TRAUMATIC SHOCK. XIII. THE PREVENTION OF IRREVERSIBILITY IN HEMORRHAGIC SHOCK BY VIVIPERFUSION OF THE LIVER

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Prolonged traumatic shock, which fails to improve in response to adequate replacement of lost blood volume or to any other known therapeutic measure, is said to be "irreversible." In this circumstance, the damage is widespread. There is diffuse biochemical injury involving intracellular enzyme systems, presumably of all tissues (1 to 5); but no available data identify the relative damage among the vital organs or tissues apart from that of the peripheral circulation. Nor is it known whether the injury to any one vital organ or tissue is a controlling factor in the survival of the remainder. Experiments herewith reported were devised to observe the effect of maintaining circulation in one vital organ, the liver, as closely as possible to normal (by cross circulation with a healthy donor dog), while the remainder of the organism is maintained in shock for a period ordinarily long enough to produce a state of "irreversibility."

The liver is an obvious choice because of its dominance in metabolic exchange and because its major dependence on venous blood for sustenance (3, 6) makes it especially vulnerable to diminished blood flow.

METHOD

Cross-circulation was performed by the use of a donor dog whose carotid blood was delivered to the liver of the dog in shock via the splenic vein in one series, or to the general circulation of the dog in shock via the jugular or femoral vein in a control series. In the early experiments of the first series, the spleen was removed under local anesthesia through an abdominal incision with aseptic precautions and the splenic vein cannulated for immediate experimentation. Because this procedure imposed a greater burden upon the liver-perfused dog than upon the control dog, the splenic pedicle in subsequent experiments was implanted subcutaneously several days or weeks in advance, and when full recovery had occurred, the cross-circulation experiment was performed as follows:

A large healthy donor dog was given 2 mgm. of morphine intramuscularly. One carotid artery, one femoral artery, and both femoral veins were cannulated through incisions under local 1 per cent procaine anesthesia without aseptic precautions. A similar dog to be shocked was likewise prepared, except that the vessels cannulated were one carotid artery, both femoral arteries, a femoral vein, and the splenic vein for liver perfusion or the jugular vein for perfusion of the general circulation. One femoral artery, not in the perfusion circuit, was used for measuring arterial pressure, and one femoral vein was used for measuring venous pressure and for transfusion (see below). Sulfanilamide was placed in all wounds after careful attention to hemostasis. Each dog received 30,000 units of penicillin and 50 mgm of the sodium salt of heparin.

A circuit was constructed with clean, but not sterile, tubing and cannulae as follows (Figure 1). The carotid artery of the donor was connected to the splenic or jugular vein (control) of the recipient; one carotid and one femoral artery of the recipient were jointly connected to one femoral vein of the donor. The largest possible cannulae were used in the recipient to donor circuit in order to facilitate adequate return flow at low arterial pressure. Glass flowmeters, constructed on Bernouille's principle, were interpolated in the inflow and outflow circuits. The "high pressure" flowmeter in the donor to recipient circuit consisted in a pair of open-end mercury manometers fused into a glass tube 8 mm. in diameter, one manometer proximal and one distal to a constriction of the tube at its center. The constriction was 5 mm. long and had an internal diameter of about 1 to 1.5 mm. This internal diameter was arrived at by trial and error until the desired flow could be obtained through it at the pressure range of the normal dog's arterial blood pressure. The "low-pressure" flowmeter, interpolated in the circuit from the dog in shock to the donor, was constructed in the same manner, but was larger in all dimensions in order to accommodate the same

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1 The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

2 In a number of instances, when the splenic vein was found not to have remained patent, the dog was used for jugular vein perfusion and thus constituted a splenectomized control preparation.
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FIG. 1. DIAGRAMMATIC REPRESENTATION OF THE VASCULAR CIRCUIT IN LIVER PERFUSION

Both the high and low pressure flowmeters are shown. The low pressure flowmeter, which contains only blood, is represented above the high pressure flowmeter, which has mercury-filled manometers.

volume flow at a pressure of 30 mm. Hg. Accordingly, the internal diameter of the chamber on either side of the constriction was about 23 mm. and of the constriction about 3 mm. The pressure on either side of the constriction was measured by the height of the column of blood in vertical, open-end glass tubes which acted as manometers just proximal and just distal to the constriction. The receiving end of this chamber carried two inlet tubes for the carotid and femoral arteries of the recipient. Both flowmeters were calibrated by the passage of dog blood at varying rates of flow, and graphs were constructed relating the pressure difference before and beyond the constriction in each flowmeter with the flow rate throughout the desired range of flow; e.g., at a flow rate of 400 ml. per minute, the difference in pressure between the manometers of the "high pressure" flowmeter was 50 mm. Hg; at the same flow rate, the pressure difference in the manometers of the "low-pressure" flowmeter was 60 mm. of blood. Since the pressure differences and flow rates varied continuously through the phases of systole and diastole, the flowmeters were not used to give an accurate measure of the total blood flow in either direction during any long period. However, the pressure difference in the "high pressure" flowmeter was a useful guide for adjusting the rate of flow from the donor dog by means of a screw clamp, and the "low pressure" flowmeter was useful in following the average rate of flow throughout the cross-circulation period.

The blood of donor and recipient were cross-matched in each instance before cross-circulation was started. Blood taken from a third healthy dog for transfusion of the donor dog, if required, and for filling the tubing of the circuits (up to 150 ml.) was cross-matched with that of donor and recipient. The cells of each dog were suspended in plasma from each of the other two, and the hanging drop observed microscopically after one-half hour at 37° C.

Heparin was placed in the tubing, and further injections of 10 to 20 mgm. of heparin were given intravenously in experiments lasting over 4 hours.

The experiment was started by causing the dog to be shocked to bleed freely from one femoral artery into a bottle suspended so that the bleeding ceased when the arterial pressure fell to 30 mm. Hg. A few minutes were allowed for equilibration at this pressure. The bottle containing this blood was disconnected and the femoral artery connected to the recipient to donor circuit. The volume of blood shed was recorded and stored in a refrigerator. Clamps on the circuits were then released and cross-circulation started.
In an early series of experiments, designated “Old Series” in Table II, flowmeters were not used. The donor bled into the recipient via rubber tubing at an undetermined rate controlled by a screw-clamp. The recipient responded to the infusion of blood by further bleeding into the suspended bottle. The recipient’s blood pressure was kept at 30 mm. Hg by syphoning off the blood which accumulated above the level established at the original bleeding. The syphoned-off blood, which accumulated at a rate varying from 200 to 500 ml. per minute, was returned as rapidly as possible to the donor. Since the return of blood to the donor was delayed while intervening glass vessels were filled, the donor blood volume was maintained by added blood taken from a third dog.

Since it has been shown (6) that the volume flow through the liver of the dog is 20 to 40 ml. per kgm. our dogs, averaging 20 kgm., would require 400 to 800 ml. per minute. Most of this flow in the normal dog is venous. The flow rate we used varied from 250 to 500 ml. per minute. This was, however, arterial blood. Moreover, there is additional flow through the recipient dog’s own hepatic artery and portal vein. If the recipient’s blood pressure began to rise above 30 mm. Hg., adjustment of the screw clamp on the donor to recipient circuit slowed the flow so as to return the level to 30 mm. Hg.

Cross-circulation was continued until the recipient showed evidence of the development of “irreversible” hemorrhagic shock. In a previous communication (7), we stated that no dependable biochemical or physiologic basis for identifying the onset of “irreversibility,” except the test of transfusion itself, had been brought forward. From extensive experience with hemorrhagic shock we find that most dogs unanesthetized but given one 2 mgm. dose of morphine, develop “irreversibility” after 2 hours at a blood pressure of 30 mm. Hg; but, an occasional dog will be “irreversible” well before 2 hours or will not be “irreversible” until 6 hours or more. Size, breed, age, nutrition, general physical condition, and environmental temperature alter resistance. Hence, the duration of the hypotensive period alone will not serve as a criterion of the onset of “irreversibility.” We observed, however, that “irreversibility” to transfusion can be predicted with some confidence under the following circumstances:

If a major artery of the unanesthetized dog bleeds into an elevated blood reservoir containing heparin (Lamson technique (8)) and is continuously connected so that the blood pressure reaches and remains at 30 mm. Hg, the blood level in the reservoir remains constant for a varying period until blood begins to return from the reservoir to the artery. When the volume returned (“taken-up”) equals or exceeds one-third of the amount bled, the rapid return of the remainder of the shed blood will fail to exert a sustained therapeutic effect in over 90 per cent of all such dogs (Table I); i.e., “irreversible” shock will have developed. Further transfusions of blood thereafter are of no avail (7). In most dogs, this process of “taking-up” begins after some 1 1/2 to 3 hours (maximum range 1/2 to 7 hours) at a hypotension of 30 mm. Hg. Many dogs will be “irreversible” before one-third of the shed volume is “taken-up,” and an occasional one before any blood is “taken-up.” It is generally true that “taking-up” is progressive once begun; i.e., progressive loss of compensation by the peripheral vascular mechanism is present so that a continuously increasing blood volume is required to maintain the blood pressure at 30 mm. Hg.

In the cross-circulation preparations, “taking-up” (at the expense of the donor) cannot be directly measured, because the flowmeters are not designed to indicate a cumulative discrepancy amounting to a few hundred ml. of blood developing after a period of hours. Donor flow in excess of return flow from the recipient was recognized by a decline in donor blood pressure. Although the donor dog compensates for a partial loss to the recipient before the donor’s blood pressure falls, “taking-up,” for the purpose of these experiments, was considered not to have started until the fall in blood pressure was noted. The donor’s condition was sustained, and his blood pressure kept above 100 mm. Hg by transfusion of blood from a third dog as needed. The volume of blood required to restore the donor’s starting pressure was used as a rough index of the volume of “taking-up” by the recipient. When this volume reached one-third to one-half of the volume originally bled from the recipient, the shock period was terminated. This method, though inexact, underestimates “taking-up” and constitutes, therefore, a more rigid test of the benefit of liver-perfusion. The reliability of the method as a means of producing “irreversibility” is attested to by the almost uniformly fatal issue in the control series (Tables II and III).

To determine whether the recorded blood pressure of the recipient during the perfusion period is the true peripheral blood pressure, the inflow and outflow tubes of the recipient dog were momentarily occluded simultaneously now and then and the blood pressure observed. The blood pressure in these circumstances never rose more than 5 mm. Hg, if the manometer was connected to an artery which was not in the circuit; but if the manometer was connected by a T-tube to the artery that was used for returning blood to the donor animal, falsely low values were recorded. For this reason, the manometer was always attached to a separate femoral artery.

<table>
<thead>
<tr>
<th>Shock duration</th>
<th>Number of dogs</th>
<th>Number of dogs “irreversible”</th>
<th>Per cent “irreversible”</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 2</td>
<td>12</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>2 to 3</td>
<td>24</td>
<td>22</td>
<td>92</td>
</tr>
<tr>
<td>3 to 4</td>
<td>15</td>
<td>14</td>
<td>93</td>
</tr>
<tr>
<td>4 to 7</td>
<td>13</td>
<td>12</td>
<td>93</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>60</td>
<td>94.5</td>
</tr>
</tbody>
</table>
Peripheral venous pressure measurements were made in 2 jugular perfusion experiments (P 11, P 13) and in 1 liver perfusion experiment (P 12). Normal pressures were 5.4 cm., 6.0 cm. and 4.5 cm. of water respectively. During the cross-circulation period the venous pressures were 4.5 cm., 2.5-3.5 cm. and 2.0 cm. of water respectively. Following transfusion, the venous pressure in dogs P 12 and P 13 was 5.0 cm. of water. Hence, systemic venous pressure did not rise above normal in any phase of the experiments.

At the end of the shock period cross-circulation was terminated by clamping the tubing, returning blood in the tubing to the donor, and rapidly transfusing the recipient with his own originally shed blood. Both dogs received in addition 50 to 150 ml. of physiologic saline intravenously. All vessels were then ligated, the wounds checked for hemostasis (0.1 per cent protamine solution was sprayed into wounds for undue oozing), coated with sulfanilamide, and closed. Closure was delayed in the few experiments where total amino acid determinations were made and in the recipient until after the blood pressure had been followed for at least 1 hour. After removal from the table, water was offered and evidence of bloody diarrhea watched for.

Blood lactic acid was determined by the method of Barker and Summerson (9), blood pyruvic acid by the method of Bueding and Wortis (10), blood amino acid by the colorimetric method of Frame, Russell, and Wilhelmi (11) and blood non-protein nitrogen by the method of Koch and McMeekin (12). Arterial blood was used.

**RESULTS**

The results shown in Tables II and III are divided into 2 groups. Table II lists the experiments which were performed before flowmeters were used ("Old Series"); Table III lists the experiments with flowmeters. In 5 of the experiments of Table III, the splenic pedicle was prepared for extraperitoneal cannulation several days before the cross-circulation experiments were performed. The results of control experiments, in which cross-circulation was done via the jugular vein instead of the splenic vein, are listed in each table.

Table II shows that all 5 liver-perfused dogs survived, whereas the 6 control animals did not survive longer than a few hours to 16 hours following transfusion. The average duration of shock preceding the onset of "irreversibility" was 1.8 hours for the liver-perfusion series and 2.1 hours for the control series.

Table III shows that 6 of 7 liver-perfused dogs survived following transfusion, but 9 of 11 control dogs died following transfusion.
tion of shock in the control dogs preceding the onset of "irreversibility" was 2.4 hours, and in the liver-perfused dogs 3.8 hours. Dogs whose splenic pedicles were prepared well in advance of the experiment resisted the onset of "irreversibility" longer; i.e., for an average of 4.6 hours or nearly twice that of the control dogs. Indeed, 2 of these dogs, 1 of which (P 51) had not "taken-up" after 7½ hours, showed evidence of cerebral anoxia (hyperventilation, convulsive twitching, tonic and clonic muscle spasms, nystagmus, and loud moaning). If a larger inflow of blood from the donor was temporarily allowed, the cerebral symptoms immediately vanished. In the experiment in which "taking-up" had not occurred after 7½ hours of shock, cerebral anoxia was taken as a criterion of the onset of "irreversibility" and an indication for termination of cross-circulation. (In 1 dog, not included in the series, whose course was similar, respiration ceased, and though he was resuscitated and trans fused, he continued to exhibit signs of decortication and died during the night.)

Dog P 51 showed blood levels of non-protein nitrogen of 63 mgm. per cent and of total amino acid of 98 mgm. per cent 24 hours after the experiment; 48 hours after the experiment, these levels were 48 mgm. per cent and 104 mgm. per cent, respectively. This would indicate that kidney function was not seriously impaired by a 7½-hour period of shock, but that an abnormal amino acid metabolism persisted. It has been shown (13) that the dog kidney probably is resistant to anoxia to a greater degree than the human kidney.

Dog P 36 showed signs of cerebral anoxia, as well as taking-up on termination of the cross-circulation period (4½ hours). Just before termination, arterial blood from both donor and recipient showed the same total amino nitrogen (78 mgm. per cent), a urea nitrogen of 37 mgm. per cent in the donor, and 45 mgm. per cent in the recipient.

The total amino nitrogen of both donor and recipient in the experiment on Dog P 34 was normal throughout the perfusion period. Blood lactic acid in the donor dropped from 31 to 16 mgm. per cent, but rose in the recipient from 9 to 61 mgm. per cent on termination of the shock period. This lactic acid level and those of 2 other liver-perfused recipients (P 30 and P 32) were not as high as is commonly seen (14) in hemorrhagic shock with a hypotension of 30 mm. Hg for 4½ hours. The pyruvic acid levels in these dogs paralleled the lactic acid levels without increase in the L/P ratio.

Among the jugular-perfused dogs, Dog P 27 showed a greater rise in lactic acid (from 64 mgm. per cent to 152 mgm. per cent) than occurred in the liver perfusion experiments at the end of the perfusion period. The L/P ratio rose from 22 to 39. Three hours after transfusion, the lactic acid level was back to 70 mgm. per cent and the L/P ratio was 19. These changes are very similar to those previously noted (14) in "irreversible" hemorrhagic shock. The donor lactic acid level rose from 36 to 92 mgm. per cent during the perfusion period. Three other control recipients showed lesser elevations in blood lactic acid, but these were greater than those in liver-perfused dogs.

That accumulating metabolites are cleared from the blood stream of the liver-perfused dog more efficiently than in the jugular-perfused dog is suggested from the fact that the concentration of these metabolites in the liver-perfused dog never reached the levels noted previously in "irreversibly-shocked" dogs. The number of control and liver-perfused recipients in which this comparison is made is limited, however. Since clearance of metabolites from the blood was apparently improved to a greater extent in the liver-perfused recipients, the benefit provided by the donor is not due to cross-circulation per se, but is a direct or indirect result of preserved liver function. Thus, it is possible that the increased production of metabolites in shock may be due to anoxia of the liver and that the better oxygenation of the perfused liver may decrease the production of these metabolites.

All donor animals in the series reported in Tables II and III survived following termination of cross-circulation. A few unlisted experiments had to be discarded either because the donor or recipient was in poor condition to start with or was made sick by some procedure. For example, depressor reactions due to protamine given intravenously to neutralize heparin or to foreign proteins in insufficiently cleansed tubing destroyed the validity of some experiments.

The control dogs which did not die on the table within a few hours after transfusion usually showed marked depression and weakness when
placed on the floor. They did not drink. Many showed melena which continued until death. The survival of the control dogs after transfusion ranged from 2 to 3 hours to a maximum of 18 hours. This survival period is the same as that of unperfused dogs subjected to these conditions of hemorrhagic shock. The liver-perfused dogs looked more alert, drank water and walked about. Some of these also showed melena, but this did not continue as in the case of many of the control animals.

Post mortem examination in liver-perfused dogs that died as a result of uncontrolled hemorrhage as, e.g., from a torn splenic pedicle, from protamine reaction, or as in one case, from strangulation by a tethering rope, showed very little hemorrhage in the small bowel and duodenum; whereas the control dogs, like unperfused dogs in hemorrhagic shock, showed marked hemorrhage following transfusion. When liver-perfused dogs, sacrificed soon after transfusion, were examined immediately post mortem, the livers lacked the friability and marked congestion noted in the livers of control animals that died soon after transfusion. In early experiments not reported, in which the abdomen was opened during cross-circulation, no evidence of portal congestion was seen, nor was the liver abnormal in size or appearance.

DISCUSSION

The protective effect of liver perfusion during hemorrhagic shock is due directly to the improved blood flow through the liver. The blood flow through the heart and lungs of both types of recipients is increased by the cross-circulation. This increases the work of the heart, probably without proportionate increase in coronary flow, because aortic pressure is not allowed to rise. It is doubtful that volume flow through tissues other than the heart and lungs is improved. Any benefit arising from increased blood flow through tissues other than the liver is also provided to the recipient vivi-perfused via the jugular vein.

The increased duration of shock prior to “taking-up” in the closed circuit liver perfusion experiments (Table III), as compared to the controls, indicates that benefit apart from that of survival itself is provided by perfusion of the liver. However, the cerebral damage that appears in the later phase of the prolonged cross-circulation periods suggests that protection against damage from deficient peripheral flow by vivi-perfusion of the liver is not unlimited.

So far as the evidence from these experiments goes, there is no toxemic factor involved in hemorrhagic shock, for if toxin is elaborated and injures the dog in shock, it should injure the donor as well. If the donor is not injured because it can neutralize such a toxin, the recipient should also benefit, whatever the route of vivi-perfusion. Since only the liver-perfused dog benefits, the inference is that the benefit from vivi-perfusion is not due to neutralization of toxin, and that the jugular-perfused dog succumbs to a loss of sustained liver function.

Furthermore, although other tissues suffer an equal deficiency in blood-flow in both types of recipient, the significance of the damage which occurs in tissues other than the liver is of secondary importance to that suffered by the liver itself. The central nervous system appears to be the first system to give way so long as the liver is adequately protected. We have not observed evidence of failure of function of the kidney and recent studies (13) would not lead one to expect irretrievable damage to the dog’s kidney under the conditions of these experiments. The only other tissue which on gross inspection was recognized to be damaged in the liver-perfused dog is the intestine, which showed slight transitory hemorrhage from which the animals recovered. It has been suggested (15) that myocardial failure accounts for “irreversibility” in some instances of hemorrhagic shock. We have not observed gross evidence of heart failure after transfusion in liver-perfused dogs. Hence, though serious injury to vital organs other than liver can occur as a direct consequence of deficient peripheral flow, even while liver function is being preserved, such injury seems not to be of crucial importance, nor the cause or the consequence of the onset of “irreversibility” as here defined. Complete recovery of the animal shows that no widespread “irreversible” intracellular damage, even to the central nervous system, occurs in the time period of these experiments so long as the liver is sustained.

Death after total hepatectomy resembles death in “irreversible” hemorrhagic shock in respect to the time period of survival and in several of the biochemical changes (16). Hepatectomy may
constitute a situation analogous to lost liver function in hemorrhagic shock. The importance of proper nutrition in the resistance of the organism to shock may also be related to the susceptibility of the liver to damage from shock-producing factors.

The mechanism by which protection of the liver prevents the onset of "irreversibility" remains to be explained. The phenomenon of delayed "taking-up" suggests that sustained liver function bears some relation to the integrity of the peripheral vascular mechanism. The anoxic liver in vitro is said (17) to produce a toxic substance which depresses the sensitivity of the small blood vessels of the rat mesentery to epinephrin. Thus, perfusion of the liver may prevent the elaboration of a depressor agent. On the other hand, it is possible that liver damage in shock results in the failure of the liver or some other tissue dependent upon it to elaborate a substance required for the maintenance of normal contractility of the peripheral vascular bed.

Disturbances in intermediary metabolism, so far as we have investigated them (14), provide no clue as to the nature of the process involved. Increased blood levels of lactic, pyruvic, and amino acids occur in shock, but there is no clear evidence that such changes are specific for shock; e.g., fever in the absence of shock may show the same disturbances (18). In work to be published (14), it is shown that the rise in lactic, pyruvic, and amino acids is not due to failure to clear the blood of these substances. Deamination proceeds satisfactorily when the liver is already damaged by shock. The high blood levels of these acids may signify an increased rate of production or a shift in the general level of metabolic exchange created by the generalized peripheral circulatory collapse. This may be due indirectly to failure of liver function. However, it is probably not the control of these metabolic processes, but some as yet unidentified function of the liver which is crucial for prevention of the development of "irreversibility" in hemorrhagic shock.

Experiments are in progress to determine whether the already damaged liver can be restored by beginning the vivi-perfusion not with the onset of the shock, but after "irreversibility" has been shown to be present.

**SUMMARY AND CONCLUSIONS**

1. The maintenance of adequate blood flow through the liver, while the remainder of the organism is subjected to the deficient blood flow of prolonged hemorrhagic shock, protects the organism from developing "irreversibility." Eleven of 12 dogs in hemorrhagic shock with a blood pressure of 30 mm. Hg, the livers of which received additional arterial blood by cross-circulation with healthy donor dogs, survived when transfused after a period of shock ordinarily long enough to render transfusion ineffective. Fifteen of 17 dogs similarly treated, except that the donor's blood entered the jugular instead of the splenic vein, died after the transfusion. None of the donor dogs in either group died or showed any adverse effects from the cross-circulation procedure.

2. With the perfected technique described, the liver-perfused dogs endured a hypotensive level of 30 mm. Hg for a much longer period of time than jugular-perfused dogs. In some of the liver-perfused dogs, evidence of damage to the central nervous system appeared late in the perfusion period, but this damage was transitory and disappeared after transfusion, except in isolated instances.

3. Disturbances in intermediary metabolism were less marked in shocked dogs being vivi-perfused as compared to shocked dogs not perfused, but in an equally-severe degree of hemorrhagic shock. There was no evidence, however, that survival of the liver-perfused dogs bears any relation to the lessened degree of metabolic derangement.

4. These observations indicate that loss of liver integrity is a significant factor in the collapse of the organism in advanced hemorrhagic shock and that the preservation of liver function is of crucial importance in recovery from advanced hemorrhagic shock.

5. Anoxia of other organs or tissues, produced under the conditions of these experiments, is not important in the development of "irreversibility" in hemorrhagic shock, since vivi-perfusion of the liver provides protection sufficient to produce survival while vivi-perfusion through the systemic veins does not. Whether maintenance of liver integrity protects by preventing secondary de-
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6. Further studies are in progress to see if the liver injury in advanced hemorrhagic shock can be corrected by viti-perfusion after "irreversibility" to transfusion has been shown to be present.

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