Peripheral Circulatory Changes as Criteria for Hemorrhagic Shock Therapy

By B. W. Zweifach, Ph.D.

This study of hemorrhagic shock syndrome in dogs evaluates commonly used therapeutic procedures on the basis of ability to correct specific vascular decompensatory episodes associated with progressive refractoriness to blood transfusion. Using specific criteria (vasomotion, responsiveness to vasoconstrictor stimuli, tone of arterioles and venules and capillary blood flow), it was found that pressor drugs improved blood pressure only at the expense of peripheral circulation. However, drugs such as angiotonin and especially pitressin, when added to the transfusion medium in subpressor concentrations sufficient to produce only a tonic narrowing of the terminal arterioles, brought sustained improvement in blood flow through the omental vessels. That the prognosis for successful treatment of the circulatory collapse closely parallels the sequential changes which occur in the terminal vascular bed, adds further significance to the probable causal relationship between the observed vascular derangements and the ultimate collapse of the peripheral circulation.

EXTENSIVE blood transfusion is at present the sole measure of proved value for preventing and counteracting the development of profound shock following massive hemorrhage or trauma. However, when the shock is prolonged the condition becomes increasingly refractory to blood replacement therapy. Such a syndrome can be produced regularly in dogs, where graded hemorrhage leads to a condition in which the animal can no longer gain recovery by reinfusion of the blood withdrawn—the so-called “irreversible” stage of shock. Our microscopic studies of the circulation in the omentum of dogs has indicated that the downward course of the syndrome is related to a number of sustaining or perpetuating factors, other than fluid loss, which are of paramount importance in the development of the “irreversible” condition. A primary defect would appear to be the deterioration of specific vasomotor reactions concerned with the regulation of peripheral blood flow. The establishment of these well defined reactions made it possible to use them as physiologic indices of the course of the syndrome and thereby offered a means for comparing the effectiveness of various therapeutic measures. Furthermore, the nature of the vascular derangement served as a guide for selecting agents which might contribute to the eventual recovery of the animal.

In our previous studies on the omental circulation an essential feature for recovery from shock was found to be an adequate improvement of the peripheral blood flow which was accompanied by, and appeared to depend upon, a sustained improvement in specific functional attributes of the peripheral vessels. It is the purpose of this study to compare the effectiveness of various therapeutic measures during the “irreversible” stage of hemorrhagic shock on the basis of their ability to correct the observed vascular dysfunction. No experiments were made to determine the long-range value of the measures employed, the end result looked for being a sustained improvement of the functional activity of the peripheral blood vessels for at least four to six hours, when the animals were sacrificed.

In the present paper two sets of experiments are described. The first deals with the relative effectiveness of blood and of several blood substitutes in restoring the deranged peripheral circulation. The restorative action of the fluids was found to differ according to the stage of the shock syndrome during which they were
administered. Emphasis was placed on the stage when infusion of whole blood was no longer restorative but, on the contrary, accentuated the developing atony of the peripheral blood vessels by unduly dilating them.

The second set of experiments deals with the effects of various pressor and vasotonic agents, injected per se or used to fortify the whole blood infusion. The agents were selected for their possible counteracting effects on the deranged peripheral circulation at the time when fluid infusion alone was inadequate.

In most of the studies in the literature, the stage at which the animals become unresponsive to replacement of the blood volume deficiency has been determined only after the blood lost has been replaced. The problem to be solved, however, is not irreversibility per se, as defined by the failure to respond to whole blood, but an analysis of the factors leading to such a condition. This makes the use of other, more physiologic, end points justifiable and even preferable to the more drastic procedure of allowing the animal to go into circulatory collapse twice before instituting therapy. When the syndrome has taken an unfavorable course and vascular and tissue metabolic deterioration has been initiated, time becomes a critical factor. The more prolonged the syndrome, the more likely is cellular damage to occur in organs which are sensitive to the effects of a stagnant anoxia. Blood replacement alone at this stage of the shock syndrome serves to accentuate further the developing functional derangement of the peripheral vascular system. This could be avoided by using as a criterion of the course of the syndrome the characteristic vascular changes, as observed through the microscope.

In order to permit a more direct comparison of the present experiments with similar work in other laboratories, a statistically significant number of experiments using the conventional blood-replacement end point were also carried out.

**Material and Methods**

The present report includes observations on the effectiveness of various therapeutic measures following the induction of hemorrhagic shock in 126 dogs anesthetized with pentobarbital sodium (30 mg. per kilogram of body weight) or morphine sulfate (2 to 12 mg./Kg.). The dogs were bled according to Wiggers' method of removing blood at intervals, in decreasing amounts, until the blood pressure was brought to, and kept for a protracted period at, hypotensive levels. The routine procedure was to maintain a moderate hypotension of 60 to 50 mm. Hg for two to four hours and to follow this by a drastic hypotension of 40 to 35 mm. Hg, or below, for an additional one to two hours. The blood withdrawn was citrated (final concentration of 0.2 per cent), chilled, and reinfected via the femoral or jugular vein at a designated point in the experiment.

Microscopic observations of the terminal ramifications of the peripheral vascular system were carried out on the exteriorized omentum of the dog according to the procedure previously described. Essentially this involved maintaining the exposed portion of the omentum both warm and moist by irrigation with a Ringer gelatin solution kept rigidly at body temperature.

In tissues such as the omentum, possessing alternating periods of greater and lesser blood supply, the capillary bed consists of definitely organized units of structure and function. Particular attention was paid to the centrally located metarterioles and their precapillary branches. The following vascular criteria were selected as reflecting the functional state of the capillary bed.

1. **Vasomotion.** Variations in capillary flow are occasioned by periodic caliber changes, constrictor and dilator phases, of the metarterioles and precapillaries. During the constrictor phase only the precapillaries become completely occluded, and the circulation is restricted to the preferential channels leading from arteriole to venule. During the dilator phase the precapillaries are open and the majority of the capillaries become flushed with blood. This intermittent activity of the metarterioles and precapillaries has been termed vasomotion. Under normal conditions it is an integral part of the homeostatic mechanism which ensures a supply of blood commensurate with the needs of the tissue.

2. **Tone of Arterioles and Venules.** Normally these vessels are maintained in a partially contracted state. By loss of tone is meant an undue dilatation of vessel lumina. It is also indicated by an excessive distention of the vessels following the intravenous administration of fluids.

3. **Responsiveness to Epinephrine.** Another feature of importance in the adjustment of the peripheral circulation is the occurrence of variations in the responsiveness of its muscular vessels to physiologic stimuli, such as epinephrine. This was ascertained by determining the minimal amount of epinephrine which, on topical application, produced a partial narrowing of the arterioles and precapillaries sufficient to slow markedly the flow of blood through the capillary vessels. The precise amount of epinephrine required to bring about a similar vasoconstriction was determined at regular intervals.
4. Rate of Flow. The rate and extent of the capillary circulation, especially that on the venous side, is an excellent indication of the efficiency with which peripheral circulatory adjustments are being made. A record of the changes observed in the above criteria offered a semiquantitative basis for comparing various therapeutic procedures. It also made possible a direct comparison between the physiologic status of different animals.

Results

1. The Three Stages of Vascular Reactivity during Shock

On the basis of the vascular responses observed, our studies have shown that the post-hemorrhagic syndrome consists of three phases.

A. Hyperreactive, Compensatory Stage: The immediate adjustment to the reduced blood volume was a widespread constriction of the larger arteries and veins. This was followed by an augmented activity of the terminal muscular vessels, which exhibited an increase in the frequency and amplitude of their vasomotion and an increased responsiveness to the constrictor effect of epinephrine.

B. Transitional Stage: In animals bled sufficiently to lower the blood pressure to the 40- to 50-mm. Hg range and allowed to remain in that range for two to three hours, the hyperreactive aspects of the syndrome gradually regressed and eventually were superseded by a state of diminished responsiveness.

C. Hyporeactive or Decompensatory Stage: During the several hours of drastic hypotension the responses of the terminal arterioles and precapillaries became impaired and finally depressed. The hyporeactivity in the capillary bed was associated with an inadequate return of blood from the capillary bed to the venous side of the circulation.

2. Refractoriness to Infusion Related to Vascular Dysfunction

Many investigators have demonstrated that dogs in hemorrhagic shock become with time increasingly refractory to fluid therapy. Our experiments show that the development of this unresponsive condition parallels closely the sequence of the vascular changes observed. It was found that the condition of the capillary bed at the time of fluid administration served as an excellent prognostic guide of the ability of the dog to respond. Thus, during the initial, reversible hyper-reactive stage it was possible to restore the normal dynamics of the capillary circulation by the infusion of any of the following fluids: physiologic saline (3 dogs), 5 per cent bovine albumin (4 dogs), and citrated plasma or whole blood (6 dogs). During the transitional stage, saline infusions became ineffective (3 dogs). During the latter part of the transitional and the early part of the hyporeactive stage bovine albumin also became ineffective (3 dogs). Finally, when hyporeactivity had persisted for at least sixty to ninety minutes, recovery was no longer possible, even with whole blood or plasma, irrespective of whether large amounts (up to 8 or 9 per cent of body weight) were used, or the infusion was prolonged for several hours (18 dogs).

3. Therapy During the Hyporeactive Stage

A. Procedure for Evaluating Therapeutic Measures: Wiggers and Frank and his co-workers have used as their end point the failure of the dog to recover when infused with the blood previously withdrawn. This procedure was found to aggravate the shock condition and made the physiologic state of the animal difficult to evaluate at the time that any supplementary treatment was instituted. The end point used by us was the detection of definitive circulatory criteria in the omentum by microscopic observation. The accuracy of this procedure was tested by subjecting 18 dogs to graded hemorrhage and maintaining them in extreme hypotension until the omental circulation exhibited criteria characterizing hyporeactivity. The dogs were then kept in this state for one to two hours at which time they were infused with citrated whole blood (0.2 per cent sodium citrate) equal to the amount previously withdrawn. Fifteen of the 18 dogs showed a temporary improvement of the peripheral circulation which eventually deteriorated, the dogs collapsing about one to two and one-half hours after the infusion.*

* We have in later studies infused over 50 dogs in the hyporeactive stage as determined by the omental index and found 82 per cent of the animals to be irreversible to whole blood replacement.
B. Vascular Changes following Replacement of Blood Withdrawn: The injection during the hyporeactive stage of all of the blood previously withdrawn usually raised the blood pressure to within 10 to 20 mm. Hg of the control level and set up an active flow in the capillary bed. These changes persisted. However, epinephrine, and atony of the terminal arterioles and venules persisted. The continued infusion resulted in an abnormal dilatation of the muscular vessels of the bed, further indicating the loss of their compensatory adjustment reactions. Within forty-five to sixty minutes after the blood had been administered, the capillary flow again became sluggish, considerable backflow from the venules into the capillaries developed, and fatal circulatory collapse ensued within sixty to one hundred twenty minutes thereafter.

Only three dogs showed a continued improvement of the omental circulation and ultimately

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**FIG. 1.—TABULATION OF PROTOCOL OF DOG RECEIVING PITRESSIN THERAPY AFTER UNSUCCESSFUL TREATMENT WITH WHOLE BLOOD.** Weight, 6 Kg.; anesthesia, 2 mg. morphine sulfate per kilogram of body weight; total blood loss, 41 cc. per kilogram of body weight. Bleeding procedure is indicated in text. The chart shows the changes in six criteria of the omental vessels presented in relation to the blood pressure. The degree of change is expressed by extent of deviation from the normal base-line. Epinephrine reactivity represents the response of the terminal arterioles to the topical application of the drug. Vasomotion, augmented, indicates an increase in both rate and duration of the constrictor phases; diminished vasomotion indicates an increasing predominance of the dilator phase, until the spontaneous caliber changes disappear. Abbreviations are the same as for figure 2.

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reactions, however, were transitory and began to wear off shortly after the infusion was stopped. A typical example of this sequence of changes is seen in figure 1, a detailed protocol illustrating this group of dogs. In several instances it was possible by means of repeated infusions at necessary intervals to forestall the slowing of the circulation for as long as three hours. It is of interest to note, however, that although the blood pressure was kept elevated above 80 mm. Hg during this period, there was no return of vasomotion, the arterioles and precapillaries remained refractory to epinephrine but the blood pressure remained above 80 mm. Hg during this period, there was no return of vasomotion, the arterioles and precapillaries remained refractory to epinephrine.
recovered. It is significant that the improved circulation always preceded the gradual rise of the blood pressure out of shock levels. The sequence of vascular changes leading to the recovery of the omental circulation were as follows:

Irrespective of whether the animals were reversible or irreversible, the omental circulation invariably showed an initial speeding up of flow, which appeared to be of mechanical ori-

was between 95 to 100 mm. Hg and the omental circulation appeared to be normal except for a moderate dilatation of some of the venules and small veins.

C. Restoration of Blood Volume with Several Blood Substitutes: Nine dogs were transfused during the hyporeactive stage: 3 with 5 per cent bovine albumin, 3 with an isotonic mixture of albumin and concentrated globulins, and 3 with a solution of 2 per cent sodium succinate. None of

<table>
<thead>
<tr>
<th>Pitressin Therapy</th>
<th>No. of Dogs</th>
<th>Initial Infusion Medium*</th>
<th>Time after Infusion (hrs.)</th>
<th>Condition of Animal B.P. (mm. Hg.)</th>
<th>Omental Circulation</th>
<th>Subsequent Pitressin Infusion (per Kg. body wt.)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. None</td>
<td>18</td>
<td>Whole blood</td>
<td>2-3</td>
<td>30-45</td>
<td>Slow, hyporeactive</td>
<td>None</td>
<td>2 survived</td>
</tr>
<tr>
<td>B. After unsuccess-</td>
<td>12</td>
<td>Whole blood</td>
<td>1.5-3.0</td>
<td>40-50</td>
<td>Slow, stagnant</td>
<td>0.10 p.u. in 2-3 c.c. saline</td>
<td>8 survived†</td>
</tr>
<tr>
<td>ful therapy with whole blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. After unsuccess-</td>
<td>3</td>
<td>5% albumin</td>
<td>0.5-1.0</td>
<td>50-60</td>
<td>Failing, hyporeactive</td>
<td>0.20 p.u. in 5 c.c. whole blood</td>
<td>2 survived</td>
</tr>
<tr>
<td>ful therapy with agents other than blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. Combined with whole blood (no previous therapy)</td>
<td>9</td>
<td>Whole blood + 0.06 p.u. pitressin/Kg.</td>
<td>0.5-0.8</td>
<td>85-100</td>
<td>Rapid, normal reactivity</td>
<td>0.05 p.u. in 2-3 c.c. saline only when necessary†</td>
<td>8 survived</td>
</tr>
</tbody>
</table>

p.u. = pressor units.

* Sufficient to restore blood volume to normal.

† Blood pressure and peripheral circulation restored to control levels; dogs sacrificed after three to six hours in this condition.

† Some dogs required additional injections of pitressin in order to maintain active circulation.

gin. However, in reversible cases, this was accompanied by the appearance of an improved tone in the small arterioles and precapillaries as evidenced by a narrowing of the vessels and a thickening of the wall. Vasomotion reappeared within twenty to thirty minutes, first in the precapillary branches and later in the metarterioles proper. The reactivity of these vessels to epinephrine returned to normal levels somewhat more slowly, requiring about ninety to one hundred minutes after the start of the infusion. Two to three hours after blood replacement had been completed, the blood pressure the dogs showed a sustained recovery either of the blood pressure or of the vascular reactivity. The omental vessels underwent essentially the same sequence of changes as described following unsuccessful whole-blood therapy. With 5 per cent albumin there was a transient improvement in the capillary circulation, but with no reappearance of vasomotion or restoration of the epinephrine response to normal levels. The addition of varying amounts of a concentrated globulin fraction (dog or beef blood) had no additional beneficial effect. The infusion of 2 per cent sodium succinate was least satisfac-
tory, since in 2 of the 3 dogs treated, the peripheral circulation remained almost stagnant throughout. Moreover, the response of the arterioles and precapillaries to epinephrine was actually further depressed by succinate therapy.

D. Addition of Vasconstrictor Agents to Infusion: In view of the demonstrated tendency of the muscular vessels distal to the larger arteries to lose their original compensatory capacity as the state of shock deepened, it was postulated that the addition of a vasconstrictor or vasotonic agent to the infusion mixture might be of value. A series of pressor drugs were tested, viz., epinephrine, neosynephrin, pareidine, ephedrine, and the S-ethyl derivative of iso-thio-urea. None of these agents proved to be of any sustained therapeutic value for the peripheral circulation.

(a) Epinephrine. When injected intravenously into normal control dogs the lowest concentration (0.002 to 0.02 mg. per kilogram of body weight) produced a visible narrowing of the arterioles and precapillaries, whereas the maximum concentration (0.5 to 2.0 mg./Kg.) produced an intense vasoconstriction and almost complete cessation of the capillary circulation. Ten dogs in the hyporeactive stage of shock were given epinephrine in varying dosages and in each of these animals the responses were considerably less than those observed in the controls with comparable dosages. In 4 of these which received intravenously 0.002 to 0.02 mg. of epinephrine per kilogram of body weight, there was no significant improvement either in the blood pressure or in the omental circulation. In 5 of the dogs, given higher dosages of epinephrine (0.04 to 2.0 mg./Kg.), there occurred a transient vasoconstriction of the larger arterioles, accompanied by a rise in the blood pressure from a level of 35 to 45 mm. Hg to 60 to 70 mm. Hg. This was followed by a speeding up of blood flow for a period of five to ten minutes. In one dog the same dose of epinephrine (0.002 mg./Kg.) was administered during the hyperreactive, the transitional, and twice during the hyporeactive stage. The vasocostricor effects of the third and fourth injections were significantly less than those elicited by the first two injections.

(b) Neosynephrine and Ephedrine. Injections of 0.1 to 6.0 mg. of neosynephrine per kilogram of body weight were given to 12 dogs in various stages of shock. In the normal dog these amounts produced a transient pressor effect of 10 to 100 mm. Hg respectively. In 2 dogs in the hyporeactive stage of shock concentrations below 0.3 mg. per kilogram of body weight were without effect. In 8 other dogs in shock, higher concentrations of the drug produced only a transitory speeding up of circulation through the capillary bed with no significant alteration in the tone or reactivity of the vessels.

Neosynephrin was more effective than epinephrine when given after infusion. In 2 dogs, which had been transfused with blood and were again showing signs of deteriorating, injections of 0.5 to 10.0 mg. of neosynephrin per kilogram of body weight stopped the fall in blood pressure and maintained it at a level compatible with good blood flow for twenty to thirty minutes. The animals eventually became refractory to repeated doses of the drug.

Ephedrine in concentrations of 0.1 to 0.5 mg./Kg. had no sustained restorative action on the omental circulation of 3 dogs in the hyporeactive stage of shock.

(c) Paredrine. Paredrine (20.0 to 30.0 mg./Kg. i.v.) produces a pressor effect in control dogs with only a moderate vasoconstriction of the small arteries and veins visible in the omentum. Eight dogs in shock received from 10.0 to 50.0 mg. of paredrine. Six of the animals received the drug before infusion and showed only a transitory increase in pressure and circulation. Two animals were given 10.0 mg. after the blood pressure had risen to 75 to 80 mm. Hg following a blood transfusion. The drug raised the blood pressure to 100 to 110 mm. Hg and considerably speeded the circulation through the capillary bed. This effect persisted for about twenty minutes and then wore off. As with other pressor agents, repeated injections in the hyporeactive stage of shock were progressively less effective.

(d) S-ethyl-iso-thio-urea. Three dogs received injections of 7.0 to 200.0 mg. of this drug during the hyporeactive stage of shock, with no
sustained improvement of either the omental circulation or the blood pressure.

E. Addition of Vasotonic Agents: From the above experiments it was obvious that all the pressor drugs which were used, produced their maximal pressor effect at the expense of the peripheral circulation. Peripheral blood flow was curtailed as a result of excessive vasoconstriction. Experiments were therefore carried out with what may be termed “vasotonic therapy,” in which the primary consideration was the use of drugs in dilutions sufficiently low to produce a barely perceptible narrowing of only the terminal blood vessels. Such concentrations had no constrictor effect on the larger blood vessels. Of several agents tested the most promising were found to be pitressin and angiotonin. Only six experiments were carried out with angiotonin owing to the difficulty of obtaining large amounts of this renal pressor agent. A total of forty-eight experiments were carried out with pitressin administered by several different procedures.

(a) Angiotonin.* The intravenous injection of 4 cat units of angiotonin (0.2 cc. in 5.0 cc. of saline) into 2 dogs during the hyporeactive stage of shock produced a transient increase in capillary circulation within two to four minutes and a definite narrowing of the arteriolar vessels. The blood pressure then gradually rose from 30 to 45 mm. Hg to 45 to 50 mm. Hg for about twenty minutes. This was less than the response obtained in normal dogs prior to bleeding. It was then decided to attempt to maintain a constant level of angiotonin in the blood by a slow intravenous infusion. In three dogs, up to 120 cat units of angiotonin were administered by a continuous drip infusion in 60 to 100 cc. of saline over periods of thirty to sixty minutes. Throughout the infusion the peripheral circulation improved considerably and in one dog vasomotion was temporarily reestablished. However, fifteen to twenty minutes after the infusion was ended, the circulation had again deteriorated to shock levels. One dog which had been transfused during the hyporeactive stage with all of the blood previously withdrawn and had again showed signs of circulatory failure, was given 20 cat units of angiotonin by repeated injections with no sustained beneficial effect.

(b) Pitressin in Subpressor Concentrations. Pitressin, in a pressor concentration of more than 0.15 p.u./Kg. body weight, was definitely contraindicated because it not only exaggerated the constricted state of the larger blood vessels but also exerted a deleterious effect on the heart. On the other hand, pitressin in concentrations which have no constrictor effect on the larger blood vessels and which are just below that exerting a constrictor effect on the arterioles, that is, in subpressor concentrations, produced a striking improvement in the peripheral blood flow. In a series of experiments based on reactions of the omental vessels in the dog, the concentration of pitressin best suited for such an improvement was found to be about 0.05 to 0.1 pressor units, per kilogram of body weight. The most satisfactory results were obtained with a mixture of pitressin and whole blood administered by a slow intravenous infusion.

In the experiments, pitressin was given by the following procedures:

1. Pitressin added to initial fluid infusion. Nine dogs were subjected to graded hemorrhage until they were judged to be irreversible by the hyporeactive condition of their omental circulation. The dogs were then infused with an intravenous drip of blood containing 0.05 p.u. pitressin per kilogram of body weight over a period lasting about sixty to ninety minutes, until the original volume had been restored. The typical response to such an infusion is shown in a protocol (fig. 2) of one of the dogs of this series. The blood pressure rose to about 100 to 110 mm. Hg and persisted at that level after the infusion had been completed. The blood flow in the omentum began to improve within five to ten minutes after starting the infusion. This is considerably earlier than occurs when blood alone is being infused during the irreversible stage. More significant than the early recovery of the blood flow were the gradual reappearance of vasomotion of the terminal arterioles and precapillary sphincters, a return to normal levels of their epinephrine

* Prepared by The Lilly Research Laboratories, Eli Lilly and Company.
reactivity, and a recovery of the relaxed arterioles to a partially constricted state.

In 5 of the subjects, about one hour after the infusion, the flow began to slow down, especially on the venous side. The blood pressure fell to about 80 to 85 mm. Hg. A second injection of pitressin, 0.2 p. u. in 5.0 cc. saline was then administered. This improved the peripheral blood flow and the blood pressure grad-

ually returned again to the 90 to 100 mm. Hg level. In 3 of these dogs it was found necessary to give a third and, in one, a fourth injection of pitressin. In none of the dogs did the total amount administered exceed 0.15 p. u. per kilogram of body weight, a quantity which was still subpressor.

A summary of these experiments together with the remaining pitressin data is given in table 1. This table shows that out of the total of 9 dogs the circulation of 8 could be restored to control levels. The elevated blood pressure and peripheral blood flow persisted at comparatively normal levels for about four to six hours, at which time the dogs were sacrificed.

2. Pitressin subsequent to whole blood infusion. These experiments were performed on 12 dogs to determine whether pitressin would be effective if administered after the dogs had not responded to whole blood infusion. Figure 1 is a protocol of one of these dogs and illustrates the vascular changes in the omentum and the effect produced by the subsequent pitressin therapy. The infusion of blood occasioned a rise of the blood pressure and a partial recovery of the flow in the capillary bed without a comparable reinstatement of its functional activity (return of vasomotion and of normal epinephrine reactivity). About two hours after the infusion had been given, the blood pressure had fallen to 75 mm. Hg and continued to fall while the omental circulation became increasingly hyporeactive.

At this time, pitressin (0.1 p. u. in 10 to 20 cc. saline) was injected intravenously. This was rapidly followed by a speeding up of the capillary flow and by a progressive recovery of arteriolar activity, viz., a partial narrowing of the vessels characteristic of their normal tonic state. In several cases (table 2) a second and a third injection of pitressin (each 0.2 p. u. in 2.0 cc. saline) were given at intervals of about forty minutes. Eight of the dogs showed a considerable improvement in omental reactivity which was maintained for four to six hours. The dogs were then sacrificed at which time their blood pressure was from 90 to 110 mm. Hg. Four of the dogs showed only a partial recovery of their vascular reactions and succumbed about one to three hours later.

3. Pitressin subsequent to unsuccessful therapy with agents other than blood. In the course of our therapeutic experiments a number of dogs, in the hyporeactive state, were infused with several different blood substitutes: 5.0 per cent albumin, an isotonic mixture of varying proportions of albumin and globulin, and a solution of 2.0 per cent sodium succinate. All the dogs remained in the hyporeactive state, whereupon they were given pitressin. The results are recorded in table 2. Of the 9 dogs
treated in this way, 6 showed recovery of their circulatory reactions until they were sacrificed about four to five hours after the initiation of therapy. The circulatory changes were essentially the same as those observed in the other groups of animals.

In these studies no direct causal relationship was established between the vascular phenomena observed through the microscope and the course of the shock syndrome. However, the remarkable uniformity with which the two sets of events occur through-

**Table 2.—Therapy during Irreversible Stage of Hemorrhagic Shock**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Anesthesia (mg./Kg.)</th>
<th>Blood Loss (cc./Kg.)</th>
<th>B. P. during Shock (mm. Hg.)</th>
<th>Circulation in Omentum</th>
<th>Therapy</th>
<th>Time after Initial Therapy (hrs.)</th>
<th>B. P. (mm. Hg.)</th>
<th>Circulation in Omentum</th>
<th>Effects of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Whole Blood</td>
<td>Morphine, 12</td>
<td>37</td>
<td>3.5</td>
<td>1.5</td>
<td>Hyporeactive, sluggish</td>
<td>Whole blood, 35</td>
<td>None</td>
<td>1.2</td>
<td>60-75</td>
</tr>
<tr>
<td>B. Pitressin after Unsuccessful Therapy with Whole Blood</td>
<td>Morphine, 12</td>
<td>30</td>
<td>3.6</td>
<td>2.0</td>
<td>Hyporeactive, stagnant</td>
<td>Initial Whole blood, 38 Subseq. Saline, 8</td>
<td>0.19</td>
<td>3.8</td>
<td>95-100</td>
</tr>
<tr>
<td>C. Pitressin after Unsuccessful Therapy with Agents other than Blood</td>
<td>Morphine, 12</td>
<td>36</td>
<td>4.5</td>
<td>1.5</td>
<td>Hyporeactive stagnant</td>
<td>Initial 5% albumin, 36 Subseq. Whole blood, 8</td>
<td>0.20</td>
<td>3.5</td>
<td>80-100</td>
</tr>
<tr>
<td></td>
<td>Pentobarb. 30</td>
<td>3.0</td>
<td>3.0</td>
<td>1.1</td>
<td>Hyporeactive sluggish</td>
<td>Initial Globulin-albumin, 35 Subseq. Saline, 10 Whole blood, 6</td>
<td>0.04</td>
<td>2.5</td>
<td>64-75</td>
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<tr>
<td></td>
<td>Pentobarb. 26</td>
<td>31</td>
<td>3.0</td>
<td>1.3</td>
<td>Hyporeactive stagnant</td>
<td>Initial 1.8 Na succinate Subseq. Whole blood, 18</td>
<td>0.15</td>
<td>4.0</td>
<td>100-120</td>
</tr>
<tr>
<td>D. Pitressin-Whole Blood (no previous therapy)</td>
<td>Morphine, 12</td>
<td>39</td>
<td>4.0</td>
<td>2.5</td>
<td>Hyporeactive, sluggish</td>
<td>Whole blood, 39</td>
<td>0.10</td>
<td>4.1</td>
<td>110-125</td>
</tr>
</tbody>
</table>

**Discussion**

The establishment of clearly defined functional changes in the minute blood vessels of the omentum during shock made possible a new approach to the development of therapy for this syndrome. Our previous investigations on hemorrhagic and tourniquet shock called attention to the nature of the breakdown of the functional activity of the visceral blood vessels. The establishment of clearly defined functional changes in the minute blood vessels of the omentum during shock made possible a new approach to the development of therapy for this syndrome. Our previous investigations on hemorrhagic and tourniquet shock called attention to the nature of the breakdown of the functional activity of the visceral blood vessels.7 In these studies no direct causal relationship was established between the vascular phenomena observed through the microscope and the course of the shock syndrome. However, the remarkable uniformity with which the two sets of events occur through-

out the progression of shock, makes it probable that the observed vascular dysfunction is a critical defect contributing to the circulatory insufficiency. In other studies from this laboratory, evidence of another character has been obtained which indicates a causal relationship between these vascular episodes and the metabolism of specific hepatorenal factors.

With regard to the causal relationship of the
Disturbance in the peripheral blood vessels and the blood pressure after therapy, the following observations are pertinent. It was possible temporarily to raise the blood pressure by the infusion of large amounts of fluid or by the injection of vasodepressor drugs without influencing the unfavorable outcome of the shock. In these dogs an accelerated blood flow developed only subsequent to the increased blood pressure. In those animals in which therapy was successful, an improvement in peripheral blood flow of considerable magnitude occurred at a time when changes in blood pressure were still minimal. Later, as an adequate peripheral blood flow was re-established, the blood pressure began to show a steady rise. Conversely, with the progression of shock, a deterioration of the peripheral circulation usually preceded the subsequent drop in the blood pressure and the circulatory collapse during the latter stages of the syndrome.

The necessity for overcoming the decompensatory vascular changes, which develop during the “irreversible” stage, is clearly indicated by the close correlation between the course of the syndrome following therapeutic measures and the degree of functional repair in the peripheral vascular system. In all animals in which the response to therapy was unfavorable and peripheral circulatory collapse ensued, no improvement in the omental circulation occurred, except for a transitory speeding of flow. This is in striking contrast to the course following favorable therapy during which a progressive restoration of the functional responses of the vessels accompanied the gradual improvement in blood flow and resulted in a return to normal of the integrated activity of the capillary bed.

The use of the exteriorized omentum for microscopic study placed several limitations on the experimental procedure. The subsequent effects of therapy could be followed only for four to six hours. Thereafter, prolonged exposure of the omentum added the possibility of nonspecific vascular deterioration. Furthermore, the animals, when brought out of shock, became restless and required repeated anesthesia, a procedure which complicated the posttherapeutic course. The experiments were therefore terminated at this time without testing the long-term value of any of the therapeutic procedures. Although the therapeutic implications of such experiments are limited, the studies clearly indicate that successful therapy must restore the circulatory efficiency of the peripheral vascular system. Anesthetized dogs, transfused with blood alone during the irreversible stage of hemorrhagic shock, invariably again went into fatal circulatory collapse within four to six hours. In contrast, animals treated with pitressin in vasotonic but subpressor concentrations showed at the end of four to six hours a markedly improved peripheral circulation with a restoration of many of the features of normal functional activity. These experiments would, therefore, seem to bear directly on the ultimate direction towards which treatment of “irreversibility” should be directed.

The administration of fluid sufficient to replace the deficient blood volume was of value early in shock before the mechanisms for peripheral vascular adjustment had deteriorated. Such nonspecific measures became less effective as the shock deepened. The fact that blood plasma was effective for a longer period than saline, albumin, or gelatin indicates that plasma exerts a physiologic effect beyond that imparted by its bulk and colloidal osmotic properties. Over the short range of our experiments, no immediate superiority could be detected between plasma as opposed to whole blood. There is, however, ample evidence in the literature that the anemia which frequently follows hemorrhagic shock is greatly benefited by whole blood therapy.

Mechanical restoration of the peripheral circulation is not sufficient, by itself, to correct the metabolic disturbances which during shock are inflicted by prolonged periods of inadequate circulation on organs such as the liver, kidney, heart, and brain. Recent work by Shorr, Zweifach, and Furchgott has demonstrated that the vascular decompression in the omentum is not solely the result of local impairment of blood flow but in large part can be referred to blood-borne vasodepressor principles (VDM) which originate in the liver and skeletal muscle. The therapeutic problem is therefore twofold. First, the correction of vascular dysfunction
resulting from the local accumulation of non-specific metabolites and from specific vaso-depressors (VDM) arising in organs such as liver and skeletal muscle; second, the correction of the metabolic defects in these organs as a result of which VDM continues to be elaborated and maintained at high levels in the blood.

None of the pressor agents employed (epinephrine, neosynephrin, ephedrine, or paredrine) were of value in counteracting the atony of the peripheral vessels. The progressive decrease in the responsiveness of hypotensive animals to pressor agents has been discussed by Frank and co-workers.\textsuperscript{11} Our data indicated that the impaired responsiveness is referable, at least in part, to the hyporeactive state of the muscular components of the capillary bed. Whatever pressor action these agents displayed during the terminal stages of shock, was the result of vasoconstriction of the larger blood vessels, the direct effect of which was a further curtailment of the circulation in the tissues proper. Additional evidence for the contraindication of pressor drug therapy during the hyporeactive stage was the stasis which developed in the larger veins during the period of elevated blood pressure induced by these drugs. It is of interest to note that, following transfusion, the refractoriness to pressor agents wore off in those cases which were reversible, whereas the pressor response remained depressed in animals which proved to be irreversible and eventually died.

Angiotonin gave some evidence of being a promising therapeutic agent. Because of the relatively few experiments done, we have insufficient data for this renal pressor substance. Page\textsuperscript{12} has reported that dogs subjected to hemorrhage were refractory to small doses of angiotonin (0.2 cc., or approximately 6 cat units). In our experiments, although the vascular response to angiotonin became less pronounced during the hyporeactive stage of shock, the administration of larger amounts (up to 120 cat units) by slow intravenous infusion produced a striking improvement of blood flow, despite the fact that the blood pressure rose only 30 to 40 mm. Hg above shock levels. Unfortunately, the effects were only temporary and wore off each time that the infusion was stepped.

Pitressin added in subpressor concentrations to the blood infusion brought about a significant extension of the period of effectiveness of whole blood therapy. The indications from the omental vascular criteria are that pitressin, administered subsequent to unsuccessful whole blood infusion, is not as effective as when the pitressin is administered together with the whole blood. Although these small amounts have no obvious direct pressor action, they are within the range (.02 p.u./Kg.) which produces a profound effect in unbled dogs.\textsuperscript{13} Frank, Seligman, and Fine\textsuperscript{3} were unable to obtain significant therapeutic results with pitressin when administered to dogs already found to be irreversible to whole blood or to the administration of succinate or of bicarbonate therapy. They found no increase in the number of animals which could be recovered by pitressin used subsequent to these experiments. The question remains whether the method used by them (that of testing pitressin only after the dog had failed to respond to whole blood) is appropriate for an evaluation of shock therapy. This drastic procedure involved subjecting the dog to deep shock twice in succession, first after the bleeding procedure and, second, after the temporary effects of the unsuccessful transfusion. When such procedures were used in our studies, considerable stasis was observed in the collecting venules and capillaries following the failure of the transfusion. As a result, large areas of the capillary bed remained in stasis and inactive throughout the subsequent period of therapy.

Our results with pitressin indicate the desirability of effecting a sustained improvement in the peripheral circulation through a vaso-tonic action on the terminal arterioles and precapillaries. Although pitressin has other pharmacologic effects which may militate against it being the agent of choice in irreversible shock therapy, it unquestionably prolonged the survival, for at least three to four hours, of dogs which otherwise would have died. What appears to be most significant about these experiments is the demonstration that functional repair of the peripheral vascular bed is
a necessary prerequisite for recovery from shock. It was our hope that through the use of vasotonic agents such as pitressin, we could maintain the adequate circulation for sufficiently long periods to allow the animal to repair these metabolic lesions. Our observations, being confined to a three- to six-hour period after the institution of pitressin, did not permit any long-term evaluation of this thesis. It is possible that the inadequacy of pitressin therapy in certain of our shocked animals may be ascribed to the continued elaboration of VDM. This would indicate that the metabolic derangements in the tissues are not reversed by the comparatively short periods of improved circulation in these experiments. Frank and co-workers\textsuperscript{14} by in vivo perfusion experiments obtained evidence that perfusion of the liver of shocked dogs with arterial blood from a normal donor dog for three to four hours (range from three to eight hours) is often sufficient to counteract the development of irreversibility. The recent isolation of VDM and its identification as ferritin by Mazur and Shorr\textsuperscript{15} opens up the possibility of developing measures for counteracting this specific principle and isolating the enzyme systems responsible for its inactivation.

CONCLUSION

Our experiments call attention to the prime necessity of restoring the normal functional behavior of the capillary circulation of animals in hemorrhagic shock and indicate the value in such conditions of vasotonic agents such as pitressin which appear to accelerate the recovery of the vascular bed.

\textsuperscript{12} Page, I. H.: Hypotension and loss of pressor response to angiotonin as the result of trauma to the central nervous system and severe hemorrhage. J. Exper. Med. 78: 41, 1943.
\textsuperscript{13} Hare, K., Melville, E. V., Chambers, G. H., and Hare, R. S.: The assay of antidiuretic material in blood and urine. Endocrinology 36: 323, 1945.
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