Enzyme and Function Changes after Extensive Liver Resection in Man

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Numerous papers have considered the question of what causes increased serum activity of hepatic enzymes in disease of the liver. Hypertransaminasemia was first believed to be caused by a release of enzyme from necrotic liver cells. Many studies support this view.[40] Later, it was realized that necrosis of liver cells was not a *sine qua non* for hypertransaminasemia. It was also realized that the different pattern of response of glutamic oxaloacetic transaminase (GOT) and of glutamic pyruvic transaminase (GPT) resulted from differences not only in liberation from the hepatocytes but also in the rate of elimination from serum.[40]

Concerning the cause of the increased serum alkaline phosphatase activity (AP) in hepatic disease, two main theories have been advanced: The "retention theory" argues that "extrahepatic" enzyme is retained in the circulation because of failure of the liver to excrete it.[5] The "regurgitation theory" postulates the increased serum alkaline phosphatase activity to be due to the delivery of biliary material into the circulation by way of abnormal communications between the bile canaliculi and the sinusoids.[43] Both theories are contested.

In view of the many unresolved problems regarding the cause of hyperenzymemia in liver disorders, it was considered of interest to analyze serum changes in "liver enzymes" after major resections of the liver in man. A multitude of changes can be anticipated after this operation; "mechanical" damage to hepatocytes at the sites of the resection, general disturbances of metabolism of the liver followed by steatosis, glycogen depletion etc., regenerative phenomena, and decreased excretory capacity, all of which have been considered as causes of hyperenzymemia.

An attempt is made in the present study to discover factors that could determine the extent of the hyperenzymemia occurring postoperatively and to analyse these factors. A comparison is also made between changes in serum enzyme activity and changes in "liver function tests" (serum bilirubin concentration and bromsulphalein retention).

Material and Methods

The material consists of 12 patients who underwent hepatic resections for different indications. Determinations of serum enzyme activities were performed before operation and up to 4 weeks postoperatively. At the same time, liver function was followed by means of determinations of serum bilirubin concentrations and bromsulphalein retention tests.

The following methods were used:

GOT (glutamic oxaloacetic transaminase) and GPT (glutamic pyruvic transaminase) determinations according to Karmen *et al.*,[32] modified by Ordell,[42] OCT (ornithine carbamoyl transferase) according to Reichard,[46] alkaline phosphatase according to Buch and Buch,[12] bilirubin, according to Jendrassik and Grof,[31] BSP (Bromsulphalein) retention 45 minutes after

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an injection according to Gaebler.[27] During the 12 hours immediately before operation, all patients received at least 1,000 ml. of 10% glucose solution; and during the first 7–10 postoperative days, 40–60 Gm. albumin per day in the form of albumin solution or plasma, and a minimum of 200 Gm. glucose per day. Most operations were performed as formal lobectomies or segmentectomies (usually called typical or anatomical resection) but some were done as partial or subtotal lobectomies (usually called non-anatomical or atypical resections). The operations were performed under $O_2 + N_2O$ anesthesia, in some cases with added Fluothane. (For further details regarding operative technic, see Bengmark.[6])

Case Reports

Case 1. A 54-year-old woman who was previously operated upon for carcinoma of the large bowel had a typical left lobectomy (40% of the liver parenchyma) for solitary metastasis. There were no postoperative complications.

Case 2. A 20-year-old man who sustained blunt injury to the right hepatic lobe in a traffic accident had a typical right lobectomy (60% of the parenchyma) immediately after arrival at the hospital. There were no significant postoperative complications.

Case 3. A 71-year-old woman had severe cardiovascular symptoms from hepatic metastases of intestinal carcinoid. To reduce the hormone producing tumor mass, a typical right hepatic lobectomy (60%) was performed. The tumor masses had probably reduced the size of the remaining left lobe by at least 50 per cent. Pleuritis and gastric retention were complications one week postoperatively. The preoperative high HIAA level was normal postoperatively. However, progressive hypoalbuminemia could not be satisfactorily compensated and the patient died after 3 weeks.

Case 4. A 56-year-old woman with gastric carcinoma invading the left lobe of the liver had a total gastrectomy plus typical resection of the left lateral segment (20%). Other than pleuritis postoperatively, there were no complications.

Case 5. A 58-year-old man previously had extirpation of a leiomyosarcoma in the omentum and ligation of the hepatic artery for metastases in both lobes of the liver. Left lobectomy plus atypical resection of the remaining solitary metastasis in the right lobe (totally 50%) were performed. There were no postoperative complications. (This patient has previously been reported.[2])

Case 6. A 63-year-old woman had carcinoma of the gallbladder with invasion of right lobe of the liver demonstrated at previous laparotomy. Extended right lobectomy (80%) was performed. Other than wound infection, there were no postoperative complications.

Case 7. A 42-year-old woman had carcinoma of the gallbladder with invasion of the right liver lobe demonstrated at previous laparotomy. Extended right lobectomy (80%) was performed with common duct drainage. There was a progressive increase of serum bilirubin and alkaline phosphatase until the 14th postoperative day. Jaundice was to some extent considered due to partial biliary stasis caused by an infrahepatic biliary abscess. Serum bilirubin decreased after drainage on the 14th postoperative day.

Case 8. A 50-year-old woman had previously been operated upon for carcinoma of the sigmoid colon. Typical right lobectomy for solitary metastasis (60%) was performed with common duct drainage. Other than pleuritis there were no postoperative complications.

Case 9. A 55-year-old woman who had previously been operated upon for carcinoma of the sigmoid colon had a left lobectomy for metastasis (40% resection) and common duct drainage. There were no postoperative complications.

Case 10. A 67-year-old woman had carcinoma of the gallbladder with metastases in the left hepatic lobe and deeply in the right lobe. Left lobectomy plus atypical resection of the right lobe (appr. 50% resection) were performed and the common duct was drained. There were no postoperative complications.

Case 11. A 30-year-old woman who had previously been operated upon for retroperitoneal paraganglioma had atypical right lobectomy for solitary mestatasis (60%). Immediately postoperatively, intra-abdominal bleeding necessitated relaparotomy. Otherwise there were no postoperative complications.

Case 12. A 67-year-old woman had extended right lobectomy for primary hepatic cancer (80%). There were no postoperative complications.

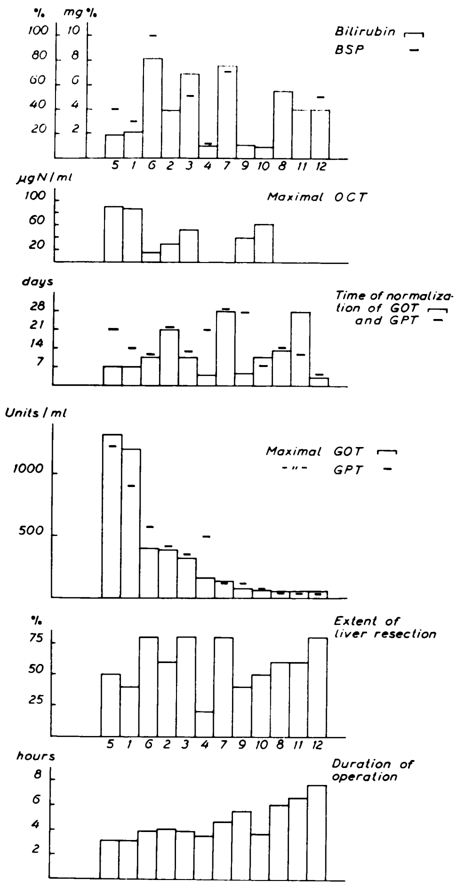
Results

Table 1 records the pattern of serum enzymes, bilirubin, and BSP changes in each patient. A surprisingly wide range of varia-

TABLE 1

Patient No.		Normal Values	Preop. Values	1 d.	2 d.	3 d.	4 d.	5 d.	6 d.	7 d.	10 d.	14 d.	21 d.	28 d.
1.	Bil.	<0.4 mg./100 ml.	0.4	1.7	2.2	2.6	3.1			2.5		0.7		0.3
	GOT	<25 u/ml.	40	900	1200	900	175			60		32		38
	GPT	<40 u/ml.	37	806	27	800	445			91		45		28
	OCT	<0.25 μg. N/ml.		51	88	91	41			2				4
	A. P.	<9 u/ml.	44	27	22	15	15			14		18		28
2.	Bil.	<0.4 mg./100 ml.		3.8	2.7		1.8			1.4	0.9	0.8	0.5	0.3
	GOT	<25 u/ml.		390	250		145			47	60	43	37	41
	GPT	<40 u/ml.		416	246			130		58	56	54	54	
	OCT	<0.25 μg. N/ml.		38	30	23	11			8	6	7	7	5
	A. P.	<9 u/ml.		7	5		8			7	9	9	11	12
3.	Bil.	<0.4 mg./100 ml.	0.2	0.7	4.3	5.2	4.1	4.4			2.7	1.0		
	GOT	<25 u/ml.	22	320	139	95	50	45			27	27		
	GPT	<40 u/ml.	11	350	300	205	155	88				35		
	OCT	<0.25 μg. N/ml.	18	48	48	23	15	6				1.0		
	A. P.	<9 u/ml.	14	10	10	10	10	12			14	8		
4.	Bil.	<0.4 mg./100 ml.	0.2		0.6	0.7	0.7	0.6	0.4		0.9	1.2	0.7	
	GOT	<25 u/ml.	30		160	56	25	23	34		29	42	40	30
	GPT	<40 u/ml.	63		500	260	130	95	88		37	43	36	37
	A. P.	<9 u/ml.	12		15	12	13	20	16		18	15		11
5.	Bil.	<0.4 mg./100 ml.	1.0	1.5	1.8		4.0			3.8	3.0			
	GOT	<25 u/ml.	200	1320	850		415			41	104			
	GPT	<40 u/ml.	108	225	1225					165				
	OCT	<0.25 μg. N/ml.		82	91		30			8	11			
	A. P.	<9 u/ml.	8	8	8		9			9	12			
6.	Bil.	<0.4 mg./100 ml.	0.5	7.2	8.7	10.1	7.9	9.2	9.1	8.4	12.2	6.1	3.3	
	GOT	<25 u/ml.	27	400	218	113	93	140	60	50	40	56	81	
	GPT	<40 u/ml.	30	570	380	220	140	200	100	79	42	67	85	
	OCT	<0.25 μg. N/ml.	19		10	15	0.5	7	5	4	4	6	9	
	A. P.	<9 u/ml.	7	9	8	8		7	8	8	9	10	16	
7.	Bil.	<0.4 mg./100 ml.	0.3	7.4	11.6			20.2	12.8	10.5		7.2	27.0	14.5
	GOT	<25 u/ml.	30	142	90			64	70	55	63		54	61
	GPT	<40 u/ml.	20	137	88				40	33	30		35	22
	A. P.	<9 u/ml.	5	6	5			7	9	12	18		10	8
8.	Bil.	<0.4 mg./100 ml.	0.5	0.3	5.5	5.1				8.0		5.4		
	GOT	<25 u/ml.	22		60	54				68		45		
	GPT	<40 u/ml.	23	20	14					42		30		
	A. P.	<9 u/ml.	12	13	9	7				7	16	41		
9.	Bil.	<0.4 mg./100 ml.	0.4	1.4	1.0	1.0		2.0		1.3	1.0	0.6	0.4	0.4
	GOT	<25 u/ml.	20	78	61	30		27		35	30	39	47	40
	GPT	<40 u/ml.	19	120	115	60		34		63	60	60	60	32
	OCT	<0.25 μg. N/ml.		26	40	18		10		2	3		1	1
	A. P.	<9 u/ml.	7	7	6	4		8		9	7	4	8	7
10.	Bil.	<0.4 mg./100 ml.	0.3		0.6	0.8		5.3		3.8	2.2	1.4	0.4	0.4
	GOT	<25 u/ml.	42		65	40		30		30	24	44	90	34
	GPT	<40 u/ml.	20		55	65		40		25	20	30		25
	OCT	<0.25 μg. N/ml.	6	63										
	A. P.	<9 u/ml.	24		12	11		13		11	14	25	19	11
11.	Bil.	<0.4 mg./100 ml.	0.5		4.2					8.4	3.0	1.0		
	GOT	<25 u/ml.	51		62					90	45	40		
	GPT	<40 u/ml.	47		47					34	17	31		
	A. P.	<9 u/ml.	51		8					9	17	18		
12.	Bil.	<0.4 mg./100 ml.	0.4	4.1	1.2	1.7	1.6		1.1		0.6			
	GOT	<25 u/ml.	26	85	47	24	12		12		10			
	GPT	<40 u/ml.	32	55	45	20	12		19		13			
	A. P.	<9 u/ml.	13	8	6	5	7		5		9			

tions in maximum GOT and GPT activity followed resections of the liver. There were pronounced elevations in some cases; in others, serum activity remains normal or almost normal. Marked elevations which occur are observed on the first or second



right or left-sided resection	L+R	L	R	R	R	L	R	L	L+R	R	R	R
atypical / typical	t+at	t	t	t	t	t	t	t	t+at	t	at	t
complications	-	-	(+)	-	+	(+)	+	-	-	(+)	+	-
remaining hepatic metastases	-	-		-	+	-	-	-	-	-	+	-
pints of blood - 24 hours per- and postop	10	8	8	16	6	5	6	6	5	4	32	12
age of patient	58	54	63	[illegible]	71	56	42	55	[illegible]	[illegible]	30	[illegible]
Fluothane anesthesia	+	-	+	+	-	+	-	+	-	+	-	+
T-tube drainage	-	-	-	-	-	-	+	+	+	+	-	+
Case number	5	1	6	2	3	4	7	9	10	8	11	12

FIG. 1. Comparison between the maximum Bil., BSP, OCT, GOT, and GPT and the time for normalization of GOT and GPT, after extensive liver resections. The patients are ordered according to the extent of the maximum GOT activity. To enable conclusions to be drawn regarding the influence of the extent of liver resection, duration of operation, remaining metastases, number of blood transfusions, and the use of anesthesia and of the T-tube, these are also documented.

postoperative day. In some cases, the GOT and in others the GPT displayed the most pronounced elevation. The time necessary for return to normal varies greatly and bears no relation to the extent of hypertransaminasemia. When hypertransaminasemia is more pronounced the GPT returns to normal somewhat later than the GOT, but this pattern is not apparent in instances of less pronounced transaminasemia. As Figure 1 shows, the extent of the hypertransaminasemia appears to bear no relation to the extent or the type of resection, whether the procedure is typical or atypical, or on the right side or left side. Nor does it seem to be correlated with age of the patients or to the presence or absence of metastases in the hepatic remnant. Patients in whom Flurotane was used do not have more hypertransaminasemia than those in whom Flurotane is not used. The number of pints of blood administered during operation or during the first 24 hours postoperatively does not seem to be related to the degree of serum transaminase elevation. An inverse relation seems to exist, however, between the duration of the operation and the degree of hypertransaminasemia. Similarly, the use of common duct drainage perhaps influences the degree of hypertransaminasemia. Thus, common duct drainage was not used in any of the six patients with maximum elevation of GOT and/or GPT above 300 units/ml., whereas it was used in five out of six patients with no elevation or an elevation below 300 units/ml.

Changes in the serum enzymes seem to be independent of simultaneous changes in liver function measured by serum bilirubin and BSP determinations. The return to normal of transaminase activity is not related to the degree of hypertransaminasemia, nor to any of the above-mentioned factors. On the other hand, impairment of the liver function, as measured in bilirubin and BSP determinations, seems to be roughly proportional to the extent of the resection. This is more apparent in Figure 2. The other factors mentioned above do not seem related to the degree of functional impairment.

Although the two most pronounced postoperative elevations of OCT activity are

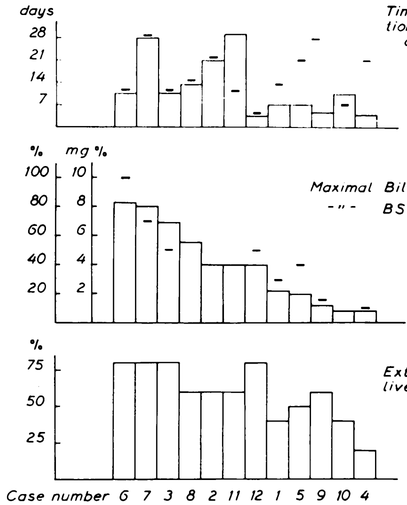


FIG. 2. Comparison between the maximum postoperative Bil. and the extent of liver resection. For comparison, the maximum BSP and the time of normalization of GOT and GPT are illustrated.

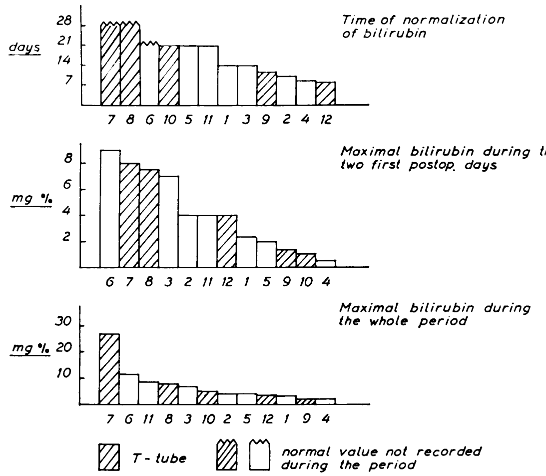


FIG. 3. Effect of T-tube drainage on the extent and duration of the postoperative hyperbilirubinemia.

seen in the two patients who display the most marked serum transaminase elevations, the pattern is not so uniform in the other patients. The time of return to normal is generally shorter and more uniform for OCT than for the transaminase.

Alkaline phosphatase activity is only slightly affected by operation. Pronounced changes are seen only in three patients with markedly elevated values preoperatively. A prompt decrease of the activity occurs in these patients. Those with preoperative normal or slightly elevated values display very small increases or decreases.

As mentioned the use of common duct drainage seems to have reduced the degree of hypertransaminasemia. Concerning the liver "function tests," bilirubin and BSP, no such effect of T-tube drainage is apparent (Fig. 3).

Discussion

The consistent finding of marked hypertransaminasemia after partial hepatectomy in experimental animals [8, 18, 19, 23, 24, 53] is not invariable in the present human material. The reason for this dissimilarity is obscure. Differences in the operative procedure *per se* do not seem to be responsible, since differences in the extent of the resection in the present observations do not influence the degree of postoperative hypertransaminasemia, which agrees with earlier experiments.[19]

A peculiar finding in man is the inverse relationship between maximum transaminase levels and duration of operation. Since the same team performed all the operations, the duration of each operation is a rough measure of the difficulties encountered. It therefore seemed important to find out whether the amount of blood administered at operation and during the first postoperative hours could be a determinant in the degree of hypetransaminasemia. Analysis of the number of blood transfusions does not support the hypothesis that lowered postoperative transaminase levels could be due to dilution of the recipient's blood.

The other "positive" observation, the use of T-tube drainage in patients with no or only slightly transaminase elevations, could be more than coincidental. Several writers [3, 54, 56, 57] recommend common duct drainage after hepatic resection with the object of diminishing the pressure within the biliary tree, thereby reducing leakage of bile from the cut surface. We do not know whether there is increased pressure within the bile ducts postoperatively, but if so, this increased pressure could be a factor in hypertransaminasemia. Experimental studies[11, 37] demonstrate that a rapid rise in serum transaminase activity occurs after sudden increase in intraductal pressure. T-tube drainage could prevent such a rise and avoid the transaminase elevation.

The lack of beneficial effect of common duct drainage on serum bilirubin elevation (Fig. 3) does not detract from the value of the T-tube, since the extent of resection seems to be the important factor in serum bilirubin elevation. This view is based on correlations observed and on earlier studies demonstrating decreased excretion of bilirubin after partial hepatectomy,[58] although excretion of bile per unit tissue of liver remnant is increased.[34]

In Case 11, no postoperative hypertransaminasemia was observed, despite no T-tube drainage, but the large amount of blood administered in connection with the operation could have had a dilution effect and explains the lack of hypertransaminasemia. Despite no proof of beneficial effect by the common duct drainage on liver "function tests," we none the less recommend this step until further experience has been obtained. Discrepancies between postoperative hypertransaminasemia in experimental animals and the irregular pattern in man and differences in extent of hypertransaminasemia between patients, are unexplained because of imperfect understanding of the cause of hypertransaminasemia. Liberation of the enzyme from damaged liver cells at the site of the resection seems improbable for several reasons: absence of hyperenzymemia in some patients despite similar resections in patients with hyperenzymemia; discrepancies between levels of elevation of transaminases, GOT and GPT, and the almost purely hepatic enzyme OCT[46] in individual patients; lack of significant increase of alkaline phosphatase despite its known presence in cells in the liver.[47] One explanation could be liberation of enzymes from cells in other parts of the liver. Opposed to this is the experimental finding of largely unchanged GOT activity per mg. wet liver despite pronounced elevation of serum activity.[8] This finding indicates increased synthesis which can be either a response to increased loss of enzyme from the liver cells or a primary phenomenon. The assumption of increased synthesis is supported by the finding of increased GOT activity per mg. of protein in mitochondrial as well as supernatant fraction.[8] Similarly, Hauss *et al.*[29] calculate that in some disorders enzyme activity in serum is greater than the total enzyme activity of the whole non-diseased organ. Finally, it should be stressed that as we cannot determine enzyme in weight units we cannot state whether there is an increased amount of enzyme or whether increased activity is a result of activation of the enzyme.

The lack of correlation between the time of return to normal of transaminases and the extent of resection indicates that the human liver is of little or no importance for elimination of serum transaminases. This is consistent with earlier experimental observations that intravenously administered GOT disappears as rapidly in partially hepatectomized animals as in animals with intact liver.[3, 4, 23] Lack of correlation between the time of return to normal and bilirubin levels and BSP was not surprising because of the low transaminase activity in bile[7, 10, 21, 22, 25, 30, 36, 49, 52] which excludes the biliary tract as a way of eliminating serum transaminases. The long period before return to normal of serum transaminase activity in some patients who had slight elevations immediately postoperatively, indicates either a continued release of enzyme from the liver or a decreased turnover of enzymes in the extravascular space.[3, 4]

In experimental animals, partial hepatectomy almost always causes increased serum AP activity.[39, 41, 48] Lack of significant postoperative increase in the serum AP in man stresses that animal experiments on serum AP in hepatic disorders are not directly applicable to man. Evidence has been presented that serum AP is eliminated via the bile in dogs.[16, 17, 35] Although no similar experiments have been performed in man, there is indirect evidence that this is true also in man.[1] If this view is correct, the "reserve capacity" seems to be much greater for AP than for bilirubin since no significant postoperative hyperphosphatasemia was observed despite marked hyperbilirubinemia. Some animal experiments indicate that elimination or reduction of the excretory apparatus is not responsible for hyperphosphatasemia in biliary obstruction; although ligation of one hepatic duct causes hyperphosphatasemia [20, 28] excision of a liver segment drained by one hepatic duct does not.[26] There are also clinical observations indicating that large parts of the human liver can be destroyed without impressive succeeding hyperphosphatasemia.[15] The unimportance of the liver for elimination of serum AP in man is also suggested by recent studies showing that at least human placental AP is eliminated in much the same way as injected plasma proteins.[45] Although these findings seem peculiar when considering the almost regular hyperphosphatasemia after partial hepatectomy in animal experiments, they would explain the lack of postoperative hyperphosphatasemia in the present studies.

If obstruction at some point of elimination is not the cause of hyperphosphatasemia in hepato-biliary disorders, what *is* the cause? The hepatic origin of the enzyme in *biliary obstruction* has been made perfectly clear by the studies of Sebesta *et al.*[50] These authors perfused isolated liver preparations and observed a significant rise in the AP activity in the perfusate after biliary obstruction. The concept of a hepatic origin of the enzyme in *liver cancer* is supported by the observed decrease of serum activity after removal of the tumor in those patients with preoperatively elevated levels. The origin of enzyme within the liver is not known. Sherlock and Walshe [51] and Kritzler and Beaubieu [33] described an increased AP activity in the vicinity of regenerating liver cells in "active" cirrhosis indicating a release of enzyme from the regenerating or necrotic liver cells. These observations have not been verified by other authors.[14, 55] Another theory is that proliferating bile duct cells are the source of the AP activity. These cells display very high AP activity.[59] Popper *et al.*[44] believe that proliferating bile ductules represent a response by the liver to injury. According to Burke [13] increased serum AP activity is an expression of regeneration of liver cells. The results of the present studies do not support this view, since no hyperphosphatasemia occurred despite marked regeneration proved at second look operations and angiographic investigations.[9]

Summary

Determinations of serum GOT, GPT, OCT, and alkaline phosphatase activity, as well as serum bilirubin concentration and bromsulphalein retention, were made before and up to 4 weeks after extensive liver resection in 12 patients. The immediate postoperative hypertransaminasemia seemed to bear no relation to the extent of the resection, but to be inversely correlated to the duration of operation. It was far less pronounced when common duct drainage was used postoperatively. Serum alkaline phosphatase activity was only slightly affected by operation, a marked alteration being observed only where there were preoperatively pronounced elevations. Serum bilirubin concentration and bromsulphalein retention appeared to depend on the extent of the resection.

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