to the empirical level of 10 Bodansky units as in the cases of obstructive jaundice: the phosphatase levels did not reach 10 Bodansky units per 100 cc. serum in 49 instances, whereas 18 cases exceeded this figure. However, the results show greater consistency if those patients whose jaundice followed upon the

TABLE II

Summary of analyses of blood in forty-one cases of jaundice with a clinical course consistent with hepatitis of indeterminate etiology ("catarrhal" jaundice)

Number	Sex	Age	Approximate duration of jaundice: Before initial blood analysis	Approximate duration of jaundice: Total duration	Bile in stool	Date	Serum: Phosphatase	Serum: Bilirubin
		years	*days*	*weeks*			*Bodansky units per 100 cc.*	*mgm. per 100 cc.*
178	♂	45	20	5	+	February 7, 1939	15.5	7.3
						February 8, 1939	13.1	9.7
						February 17, 1939	11.6	5.0
						March 8, 1939	6.9	Trace
179	♀	29	2	2	+	April 15, 1939	13.2	5.0
						April 19, 1939	10.8	4.8
						April 26, 1939	7.5	1.0
						May 3, 1939	5.0	Trace
180	♀	13	7	?	+	November 17, 1936	13.1	10.0
181	♀	51	31	10	0	June 30, 1938		25.0
					+	July 8, 1938	11.1	10.0
					+	July 18, 1938	9.3	3.9
182*	♂	48	28	12	+	July 7, 1939	10.6	8.7
						July 17, 1939	9.5	8.4
						July 21, 1939	12.1	17.8
183	♂	36	5	3.5	+	January 27, 1939	9.7	6.3
						February 3, 1939	7.7	7.2
184	♂	30	14	3	+	June 16, 1937	9.5	6.0
						June 19, 1937	8.6	2.7
185	♂	42	6	3.5	+	December 24, 1936	9.3	9.9
						January 11, 1937	5.9	2.7
186	♂	49	9	3	+	August 19, 1939	9.0	24.2
187	♂	28	28	6.5	+	January 6, 1938	8.8	12.1
						January 29, 1938	7.6	7.5
						February 15, 1938	4.4	2.5
188	♀	49	9	3	+	May 3, 1937	8.8	8.3
						May 11, 1937	6.0	5.4
						May 14, 1937	5.0	2.7
189	♀	74	25	6	+	November 6, 1936	8.4	10.3
190	♂	29	4	2	0	February 27, 1939	7.9	4.0
					+	March 6, 1939	7.1	5.0
					+	April 3, 1939	3.5	Trace
191	♂	36	10	3	0	July 15, 1937	7.9	5.0
192	♀	32	4	1.5	+	February 18, 1939	7.8	4.8
						February 20, 1939	8.5	5.3
						June 29, 1939	3.2	0
193	♂	33	42	11	+	April 25, 1939	7.7	11.5
						April 26, 1939	8.3	11.7
194	♀	22	7	3	+	September 21, 1936	7.7	10.7
195	♀	67	20	12	0	January 6, 1938	7.6	12.5
					+	January 10, 1938		6.0
196	♂	48	15	9	+	June 9, 1936	7.4	12.3
						June 12, 1936	7.8	15.0
						July 6, 1936	2.9	3.2
197	♂	23	3	1	+	October 15, 1936	7.4	2.0
198	♀	43	7	5	+	December 3, 1937	7.3	11.7
						December 15, 1937	5.4	10.1
199	♂	22	3	2	+	March 14, 1938	7.3	5.4
						March 16, 1938	6.5	8.1
						March 22, 1938	5.0	3.0
200	♂	24	4	1.5	+	October 2, 1937	7.2	6.1
						October 5, 1937	7.3	7.5
201	♀	15	26	11	+	February 25, 1939	6.8	10.4
						February 28, 1939	6.6	8.8
						March 20, 1939	7.2	8.3
						April 3, 1939	7.4	7.0
202	♀	49	75	15	+	October 13, 1937	6.8	5.0
					+	October 21, 1937	4.2	2.3
						November 16, 1937	3.1	2.0
						January 4, 1938	2.6	Trace
203	♀	20	1	1.5	+	February 11, 1938	6.7	3.8
204	♀	29	8	2.5	+	October 26, 1938	6.5	9.6
205	♀	28	8	3	+	August 4, 1938	6.4	7.8
						August 15, 1938	4.7	2.1
206	♂	37	9	2.5	0	November 25, 1938	6.1	4.5
					+	December 1, 1938	4.5	2.0
207	♂	31	22	7	0	March 2, 1939	5.8	19.0
208	♀	34	5	3	+	July 1, 1939	5.6	9.4
209	♂	39	15	3.5+	+	October 25, 1937	5.6	4.4
210	♂	22	21	4	+	July 21, 1938	5.5	15.0
						July 25, 1938		5.9
211	♂	34	8	2	+	August 9, 1938	5.4	9.4
212	♂	42	14	5+	+	August 13, 1938	5.1	21.0
						August 22, 1938	6.7	19.0
						August 30, 1938		12.3
213	♂	23	3	1.5	0	June 30, 1938	5.1	7.5
214	♀	24	3	2	+	January 12, 1938	4.8	4.2
215	♂	28	3	2	+	January 5, 1939	4.6	6.8
216	♂	32	23	13	+	October 28, 1937	4.2	18.8
						November 15, 1937	3.9	5.0
						December 16, 1937	3.5	3.5
217	♀	37	4	1.5	+	March 10, 1938	3.1	6.9
218†	♂	19	15	3.5	+	February 25, 1937	2.5	5.4

* Stone subsequently found in common duct.

† Subsequently found to have hemolytic jaundice, acquired.

TABLE III

Summary of analyses of the blood in twenty-six cases of jaundice following exposure to known hepatotoxic agents

Number	Sex	Age	Cause of jaundice	Approximate duration of jaundice		Urobilin in stool	Date	Serum	
				Before initial blood analysis	Total duration			Phosphatase	Bilirubin
		years		*days*	*weeks*			*Bodansky units per 100 cc.*	*mgm. per 100 cc.*
219	♀	53	Arsenical therapy	7	> 7	±	May 31, 1939	19.5	5.3
						±	June 5, 1939	30.9	9.9
						0	June 15, 1939	41.6	16.6
						0	June 22, 1939	31.5	13.8
						+	June 29, 1939	25.0	12.9
220	♂	29	Arsenical therapy	20	8	0	May 20, 1938	17.6	17.0
						±	June 1, 1938	13.8	15.0
						+	June 14, 1938	11.6	12.5
						+	June 21, 1938	11.8	9.4
221	♂	35	Arsenical therapy	70+	14+	+	July 24, 1939	16.7	6.5
						+	July 28, 1939	14.9	6.5
						+	August 18, 1939	24.7	4.7
222	♀	22	Cinchophen	20	8	+	April 21, 1939	15.8	4.0
						+	May 1, 1939	13.8	2.0
223	♀	25	Arsenical therapy	7	> 3	+	June 8, 1939	14.5	17.0
224	♀	57	Arsenical therapy	7	8	0	January 19, 1937	14.0	14.2
						+	January 26, 1937	7.8	15.0
						+	February 2, 1937	11.2	12.5
						+	March 4, 1937	6.8	2.0
225	♀	36	Arsenical therapy	60±	25	0	July 26, 1938	12.7	10.4
						±	September 1, 1938	18.5	15.0
						+	September 13, 1938	20.1	11.7
						+	September 27, 1938	13.9	9.4
226	♂	19	Arsenical therapy	7	4	+	March 9, 1938	12.2	7.0
						+	March 22, 1938	14.3	2.2
227	♂	53	Arsenical therapy	9	20	+	March 17, 1938	12.1	13.2
						+	March 21, 1938	9.0	7.4
228	♂	33	Sulfanilamide	2	1		April 8, 1937	11.3	1.0
							July 10, 1939	11.4	
							July 16, 1939	9.1	Trace
229	♂	24	Arsenical therapy	6	2+	+	March 27, 1939	10.8	7.9
						+	April 3, 1939	20.4	11.5
230	♂	30	Sulfanilamide	5	5	+	May 24, 1937	10.4	2.0
							June 1, 1937	11.9	2.0
							June 7, 1937	10.5	7.1
							June 16, 1937	10.9	2.0
							June 28, 1937	6.1	1.0
231	♂	43	Arsenical therapy	63	13	+	July 29, 1939	10.0	16.0
							August 7, 1939	9.0	16.5
232	♀	57	Phosphorus*	2	4	?	August 11, 1938	8.7	2.7
233	♂	26	Arsenical therapy	?	?	+	February 3, 1937	8.4	8.3
							March 9, 1937	3.2	Trace
234	♂	46	Arsenical therapy	14	4	+	June 14, 1937	8.2	4.2
						+	June 24, 1937	6.2	3.0

TABLE III—*Continued*

Number	Sex	Age	Cause of jaundice	Approximate duration of jaundice		Urobilin in stool	Date	Serum	
				Before initial blood analysis	Total duration			Phosphatase	Bilirubin
		years		*days*	*weeks*			*Bodansky units per 100 cc.*	*mgm. per 100 cc.*
235	♀	38	Sulfapyridine	1	5	+	January 24, 1939	7.9	6.5
						+	January 27, 1939	13.6	2.0
						+	February 1, 1939	8.4	Trace
236	♂	37	Arsenical therapy	15	4+	+	January 14, 1937	7.5	15.0
						+	January 18, 1937	4.6	14.4
						+	January 21, 1939	4.1	11.2
237	♀	35	Arsenical therapy	35	12	+	June 3, 1938	6.9	13.0
						+	June 13, 1938	8.7	9.4
						+	June 27, 1938	8.9	5.0
						+	July 5, 1938	8.6	4.3
238	♂	34	Arsenical therapy	16	4	+	February 5, 1937	6.5	11.4
239	♂	71	Carbon tetrachloride*	7	1	+	March 22, 1937	6.3	14.0
240	♂	22	Arsenical therapy	60±	10	0	August 26, 1936	6.0	8.3
241	♀	32	Sulfapyridine	1	< 1	+	December 27, 1938	4.9	3.8
						+	January 5, 1939	3.3	1.5
242	♀	37	Carbon tetrachloride	?	2±	+	May 22, 1937	4.7	4.5
						+	May 29, 1937	4.4	3.5
						+	June 2, 1937	5.0	4.0
						+	June 8, 1937	4.6	2.0
243	♀	47	Sulfanilamide	?	1	+	December 24, 1937	4.1	Trace
						+	January 3, 1938	7.6	2.0
244	♂	42	Sulfanilamide	1	3	+	April 9, 1937	3.1	3.0

* Fatal termination.

administration of hepatotoxic drugs are segregated from the miscellany of cases which it is convenient clinically to group together as "hepatitis." This division, for which there is other justification, ordinarily can be made without difficulty by reference to the case history.

Table II includes 41 patients with jaundice of indeterminate etiology in whom the clinical course, with few exceptions, was typical of so-called "catarrhal" jaundice. The phosphatase activity of the serum in all but 5 of these patients was less than 10 Bodansky units per 100 cc. The 5 exceptions include one 13-year-old patient whose serum phosphatase level of 13.1 Bodansky units was little, if at all, above the normal maximum for that age period. In many of the cases in this group with comparatively little rise in serum phosphatase activity, the degree of jaundice and the clinical course were indicative of severe parenchymal involvement. In some, acholic stools were present for variable, occasionally protracted periods.

Table III includes 26 patients with jaundice following exposure to known hepatotoxic agents, for the most part luetics after intravenous administration of arsphenamine. In some of these, icterus developed rapidly early in the course of treatment, the highest values in Table III falling in this group. In others, icterus appeared as late as 6 months following cessation of treatment.

The dispersion in the cases comprising Table III is striking: no less than 14 cases (about half) presented serum phosphatase values greater than 10 Bodansky units at some time in the course of their jaundice, in one instance reaching a level of 41.6 Bodansky units per 100 cc. serum. There is some evidence that the dispersion in serum phosphatase values observed in arsphenamine

jaundice may have clinical significance since many patients with markedly increased serum phosphatase activity also presented other peculiarities (clinical as well as in laboratory data) suggesting an obstructive rather than hepatogenous type of jaundice. For example, Hanger (6) pointed out that the sera of patients with arsphenamine jaundice and markedly increased serum phosphatase activity fail to flocculate cephalin-cholesterol emulsions, a sensitive test for hepatitis. Moreover, the serum cholesterol values in this group rose, in contrast to the usually normal or lowered levels in hepatogenous jaundice; the rise occurring after icterus had been present for some time and tending to persist after jaundice had subsided. Clinically, this group was characterized (6) by acute onset in the form of a typical delayed reaction to the second or third arsphenamine injection; by intense icterus and pruritus, acholic stools for long periods, and relative freedom from gastrointestinal upsets.

The cases in Table III with little rise in serum phosphatase activity, on the other hand, for the most part presented a clinical and laboratory picture more in keeping with that of hepatogenous jaundice.

3. Hemolytic jaundice

Table IV summarizes the results in 12 of our patients with hemolytic jaundice of diverse etiology. Case 245 was an infant who was deeply icteric at birth, the hyperbilirubinemia gradually subsiding within 6 weeks; an instance, apparently, of unusually severe and protracted "physiologi-

TABLE IV

Summary of analyses of the blood in twelve cases of hemolytic jaundice

Number	Sex	Age	Date	Serum		Diagnosis
				Phosphatase	Bilirubin	
		years		*Bodansky units per 100 cc.*	*mgm. per 100 cc.*	
245	♂	2 weeks	January 22, 1937	13.7	15.0 (direct reaction)	Unusually marked "physiological jaundice" of newborn with protracted but benign course.
			February 2, 1937		7.4	
246	♂	28	December 19, 1935		18.9 (direct reaction)	Sickle cell anemia with related bone changes; hemolytic crises.
			December 23, 1935	13.6	10.0 (direct reaction)	
			December 27, 1935	9.9	9.4 (direct reaction)	
			February 3, 1936	5.8	5.4 (biphasic reaction)	
			May 12, 1937	3.5	6.1 (indirect reaction)	
			December 11, 1937	3.9	3.4	
			September 17, 1938	3.8	25.0 (direct reaction)	Hemolytic crisis.
			September 23, 1938	3.5	4.0 (direct reaction)	
247	♂	57	May 1, 1939	3.9	5.4 (biphasic reaction)	Familial (spherocytic) hemolytic jaundice.
248	♀	36	June 20, 1938	3.8	2.9 (indirect reaction)	Familial (spherocytic) hemolytic jaundice.
249	♂	18	May 5, 1937	2.6	4.7 (indirect reaction)	Acquired hemolytic jaundice, cause unknown; splenomegaly.
250	♀	58	September 22, 1938	2.6	2.0 (indirect reaction)	Pernicious anemia.
251	♂	57	May 13, 1938	2.5	3.0 (indirect reaction)	Pernicious anemia.
252	♀	70	June 1, 1936	2.3	2.0 (indirect reaction)	Pernicious anemia.
253	♂	62	June 15, 1937	2.3	3.4 (indirect reaction)	Pernicious anemia.
254	♂	35	July 20, 1938	2.0	3.0 (indirect reaction)	Familial (spherocytic) hemolytic jaundice.
255	♂	74	May 27, 1938	2.0	2.0 (indirect reaction)	Pernicious anemia.
256	♀	61	March 19, 1937	1.9	2.0 (indirect reaction)	Pernicious anemia.

cal" jaundice. The value 13.7 Bodansky units per 100 cc. is little, if at all, above the normal maximum for that age period. Case 246 was a colored male with severe sickle cell anemia and related skeletal changes who experienced several episodes of recurring jaundice. The first of these, in 1935, was an afebrile attack of deep jaundice which subsided spontaneously after 2 weeks. Marked enlargement and tenderness of the liver, choluria, normal stools and negative x-rays for opaque biliary calculi, characterized this episode, the precise nature of which remained uncertain. In 1938, severe jaundice recurred with a sharp drop in the erythrocyte count typical of "hemolytic crisis." Because of painful attacks suggesting biliary colic and x-ray evidence of gall bladder disease, the possibility of obstruction due to pigment stones was suggested. The serum phosphatase level was within normal limits despite very marked hyperbilirubinemia. Exploration revealed calcium bilirubinate "mud" in the gall bladder but no obstruction of the common bile duct, which was not dilated and through which saline could be irrigated freely.

As indicated in Table IV, the phosphatase activity of the serum is consistently within normal limits in hemolytic jaundice. There is no difficulty in establishing the diagnosis of hemolytic jaundice on other grounds, however, and we regard the use of the method in this type of jaundice as of chiefly theoretical interest; though in occasional obscure instances such as Case 246 the determination may be of distinct aid.

4. Cirrhosis of the liver

Table V summarizes our results in 30 patients with cirrhosis of the liver in whom the diagnosis could be established at necropsy or by liver biopsy. This is a heterogeneous group. The majority of subjects were chronic alcoholics and at necropsy many were found to have a fatty type of Laënnec's cirrhosis specified as "alcoholic" cirrhosis (7); when fatty degeneration was not striking but fibrosis was the chief abnormality, the findings are designated more generally as Laënnec's cirrhosis. The presence of extreme atrophy is recorded. The series further comprises 3 cases of "cardiac" cirrhosis in patients with long-standing cardiac failure; 3 cases of hemochromatosis; 2 cases of "toxic" cirrhosis associated with hyperthyroidism; and 1 case of schistosomiasis of the liver with cirrhotic changes. Cases 257 and 263 were relatively young persons. In the former the clinical course was that of sub-acute yellow liver atrophy, though the pathological findings were not so classified. Our proven instances of biliary cirrhosis were all patients with chronic obstructive jaundice and are included in Table I.

These patients for the most part presented the picture of hepatic cirrhosis in its more advanced stages. We have recorded the results of serum protein analyses (Howe's method was used) to afford another criterion of the degree of hepatic pathology. The highest value for serum phosphatase activity observed in this group was 20.3 Bodansky units per 100 cc. In only 6 patients were serum phosphatase levels of 10 Bodansky units or over obtained and 3 of these inconstantly exceeded that figure. Almost half of this group of advanced cirrhotics were found on at least one occasion to have essentially normal serum phosphatase levels. The results indicate that even advanced hepatic cirrhosis of the type included in Table V usually effects little rise in serum phosphatase activity. In biliary cirrhosis the values are quite consistently elevated.

5. Neoplastic involvement of the liver

Four proven cases of primary carcinoma of the liver (Table VIA); 10 cases of malignancy proven not to have liver involvement (Table VIB); and 22 cases of malignancy with proven metastases to the liver (Table VIC). In 2 of the cases of primary carcinoma of the liver, the tumor had its origin in the intrahepatic biliary system (cholangioma), 2 arose from hepatic cells (hepatoma) in association with advanced Laënnec's cirrhosis. Not included in Table VI are 2 cases of carcinoma arising from the junction of the main hepatic ducts, which are recorded in Table IB (Cases 154 and 156) as instances of obstructive jaundice due to carcinoma at the origin of the common bile duct; being in effect, if not literally, instances of extrahepatic duct obstruction. The serum phosphatase activity of the cases comprising Table VIA was distinctly elevated, the values ranging from 33.1 to 11.5 Bodansky units per 100 cc. In 2 previously recorded instances of

primary carcinoma of the liver (Cases 99 and 118), the serum phosphatase levels were somewhat lower but still above those of most cases of uncomplicated hepatic cirrhosis. It would appear that the serum phosphatase activity tends to be higher in patients with primary carcinoma of the liver than in uncomplicated Laënnec's cirrhosis, with which the condition is most frequently confused clinically.

In considering patients with malignancy other than primary carcinoma of the liver, it is apparent from our data that the serum phosphatase level depends largely upon the presence or absence of metastases to the liver or skeleton. In Table VIB are recorded serum phosphatase values obtained in 10 patients with neoplasia shown at necropsy not to have involved the liver. Cases 291 and 292, however, had extensive osteoplastic metastases to bone and are included to illustrate the marked increase in serum phosphatase activity usually accompanying this type of metastatic spread. Cases 293 and 294 exhibited a significant rise in serum phosphatase activity although no metastases were noted in the liver or bones at

TABLE V

Summary of analyses of the blood in thirty proven cases of cirrhosis of the liver

Number	Sex	Age	Basis for diagnosis	Duration of jaundice at time of blood analysis	Bile in stool	Date	Serum						Remarks
							Phosphatase	Bilirubin	Total protein	Albumin	Globulin	Euglobulin	
		years					*Bodansky units per 100 cc.*	*mgm. per cent*	*per cent*	*per cent*	*per cent*	*per cent*	
257	♀	21	Autopsy	5 months	0	April 28, 1938	15.4	17.3	9.6	2.5	7.1	3.6	Diffuse atrophic Laënnec's cirrhosis; ascites, cholemia.
					0	May 13, 1938	13.9	16.0	9.7	2.6	7.1		
					0	May 25, 1938	11.4	15.0	8.5	2.4	6.1	2.9	
					±	June 17, 1938	18.7	15.0	7.6	2.6	5.0	2.0	
					±	July 5, 1938	14.5	13.4	8.0	2.6	5.4	2.0	
					±	July 26, 1938	11.3	15.0	7.8	2.6	5.2	1.3	
258	♀	35	Liver biopsy	Not known	+	May 26, 1937	14.7	3.2	7.3	2.8	4.5	1.2	Chronic alcoholism. Laënnec's cirrhosis, diffuse, with hepatosplenomegaly.
					+	December 17, 1937	20.0	2.5	8.1	3.6	4.5	1.4	
					+	May 3, 1938	20.3	2.0	7.2	2.8	4.4	1.6	
					+	November 30, 1938	15.5	2.5	7.2	3.2	4.0	0.9	
					+	May 16, 1939	14.1	3.0	7.7	3.6	4.3	0.8	
259	♀	43	Autopsy	Not jaundiced	+	April 28, 1937	10.6	0	5.0	2.6	2.4	0.4	Diffuse "cardiac" cirrhosis; adherent pericardium.
					+	May 20, 1937	10.9	0	5.2	3.0	2.2	0.6	
					+	June 14, 1937	4.4	0	5.1	2.1	3.0		
260	♂	32	Autopsy	Not jaundiced	+	November 13, 1936	10.1	1.0	4.2	2.6	1.6	0.3	Post-operative gastro-jejunal-colic fistula, malnutrition. Fatty liver, diffuse Laënnec's cirrhosis.
261	♀	43	Autopsy	Not jaundiced	+	April 20, 1938	9.2	1.0	6.7	3.6	3.1	0.3	Chronic alcoholism. Diffuse alcoholic cirrhosis. No marked atrophy.
					+	May 16, 1938	4.7	0	7.1	3.6	3.5	0.5	
262	♀	52	Autopsy	1 week	+	August 11, 1938	8.5	9.5	6.3	3.1	3.2	0.6	Chronic alcoholism. Diffuse cirrhosis, unclassified type, superimposed hepatitis ?
263	♀	11	Liver biopsy	1 month	±	December 2, 1936	8.4	4.2	7.3	2.4	4.9		Diffuse Laënnec's cirrhosis with atrophy.
						December 22, 1936	8.7						
264	♀	45	Autopsy	Not jaundiced	+	November 22, 1937	8.2	0	8.5	5.9	2.6		Marked "cardiac" cirrhosis, hepatomegaly. Rheumatic cardiac disease.
						December 1, 1937	7.4	trace	6.8	3.2	3.6		
265	♂	64	Autopsy	Not known	+	May 31, 1938	8.1	2.2	5.9	2.1	3.8	0.9	Chronic alcoholism. Atrophic Laënnec's cirrhosis. Ascites.
266	♂	60	Autopsy	Not jaundiced	+	January 13, 1937	7.7	2.0	6.1	1.5	4.6	1.6	Chronic alcoholism. Atrophic Laënnec's cirrhosis, ascites.
267	♀	59	Autopsy	Not known	+	January 12, 1937	7.3	6.5					Chronic alcoholism. Diffuse alcoholic cirrhosis, ascites.
					+	January 20, 1937	6.6	9.6					
268	♀	37	Autopsy	1 week	+	March 24, 1939	6.4	2.0	6.2	3.5	2.7	0.6	Hyperthyroidism with patchy cirrhosis.
					+	March 31, 1939	6.2	3.4	6.2	3.2	3.0	0.6	
269	♀	65	Autopsy	Not jaundiced	+	January 27, 1939	6.2	trace	6.9	4.0	2.9	0.6	Hyperthyroidism with diffuse cirrhosis.
270	♂	29	Liver biopsy	Not jaundiced	+	February 15, 1939	5.9	0	5.7	3.3	2.4		Diffusely nodular liver, no atrophy. Moderately advanced Laënnec's cirrhosis.
					+	March 14, 1939	10.0	trace	7.2	3.4	3.8		
271	♂	48	Autopsy	3 months	+	October 28, 1938	5.8	2.0	6.1	1.8	4.3	1.2	Diffuse Laënnec's cirrhosis with atrophy. Ascites.
					+	November 28, 1938	10.1	3.3	5.9	1.8	4.1	1.1	
					+	December 15, 1938	7.4	3.8	6.3	1.7	4.6	1.3	
					+	January 25, 1939	10.7	3.0	6.2	2.0	4.2	1.1	

TABLE V—*Continued*

Number	Sex	Age	Basis for diagnosis	Duration of jaundice at time of blood analysis	Bile in stool	Date	Serum						Remarks
							Phosphatase	Bilirubin	Total protein	Albumin	Globulin	Euglobulin	
		years					*Bodansky units per 100 cc.*	*mgm. per cent*	*per cent*	*per cent*	*per cent*	*per cent*	
272	♀	43	Autopsy	Not jaundiced	+	December 31, 1936	5.7	2.0	6.3	2.2	4.1	1.2	Atrophic Laënnec's cirrhosis, diffuse. Ascites.
					+	January 11, 1937	6.9	trace	8.2	2.0	6.2	2.7	
					+	January 20, 1937	6.1	trace	8.2	2.2	6.0	2.3	
					+	January 27, 1937	5.4	trace	8.7	2.4	6.3	2.7	
					+	December 20, 1937	3.6	2.0	8.5	2.1	6.4	3.3	
					+	February 25, 1938	3.6	trace	6.8	2.0	4.8	2.4	
273	♂	47	Autopsy	Not jaundiced	+	March 16, 1937	4.7	0	7.0	3.9	3.1	0.4	Diffuse "cardiac" cirrhosis; coronary sclerosis, hepatomegaly (congestive).
274	♂	57	Autopsy	3 weeks	0	December 11, 1937	4.7	15.0	6.2	2.3	3.9	1.4	Diffuse Laënnec's cirrhosis with atrophy; acute cholangeitis; ascites.
275	♂	60	Autopsy	2 weeks	0	February 27, 1939	4.4	24.2	6.7	2.3	4.4	1.8	Chronic alcoholism. Atrophic Laënnec's cirrhosis, diffuse. Ascites, cholecystitis.
					0	March 2, 1939	3.8	27.0	7.2	2.5	4.7	1.3	
276	♂	54	Skin biopsy	Not jaundiced	+	June 7, 1937	4.2	0	7.2	4.2	3.0	0.4	Hemochromatosis. Hepatomegaly, diabetes.
277	♀	40	Autopsy	Not jaundiced	+	September 24, 1937	3.9	0	6.9	2.7	4.2	1.4	Diffuse Laënnec's cirrhosis, early. Lues.
278	♀	54	Autopsy	1 week	±	February 24, 1939	4.2	29.0	6.8	2.6	4.2	0.7	Chronic alcoholism, diffuse alcoholic cirrhosis; ascites.
279	♂	52	Celiotomy	Not jaundiced	+	January 25, 1937	3.6	trace	5.5	2.2	3.3	0.7	Chronic alcoholism. Diffuse cirrhosis.
280	♀	68	Autopsy	Not jaundiced	+	January 15, 1937	3.4	trace	6.9	4.1	2.8	0.6	Coarse lobular cirrhosis, luetic.
281	♂	64	Autopsy	Not jaundiced	+	January 14, 1936	3.3	2.0	6.5	3.6	2.9		Hemochromatosis. Diffuse cirrhosis with hepatomegaly.
282	♂	59	Autopsy	Not known	+	June 8, 1937	3.2	6.5	7.1	3.6	3.5	1.2	Chronic alcoholism. Diffuse Laënnec's cirrhosis, no atrophy.
283	♂	74	Autopsy	Not jaundiced	+	March 22, 1939	3.1	1.5	7.1	4.0	3.1	0.3	Diffuse Laënnec's cirrhosis, moderately advanced.
284	♂	47	Autopsy	Not jaundiced	+	September 20, 1937	2.7	2.0	6.3	3.7	2.6		Hemochromatosis. Hepatomegaly, marked cirrhosis, diabetes.
					+	December 22, 1937	2.8	1.0	6.3	4.2	2.1	0.1	
285	♀	31	Liver biopsy	Not known	+	October 2, 1936	2.5	3.1					Schistosomiasis; diffuse cirrhosis.
286	♀	24	Liver biopsy	Not known	+	December 13, 1935	1.5	3.3	5.5	3.4	2.1		Diffuse Laënnec's cirrhosis, moderately advanced.

necropsy. This result is contrary to our usual experience, as indicated by the essentially normal values of the remaining cases in Table VIB.

Table VIC comprises 22 cases of neoplasm with proven metastatic involvement of the liver, exclusive of all subjects in whom the primary tumor originated from or by extension impinged upon the extrahepatic biliary tract. Excluded also are all patients with bone metastases demonstrable by x-ray or at necropsy, with the exception of Case 320. It is assumed that with these restrictions, a distinct increase in serum phosphatase activity may be attributed to the presence of secondary metastases to the liver.

The serum phosphatase level was found to be variable in this group, ranging from 23.9 to 4.0 Bodansky units per 100 cc. The values in 17 cases exceeded the maximum we usually find in non-metastasizing malignancy (Table VIB). There were 5 instances, however, with serum phosphatase activity less than 5 Bodansky units, despite definite metastatic involvement of the liver; and Case 320 presented both hepatic and skeletal (osteolytic) metastases without any significant rise in serum phosphatase activity (an exceptional occurrence in our experience). The patients with little or no elevation in serum phosphatase level were not icteric.

In general, the serum phosphatase activity tends to be higher in patients with diffuse spread of large nodules throughout the liver. Our highest values were in patients who showed jaundice, though some were only slightly icteric (Cases 301, 302); and in several instances the serum phos-

TABLE VI

Summary of analyses of the blood in four proven cases of primary carcinoma of the liver; ten cases of malignancy without liver metastases; and twenty-two cases of malignancy with proven involvement of the liver

Number	Sex	Age	Primary tumor; basis for diagnosis	Serum		Remarks
				Phosphatase	Bilirubin	
		years		*Bodansky units per 100 cc.*	*mgm. per 100 cc.*	
A. PRIMARY CARCINOMA OF THE LIVER						
287	♀	41	Cholangioma (autopsy)	25.8	4.7	April 20, 1938
				33.1	4.4	May 9, 1938
				29.7	3.2	June 1, 1938
288	♂	65	Hepatoma, cirrhosis (liver biopsy)	16.8	4.0	January 6, 1938
				27.4	7.5	January 24, 1938
289	♂	38	Hepatoma, cirrhosis (liver biopsy)	16.3	3.0	June 1, 1939
290	♀	57	Cholangioma (autopsy)	11.5	2.5	June 29, 1937
B. MALIGNANCY WITHOUT LIVER METASTASES						
291	♂	67	Carcinoma of prostate gland (autopsy)	44.4	0	Extensive osteoplastic metastases to bone.
292	♂	61	Carcinoma of prostate gland (autopsy)	21.6	0	Extensive osteoplastic metastases to bone.
293	♀	43	Melanosarcoma (autopsy)	7.8	trace	Brain metastases; focal necroses of liver.
				3.9	0	
294	♂	57	Carcinoma of colon (autopsy)	7.4	0	Large local abscess formation.
295	♂	71	Carcinoma of stomach (autopsy)	4.9	1.0	Local metastases to nodes.
296	♀	60	Carcinoma of lung (autopsy)	4.5	0	Metastases to lung, lymph nodes.
297	♂	55	Oat cell tumor of lung (autopsy)	4.1	0	Metastases to brain, adrenals, etc.
298	♀	47	Lymphosarcoma (autopsy)	3.9	0	Metastases to spleen, pelvis.
299	♂	70	Carcinoma of colon (autopsy)	3.4	0	No metastases.
300	♀	70	Lymphosarcoma (autopsy)	3.2	0	Metastases to lung, skin, spleen, etc.
C. MALIGNANCY WITH LIVER METASTASES						
301	♀	43	Primary not known (liver biopsy)	23.9	2.5	Many liver metastases; jaundiced 1 year.
302	♂	39	Carcinoma of esophagus (autopsy)	21.5	2.7	Many liver metastases.
303	♂	32	Reticulum cell sarcoma (autopsy)	20.7	5.0	Many liver metastases.
304	♀	63	Carcinoma of colon (liver biopsy)	19.8	9.6	Many liver metastases; jaundiced 1 month.
305	♀	36	Carcinoma of stomach (autopsy)	18.8	trace	Many liver metastases.
306	♀	82	Carcinoma of tail of pancreas (autopsy)	18.3	0	Many liver metastases.
307	♂	74	Primary not known (autopsy)	13.1	7.4	Many liver metastases; duration of jaundice not known.
308	♂	47	Primary not known (celiotomy)	12.3	0.5	Many liver metastases.
309	♂	60	Carcinoma of bronchus (autopsy)	10.4	2.7	Many liver metastases.
310	♂	60	Sarcoma ? of testis (autopsy)	9.7	trace	Diffuse microscopic infiltration of liver; no gross nodules.
311	♀	52	Melanosarcoma (liver biopsy)	9.0	8.3	Many liver metastases. Duration of jaundice not known.
312	♂	63	Carcinoma of kidney (autopsy)	8.5	0	Many liver metastases.
313	♂	69	Carcinoma of prostate gland (autopsy)	8.4	0	Many liver metastases. (Early bone invasion, osteolytic).
314	♀	51	Carcinoma of cervix (autopsy)	7.5	0	Many liver metastases.
315	♀	40	Krukenberg tumor (autopsy)	6.7	trace	Many liver metastases; extensive osteolytic bone metastases.
316	♀	35	Carcinoma of rectum (liver biopsy)	6.5	trace	Many liver metastases.
317	♂	54	Carcinoma of stomach (autopsy)	6.3	0	Slight infiltration of liver.
318	♂	62	Primary not known (liver biopsy)	4.9	trace	Many liver metastases.
319	♀	63	Carcinoma of colon (autopsy)	4.4	0	Many liver metastases.
320	♂	50	Oat cell tumor of lung (autopsy)	4.2	0	Few liver metastases; extensive osteolytic bone infiltration.
321	♂	56	Hodgkin's sarcoma (autopsy)	4.1	0	Several liver metastases.
322	♂	63	Carcinoma of colon (autopsy)	4.0	trace	One nodule in liver.

phatase level was distinctly increased before jaundice developed (Cases 305, 306, 308). It has been our experience that significantly increased serum phosphatase activity occurs more consistently in this group of patients than does hyperbilirubinemia. Some of the most striking examples of this are not included in Table VI because, though the diagnosis of malignancy with liver metastases was obvious clinically, permission for autopsy and proof of the diagnosis could not be obtained.

6. Liver abscess; chronic passive congestion of the liver; miscellaneous disorders of the liver; cases of gall bladder disease with indeterminate effect upon the patency of the common bile duct

Table VIIA includes 9 cases of liver abscess of diverse etiology. The diagnosis was established by exploration or necropsy except in 2 patients with amebic abscess in whom the diagnosis would seem beyond reasonable doubt on clinical and laboratory grounds. The serum phosphatase activity was variable but definitely increased in every instance, ranging from 7.9 to 49.4 Bodansky units per 100 cc. The highest serum phosphatase levels occurred in jaundiced patients.

Table VIIB includes 10 patients with marked chronic passive congestion of the liver in decompensated cardiacs of long standing who at necropsy were found to have little or no "cardiac" cirrhosis. Congestive failure may cause some increase in serum phosphatase activity, particularly in patients who develop clinically demonstrable jaundice; 2 such patients in our series (Cases 332 and 333) reaching levels of 8.6 Bodansky units per 100 cc. In 4 instances, the values were within normal limits despite the presence of marked congestive hepatomegaly.

TABLE VII

Summary of analyses of the blood in nine cases of liver abscess; ten cases of chronic passive congestion of the liver; eight cases of miscellaneous disorders of the liver; and nine cases of gall bladder disease with indeterminate effect upon the patency of the common bile duct

Number	Sex	Age	Diagnosis	Date	Serum		Remarks
					Phosphatase	Bilirubin	
		years			*Bodansky units per 100 cc.*	*mgm. per 100 cc.*	
A. LIVER ABSCESS							
323	♂	59	Ruptured viscus? (operation)	May 29, 1939	42.1	4.0	Sub- and intrahepatic abscess at hilum. Jaundiced one week.
324	♂	21	Miliary tuberculosis (autopsy)	July 26, 1938	26.6	4.7	Disseminated tubercular abscesses of liver. Jaundiced one week.
				August 9, 1938	18.0	11.5	
325	♀	27	Sepsis (autopsy)	September 22, 1937	15.2	7.0	Large hilar abscess obstructing main hepatic ducts. Jaundiced two years, intermittently.
				November 16, 1937	49.4	3.5	
				December 9, 1937	39.6		
				December 20, 1937	34.5	2.9	
326	♀	52	Post-operative infection (operation)	November 23, 1938	14.0	0	Multiple liver abscesses.
327	♀	26	Tularemia ? (autopsy)	October 13, 1937	13.4	trace	Multiple intra- and subhepatic abscesses.
				October 22, 1937	17.0	0	
				January 10, 1938	19.1	3.9	
328	♂	32	Multiple liver abscesses (operation)	December 11, 1937	10.3	3.0	Following empyema of gall bladder.
				December 28, 1937	7.2	3.0	
329	♂	70	Amebic abscess (clinical)	November 1, 1937	9.5	2.1	Amebic cysts in stool, fever, etc.
				January 19, 1939	8.2	0	Recurrence.
330	♂	26	Amebic abscess (operation)	May 17, 1939	8.1	2.0	Recurrence.
331	♂	44	Amebic abscess (clinical)	January 28, 1938	7.9	0	Amebae in stool; fever, etc.
B. CHRONIC PASSIVE CONGESTION OF THE LIVER (Autopsy diagnoses in every instance)							
332	♂	52	Myocardial infarctions	March 23, 1938	8.6	1.0	
333	♀	53	Arteriolar sclerosis	January 19, 1937	8.6	2.0	
334	♂	49	Myocardial infarctions	February 3, 1938	8.2	2.0	
				November 21, 1938	6.1	trace	
335	♀	48	Rheumatic valvular disease	March 10, 1937	8.0	3.2	
336	♀	16	Rheumatic pancarditis	January 22, 1934	7.1	0	
337	♂	37	Rheumatic pericarditis	April 22, 1937	6.7	2.5	
338	♂	15	Rheumatic pancarditis	October 21, 1938	3.9	8.3	Terminal Friedlaender pneumonia.
339	♂	38	Bacterial endocarditis	October 28, 1937	3.3	0	
340	♂	41	Bacterial endocarditis	November 14, 1938	2.5	0	
341	♂	60	Arteriolar sclerosis	December 11, 1937	2.3	1.0	

TABLE VII—*Continued*

Number	Sex	Age	Diagnosis	Date	Serum		Remarks
					Phosphatase	Bilirubin	
		years			*Bodansky units per 100 cc.*	*mgm. per 100 cc.*	
C. MISCELLANEOUS DISORDERS OF THE LIVER							
342	♀	75	Stone in common duct (operation)	June 18, 1938	20.0	2.0	Localized Paget's disease, pelvis.
343	♂	64	Stone in common duct (operation)	March 5, 1935	17.9	3.0	Localized Paget's disease, pelvis.
344	♂	48	Pneumonia, septicemia (autopsy)	January 6, 1937	4.8	9.0	Complicated by jaundice.
345	♂	26	Pneumonia (clinical)	March 26, 1937	1.7	2.8	Complicated by jaundice.
				April 2, 1937	5.0	2.0	
				April 13, 1937	4.0	0	
346	♂	70	Pneumonia, empyema, uremia (autopsy)	January 18, 1937	7.7	6.9	Complicated by jaundice.
				February 8, 1937	12.9	1.0	
				February 10, 1937	22.4	1.0	
347	♀	58	Tuberculosis of liver (liver biopsy)	January 28, 1939	14.4	2.0	Extensive infiltration.
348	♂	35	Hodgkin's disease (autopsy)	June 9, 1936	7.3	9.0	Extensive infiltration of portal areas.
349	♀	28	Echinococcus cyst of liver (operation)	September 6, 1938	4.6	trace	Left lobe of liver involved.
				March 17, 1939	4.5	trace	
D. CHRONIC GALL BLADDER DISEASE							
350	♀	54	Cholelithiasis (operation)	October 30, 1937	19.6	15.0	Operation December 7, 1937, no stone in common duct.
				November 13, 1937	10.0	9.0	
				November 22, 1937	7.5	2.9	
351	♀	63	Cholelithiasis (operation)	May 25, 1937	18.0	6.0	Operation June 8, 1937, no stone in common duct.
				May 29, 1937		1.0	
352	♀	50	Cholelithiasis (operation)	March 6, 1938	11.9	6.0	Operation March 14, 1938, no stone in common duct.
				March 8, 1938	8.7	trace	
353	♀	40	Cholelithiasis (operation)	September 29, 1938	7.3	7.5	Operation October 4, 1938, no stone in common duct.
354	♀	19	Cholelithiasis (operation)	October 2, 1936	3.0	8.3	Operation October 14, 1936, no stone in common duct.
				October 5, 1936		3.2	
355	♀	61	Cholelithiasis (operation)	March 13, 1936	3.6	trace	Operation March 16, 1936, no stone in common duct.
356	♂	56	Cholelithiasis (operation)	March 20, 1939	4.4	trace	Operation March 25, 1938, no stone in common duct.
357	♀	59	Cholelithiasis (operation)	May 26, 1939	3.6	0	Operation June 6, 1939, no stone in common duct.
358	♂	30	Cholelithiasis (operation)	March 7, 1939	6.5	6.2	Operation March 16, 1939, no stone in common duct; spasm of sphincter of Oddi?
				March 13, 1939	5.7	11.5	
				March 20, 1939	2.3	17.0	
				March 29, 1939	7.2	6.3	
				April 10, 1939	5.4	2.7	

Eight patients with miscellaneous types of hepatic disease are included in Table VIIC. Cases 342 and 343 illustrate difficulties in the application of the serum phosphatase determination to the differential diagnosis of jaundice in patients with bone disease. In both instances a marked increase in serum phosphatase activity, with slight jaundice, was noted but was not interpretable because Paget's disease was present (localized lesions not apparent clinically but disclosed incidentally by x-rays). These patients subsequently proved to have stone in the common duct. In a previously recorded instance (Case 116) confusingly high serum phosphatase values due to clinically unrecognizable Paget's disease were obtained in a case of hepatitis.

Jaundice developing in patients with pneumonia ("toxic" or "infective" jaundice) usually is associated with comparatively little increase in serum phosphatase activity, as shown in Cases 344 and 345. In Case 346, whose course was complicated by empyema, there was a terminal rise in the serum phosphatase activity to 22.4 Bodansky units per 100 cc., a level we have not encountered otherwise in this type of case. There was no adequate explanation for this increase at autopsy, which disclosed only focal necroses of the liver. Case 347, with serum phosphatase of 14.4 Bodansky units, was found to have tubercles extensively involving the liver. Case 348 had Hodgkin's disease of the liver, confined to the portal areas. Case 349 is of interest because a very large echinococcus cyst was present but did not effect a significant rise in serum phosphatase activity. The cyst involved the left lobe of the liver, which may have some bearing on the result.

Table VIID comprises 9 cases of gall bladder disease with jaundice, a large and important clinical group but one which presents many difficulties in classification. Several investigators in this field have regarded all such cases as jaundice due to obstruction of the common bile duct, irrespective of whether or not operation disclosed a stone in the common duct; apparently on the assumption that mechanical obstruction or sphincter spasm are the sole causes of jaundice under these circumstances. So far as evaluation of the serum phosphatase determination is concerned, we have preferred to classify as obstructive jaundice only those cases of biliary tract disease in which mechanical obstruction of the common bile duct could be demonstrated at operation or autopsy. Patients in whom no such obstruction was found have been regarded for the present purpose as unclassifiable and were omitted from our statistical series. In some of our patients in this category (Cases 350, 351, and 352), serum phosphatase values over 10 Bodansky units were associated with definite hyperbilirubinemia and typical biliary colic suggesting stone in the common bile duct; there was spontaneous cessation of pain and rapid subsidence of jaundice, and operation about 1 week thereafter disclosed cholelithiasis but no stone in or dilatation of the common duct. This sequence of events is consistent with spontaneous passage of a stone in the common duct but proof is wanting. In other instances (Cases 353 and 354), the clinical course and the operative findings were the same, definite jaundice was present but the serum phosphatase level showed little or no increase. It is impossible to say whether a stone occluded the common duct at the time the patient was icteric and the serum phosphatase failed to rise to its usual level; or whether the jaundice was caused by transitory infection of the biliary tract or hepatitis. Even more difficult of interpretation are instances in which the first serum phosphatase determination was made after jaundice had subsided spontaneously (Case 355), conditions under which the method is without value. Cases 356 and 357 illustrate essentially normal serum phosphatase values characteristic of chronic gall bladder disease uncomplicated by jaundice.

Another source of error inherent in our classification of obstruction of the extrahepatic biliary tract on the basis of mechanical occlusion lies in the possible inadvertent exclusion of obstruction due to spasm of the sphincter of Oddi. In those instances in which this mechanism was suggested at operation as the cause of icterus, it was not possible to obtain convincing objective proof of the causal relation of spasm to jaundice. For example, Case 358 was found to have cholecystitis and cholelithiasis but no stone in or dilatation of the common bile duct at operation (at which time the serum bilirubin was markedly elevated but the serum phosphatase activity insignificantly increased). Cholangiograms showed some narrowing of the distal end of the common duct, without delay in emptying. Liver biopsy was variously interpreted as hepatitis or essentially normal liver but was not thought to suggest obstructive jaundice. Manometer readings of bile duct pressure after injection of saline into the drainage tube gave equivocal results. The jaundice increased after operation, then slowly subsided.

ANALYSIS AND DISCUSSION OF TOTAL SERIES OF OBSERVATIONS 1933 TO 1939

1. *Distribution of serum phosphatase values in major diseases of the liver and biliary tract*

Perhaps the clearest summary of our results is afforded by an analysis of their distribution in certain common disorders of the liver and biliary tract. The total number of such cases available for analysis is 308, the several categories of disease considered and their respective representation being indicated in Table VIII. For reasons stated elsewhere, observations in children are excluded. Only the initial values obtained in each patient were employed for purposes of analysis, but an exception was made in Case 246 for reasons evident in the text. Patients with biliary cirrhosis (including Case 73 (1)) are classified according to the type of biliary tract obstruction and do not appear in the cirrhosis group.

Of a total of 34 patients with jaundice due to stone obstructing the common bile duct, 5 or roughly 15 per cent had serum phosphatase levels less than 10 Bodansky units per 100 cc.; as did 2 or roughly 5 per cent of 45 patients with noncalculous common bile duct obstruction (chiefly carcinoma of the head of the pancreas). Consid-

TABLE VIII

Distribution of serum phosphatase values in major disorders of the liver and biliary tract; analysis of results in 308 adults (initial values only)

Diagnosis	Total number of cases	Distribution of cases by phosphatase values				
		Zone of normal values		Zone of indeterminate diagnostic significance		
		<4.0	4.1–9.0	9.1–12.0	12.1–25.0	>25.0
		Bodansky units per 100 cc.				
Stone in common bile duct	34	0	5	5	21	3
Non-calculous obstruction of common bile duct	45	0	1	5	25	14
"Catarrhal" jaundice	69	8	48	8	4	1
Jaundice after hepatotoxic drugs	38	2	18	4	13	1
Hemolytic jaundice	13	13	0	0	0	0
Hepatic cirrhosis (non-biliary)	44	14	20	5	4	1
Neoplastic involvement of liver	47	4	18	5	18	2
Liver abscess	10	0	2	3	3	2
Chronic passive congestion of liver	8	3	5	0	0	0

ering the 79 cases of proven obstructive jaundice as a whole, about 10 per cent failed to show phosphatase levels over 10 Bodansky units per 100 cc. serum. Of a total of 107 cases classified as "hepatitis," 82 or roughly 75 per cent had serum phosphatase levels less than 10 Bodansky units per 100 cc. If, as we have proposed, patients with jaundice following exposure to hepatotoxic agents be excluded from the heterogeneous "hepatitis" group, then 62 of the 69 remaining cases (90 per cent) had serum phosphatase levels less than 10 Bodansky units per 100 cc.

There would seem to be little point in further pursuing the analysis along these lines because, in practice, many values that are slightly above or below 10 Bodansky units are of indeterminate diagnostic significance. This difficulty is recognized in the distribution of values as summarized in Table VIII, which gives a more representative picture of the applicability of the serum phosphatase determination in our hands. It will be noted that 6 of 79 patients with proven common duct obstruction had serum phosphatase levels not exceeding 9.0 Bodansky units per 100 cc., 5 being instances of choledocholithiasis with incomplete or intermittent occlusion. The values in 10 patients of this group further fell into the indeterminate zone of 9.1 to 12.0 Bodansky units. Sixty-three or 80 per cent of the total number of cases with jaundice due to gross common duct obstruction showed serum phosphatase values over 12.0 Bodansky units per 100 cc. Values over 25 Bodansky units were obtained usually but not invariably in patients with complete and protracted obstruction of the common bile duct due to neoplasm.

In "catarrhal" jaundice, on the other hand, 56 of 69 cases (about 80 per cent) had serum phosphatase levels less than 9.0 Bodansky units per 100 cc., 8 were at indeterminate levels and 5 (about 7 per cent) exceeded 12.0 Bodansky units. When the relation of serum phosphatase to serum bilirubin levels in these two major types of jaundice is taken into consideration, the differences between them become even more striking. Those patients with obstructive jaundice who showed little increase in serum phosphatase activity had relatively slight hyperbilirubinemia, as obstruction was incomplete; whereas even marked jaundice of hepatogenous origin was associated for the most part with comparatively little elevation in serum phosphatase activity.

The distribution of serum phosphatase values in hemolytic jaundice and in chronic passive congestion of the liver is limited to the normal range or slightly above, as already indicated. In patients with liver abscess the values are preponderantly in the range of obstructive jaundice or fall within the zone of indeterminate significance. Thirty-four of 44 cases (about 75 per cent) of cirrhosis other than biliary cirrhosis had serum phosphatase levels less than 9.0 Bodansky units per 100 cc., and 5 fell within the indeterminate zone.

The distribution of serum phosphatase values in two categories of liver disease deserves special comment because a double peak in the incidence curve appears, one within the "hepatitis" zone, the other in the zone of obstructive jaundice. These are the group with jaundice due to hepatotoxic drugs and the series comprising patients with neoplastic involvement of the liver. In the former, as already indicated, there is some evidence that two distinct types of jaundice may be present. In the latter group, the spread in serum phosphatase values appears to relate to the number and distribution of metastases in the liver.

2. Clinical usefulness and limitations of the determination of serum phosphatase activity as applied to diseases of the liver and biliary tract

A. Evaluation of the method as a supplementary aid to the clinical differentiation of the several types of jaundice. The chief usefulness of the determination of serum phosphatase activity derives, we believe, from the consistency with which distinctly increased values accompany obstruction of the extrahepatic biliary tract. We have found it helpful to recognize that jaundice in patients with serum phosphatase levels less than 10 Bodansky units per 100 cc. is probably not due to gross obstruction of the common bile duct. When exploration was contemplated in such patients, it proved good policy to observe the patient further until additional clinical and laboratory data could be obtained.

While the absence of significantly increased serum phosphatase activity in icteric patients is valid evidence against obstruction of the common bile duct, in our experience, it does *not* follow that a serum phosphatase value greater than 10 Bodansky units accompanying jaundice automatically marks the patient for exploration. The finding of a serum phosphatase level exceeding 10 Bodansky units per 100 cc. in icteric patients, to be sure, is consistent with the clinical diagnosis of obstructive jaundice. But in addition to obstruction of the extrahepatic biliary tract warranting surgical intervention, marked elevations in serum phosphatase activity also occur frequently in arsphenamine jaundice and with liver metastases, occasionally in hepatitis and other liver diseases requiring conservative management, and in a variety of skeletal disorders. It was sometimes but not always possible for us to exclude these further possibilities by careful history-taking and appropriate roentgenographic and clinical studies.

To indicate what seems to us to be a particular advantage of the serum phosphatase determination in the differential diagnosis of jaundice requires a consideration of certain difficulties inherent in the clinical application of any physiological aid to the diagnosis of liver disease. As pointed out by several investigators (8, 9), the simple but arbitrary division of clinical jaundice into three discrete categories, obstructive, hepatogenous and hemolytic, however convenient clinically, does not adequately define the mechanisms actually operating in many patients. The initial or predominant cause of jaundice may fall into one or another of these distinct categories, but serious disturbance of one mechanism soon involves others and this complexity is reflected in equivocal or confusing results with the test employed. The disadvantage of most liver function tests used in the differential diagnosis of jaundice lies in the circumstance that they provide only negative evidence for obstruction; that is, mechanical obstruction of the common bile duct is suggested by the *absence* of any significant alteration in a given function of the liver in patients with jaundice. While this often suffices, if significant liver parenchymal injury complicates obstruction (as with cholangeitis or biliary cirrhosis developing in protracted obstructive jaundice) then the negative effect of obstruction may be superseded by the positive effects of secondary inflammatory or degenerative changes. Under these circumstances, liver function tests not infrequently give equivocal or confusing results and the possibility of error is not minimized by a multiplicity of such tests all having much the same limitation.

It would seem desirable rather to complement the liver function tests with some positive measure of biliary tract obstruction. We find the determination of serum phosphatase activity satisfactory for this purpose, since inflammatory or cirrhotic changes secondary to common bile duct obstruction do not ordinarily significantly lower the phosphatase level of the serum. Other positive indices of biliary tract obstruction, such as the total cholesterol content of the serum, have proved less consistently helpful in our hands (Table I), particularly in the clinically important group of patients with incomplete mechanical obstruction of the common bile duct. The range of variation in the serum cholesterol content of different normal subjects, moreover, is extremely broad so that interpretation of values in any one case of jaundice may be difficult; whereas we find the range of variation in serum phosphatase activity in the normal adult relatively narrow and the many-fold increase encountered in obstructive jaundice facilitates interpretation of results.

There are further minor advantages that recommend the serum phosphatase determination for

test purposes in jaundiced patients: it does not require the administration of substances that may or may not be innocuous to the disordered liver; and it is not significantly affected by renal disease, in our experience.

As to the disadvantages of the method, there are several that limit its applicability in the differentiation of the several types of jaundice. The foremost of these is overlapping of serum phosphatase values in the obstructive and hepatogenous groups of jaundiced patients. The degree of overlapping noted by different investigators has varied extraordinarily, some finding it so large as to disqualify the method for differential diagnosis (3b, 3f), others finding the overlapping of values sufficient to limit but not invalidate the usefulness of the determination (3c, 3h). There is general though not unanimous agreement, however, regarding the relative consistency of distinctly increased serum phosphatase levels in jaundice due to obstruction of the common bile duct. As suggested elsewhere (1), these discrepancies in experience may be ascribable, in part, to variations in technique of the serum phosphatase determination, in the classification of clinical material, or in the adequacy of evidence adduced for the classification of cases.

The differentiation of obstructive from hepatogenous jaundice is further confused by overlapping of serum phosphatase values obtained in other diseases of the liver and biliary tract, as shown in our tables. Consequently, we feel that the chief usefulness of the determination in the differential diagnosis of jaundice is in excluding, with high probability, obstruction of the common bile duct as a cause of jaundice in patients showing no marked increase in serum phosphatase activity.

Another difficulty with the serum phosphatase determination as applied to the differential diagnosis of jaundice lies in its lack of specificity. As is well known (10, 11, 12, 13), the phosphatase activity of the serum is increased in a variety of skeletal disorders, notably Paget's disease, rickets, carcinoma with bone metastases, particularly of the osteoplastic type, hyperparathyroidism and osteogenic sarcoma. The serum phosphatase level cannot be applied to the diagnosis of disease of the liver or biliary tract in patients presenting any of these bone conditions. Ordinarily, appreciation of this limitation avoids confusion because the skeletal disorder is readily recognizable. But errors occur occasionally when localized Paget's disease or metastatic bone involvement, discoverable only by appropriate x-rays, is overlooked. Apart from these skeletal disorders, no other conditions significantly affect the serum phosphatase level consistently enough to interfere seriously with the use of the method in jaundice, so far as we could discover. If skeletal disease can be ruled out, it has been our experience that patients with definitely elevated serum phosphatase level, whether jaundiced or not, generally prove to have one or another type of liver disease.

Further difficulties with the serum phosphatase determination are encountered when it is applied to the differential diagnosis of jaundice in children. The method appears to be of no value in an important problem of this kind in infants: the differentiation of congenital atresia of the bile ducts from "physiological jaundice." Throughout the period of skeletal growth, the range of normal variation in serum phosphatase activity is so broad and ill-defined (roughly 4 to 12 or more Bodansky units per 100 cc.), that the values obtained in hepatitis in children are confusingly high (3a, 3g). Although our experience with this age period has been limited, we feel that for the present the method is not applicable to growing children.

Finally, as already indicated, we find the serum phosphatase determination of little value in the diagnosis of Laënnec's cirrhosis and of largely academic interest in hemolytic jaundice.

B. The determination of serum phosphatase activity as an aid in the diagnosis of complications following surgery of the biliary tract. In all, 24 patients with obstructive jaundice were studied both before and after attempted relief of common duct obstruction by surgical measures. Because of the complexities involved, our data are too incomplete for any but the most general inferences, and in 3 patients are wholly inadequate for analysis.

Decompression by establishment of external or internal biliary fistulae in obstructive jaundice, if successful in effecting adequate drainage and if not complicated by infection, resulted in a roughly parallel fall in both serum bilirubin and phosphatase levels (Cases 5, 11, 18, 21, 23, 125, 128, 151,

155). The post-operative course under these circumstances was usually uneventful. When exploration disclosed that obstruction of the common bile duct was due to carcinoma so extensive as to discourage any attempt at drainage, or when an unsuccessful attempt at drainage was made, both serum bilirubin and phosphatase showed a parallel tendency to remain elevated or to rise further (Cases 2, 22, 168).

In many patients both serum bilirubin and serum phosphatase levels fell following establishment of biliary drainage but a secondary rise in serum phosphatase activity was noted, not necessarily associated with a comparable rise in serum bilirubin. Meranze, Meranze and Rothman (3h) called attention to this phenomenon and pointed out that it occurred usually when convalescence was stormy, an observation that coincides in general with our experience. The significance of this secondary rise in serum phosphatase activity appears to depend largely upon the nature of the obstruction and the type of operation performed. In patients with stone in the common duct, the principal cause was infection such as subphrenic abscess involving the hilum of the liver (Case 133) or cholangeitis (Case 138). In patients with carcinomatous obstruction of the common duct, a late recurrence of serum phosphatase activity after establishment of internal biliary fistulae was associated with cholangeitis leading to closure of the stoma and to multiple liver abscesses (Case 10); with the development of liver metastases (Case 162); or with cholangeitis and liver metastases (Case 21). The association of increased serum phosphatase activity with complications attending the development of protracted biliary fistulae after cholecystectomy has already been illustrated by three case summaries.

Although our data are incomplete, there would appear to be a general correlation between the post-operative serum phosphatase level and the success of surgical procedures in the establishment of adequate biliary drainage. In this sense, serum phosphatase determinations may aid in the anticipation of certain post-operative complications, particularly in the development of cholangeitis or of liver metastases (the serum bilirubin level being an uncertain guide). Limitations in the use of the determination for this purpose are illustrated by instances in which convalescence was without serious incident yet the fall in serum phosphatase was either very slow (Case 17) or was interrupted by a slight rise without apparent cause (Case 126). One patient (Case 139), who developed peritonitis postoperatively, showed a fall in serum phosphatase activity associated with a distinct rise in serum bilirubin. Necropsy disclosed extensive liver necrosis suggesting 'toxic' hepatitis.

C. Serum phosphatase determination as a means of early detection of metastases in malignancy. The liver is a site of predilection for distant metastases in many types of tumor but because of difficulties in the early detection of liver metastases by any means short of exploration, the recognition of metastatic liver involvement is frequently delayed until palpable nodules become obvious. Jaundice, as is well known, is a late and inconstant manifestation of metastatic malignancy. It has been our experience that usually before there is any demonstrable liver enlargement, the serum phosphatase activity of patients with liver metastases often shows a distinct rise (14, 12, 1). On a number of occasions, the increased serum phosphatase level was the only objective evidence we could obtain of the presence of metastatic liver involvement demonstrated by exploration or necropsy shortly thereafter. However, the absence of a significant rise in the serum phosphatase level does not exclude the possibility of metastatic liver involvement since some patients with essentially normal serum phosphatase levels nevertheless proved to have liver metastases (1, 12, 13, 15), usually a few small nodules but sometimes more extensive invasion. Apparently, chance variations in the distribution and size of metastases affect the reliability of the method, particularly when few nodules are present, and limit the usefulness of the serum phosphatase determination for this purpose. Moreover, if jaundice is absent, it is necessary to exclude metastatic involvement of the skeleton (usually but not always possible by x-ray) before concluding that increased serum phosphatase activity is due to liver metastases; though it is often immaterial, as when ablation of a primary tumor is contemplated, whether secondaries involve liver or skeleton, so long as they can be detected early.

It is our impression that, as emphasized by Meranze, Meranze and Rothman (15), valid early

evidence for metastases may be afforded by the finding of a definitely elevated serum phosphatase level in patients known to have malignancy. This obviously does not apply if other causes of increased serum phosphatase activity (Paget's disease, etc.) are present or if the primary tumor itself may be responsible for such an increase (osteogenic sarcoma, primary tumors obstructing the biliary tract). It should be kept in mind that the serum phosphatase level is not affected by metastases to such organs as lungs and may not be significantly affected by either liver or bone metastases (particularly of the osteolytic type) or both (see Case 320).

3. Mechanisms regulating the behavior of the serum phosphatase level in disease of the liver and biliary tract

According to the prevailing concept (10), "alkaline" serum phosphatase[8] originates for the most part in bone-producing cells (an assumption based chiefly upon the high phosphatase activity of bone) and, after escaping into the circulating fluids, is excreted in the bile (an assumption based upon the high phosphatase activity of the bile). Clinical experience, on the whole, is in good agreement with this theory. Serum phosphatase determinations in a wide variety of diseases have shown, empirically, that appreciable elevations in serum phosphatase activity are observed consistently in only two general pathological states: (*1*) diseases of the skeletal system in which there is active, widespread formation of bone or cartilage (11, 12, 13, 17); (*2*) diseases of the liver and biliary system in which there is obvious or presumptive impingement upon the excretory channels (biliary tract), whether extra- or intrahepatic. That skeletal disorders characterized by increased osteogenesis cause elevated serum phosphatase levels is understandable, on the basis of the experimental evidence for the osseous origin of "alkaline" phosphatase, as due to increased *formation* of the enzyme. That hepatic disorders of the obstructive type cause increased serum phosphatase activity would be anticipated as a result of *retention* of the enzyme due to blocking of its excretory channel, the biliary tract. The prevailing concept therefore affords an explanation for the occurrence of a common phenomenon (increased serum phosphatase activity) in diseases that are otherwise extremely heterogeneous in character.

There is a diversity of opinion regarding the validity of the "retention" theory as applied to the increased serum phosphatase activity observed in some hepatic disorders. It is wholly probable that even if blocking of the excretory biliary channels results in retention of phosphatase in the serum, other factors also affect the serum phosphatase level in obstructive jaundice. It is difficult otherwise to explain the wide range in serum phosphatase activity in different patients each having complete and protracted obstruction of the common bile duct (from 113.1 to 9.6 Bodansky units per 100 cc. in our cases of carcinoma of the head of the pancreas). Evidently, the level of serum phosphatase at which equilibrium is re-established in the blood following common duct obstruction does not depend solely upon the degree of obstruction. It would seem likely that the rate of phosphatase formation and the adequacy of other methods of disposing of serum phosphatase (by mechanisms as yet unknown) play a rôle here. That these other factors are operative does not imply, however, that the "retention" theory is invalid.

Several alternative explanations have been offered in lieu of the "retention" theory. Thannhauser and his associates have interpreted their clinical and experimental studies (18, 19) to signify that the increased serum phosphatase activity observed in sundry diseases, including obstructive jaundice, is due not to increased concentration of the enzyme in the blood but rather to the effect of an activator on the enzyme. This hypothesis is based upon their observation that ascorbic acid activates serum phosphatase (20), a phenomenon subsequent studies (21, 22) proved to be an artefact. The activity of "alkaline" phosphatase is slightly inhibited by bile salts (23).

Another explanation for the behavior of the serum phosphatase level in diseases of the liver and biliary tract lies in the possible hepatogenous origin of at least part of the "alkaline" phosphatase content of serum. Bodansky has shown (24) that nutritional factors may influence the

[8] For the sake of simplicity we have referred to the serum phosphatases as "phosphatase." In reality, at least one "alkaline" and at least one "acid" phosphatase system is present in serum.

" alkaline " phosphatase activity of the serum and has raised the question of extra-osseous sources of the enzyme (25). Liver tissue is known to contain appreciable amounts of both " alkaline " and " acid " phosphatases. It is possible that the behavior of the serum phosphatase in hepatic disease is due not to retention of a phosphatase of osseous origin but to varying effects of hepatic disease upon the elaboration and secretion of phosphatase by the liver parenchyma. Much of the evidence now available, both experimental and clinical, is interpretable either way. Current discussion along these lines is reminiscent of the controversy which prevailed regarding the hepatic vs. extra-hepatic origin of the bile pigments until incontrovertible proof of their chiefly extrahepatic origin was obtained (26).

No such definitive evidence is now available, one way or the other, concerning the validity of the " retention " theory of the behavior of serum phosphatase levels in disease of the liver and biliary tract. Such evidence must be obtained by proper experiment. But so far as clinical observations go, the distribution of our data on adults (Table VIII) is consistent, on the whole, with the " retention " theory. Gross obstruction of the common bile duct quite regularly results in markedly increased serum phosphatase activity, the exceptions occurring chiefly with incomplete or intermittent obstruction. Interposition of masses in the liver substance (tumor nodules, liver abscess, etc.) that might block off major intrahepatic biliary passages likewise leads to elevated serum phosphatase values. Hepatogenous or " catarrhal " jaundice usually causes relatively little increase in serum phosphatase activity as compared with the degree of hyperbilirubinemia; not more than might well be due to varying intrahepatic obstruction of the finer biliary radicles. Hemolytic jaundice does not ordinarily affect the serum phosphatase level. The varying serum phosphatase levels observed in jaundice due to hepatotoxic drugs accord with other criteria in patients with high levels and are all indicative of the possibility of intrahepatic biliary obstruction. Fibrosis of the portal areas (or about the central veins) seems not to disrupt the biliary tract in most instances, judging by the preponderance of cases with little or no jaundice and comparatively little increase in serum phosphatase activity; apparently new bile duct proliferation maintains the integrity of the excretory channels. But when disorganization of the biliary tract, with jaundice, occurs in Laënnec's cirrhosis (due to complications like infection or neoplastic degeneration), the serum phosphatase level rises.

On the other hand, it is clear that markedly increased serum phosphatase activity may occur with little or no hyperbilirubinemia (as, for instance, with metastatic liver malignancy) and this dissociation has seemed to some (27, 28) incompatible with the " retention " theory: both phosphatase and bilirubin being constituents of bile, obstruction of the biliary tract sufficient to cause retention of phosphatase ought to be associated with a comparable degree of bilirubin retention. This would follow, of course, if the blood levels of both bilirubin and phosphatase depended solely upon their common rate of excretion in the bile. However, bile pigments are excreted in the urine when there is biliary obstruction with retention of bile in the blood, whereas the human kidney appears to be impermeable to " alkaline " serum phosphatase.[4] This difference with respect to renal excretion affords a possible explanation for the occurrence of increased serum phosphatase activity with little or no jaundice, a dissociation which does not seem to us to disqualify the " retention " theory. In hepatitis, the absence of appreciable increase in phosphatase activity, despite marked hyperbilirubinemia due to blocking of bile pigments by the disordered parenchyma, suggests possible shunting of the enzyme around the polygonal cells.

The increased serum phosphatase activity sometimes observed in patients with external biliary fistulae draining bile likewise appears to be incongruous with the " retention " theory, since under these circumstances bile, and therefore

[4] That is, the " alkaline " phosphatase activity of human urine is negligible in jaundiced (or normal) human subjects. Interestingly enough, in the cat, the one species in which " alkaline " phosphatase is known to be present in appreciable amounts in the urine (29), ligation of the common bile duct causes little or no rise in serum phosphatase activity (30).

In passing, it might be noted that dissociation of serum bilirubin and phosphatase is not peculiar to phosphatase among bile constituents. For example, a similar dissociation between serum bilirubin and total cholesterol values is the rule in hepatogenous jaundice.

phosphatase, is certainly being excreted. The validity of this inconsistency would seem to depend upon whether or not the excretion of phosphatase in a given instance is adequate, always a difficult matter to appraise. The fairly consistent occurrence of clinical complications, when such dissociation was observed by us, leads to the suspicion that drainage under those circumstances may not be as adequate as would appear. It is interesting to note in this connection that patients with seemingly free drainage of bile through external fistulae may show other peculiarities such as increased serum cholesterol (31) and rather marked increase in bromsulfalein retention (9).

A more convincing inconsistency of the "retention" theory encountered in our clinical material, however, was that presented by infants with jaundice due to congenital atresia of the bile ducts. In spite of typical obstructive jaundice, the serum phosphatase level in this condition has been found to be within or only moderately above the normal range in infants. We obtained values of 11.1 and 6.3 Bodansky units per 100 cc. respectively in 2 such previously recorded instances (Cases 112 and 113; see Donovan (32) for clinical details). Similar results have been obtained by other investigators (3f, 3i). Another case reported here (Case 173) showed a level of 17.1 Bodansky units, a value which we regard as definitely elevated but probably less than might be anticipated in obstructive jaundice at this age period. It remains to be determined whether these unexpected results signify that the "retention" theory is untenable or whether they are ascribable to some as yet unknown peculiarity of the phosphatase metabolism in the infant.

SUMMARY

Our experience during the period 1933 to 1939 with serum phosphatase determinations (Bodansky method) in disorders of the liver and biliary tract is summarized. An analysis was made of the results in over 300 adult patients in whom the diagnosis, apart from the hepatitides, could be established at operation or autopsy.

Of 79 adults with proven obstruction of the common bile duct, 72 (roughly 90 per cent) had serum phosphatase levels more than 10 Bodansky units per 100 cc. In the "hepatitis" group, 82 of 107 adult cases had serum phosphatase levels less than 10 Bodansky units per 100 cc.; but if, as we have proposed, patients with jaundice following exposure to hepatotoxic agents be segregated from the "catarrhal" jaundice group, then 62 of the 69 latter cases (roughly 90 per cent) had serum phosphatase levels less than 10 Bodansky units per 100 cc. There is a striking dispersion in the serum phosphatase values of patients with jaundice following exposure to hepatotoxic agents, especially arsphenamine. This dispersion may have clinical significance.

Hemolytic jaundice was associated with normal serum phosphatase values. Of 44 patients with advanced cirrhosis (exclusive of biliary cirrhosis), 34 had serum phosphatase values less than 9 Bodansky units per 100 cc. Forty-seven patients with proven neoplastic involvement of the liver showed a wide dispersion in serum phosphatase levels, depending apparently upon the number and location of metastases. Chronic passive congestion of the liver caused little or no elevation in serum phosphatase activity; liver abscess was usually associated with distinctly increased values.

We find the determination of serum phosphatase activity of limited but definite value as a supplementary aid to the clinical differentiation of the several types of jaundice. It is useful particularly in ruling out obstruction of the extrahepatic biliary tract, an improbable cause of jaundice in patients with serum phosphatase values less than 10 Bodansky units per 100 cc. When applied to the differential diagnosis of jaundice, the following sources of error should be recognized: (*a*) overlapping of values in the obstructive and hepatogenous groups of jaundice (about 10 per cent in either direction, in our experience); (*b*) unspecificity, as certain skeletal disorders increase serum phosphatase activity; (*c*) inapplicability to jaundice in children, particularly in congenital atresia of the bile duct.

The determination of serum phosphatase activity may be useful also in anticipating certain complications following surgery of the biliary tract. Pre- and post-operative determinations in 24 patients with obstructive jaundice disclosed a distinct correlation between post-operative serum phosphatase trends and the post-operative clinical course.

Furthermore, the determination of serum phosphatase activity is of some value in the relatively early detection of liver or skeletal metastases in patients known to have malignancy.

Possible mechanisms regulating the serum phosphatase level in disorders of the liver and biliary tract are considered, with special reference to the "retention" theory. To judge from our empirical clinical experience, the serum phosphatase level in the adult is a sensitive criterion of the integrity of the excretory biliary channels, extra- and intra-hepatic, affording *positive* evidence for obstruction. It is suggested that the determination be employed to complement "liver function" tests, which measure impairment of a given function of the liver parenchyma but provide merely *negative* evidence for obstruction; and the dye retention tests which are inapplicable in jaundiced patients.

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