BLOOD PLASMA PROTEINS IN RATS FOLLOWING PARTIAL HEPATECTOMY AND LAPAROTOMY*

BY ALFRED CHANUTIN, J. C. HORTENSTINE, W. S. COLE, AND STEPHAN LUDEWIG

(From the Laboratory of Physiological Chemistry, University of Virginia, University)

(Received for publication, January 3, 1938)

The present communication is a study of the changes in albumin, globulin, fibrin, total protein, and albumin to globulin ratios in the plasma of rats following partial hepatectomy. Similar observations were made after laparotomy and in normal animals for comparison. Partial hepatectomy seemed particularly appropriate to the study of the rôle of the liver in the fabrication of plasma proteins for several reasons. In the first place, 70 per cent of the liver substance can be removed safely (1, 2). In the second place, regenerative changes following this operation have been studied in detail. For example, it has been shown that during the first 24 hours there is no mitotic activity and the water content of the liver stump is markedly decreased, probably from the increased deposition of fat. Evidences of regeneration are most marked on the 3rd day. The water content, number of cells, size of the cells, the chemical composition, and weight change rapidly then and the liver appears to be normal about the 14th day. In the third place, previous methods which made use of total hepatectomy (3), hepatotoxic chemicals (4), Eck fistula animals (5), and patients with liver disease (6) did not lend themselves to quantitative comparisons because of the lack of any uniformity in the pathological physiology.

Inbred male albino rats, 60 days of age, of Wistar stock, raised in this laboratory were used. Partial hepatectomy, under ether anesthesia, was carried out according to the procedure of Higgins and Anderson (1); 60 to 75 per cent of the total liver tissue was

* This investigation was made possible by the Edward N. Gibbs Prize Fund of the New York Academy of Medicine.
removed. Other animals were subjected to laparotomy alone, at which time the liver was handled and the intestines exposed for a period similar to that occupied by partial hepatectomy. The animals were fed a stock diet and were allowed food and water up to the time they were sacrificed. Intact animals served as controls. Blood was drawn from the abdominal aorta and was prevented from clotting by use of uniform concentrations of potassium oxalate. Globulin was precipitated with 22.2 per cent sodium sulfate and filtered through a Whatman No. 50 filter paper after incubation overnight. Fibrin was prepared for analysis from 1.0 cc. of plasma according to Cullen and Van Slyke's method (7). Protein nitrogen was determined by the micro-Kjeldahl procedure. Non-protein nitrogen was determined according to the procedure of Daly (8). Albumin and globulin were determined in each individual animal. Animals with gross signs of wound infection were not studied.

Results

The results obtained on each rat subjected to laparotomy and partial hepatectomy are presented graphically in Figs. 1 to 5. The maximum and minimum variations in the "control" values for total nitrogen, albumin, globulin, and fibrin in the plasma of the intact rats are represented by two lines in each figure.

The values for fibrin in the laparotomized and partially hepa-
tectomized rats are represented in Fig. 1. Since the concentration of fibrin is comparatively small, the scale has been magnified in Fig. 1. It can be seen that laparotomy exerts a profound influence, as is evidenced by the fibrin concentrations on the 1st day. These values decrease slowly and only two fall within the control range during the first 9 days, while the majority remain elevated until the 18th day. After hepatectomy there is a marked variation in the fibrin concentrations on the 1st day, but it is striking that removal of liver tissue has not been followed by the marked rise seen after laparotomy. The highest concentrations after partial hepatectomy were obtained during the 4th to 10th day. Thereafter there was a gradual general decrease in fibrin concentra-
tion, but the control range was not consistently reached by the 30th day after hepatectomy. The results seem to confirm previous evidence that the liver is of primary importance in the manufacture of fibrinogen.
The average of the albumin concentration is definitely decreased during the first 12 days after laparotomy (Fig. 2). By the 18th day all were within the control range. In the partially hepatectomized rats, the albumin concentrations decreased on the 1st day. On the 2nd and 3rd days, not a single value was within the control range. The albumin concentrations tended to remain low until the 18th day, when most of the values fell within the control range.

There appeared to be only a slight effect on the plasma globulin concentrations in the laparotomized animals during the first 6 days after operation (Fig. 3). After this time the globulin values tended to remain elevated until the end of the experiment on the 30th day. After partial hepatectomy the globulin is lowered on
the 1st day and is followed by an immediate rise to the control level on the 3rd day. After this there is an increase in the mean values, although the majority are within the control limits. The total nitrogen concentrations remained within the control range in the laparotomized rat with a few exceptions (Fig. 4). The effect of partial hepatectomy was manifested by results well below the control level during the first 5 days. Values fluctuated until the 16th day, after which practically all values were normal.
Fig. 3. Individual and mean values for globulin nitrogen following partial hepatectomy and laparotomy.

The albumin to globulin ratios of the laparotomized rats tended to remain low because of the proportionately greater increase in the globulin fraction. The ratios of the partially hepatectomized
rats remained normal during the 1st day, which demonstrates an equal effect on albumin and globulin. After this time the more rapid regeneration of globulin in the respective animals manifested itself in the large number of low ratios. Most of the values were within the control range after the 18th day (Fig. 5).

Fig. 4. Individual and mean values for total protein nitrogen following partial hepatectomy and laparotomy.
The effects of laparotomy and partial hepatectomy on the albumin, globulin, and fibrin of the plasma are compared in Fig. 6, in which average values are plotted. The distribution around the average of the "normal" values of the control intact rats was not essentially changed between the 60th and 90th days of life.

It will be seen that there is an obvious effect on the plasma proteins following the control laparotomy operation. There is an immediate and prolonged decrease of the plasma albumin which is difficult to explain unless one assumes that tissue damage reduces...
the stimulus to albumin formation. There is an immediate and very sustained rise in the plasma globulin which indicates that the operative procedure of laparotomy alone stimulates globulin production at once and for a long period. There is an immediate but less sustained elevation of the plasma fibrin which appears attributable also to the tissue injury per se.

At first glance, it seems that the more marked alterations in the plasma proteins which occur after the partial heptectomy might be ascribed to the greater operative procedure and the greater postoperative disturbance. The effect on the plasma albumin is of the same kind as that following laparotomy alone and only the degree is accentuated. This further decrease in the plasma albumin cannot with certainty be attributed to the reduced liver substance rather than to the larger operation, but it would be difficult to devise any operative procedure which would serve as an adequate control to determine this point. On the other hand, the plasma globulin and fibrin do not increase over the laparotomy levels in the first few days after operation when the tissue injury
is at its greatest and the liver function at its least. The most probable explanation for this fact appears to be that the deficient liver cannot meet the stimulus for increased production of globulin and fibrin. If this is true, one must conclude that the liver is intimately associated with the fabrication of these substances.

The abnormal distribution of plasma albumin and globulin associated with pathological livers is assumed by most investigators to be the direct effect of hepatic insufficiency. This may possibly account for the decreased albumin but not for the increased globulin. In conditions in which the liver is not directly involved, such as malnutrition, renal diseases, and plasmapheresis, similar plasma protein changes are noted. At present there is no evidence for associating the liver directly with the plasma albumin- and globulin-regenerating mechanism.

SUMMARY

The concentration of blood plasma fibrin, albumin, and globulin was determined at frequent intervals in rats subjected to partial hepatectomy and to laparotomy alone.

A decrease in all these fractions was noted on the 1st day after partial hepatectomy. Fibrin and globulin concentrations increased on the 2nd and 3rd days and tended to remain above the normal values for the 30 day period of observation. The albumin concentration remained depressed until the 4th week after operation.

Laparotomy was followed immediately by increases in the concentration of fibrin and globulin and a decrease in the albumin. The globulin fraction remained high during the entire period of observation, and albumin and fibrin approached normal about the 18th day.

The most important effect of tissue injury and reduction of liver tissue is in the prolonged reduction of the plasma albumin which is accompanied by increased globulin concentrations.

These experiments do not necessarily support the thesis that the liver is directly involved in the fabrication of plasma proteins.

BIBLIOGRAPHY
