# BIOCHEMICAL STUDIES ON SHOCK

## III. The Rôle of the Liver and the Hepatic Circulation in the Metabolic Changes during Hemorrhagic Shock in the Rat and the Cat*

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It has already been shown (1, 2) that certain of the changes in the metabolism of carbohydrate and protein and their degradation products during hemorrhagic shock are determined in part by alterations in hepatic function and in part by the effects of circulatory failure on peripheral tissue metabolism. In these reports it was suggested that the liver becomes less able to absorb and deaminate amino acids because of hepatic anoxia resulting from a failing oxygen supply to that organ. The experiments to be reported here are designed to show, first that there is a decreased oxygen supply to the liver during shock and that this decrease can be correlated with certain other changes occurring during shock, and secondly that diminishing the blood supply to the liver by surgical means will influence the ability of that organ to dispose of amino acids. The comparative rôles of the arterial and venous circulation to the liver for the maintenance of its function normally and during shock are also considered and quantitative data are presented concerning the liver's ability to withstand total anoxia.

### *Methods*

Whole blood and plasma amino nitrogen levels were determined by the method of Frame, Russell, and Wilhelmi (3); blood oxygen by the micro method of Roughton and Scholander (4), and expressed as per cent saturation; and hemoglobin with the Evelyn colorimeter. The blood oxygen is expressed as per cent saturation rather than content since the percentage saturation is an index of the $O_2$ tension in the tissues. Blood pressure in the rat was estimated by direct cannulation of the carotid artery, heparin in saline being used as anticoagulant. For the cat, 5 per cent sodium sulfate solution was used to prevent coagulation during blood pressure measurement from the carotid artery.

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All experiments were carried out under sodium pentobarbital anesthesia (4 mg. per 100 gm. for rats and 25 to 40 mg. per kilo for cats administered intraperitoneally). In those experiments in which the hepatic circulation was altered surgically no further anesthesia was given after the initial dose.

The hepatic arterial circulation was occluded by ligating the celiac axis and all the branches of it which could be found. While this resulted in impairment of circulation to certain other organs such as the stomach and spleen, made apparent in a few cases by slight hemorrhage into the stomach, there was never any evidence of shock in these experiments and, with a very few exceptions, all animals survived. Although it is possible that some arterial circulation *via* collaterals to the liver persisted it was felt to be unlikely that they could contribute a significant amount of blood to the liver in a brief experiment.

Evisceration was performed by the method described in the previous report (2).

Since it is not possible to occlude the portal vein, leaving the hepatic arterial circulation intact, without producing marked venous engorgement of the gastrointestinal tract with eventual shock, an operation was devised for the rat whereby the arterial circulation to the liver could be preserved while that by the portal vein was eliminated.

In this operation the branches of the celiac axis and of the hepatic artery are tied off separately and the entire gastrointestinal tract removed with spleen and pancreas, leaving the hepatic artery patent as the only blood supply to the liver. The first step is to ligate the splenic pedicle and remove the spleen. Ligatures are then tied about the rectum, inferior and superior mesenteric arteries in that order. The rectum and superior and inferior mesenteric arteries are then divided between ligatures and the large intestine, ileum, and jejunum gently freed. At the point in the third part of the duodenum beyond which arterial circulation has been occluded a ligature is tied. This point is apparent from its anemic appearance as compared to the remaining duodenum and stomach. After the remaining mesentery has been ligated the intestine is divided at the above point and removed, leaving the stomach, pancreas, and part of the duodenum still to be removed. The stomach is pulled down and the arteries and veins supplying the lower esophagus and the cardia of the stomach are doubly ligated and divided. A hemostat is placed on the esophagus which is then divided distally. The remaining mesentery to the stomach and duodenum is then ligated step by step close to these viscera and the stomach and duodenum are removed. The hemostat on the esophagus is released and its lumen is reopened. Any bleeding in the mesenteric stump is controlled by careful use of hemostats and by pressure. In the final steps of the operation great care must be used not to include the hepatic artery in the ligatures. The portal vein and its branches should be tied off last to avoid back-flow of blood into the stomach and duodenum. Since, in contrast to the other evisceration operation, slight to moderate blood loss is unavoidable, it has been found advisable to administer a small blood transfusion (1 to 3 cc. depending on the amount of blood lost) immediately postoperatively to avoid the development of shock. The criterion for the success of the operation, *i.e.*, hepatic artery patent and the absence of postoperative shock, is the fact that the nembutal anesthesia wears off and the animals exhibit normal activity. The animals which failed to come out of the anesthesia or in

which more than a few tenths of a cubic centimeter of blood was found in the peritoneal cavity postoperatively were discarded. With practice the procedure can be carried out in from 10 to 20 minutes. In the studies on total hepatic anoxia the rats were prepared as above and a clamp was then applied to the celiac axis (hepatic artery) for the desired period, thereby completely occluding the blood supply to the liver.

## RESULTS

### *The Oxygen Supply to the Liver during Shock*

Since the major blood supply to the liver is by the portal vein which has been estimated to account for as much as 80 per cent of the oxygen brought to the liver under normal circumstances (5), a study was made of the oxygen saturation of portal venous blood during hemorrhage and shock in eleven rats. This was correlated with the arterial blood pressure, which can be considered as a rough measure of the arterial circulation to the liver, and with the blood amino nitrogen concentration. The latter has already been shown to be a reliable index of the degree of circulatory depression in the rat and is an indication of the rate at which the liver deals with circulating amino acids. The arterial oxygen saturation shows little change during shock except terminally (6) so it was not generally followed in the experiments on rats, although it was determined in those on cats.

In these experiments the rats were bled until the blood pressure had fallen to a desired level which varied in different animals. Fig. 1 is a graphic representation of the relationship between the blood amino nitrogen levels and the portal venous oxygen saturation during hemorrhage in eleven rats. A high degree of negative correlation between the two is evident, the amino acids being high when the portal oxygen is low. Similarly, a high negative correlation is found between the arterial blood pressure and the blood amino acid concentrations, with a correlation coefficient of $-0.660$ in 44 determinations. Fig. 7 of an earlier paper (1) demonstrates this relationship in another series of rats. The fall in portal oxygen saturation closely parallels the fall in blood pressure, as Fig. 2 demonstrates. These data suggest a close relationship between the oxygen supply to the liver, as measured by the portal venous $O_2$ saturation and the falling blood pressure, and the failing ability of that organ to assimilate amino acids.

Since measurement of the portal venous oxygen saturation is not a convenient method of following the course of shock, simultaneous studies were made of the peripheral venous (tail vein) $O_2$ saturations, the portal venous $O_2$ saturation, the blood pressure, and blood amino acids in six rats. In another eight rats tail and portal venous $O_2$ saturations alone were followed during hemorrhage. Fig. 3 summarizes the data on the peripheral and portal venous $O_2$ saturations.

Although the correlation coefficient is high (r = +0.792, n = 35), it is interesting that the correlation between the blood amino nitrogen and the tail vein oxygen is lower (r = −0.617, n = 48) than that between blood amino nitrogen and portal vein $O_2$ saturation (r = − 0.714). Likewise the correlation between the tail vein $O_2$ saturation and the blood pressure (r = +0.505,

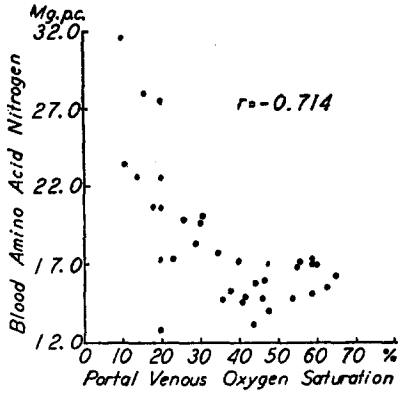


FIG. 1. The blood amino nitrogen and portal venous oxygen saturation during hemorrhage and shock in eleven rats. In this and subsequent figures "r" represents the correlation coefficient.

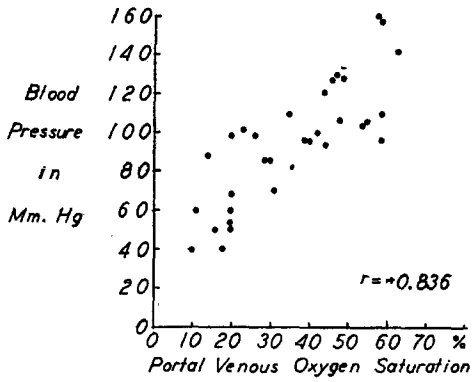


FIG. 2. The arterial blood pressure and portal venous oxygen saturation during hemorrhage and shock in rats.

n = 29) is lower than that between the portal $O_2$ saturation and the B. P. For practical purposes, however, the peripheral venous oxygen saturation gives a very good indication of the state of the circulation during hemorrhages as has already been suggested by several investigators (7).

Fig. 4 illustrates the above relationships in two rats, in both of which it is seen that the $O_2$ saturation of the venous blood was a better measure of the status of the animal than was the blood pressure, when both were compared to the blood

amino nitrogen. The latter we have already shown to be a very reliable prognostic index in the rat (1). In the first case (*a*) the blood pressure fell quite

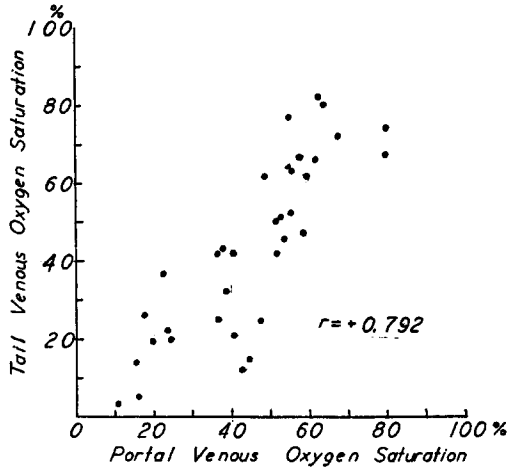


FIG. 3. The tail venous and portal venous oxygen saturations during hemorrhage and shock in rats.

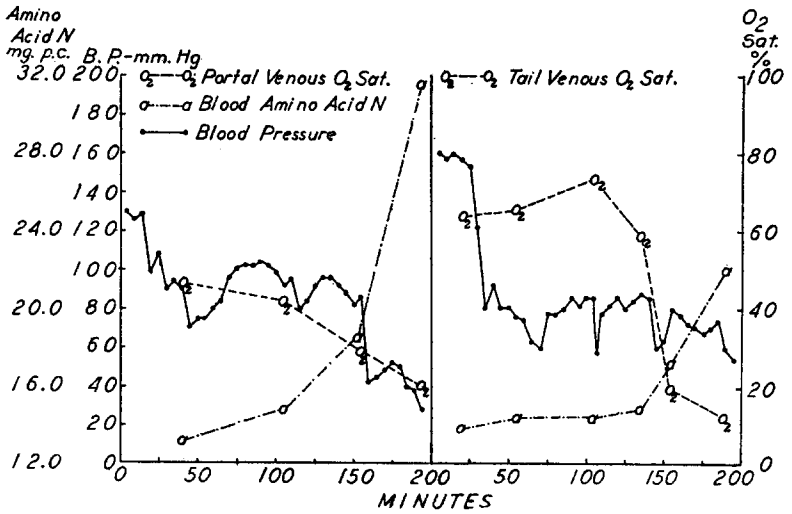


FIG. 4. The blood amino nitrogen, blood pressure, and portal and tail venous oxygen saturations in two rats subjected to fatal hemorrhagic shock.

rapidly to a level of 70 mm. of Hg, but then climbed back to 90 to 100 mm. of Hg, where it remained for an hour and a quarter before falling again to low levels. Nevertheless, the portal $O_2$ saturation was falling progressively and the amino nitrogen began to rise early, an ominous prognostic sign In contrast is

the second rat in which the blood pressure fell to and remained at low levels while the peripheral venous $O_2$ saturation was maintained at a normal level for several hours and concomitantly the blood amino nitrogen showed no change. With further bleeding, however, the $O_2$ saturation finally fell and with this there was a sharp rise in the blood amino nitrogen and death. Most rats showed a closer correspondence between the blood pressure and venous oxygen than these two. In a few, however, the amino nitrogen seemed to follow the blood pressure closer than the venous oxygen saturation. In control experiments in which there was no bleeding, none of the blood constituents studied here showed any significant changes in periods comparable to the above experiments.

While the data on portal venous $O_2$ saturation and arterial blood pressure are strongly suggestive of a causal relationship between hepatic anoxia and a failure to dispose of amino acids, without measurement of the hepatic venous $O_2$ content the degree of hepatic anoxia could not be established with certainty. It has been shown by others (6) and confirmed by us in the rat that the arterial oxygen saturation shows little change during shock except terminally. Indeed in some cases it is still normal even at death. It is thus conceivable that an increased oxygen supply might reach the liver *via* the hepatic artery during shock to compensate for the decreased venous supply. Since it is technically very difficult to obtain hepatic venous blood from the rat, cats were used in these experiments. Further, in experiments to be described below, the effects of occlusion of the hepatic artery in the normal and shocked rat were studied in order to establish the dominant rôle of the portal vein in maintaining a normal oxygen supply to the liver.

Five cats anesthetized with nembutal were bled from the carotid artery at intervals and in such amounts as were necessary to maintain the blood pressure between 60 and 80 mm. Hg for 2 to 3 hours. When the pressure fell below 60 mm. Hg and showed no evidence of a spontaneous rise blood was transfused into the femoral vein until amounts almost equal to that originally withdrawn had been replaced. In spite of this all the animals died. Samples were withdrawn at intervals from the carotid artery, femoral vein, portal vein, and hepatic vein for measurement of the oxygen saturation while the plasma amino acid level was also determined on the arterial blood. Fig. 5 shows the results of a typical experiment. Here it is seen that the arterial $O_2$ was maintained at normal levels as long as it was followed, while the venous $O_2$ saturations fell early reaching very low levels. In this particular case the hepatic venous $O_2$ saturation had fallen to 22 per cent in an hour, when the B. P. had reached 80 mm. Unfortunately no further hepatic vein samples were taken from this cat. However, a similar early fall occurred in other cats and was progressive: in two cats it reached 0 and 3 per cent at 30 and 20 minutes respectively before death (Table I). This striking degree of oxygen unsaturation indicates a very low level of oxygen available to the hepatic tissue. In most cases, the femoral vein $O_2$ fell more rapidly than the portal vein $O_2$ suggesting that peripheral vasocon-

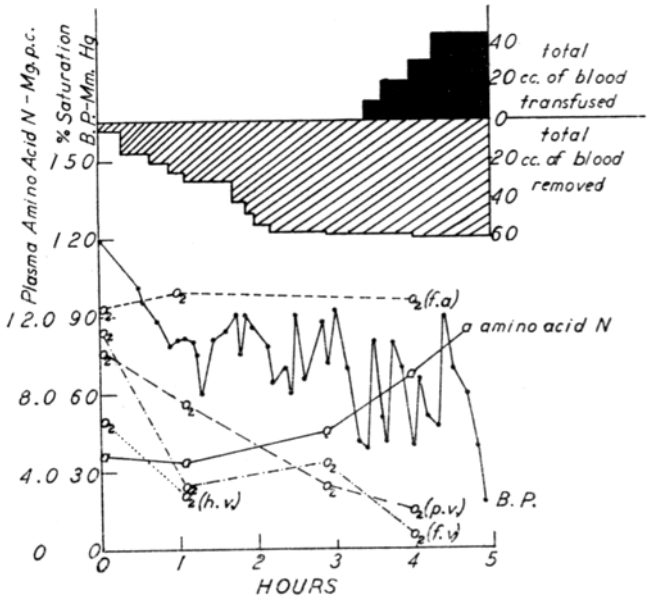


FIG. 5. The effect of hemorrhage and shock on the plasma amino nitrogen, blood pressure, and oxygen saturation in the femoral artery (f.a.), the femoral vein (f.v.), the portal vein (p.v.), and the hepatic vein (h.v.) in a 2.3 kilo cat.

TABLE I

| Blood pressure | Oxygen as per cent saturation | | | | Plasma amino acid N |
|---|---|---|---|---|---|
| | Femoral artery | Femoral vein | Portal vein | Hepatic vein | |
| *mm. Hg* | | | | | *mg. per cent* |
| 190* | 99 | 80 | 56 | 59 | 5.8 |
| 130* | 82 | 75 | 68 | 45 | 4.2 |
| 144* | 87 | 69 | 76 | 74 | 5.6 |
| 115* | 92 | 89 | 77 | 50 | 4.8 |
| 114* | 84 | 70 | 66 | 77 | 4.9 |
| 104 | 100 | 19 | 18 | 21 | 7.6 |
| 84 | 98 | 43 | 12 | 0 | 4.8 |
| 80 | 99 | 22 | 56 | 22 | 4.3 |
| 70 | — | 34 | 26 | — | 6.0 |
| 70 | 95 | 28 | 40 | 30 | 6.0 |
| 60 | — | 3 | — | — | 11.8 |
| 50 | 95 | 7 | — | — | 8.9 |
| 50 | — | — | 14 | — | 11.3 |
| 50 | 85 | 5 | 16 | 3 | 7.4 |
| 40 | 90 | 21 | 18 | 11 | 6.2 |
| 50 | — | — | — | — | 8.0 |
| 40 | — | — | — | — | 8.7 |
| 30 | — | — | — | — | 7.8 |

* Initial specimens.

striction was a significant factor. This is further borne out by one cat whose blood pressure was well maintained despite hemorrhage but whose venous oxygen saturation had fallen to 20 per cent 1 hour after bleeding was begun. The amino nitrogen rise in the plasma occurs somewhat later than in the rat and is not as striking in degree. Since the metabolic rate per unit weight in the cat is slower than in the rat it seems likely that the difference in degree between the amino nitrogen rise in the cat and rat may be due to a slower rate of peripheral protein breakdown by the former. This is borne out by the fact that following complete elimination of the liver from the circulation by evisceration the rise in blood amino acids in the cat is much more gradual than in the rat (8). Table I summarizes the data on the five cats.

### *The Effect of Restriction of Hepatic Blood Supply on the Blood Amino Nitrogen Levels*

It has now been shown that shock is associated with a marked decrease in oxygen supply to the liver and with this there is a rise in the blood amino nitrogen. In order to demonstrate that there is a causal relationship between the decrease in $O_2$ supply to the liver because of shock and the rise in amino nitrogen, experiments were devised to show whether decreasing the blood supply to the liver by surgical means would also cause a rise in the blood amino acids. For this purpose the behavior of the blood amino nitrogen was compared under circumstances in which the liver received blood only through the portal vein, or only through the hepatic artery, or in which the hepatic circulation was completely occluded for varying periods of time.

(*a*) *The Portal Vein as Sole Blood Supply: Hepatic Artery Ligation.*—

Although various investigators have disagreed as to whether the hepatic arterial supply to the liver is essential to its function, most are in agreement that the major blood supply to the liver is *via* the portal vein (9). Our data suggest that changes in the portal circulation are of major importance in influencing liver function during shock and that the hepatic artery plays only a minor rôle. In Fig. 6 are recorded the effects of hepatic artery ligation on the levels of the blood amino nitrogen in twelve normal rats which were examined up to 24 hours postoperatively. It will be noted that this procedure had no effect on the ability of the liver to handle amino acids. These rats survived indefinitely, with the exception of two that developed an intestinal obstruction postoperatively.

Although this procedure had no effect on the normal rat, it was thought possible that if a strain were put on the circulation by subjecting the animal to a hemorrhage which would have little or no effect on the blood amino nitrogen of the normal rat, the rats with ligated hepatic arteries would show a rise in blood amino nitrogen if the hepatic arterial blood were an essential factor in protecting

the liver. Fig. 6 shows that there is no significant difference between the blood amino nitrogen levels of six normal and seven hepatic artery ligated rats after a hemorrhage equivalent to 2 per cent of the body weight. These experiments were all performed immediately after ligation so that the likelihood of there being very active collateral arterial circulation to the liver is not great.

(*b*) *Hepatic Artery As Sole Blood Supply.*—

The liver whose sole blood supply is by the portal vein would thus seem to be quite competent to deaminate amino acids at a normal rate and to have as great a margin of safety as the normal liver in the rat. That being the case, it was of interest to determine whether the liver which receives blood only from the hepatic artery can maintain its function. For this purpose an operation was

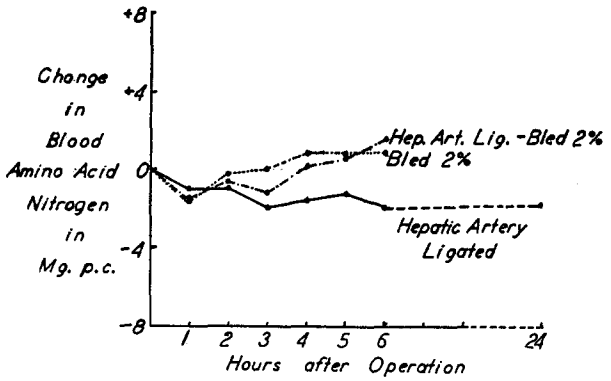


FIG. 6. The effect of hepatic artery ligation on the blood amino nitrogen of nine normal rats and of seven rats subjected to a hemorrhage equivalent to 2 per cent of the body weight as compared to six normal rats bled the same amount.

devised whereby the viscera were removed along with the portal vein, while the hepatic artery was left intact and patent. This operation has been described under the section on methods. It is, of course, realized at the outset that such an animal lacking viscera including pancreas is not normal and any results from it must be interpreted with caution. These animals recover from the operation and live as long as 36 hours, eventually succumbing to peritonitis and diabetes. The blood sugar usually reaches 200 or more mg. per cent after 24 hours. Nevertheless it is felt that observations on the blood amino nitrogen of these rats may be a valid indication of liver function during the first 7 hours postoperatively, provided care is taken to prevent postoperative shock by transfusion and provided only those animals are used which survive at least 15 to 20 hours. When the blood amino nitrogen levels of these rats are compared to hepatic artery ligated rats and totally eviscerated rats (functionally hepatectomized) (Fig. 7) it is seen that the hepatic artery alone can maintain hepatic

function for some hours, since the rise in amino nitrogen is slight, although definitely greater than the normal. Furthermore, in contrast to the eviscerate rat in which the amino nitrogen rises rapidly and the animal fails to come out of the nembutal anesthesia, rats in which the hepatic artery alone is patent regain consciousness postoperatively. But while this rat retains considerable ability to dispose of amino acids, its margin of safety is very small. Only a small amount of hemorrhage with resultant fall in blood pressure and flow causes a rapid rise in the blood amino nitrogen. This is to be compared to the situation in the hepatic artery ligated rats which could stand a 2 per cent hemorrhage

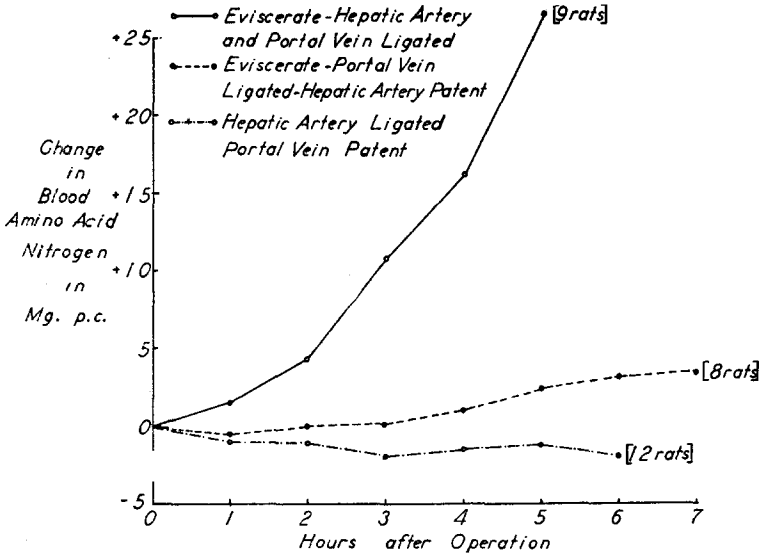


FIG. 7. The comparative effects on the blood amino nitrogen of the rat of complete exclusion of the hepatic circulation, of exclusion of the portal circulation, and of exclusion of the hepatic arterial circulation.

without causing a greater than normal rise in blood amino nitrogen. Decreasing the blood supply of the liver below that contributed by the hepatic artery normally results in a decreased ability by the liver to dispose of circulating amino acids.

(*c*) *Effect of Complete Occlusion of Hepatic Circulation for Various Periods.*—

The experimental results so far described indicate that amino acids accumulate in the blood if the blood flow to the liver is sufficiently reduced, as it may be during shock. But they do not demonstrate whether this phenomenon during shock is prehepatic, *i.e.*, that hepatic blood flow is so impaired that amino acids are supplied to the liver at a slower rate than normal even though they

may be produced abnormally rapidly in the periphery (2) or whether it is intrinsically hepatic, *i.e.*, the liver loses its ability to take up or deaminate amino acids because of anoxia. By use of the preparation in which the liver receives its blood supply only through the hepatic artery this question was subjected to analysis. Rats were prepared as described above, a small bulldog clamp was placed on the hepatic artery for 15, 30, 45, 60, 90, and 120 minutes and the blood amino nitrogen levels followed for 7 hours. In all cases the rats came out of the anesthesia after the clamp was removed, but the period for which anesthesia persisted depended on how long the hepatic circulation was

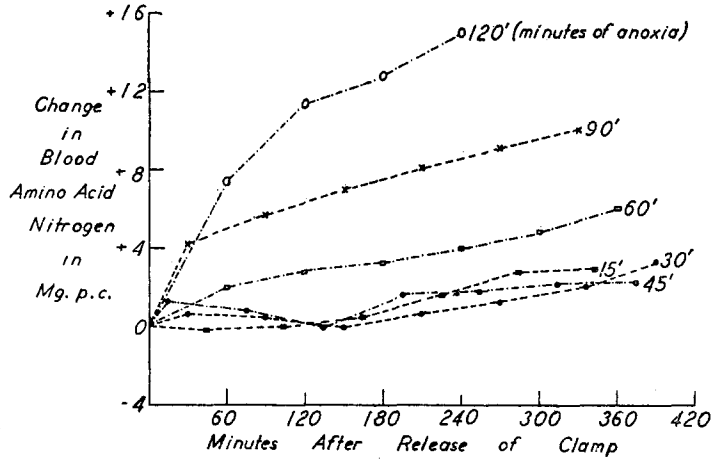


FIG. 8. The effect of complete occlusion of the hepatic circulation for 15 to 120 minutes on the blood amino nitrogen levels of the rat. Note that with less than 60 minutes of anoxia the liver subsequently is able to clear amino acids from the blood as well as the control, plotted in Fig. 7 (eviscerate–portal vein ligated-hepatic artery patent).

occluded. On clamping the artery the liver became deeply cyanotic and there was no evidence from its appearance that any circulation persisted. On releasing the clamp the normal color of the liver reappeared slowly and in an irregular manner. In those in which the circulation was obstructed for 30 minutes or more gross infarcts could be seen but the major bulk of the liver showed a normal color. Microscopically, small to large infarcts could be found in all the livers in which the hepatic artery was the sole remaining source of blood even when the artery was not occluded at all. All the rats reported here survived at least 12 hours and many, including those totally anoxic for 60 minutes or more, lived 24 or more hours postoperatively. The results (Fig. 8) show that the liver can be subjected to a considerable period of anoxia before its ability to handle amino acids is irreversibly damaged. When the liver circula-

tion is occluded for 30 minutes or more, amino acids increase in the blood during the 1st hour, but in the case of the 30 minute and 45 minute occlusion this is apparently an accumulation taking place while the liver is out of the circulation because on release of the clamp the blood amino nitrogen returns to the control level in the subsequent hours. With 1 hour of anoxia, however, a definite break occurs. The amino nitrogen of the blood rises progressively indicating intrinsic damage to the deaminating mechanism of the liver after this amount of anoxia in this particular preparation.

## DISCUSSION

The material presented in this series of papers would suggest that a combination of extrinsic and intrinsic factors determine hepatic function during peripheral circulatory failure. Other workers have published data indicating that the hepatic circulation fails in shock. Blalock and Levy (10) noted a 53 per cent decrease in portal blood flow in dogs after only a moderate hemorrhage. McMichael (5) during the course of his studies on the oxygen supply of the liver in the cat comments on the decrease in portal and hepatic venous oxygen contents in those animals which were failing. Wood *et al.* (11) reported a low portal vein oxygen content in dogs after hemorrhage. The decrease in oxygen supply to the liver of the rat and cat during shock is confirmed in the present report and its relation to hepatic function is made clear by the high degree of correlation between the fall in portal venous oxygen saturation and fall in blood pressure and the rise in the blood amino acids.

The low hepatic vein oxygen saturation in shock is indirect evidence that the hepatic circulation as a whole is reduced, and the data suggest that any compensatory rôle by the hepatic artery in maintaining the blood flow to the liver during shock is not adequate. In the literature (9) there is still considerable disagreement on how essential the hepatic artery and portal vein are respectively to the integrity of the liver. The fact that ligation of the hepatic artery of the rat does not influence the blood amino acids either in an otherwise normal rat or in one subjected to a small hemorrhage when compared to a normal or bled control indicates that, in this species at least, the hepatic artery is not essential to the hepatic function of the metabolism of amino acids. In contrast, on elimination of the portal vein, this ability of the liver is just barely maintained and any reduction in the arterial blood flow because of hemorrhage elsewhere results in a rapid rise in blood amino acids. It would thus appear probable that in shock the portal venous circulation is the main determining factor in the ability of the liver to clear amino acids from the blood and that the hepatic artery cannot play a very significant rôle in compensating for portal venous insufficiency due to shock.

Although it seems that the hepatic circulation in shock may be sufficiently depressed to account for a prehepatic accumulation of amino acids in the blood,

the experiments on the complete occlusion of the liver circulation show that if anoxia is sufficiently prolonged irreversible damage takes place. What functions other than those of handling amino acids are damaged and how soon are not yet known. That the liver is damaged during shock is suggested in many studies on the pathology of both clinical and experimental shock (12), but in general few studies of liver function have been made during the course of shock. Similarly under the conditions of the experiments reported in these papers there is evidence that the degree and duration of anoxia is sufficient to damage the liver. Russell, Long, and Wilhelmi, in the paper to follow (13), show that there is a significant depression in the oxygen consumption of liver slices from shocked rats. The decrease in oxygen consumption correlates well with the degree of shock as measured by the blood amino nitrogen levels. Further, as will be reported later (14) there is a profound change in the electrolyte pattern of the liver in severe shock due to hemorrhage. This is similar to that which has already been reported by Clarke and Cleghorn (15) after traumatic shock in the rat.

With respect to protein and amino acid metabolism the course of events during peripheral circulatory failure may be visualized as follows. By mechanisms varying in different types of shock the circulating blood volume is decreased and with this there is a diminution in blood flow. This results in a diminished supply of oxygen to the tissues, the first of which to be affected are probably the peripheral tissues, particularly the extremities, and the liver. An increased rate of peripheral protein breakdown ensues from the anoxia and the amino acids and other products resulting therefrom begin to accumulate in the blood since they either are not taken up or are not deaminated sufficiently rapidly by the liver. If the hepatic anoxia persists long enough actual damage to the liver probably occurs and this organ then begins to lose its ability to deal with even those amino acids that pass through it. One may speculate on a possible relation between this stage and the so called irreversible phase of shock but further study is necessary to clearly establish this relationship. As has already been indicated in the previous paper, the fall in blood sugar and the mounting blood lactate, pyruvate, and lactate/pyruvate ratio are manifestations of peripheral anoxia rather than an indication of hepatic insufficiency.

## SUMMARY

1. In a series of rats subjected to hemorrhage and shock a high negative correlation was found between the portal and peripheral venous oxygen saturations and the arterial blood pressure on the one hand, and the blood amino nitrogen levels on the other, and a high positive correlation between the portal and the peripheral oxygen saturations and between each of these and the blood pressure.

2. In five cats subjected to hemorrhage and shock the rise in plasma amino

nitrogen and the fall in peripheral and portal venous oxygen saturations were confirmed. Further it was shown that the hepatic vein oxygen saturation falls early in shock while the arterial oxygen saturation showed no alteration except terminally, when it may fall also.

3. Ligation of the hepatic artery in rats did not affect the liver's ability to deaminate amino acids. Hemorrhage in a series of hepatic artery ligated rats did not produce any greater rise in the blood amino nitrogen than a similar hemorrhage in normal rats. The hepatic artery probably cannot compensate to any degree for the decrease in portal blood flow in shock.

4. An operation was devised whereby the viscera and portal circulation of the rat were eliminated and the liver maintained only on its arterial circulation. The ability of such a liver to metabolize amino acids was found to be less than either the normal or the hepatic artery ligated liver and to have very little reserve.

5. On complete occlusion of the circulation to the rat liver this organ was found to resist anoxia up to 45 minutes. With further anoxia irreversible damage to this organ's ability to handle amino acids occurred.

6. It is concluded that the blood amino nitrogen rise during shock results from an increased breakdown of protein in the peripheral tissues, the products of which accumulate either because they do not circulate through the liver at a sufficiently rapid rate or because with continued anoxia intrinsic damage may occur to the hepatic parenchyma so that it cannot dispose of amino acids.

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