PLASMA PROTHROMBIN: EFFECT OF PARTIAL HEPATECTOMY*

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In previous publications, Smith, Warner, and Brinkhous (1, 2) have noted a profound fall in plasma prothrombin in dogs having chloroform or phosphorus intoxication. The fall corresponds fairly closely to the degree of liver injury, and the prothrombin returns to normal as the liver regenerates. This evidence indicates that the liver plays an essential rôle in the manufacture of prothrombin. Further support for this conclusion is obtained by experiments presented at this time, showing that partial hepatectomy in rats also causes lowering of the plasma prothrombin level. The degree of lowering is somewhat variable from rat to rat, but in many instances the prothrombin falls to very low levels during the first 24 hours after operation. The prothrombin level returns to normal in the period required for restoration of the liver to normal weight.

Methods

Albino rats were used in all cases. Throughout the experiment they were kept on a diet of dog chow.[1] Rats in three different age groups were used. The youngest rats ranged in weight from 90 to 100 gm., the next group from 150 to 200 gm., and the oldest from 250 to 400 gm. The results obtained in the three different groups were essentially the same. Under ether anesthesia the liver was exposed and the large median lobe and the left lateral lobe were removed by the technique of Higgins and Anderson (3). It is estimated that about 60 per cent of the liver was excised in these animals. In addition, the right lateral lobe was

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[1] Purina Mills, St. Louis.

partially removed in a few cases, leaving intact only the Spigelian lobe and the stumps of the other lobes. In these cases only about 25 per cent of the liver was left behind. Prothrombin analyses were made by the method developed in this laboratory (1, 2). Blood for the analyses was drawn from the jugular vein into a 1 cc. syringe containing isotonic potassium oxalate. To avoid making the rats anemic, the individual animals were bled infrequently, but at intervals designed to cover the entire recovery period. Fibrinogen determinations were made according to the technique of Jones and Smith (4) on a number of the rats postoperatively.

EXPERIMENTAL RESULTS

The postoperative prothrombin values obtained in 39 rats are shown in Table I. The prothrombin values are tabulated in per cent of normal. In the first 9 rats shown in this table, approximately 75 per cent of the liver was removed; in the other experiments only 60 per cent. In both groups the prothrombin commonly falls to 30 to 40 per cent of normal within the first 24 hours. However, with the more drastic operation the level sometimes falls to less than 30 per cent, and in the milder operation many of the animals maintained levels of 70 per cent or more. On removal of 75 per cent of the liver, a number of animals died within 24 hours after operation. Autopsy in this group occasionally showed massive hemorrhage into the peritoneal cavity or into the tissues adjacent to the incision. Evidently, removal of this amount of liver at times permits the plasma prothrombin to fall to critical levels. No evidence of excessive hemorrhage was encountered in the animals in which only 60 per cent of the liver was removed.

The fall in prothrombin appears to reach its maximum within 24 hours. Blood samples following removal of liver tissue drawn within the first hour showed little or no fall. At the end of 6 hours the fall is often maximal. No doubt the formation of fibrinous exudate at the site of operation increases the consumption of prothrombin beyond normal limits, thus accelerating the decline. The normal intact liver is able to meet such demands, for in several control experiments simple laparotomy was performed and after some trauma to the peritoneal surfaces the incision was sutured in the usual way. The amount of exudate formed was almost as much as in the ablation experiments, yet the prothrombin showed no fall whatever. In several control experiments pieces of fresh rat liver were placed in the

TABLE I

Plasma Prothrombin Following Partial Hepatectomy

Rat No.	Prothrombin (per cent of normal) at intervals following hepatectomy							
	20–60 min.	6–7 hrs.	1 day	2–3 days	4–6 days	8–13 days	14–17 days	18–32 days
			75 per cent of liver removed					
1			17					
2			27					
3			36					
4			37	65		96		
5			39					
6			46			84	83	
7			63		55	77		123
8			63		74	85		100
9			65		62	95		81
			60 per cent of liver removed					
10		30						
11		34	32	36				
12		37	33	42	73			89
13		38	33	30	67			93
14			35					102
15			36					
16	65		37					
17				46			85	97
18					58			98
19				50		84	97	
20			41		65			
21	104		42		83	94		
22	100		46		72	83		
23			51					
24			56		113		100	
25			60					
26			63		84		102	
27	66							
28			66					
29			66					97
30			71		67			100
31			75					96
32			80					
33			84		73			105
34			85					
35			88					
36					88			
37						88		
38							100	
39			100					

peritoneal cavity to serve as a control for the autolyzed bits of liver tissue left at the stumps of resected lobes in the hepatectomized animals. These animals likewise showed no fall in plasma prothrombin at any time.

The return of prothrombin toward normal levels is manifest within 3 to 6 days, but as a rule is not complete until 10 days to 3 weeks have elapsed. Exudate formation subsides long before the prothrombin reaches normal values. The subnormal values are thus to be correlated with defective production of prothrombin, not with excessive utilization. It cannot be denied that trauma to the residual liver may decrease its functional capacity for a period of several days. We believe, however, that the actual loss of liver substance is mainly responsible for the deficient production of prothrombin. Our experiments are in accord with the work of Higgins and Anderson (3) which showed that 10 days to 3 weeks must elapse before the liver has returned completely to normal size. This period corresponds with the period of subnormal prothrombin production.

These liver ablation experiments support our work on chloroform intoxication (1, 2). In both cases an observable defect in liver tissue is associated with a marked fall in plasma prothrombin. It is conceivable that chloroform may injure other organs, though all investigators agree that the liver lesions are the only conspicuous lesions. The ablation experiments offer no injury to other organs. It is thus necessary to conclude that the liver is vitally concerned in the manufacture of prothrombin.

The fibrinogen values obtained on a number of rats postoperatively were all normal or above normal This indicates that the reduction in liver function, although sufficient to result in a decrease in prothrombin, was not sufficient to reduce the fibrinogen. Evidently the reserve capacity for prothrombin manufacture is less than in the case of fibrinogen. This is in accord with experiments from this laboratory (2) which show that mild chloroform injury in dogs produces a fall in plasma prothrombin, but not in plasma fibrinogen.

SUMMARY

Extirpation of a large portion of the liver in rats results in a marked decrease in the plasma prothrombin. The plasma prothrombin level

gradually returns to normal during the period required for restoration of the liver to its normal weight. The decrease in prothrombin incident to partial hepatectomy supports the thesis that the liver is concerned in the manufacture of plasma prothrombin.

BIBLIOGRAPHY

1. Warner, E. D., Brinkhous, K. M., and Smith, H. P., *Am. J. Physiol.*, 1936, **114**, 667.
2. Smith, H. P., Warner, E. D., and Brinkhous, K. M., *J. Exp. Med.*, 1937, **66**, 801.
3. Higgins, G. M., and Anderson, R. M., *Arch. Path.*, 1931, **12**, 186.
4. Jones, T. B., and Smith, H. P., *Am. J. Physiol.*, 1930, **94**, 144.