The Nature of Irreversible Shock:

Experimental and Clinical Observations *

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The search for truth is in one way hard and in another easy,
For it is evident that no one can master it fully, nor miss it wholly,
But each adds a little to our knowledge of nature,
And from all the facts assembled, there arises a certain grandeur.—*Aristotle*

IN recent years we have reached an impasse in our efforts to increase the survival rate of patients in shock who respond poorly to blood replacement. These patients are thought to be in irreversible shock. While it is never possible to define irreversible shock in patients with the same precision that it can be done in animals in the experimental laboratory, the criteria of poor response to blood or fluid infusion is, we believe, a working definition which will satisfy most physicians.

A frequent cause of severe or irreversible shock is infection with gram-negative bacteria with their contained endotoxins. This is not to say that infection is the cause of all cases of irreversible shock. However, many patients who suffer an initial insult not necessarily related to bacterial contamination often die of gram-negative septicemia complicating their injury. Moreover, we hope to indicate here that while various events causing shock are obviously different (such as trauma, pure hemorrhage, burns, infections with gram-negative bacteria with their contained endotoxins or gram-positive bacteria with their elaborated exotoxins, or even certain types of "low output" syndrome due to myocardial failure) and initially may have widely varying effects on metabolic balance, they apparently have in common a similar disturbance in the peripheral circulation (Fig. 1).

Many believe that the heart is a stronger determinant in the genesis of irreversible shock than the peripheral circulation. Yet the studies of others indicate that in many circumstances, the heart is better able to resist the deleterious effects of hypoxia than the peripheral circulation and, indeed, the heart is as dependent on the adequacy of the peripheral circulation for proper function as on its own coronary circulation.[5, 33, 34]

A Concept of Irreversible Shock

Before formulating our plan of treatment for severe shock resulting from the various forms of trauma listed above, we should first review the physiology of shock. The effects of trauma on adrenal function are widely appreciated. With oligemic hypo-

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tension there is an increased outpouring of corticosteroids and epinephrine. In addition, increased sympathetic nerve activity liberates increased amounts of norepinephrine at myoneural junctions, which stimulate alpha receptors in effector organs.[3] The effect of this on the peripheral circulation in the viscera and skin and to a lesser extent in the muscle masses is an intense vasoconstriction in precapillary arteriolar sphincters as well as in postcapillary venular sphincters. This process shown in Figure 2 can best be characterized by the term ischemic anoxia, for the affected tissues are pale and relatively bloodless. The result of this reaction is to preserve, at all costs, blood flow to the brain and heart, the cerebral and coronary circulatory systems being little affected by the vasoconstrictive effects of the catecholamines (epinephrine and norepinephrine). Shock at this phase of ischemic anoxia is usually readily reversible and prompt use of blood or suitable substitutes restores circulatory dynamics to their normal state. Moreover, the intense vasoconstriction itself provides for autotransfusion, since reduced hydrostatic pressure in the capillary beds allows the plasma colloid osmotic pressure in the capillaries to draw greater than normal volumes of fluid back into the vascular space at the venous end of the capillary (inset, Fig. 2).

If, however, the shock is prolonged, then the situation in the tissues gradually

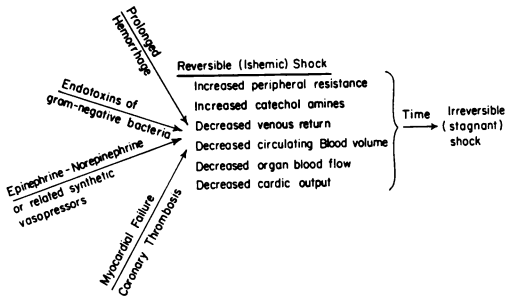

FIG. 1. A concept of shock in which various stresses result in a common hemodynamic disturbance.

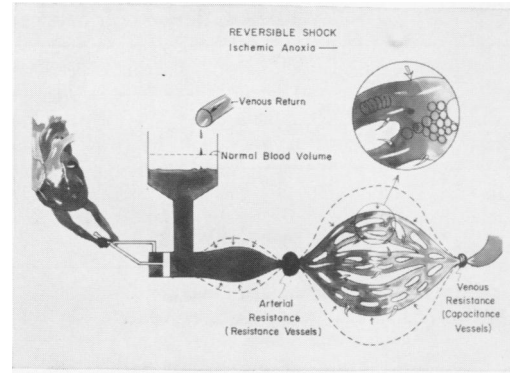

FIG. 2. Reversible shock or ischemic anoxia is characterized by intense vasoconstriction of arterioles and venules on either side of the capillary bed. The result is a smaller vascular space which more adequately fits the diminished circulating blood volume. As a result of the vasoconstriction, hydrostatic pressure within the capillaries falls, allowing the plasma colloid osmotic pressure to draw additional extravascular fluid into the circulation to aid in restoration of the blood volume.

changes from pale, ischemic anoxia to congested, stagnant anoxia. Now we are approaching irreversible shock (Fig. 3). The progression of events leading to this stage

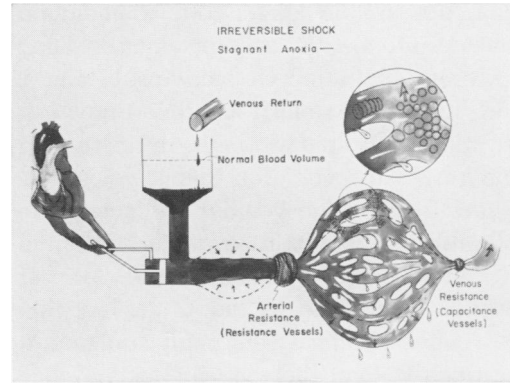

FIG. 3. Irreversible shock or stagnant anoxia is characterized by a loss of tone of arteriolar sphincters while venular sphincters are still able to retain their tone. Now blood can get into the capillary beds in increasing amounts, but is unable to leave due to the venous obstruction. This increasing stagnation of blood increases hydrostatic pressure in the capillary beds and tends to further deplete an already diminished blood volume by driving additional fluid out of the capillary. Restoration of blood volume at this time may not restore the circulation to normal unless something is also done to restore the normal dynamics in the microcirculation.

TABLE 1. *Hemorrhagic Shock at 35 mm. Hg Mean Arterial Pressure*[1]

No. Dogs	Level of Hypotension mm. Hg	Time of Retransfusion Hours	Maximal Bleeding Volume ml./Kg.	Maximal Bleeding Volume % Blood Volume	% Uptake at Time of Retransfusion	% Plasma Loss 2 Hours Following Retransfusion	No. Survivors[2]
10	35	2	61.0±4.1	61.8±8.3	6.36± 5.1	7.5± 9.3	9
10	35	3	56.8±6.1	62.5±6.4	17 ±11	18 ± 6.5	5
10	35	4–4.5	57.7±4.3	57.5±7.2	34.3±10	29.4±15	1

[1] Mean values with standard deviations.
[2] Alive 72 hours following an experiment.

appears to be as follows. As a result of the vasoconstriction in arterioles and venules, products of metabolism accumulate leading to acidosis and lowered pH which causes these same vessels to be less responsive to the effects of the catecholamines. This in turn results in increased norepinephrine liberation by the sympathetic nervous system and increased epinephrine secretion by the adrenal medulla to maintain vasoconstriction in the face of the increasing acidosis and, hence, decreasing effectiveness of these substances. Eventually, if shock is prolonged, the arteriolar sphincters are no longer able to maintain tone despite heroic attempts by the body to secrete additional vasoactive substances. With loss of arteriolar tone, blood now can get into the capillary beds in increasing amounts. However, for some yet unexplained reason, the venular sphincters are still able to maintain reasonably normal tone in the face of the severe acidosis of shock.[10, 21] This may be due to the fact that the venular sphincters normally function at a lower pH than those on the arterial side and are therefore able to continue to function at the low pH characteristic of shock. At any event, the inevitable result now is that blood has difficulty in leaving these stagnant capillary beds. Hydrostatic pressure within the congested capillaries increases above colloid osmotic pressure and fluid begins to leave the circulation in increasing amounts (inset Fig. 3). Significant losses (30–40%) of the plasma volume occurring in this manner can be measured in dogs suffering shock from a variety of causes.[11]

As this process of stagnation continues, ischemia may become so severe that the capillaries lose their integrity and slough, allowing whole blood to suffuse into the tissues. This further reduces the blood volume and irreversible shock is at hand. It is now clear why added blood, plasma or plasma substitutes at this stage are palliative rather than curative, for the added fluids eventually also end in the stagnant peripheral pools unless normal tone in arterial and venous sphincters can be restored.

The effect of this process on the heart is dramatic. The increasing congestion diminishes venous return which, in turn, lowers cardiac output and coronary flow. Moreover, the lowered blood pH further decreases cardiac efficiency. Eventually cardiac function deteriorates and arrest or fibrillation supervenes.

It bears emphasis again that in the experimental animal this cardiac failure is not the primary cause of the irreversible shock, for a number of investigators have shown that if venous return and pH are artificially supported cardiac efficiency returns temporarily to normal even in the face of extensive and irreversible visceral tissue damage.[5, 33, 34]

Irreversible Hemorrhagic Shock

If this hypothesis is correct, what evidence have we to support us? First let us

briefly review the problem of irreversible hemorrhagic shock as it is produced in the laboratory.[12-14]

If dogs are bled to a mean pressure of 35 Hg and maintained at this level, the following pattern of events occurs. Initially, there is a period of rapid bleeding lasting a few minutes to reach the 35 mm. Hg level, followed by additional bleeding in small amounts as vasoconstriction becomes more intense and fluids are drawn into the vascular system due to lowering of hydrostatic pressure in the capillaries. Maximal bleed-out is usually complete by 60 minutes (1.5 ± .48 hours) at which time the dogs have lost 50 to 60 per cent of the measured blood volume. The dogs are then relatively stable for another hour with no net exchange of blood between dog and blood reservoir. This is the period of reversible or ischemic anoxia in the tissues and retransfusion with all shed blood at this time, two hours after the start of bleeding, results in a prompt return of blood pressure to normal. Almost all dogs will survive this period of hemorrhagic shock (Table 1).

If, however, the oligemic hypotension is prolonged beyond two hours, then the dogs begin to enter the phase of irreversible or stagnant anoxia of the tissues. As a result they begin to take up blood from the reservoir in order to replace blood lost from the active circulation, which lowers mean pressure below 35 mm. Hg. Retransfusion of shed blood at three hours may restore blood pressure to normal, but in many dogs (50%) there is a second bout of hypotension due to continued pooling of blood in damaged viscera and death occurs.

If retransfusion is delayed until four hours, a variable amount of the shed blood will have already been taken up spontaneously by the dog to support a failing circulation. This varies from 5 to 50 per cent, with an average of 26 ± 5.9 per cent in 100 dogs. Regardless, the remaining blood is returned to the dog and this is followed by a

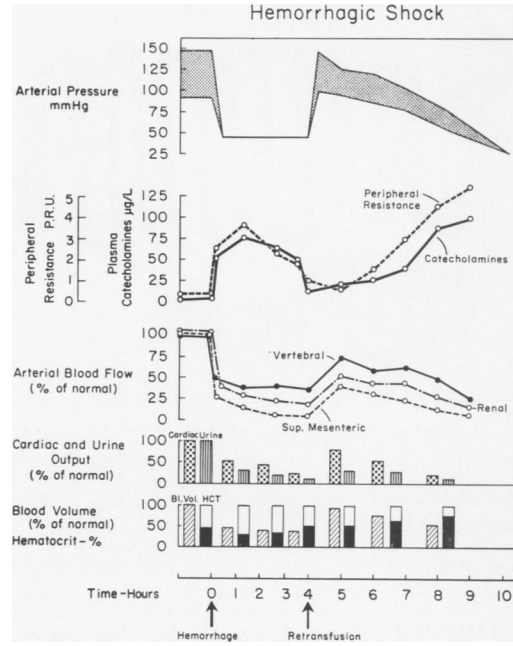

FIG. 4. Typical irreversible hemorrhagic shock in the dog.

return of the dog's systemic arterial pressure to or toward normal (Fig. 4). This return to normotension is short-lived, however, for the arterial pressure soon begins to decline again and 90 per cent of the dogs die.

Accompanying this post-transfusion hypotension is a watery diarrhea which soon becomes hemorrhagic. In some instances the diarrhea may have started before retransfusion, especially if uptake of blood from the reservoir has been excessive before retransfusion. At this time, blood volume measurements will again show a deficit in the dog. Additional blood or fluids will temporarily prolong life, but survival is not increased by fluid therapy alone.

Catecholamines in Hemorrhagic Shock. By the time of maximal bleed-out, the concentrations of plasma catecholamines (epinephrine and norepinephrine) reach high levels (Fig. 4). The peaks of these endogenous vasopressor substances can be correlated with the severity of the hypotension, for the values return to more normal

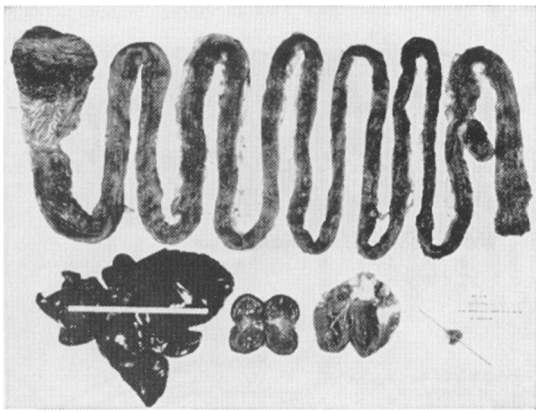

FIG. 5. Viscera from a dog dead of irreversible hemorrhagic shock. A chronic end-to-side portacaval shunt had been made some weeks prior to the experiment. At autopsy, the shunt was widely patent, yet the dog still had developed hemorrhagic necrosis of the bowel which is characteristic of irreversible shock in the dog. These findings indicate that hepatic venous constriction with secondary portal venous system congestion is not the cause of the intestinal findings; rather, the intestinal pathology is a primary result of the ischemic and stagnant anoxia of shock.

levels with the advent of retransfusion. But, as the dog again becomes hypotensive following retransfusion due to pooling of blood in the viscera and to losses from the gut as bloody diarrhea, the catecholamines once again progressively increase until death occurs.

Blood Volume. Initially when the dog is being bled, equal amounts of the red cell and plasma volume are lost. Such measurements are made with Evans blue dye (T-1824) or radioactive iodinated albumen (I^{131}) for the plasma volume and radioactive chromium (Cr^{51}) for the red cell volume. With these substances, measurements of blood volume can be made serially throughout the experiment.

When maximal bleeding volume is reached, there is still more blood remaining in the circulation than would be predicted from subtraction of the volume of blood in the reservoir from the measured prebleeding blood volume. This is due to passage of fluids into the vascular system as a result of reduced hydrostatic pressure in the capillaries and causes a lowering of the venous hematocrit when compared to the prebleeding level. However, towards the end of the 4-hour period of hemorrhagic shock, the hematocrit begins to rise again as plasma is lost into the tissues. This is particularly marked in those dogs which take up excessive amounts of blood from the reservoir in order to maintain the preset hypotensive level of 35 mm. Hg mean arterial pressure. The uptake of blood from the reservoir is a sign of failure of the dog to maintain arteriolar vasoconstriction in the peripheral circulation. Consequently, the size of the vascular bed begins to expand and blood must be taken up from the reservoir to fill this increasing space. The increased hydrostatic pressures in congested capillary beds resulting from the pooling of blood at this stage forces plasma out of the vascular space and is apparently responsible for the hemoconcentration usually seen late in the period of hemorrhagic shock.

Following retransfusion, the blood volume returns to or near normal values, only to fall again within a short time as pooling in the visceral and peripheral vascular beds continues unabated. In the intestine, this sequence of events is especially severe and as the period of stagnant anoxia becomes prolonged, there is actual tissue necrosis and loss of integrity of the mucosa of the bowel so that blood passes directly into the bowel lumen. Bloody diarrhea is the manifestation of this turn of events and results in further depletions of blood volume.

Examination of the microcirculation of the bowel mesentery after retransfusion at four hours, represents what is occurring in the viscera and gives evidence for the source of the blood volume loss; for there is now an ever increasing vasodilation with resultant pooling of blood in capillary beds. This congestion is seen grossly as a hemorrhagic suffusion of the small bowel mucosa which leads subsequently to necrosis and bloody diarrhea. The kidneys and liver are also affected by this process, but the find-

ings are most marked at autopsy in the intestine of the dog.

Autopsy Findings. Dogs dead of irreversible hemorrhagic shock present a characteristic picture. The intestinal mucosa is congested and necrotic. The liver is also congested and shows some cellular necrosis around the central veins. The cortices of the kidneys are congested and there are varying amounts of tubular damage present. A similar congestion is noted in the lungs. There are less severe changes in other organs such as subendothelial hemorrhages in the atria and ventricles of the heart.

The intestinal findings in the dog have often in the past been said to be a secondary result of hepatic vein vasoconstriction with resultant portal bed congestion. Nevertheless, dogs with chronic end-to-side portacaval shunts show the same degree of hemorrhagic necrosis of the small bowel mucosa as normal dogs, even though all their portal vein blood bypasses the liver (Fig. 5). Hence, the intestinal changes in the dog appear to be primary and not secondary to liver congestion.

Electrolytes and Blood pH. There are quite marked shifts in electrolytes during hemorrhagic shock experiments. Serum potassium level elevations are especially striking. However, the hyperkalemia as well as other electrolyte changes appear to be the result of the irreversible state rather than its cause. A similar statement can be made for pH changes during shock. There is always a lowering of blood pH as shock progresses, but this shift does not appear to have prognostic significance; nor does prevention or correction of pH shifts or electrolyte changes during or after the bleeding change the course of the experiment.

Hemodynamic Manifestations of Shock. The high levels of circulating catecholamines present during the various phases of the hemorrhagic shock experiments cause severe alterations in blood flow to visceral organs, total and individual organ resistance, blood volume and venous return. Cardiac output in turn is also depressed. Finally, the peripheral ischemia attendant on the shock process results in lowered pH which further depresses cardiac function. A consistent finding is that blood flow, as measured with the electromagnetic flow meter, to the intestine, kidney and liver is consistently decreased to greater degrees than blood flow to other organs. Thus, while all the tissues of the body suffer from reduced flow during shock, these visceral organs apparently receive a smaller proportion of the reduced cardiac output than usual (Fig. 6). A significant corollary to this finding is that perfusion of the intestinal circulation of the dogs during hemorrhagic shock with arterial blood from a donor dog at normal pressure and flow will prevent the death of the perfused dog following retransfusion. This also is true in dogs with previously constructed portacaval shunts, indicating that the salutary effects of intestinal perfusion via the superior mesenteric artery are not due to indirect liver perfusion via the portal vein. Perfusion of other organs during shock does not produce the same salutary effects (Table 2).[12]

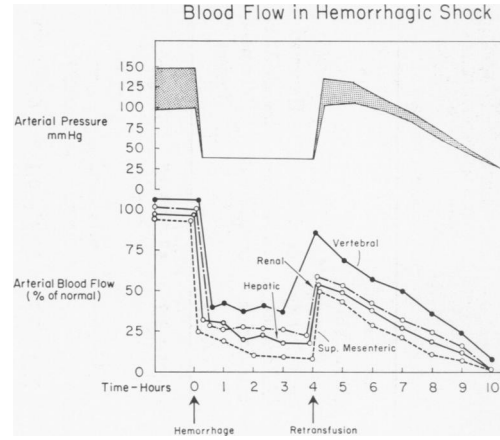

FIG. 6. Organ blood flow of dogs in hemorrhagic shock is consistently depressed to the lowest levels in the splanchnic viscera. This initially provides for a more adequate flow to the coronary and cerebral circulations, which are relatively insensitive to vasoactive substances, but if long continued results in damage to the deprived viscera.

TABLE 2. *Results in Perfusion Studies*[1,2]

Group	Type of Perfusion	No. Dogs	No. Survivors[3]	Maximal Bleeding Volume		Perfusion		Hours in Shock	Blood Volume Change Immediately After Retransfusion in %	Mean Plasma Loss 2 Hours After Retransfusion in %	Hours to Death After Retransfusion
				ml./Kg.	% Blood Volume	Start in Hours After Hemorrhage	Flow ml./Kg./min.				
I	Superior mesenteric arterial	30	27	60.0±9.4	58.6±7.6	1.48±0.38	8.84±2.2	4.90±0.23	6.21±4.2	18.6±10.7	—
II	Superior mesenteric arterial-Eck fistula	10	9	50.9±3.9	51.5±3.9	1.01±0.28	9.52±2.3	5.0 ±0.2	7.33±6.3	9.79±3.2	—
III	None-normal dogs	15	1	57.3±5.5	53.5±4.6	—	—	4.40±0.40	7.21±3.3	28.8 ±9.1	6.39±3.9
IV	None-Eck fistula	8	0	56.0±8.6	53.0±5.3	—	—	4.92±0.06	9.10±3.9	22.7 ±6.8	18.5 ±9.1
V	None-antibiotic sterilization of gut	10	1	57.0±6.4	58.7±6.8	—	—	4.80±1.2	14.1 ±9.8	26.5±13	6.21±6.5
VI	Inferior vena caval	10	2	60.4±9.3	56.0±4.5	1.30±0.07	9.0 ±0.92	4.94±0.29	6.87±4.0	23.1±13	5.86±3.1
VII	Inferior vena caval-Eck fistula	3	0	61.5±6.0	56.4±2.1	1.33±0.30	8.41±1.1	4.98±0.10	9.53±3.1	22.6 ±6.4	20.5 ±7.1
VIII	Lower abdominal aortic	10	2	57.8±6.4	57.3±5.6	1.32±0.19	10.9 ±0.20	4.64±0.2	7.60±4.6	25.6 ±9.1	7.03±6.1
IX	Celiac axial	10	4	63.7±9.0	57.8±7.3	1.37±0.23	9.86±0.72	4.97±0.14	4.98±5.1	15.4±10	12.5 ±6.8
X	Portal	10	3	43.9±14	51.2±7.3	1.44±0.36	10.9 ±2.2	4.95±0.10	8.34±3.4	19.3 ±9.5	9.64±4.5
XI	Carotid	10	2	51.3±7.9	53.9±8.0	1.25±0.19	8.72±0.83	4.92±0.06	7.81±6.9	21.1±10	26.2 ±4.0

[1] Mean values with standard deviations.
[2] Hemorrhagic shock at 35 mm. Hg mean arterial blood pressure for all groups.
[3] Alive 72 hours following an experiment.

The Role of Bacteria Within the Intestinal Lumen. It is tempting, when interpreting the perfusion results, to indict the bacteria within the bowel lumen as the cause of irreversible shock, since they are presumed to escape into the systemic circulation as a result of the destruction of the barrier of the intestinal mucosa. Yet in our experience, bacteremia is not a concomitant of irreversible shock (Table 3). Moreover, pretreatment of dogs with oral neomycin, sulfasuxidine and streptomycin for several days, so that stool cultures on the day of an experiment are sterile for both aerobic and anaerobic organisms, does not influence the results of hemorrhagic shock experiments in our hands (Table 4). The course prior to death and the hemorrhagic necrosis of the intestinal mucosa at autopsy do not differ in these dogs from other dogs not receiving oral antibiotics.

Heparin has also been given in large doses, up to 30 mg./Kg. intravenously, prior to hemorrhagic shock to prevent the formation of microthrombi in the stagnant capillary beds of the intestine during the period of shock. This treatment also fails to prevent the intestinal changes of irreversible hemorrhagic shock (Table 4). From these observations, we think that the significance of the intestine lays in the susceptibility of

TABLE 3. *Blood Cultures in Normal and Shocked Dogs*

	No. Dogs Studied	No. Positive Blood Cultures
Normals (No shock)	56	11
Hemorrhagic Shock		
Survivors	25	4
Fatalities	25	6
Endotoxin Shock		
Survivors	10	3
Fatalities	10	3

TABLE 4. *Evaluation of Heparin and Oral Antibiotics in Preventing Irreversible Hemorrhagic Shock*[1,2]

Group	No. Dogs	Body Weight Kg.	Pre-hemorrhage MABP mm. Hg	Pre-hemorrhage Blood Vol. ml./Kg.	Pre-hemorrhage Hematocrit %	Maximal Bleeding Volume Retransfusion (MBV) ml./Kg.	% BV	% Uptake	Time in Hours	No. Survivors	Fatalities Time to Death in Hours	Mean Plasma Loss 2 Hours Following Retransfusion in %
Control	16	19.1±3.2	124±12	99.5± 9.8	51±5	57.7±4.3	57.5±7.2	34.3± 10	4.63±1.6	1	7.49±6.3	27.4±15
Heparin 30 mg./Kg. i.v.	10	17.9±2.3	121±12	97.3±16	48±5	55.8±9.6	59.3±6.3	36.4±7.4	4.88±0.98	0	4.18±2.4	29.1±10
Neomycin-sulfasuxidine 7 days prior to shock	10	17.4±2.6	130±15	94.8±12	47±7	55.2±7.3	58.7±5.4	32.9±6.9	4.90±1.0	0	8.1 ±4.7	28.3± 7.9

[1] Hemorrhagic shock at 35 mm. Hg mean arterial blood pressure (MABP) with retransfusion at end point of cardiorespiratory failure or 40 per cent uptake of maximal bleeding volume, whichever occurred first.

[2] Mean values with standard deviations.

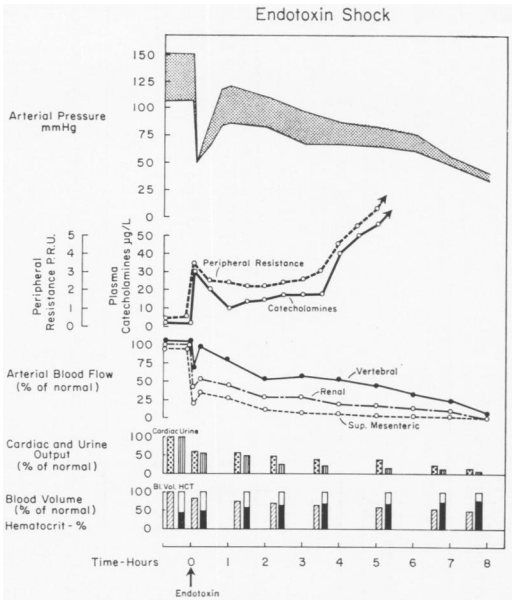

FIG. 7. Typical shock in the dog due to the endotoxin of Escherichia coli bacteria. The effects of the endotoxins of the various other gram-negative bacteria are similar.

its arterioles and venules to the profound vasoconstriction occurring during shock; the blood volume losses and tissue destruction alone resulting from stagnant anoxia being enough to cause the death of the animals. Such a conclusion is supported by the results of shock experiments in germ-free animals carried out by others.[35]

Shock Due to Endotoxins of Gram-negative Bacteria. The terrifying aspects of gram-negative septicemia and shock are feared by all physicians. It is now known that endotoxin, a complex lipopolysaccharide, within the cell wall of gram-negative bacteria accounts for the lethality of these organisms. It is less well known, however, that the manner in which endotoxin causes shock in man and animals is by its sympathomimetic-effect resulting in intense vasospasm in small arteries and veins in selected visceral organs, with the principal effects occurring in the lungs, bowel and kidneys.[7, 8, 13, 15] The sympathomimetic effects of endotoxin have a twofold origin. First, endotoxin increases the plasma levels of catecholamines and, secondly, the endotoxin combines with some formed element in the blood, probably the leucocyte, to form an additional potent sympathomimetic substance.[30]

The experimental counterpart of clinical bacterial shock can be produced in the dog by the intravenous injection of endotoxin obtained from killed Escherichia coli bacteria. It should be noted, however, that endotoxins of all gram-negative bacteria have a similar action, the major difference being that endotoxins from the various gram-negative bacteria vary in potency.

When endotoxin of Escherichia coli bacteria is injected intravenously in adult dogs, a typical picture is seen (Fig. 7). Immediately, there is a rapid fall in blood pressure followed by recovery in a few minutes. The cause of this initial hypotension is a trapping of blood within the portal system as a result of transient hepatic venous constriction due to histamine release. This initial event can be abolished by a portacaval shunt but the lethality of the endotoxin is not altered.[18]

A second bout of hypotension occurs in one to two hours following injection of the endotoxin. This fall is more gradual and

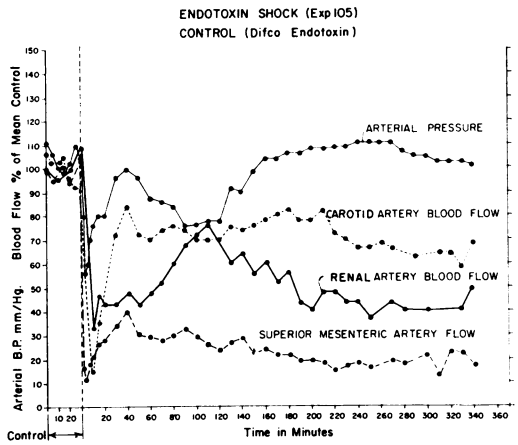

FIG. 8. In endotoxin shock, the splanchnic viscera again suffer profound decreases in blood flow resulting in tissue destruction if the period of deprivation is prolonged.

TABLE 5. *Endotoxin Shock*[1]

Group	No. Dogs	No. Survivors[2]	Fatalities—Duration of Survival (Hours)	Measurements—6 Hours After Endotoxin: Hematocrit Increase %	Measurements—6 Hours After Endotoxin: Plasma Volume Loss %
Controls (no treatment)	90	6	10.3±5.5	36.1±14	34.8±13
Administration[3] of Blood	10	0	12.2±5.5	39.2±19	—
Plasma[3]	10	0	16.5±6.1	—	—

[1] Mean values with standard deviations.
[2] Alive 72 hours following an experiment.
[3] Administered in volumes sufficient to maintain systolic arterial pressure at 100 mm. Hg.

spontaneous recovery does not occur. If at this time the visceral tissues are examined, they are pale and ischemic in appearance. Examination of the microcirculation reveals vasospasm in arterioles and venules. This is the period of ischemic anoxia or reversible shock due to endotoxin and it is possible with proper treatment to prevent the death of the animals at this stage.[14]

Measurement of organ blood flow to various organs of the dog during endotoxin shock shows that, again, the splanchnic organs suffer profound decreases in arterial blood flow (Fig. 8). The decreased organ blood flow is much greater in proportion than the decrease in cardiac output, emphasizing the sensitivity of the splanchnic circulation to the increased vasoactivity following endotoxin injection.

When the period of hypotension induced by the endotoxin approaches 4 hours, the visceral tissues become hemorrhagic or congested in appearance and the dog has reached the stage of stagnant anoxia or irreversible shock. Examination of the microcirculation at this time shows dilated arteriolar sphincters and congested capillaries which cannot be distinguished from the microcirculation in irreversible hemorrhagic shock. The loss of a portion of this circulating blood volume into congested peripheral vascular beds is a constant concomitant of the hypotension associated with gram-negative bacterial shock. Moreover, added blood or suitable substitutes will temporarily restore blood pressure in such dogs but again, as in irreversible hemorrhagic shock, the added fluids are also soon lost from the effective circulating blood volume and the dogs ultimately die because of an uncorrected disturbance in the peripheral circulation (Table 5).

Autopsy Findings. The autopsy findings in dogs dead of endotoxin shock are identical with those previously described for irreversible hemorrhagic shock. The principal damage is in the small intestine where extensive hemorrhagic necrosis of the mucosa is found. The lungs, liver and kidneys also show evidence of the stagnant anoxic process.

Epinephrine Shock. Before proceeding to treatment studies, let us examine the hemodynamic disturbances caused by epinephrine or related drugs. A lethal form of shock can be produced in the dog by the intravenous administration of 17 γ/Kg./min. of epinephrine for 90 minutes[15] (Fig. 9). This produces initially an intense ischemic anoxia which is followed in time by congestion and stagnation within the visceral organs. The effect on blood flow and resistance in visceral organs is similar to that already discussed for hemorrhagic and endotoxin shock. Moreover, autopsy findings are also similar with the intestine, kidneys, liver and lungs showing severe congestive changes (Table 6).

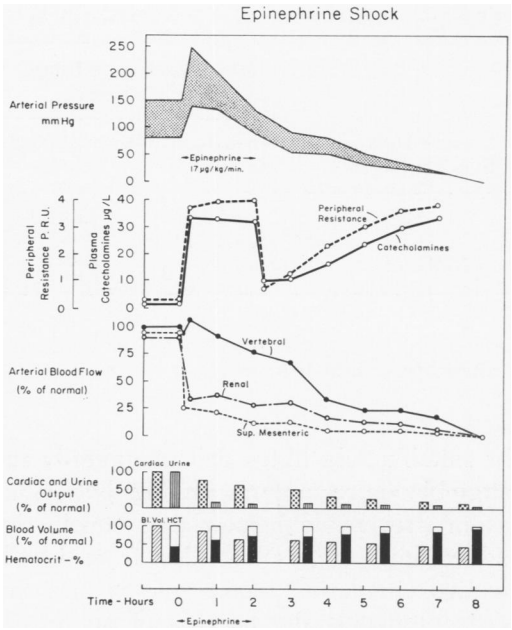

FIG. 9. Typical shock in the dog caused by the administration of epinephrine. An identical picture can be obtained by using l-norepinephrine (Levophed), metaraminol (Aramine), or any of the other related vasopressor drugs in place of epinephrine.

Coronary Shock and Shock Following Cardiopulmonary Bypass. The experimental counterpart of clinical shock following myocardial infarction can be duplicated in the laboratory by the injection of microspheres of varying sizes directly into the coronary arteries by methods previously described. Surprisingly, we see again a picture similar to that already described above (Fig. 10). Cardiac output is, of course, decreased but there is also an immediate increase in plasma catecholamines. These vasoactive substances act primarily on sensitive visceral beds to increase total peripheral resistance and profoundly decrease organ blood flow. As a result, the efficiency of an already weakened heart is further depressed by the increase in total peripheral resistance, metabolic acidosis and a decreased venous return resulting from this peripheral vascular disturbance.

Measurements in patients suffering shock following myocardial infarcts are sparse, but, in general, most studies show that there are varying increases in catecholamines and total peripheral resistance accompanying such catastrophes.[26] The extent of the patient's ability to increase his total peripheral resistance, as in the dog, determines the severity of the accompanying hypotension and shock.

Still another form of shock accompanying myocardial failure is seen clinically following prolonged cardiopulmonary bypass for repair of difficult congenital or acquired heart defects. Here, in contrast to coronary shock, we have more information from clinical observations than from the laboratory. During cardiopulmonary bypass there are significant elevations of plasma, epinephrine and norepinephrine which are directly proportional to the length of the bypass [25] (Fig. 11). Patients having a prolonged bypass often exhibit the "low output syndrome" following surgery.[16] This syndrome is characterized by cyanosis and

TABLE 6. *Epinephrine Shock*

(16–17 µg./Kg./min. × 120 min.)[1]

Group	No. Dogs	No. Survivors	Duration Survival in Hours	Hematocrit Increase %	Plasma Loss %
Controls	10	1	19.9±16	29.7± 9.3	40.4± 9.9
Hydrocortisone, 15–25 mg./Kg. i.v. 60 min. prior to epinephrine injection	10	8		25.3±12	29.7±11

[1] Mean values with standard deviations.

coolness of the extremities, oliguria or anuria, blood volume deficits in the face of elevated venous pressures, narrowed pulse pressures and low cardiac outputs. All of these signs are characteristic of a shock-like state with increased peripheral resistance and a failing heart. Thus it is our feeling that prolonged cardiopulmonary bypass is a form of controlled clinical shock, since all the chemical, hemodynamic and clinical criteria for its diagnosis are present. Finally, at autopsy such patients exhibit varying degrees of congestion in the splanchnic viscera and in the lungs.

Treatment of Shock

The pathogenesis of various types of shock has been described. These observations indicate that disturbances in the balance between arteriolar and venous resistance may be at fault in the genesis of lethal shock due to various causes. Moreover, excessive sympathomimetic tone appears to be responsible for this imbalance. The question now is to choose treatment which will correct the resulting disturbance in the peripheral circulation. There are three areas where the sympathomimetic response to stress can be altered[3] (Fig. 12). We can depress sympathetic activity by drugs which act on sympathetic ganglia, or by drugs which act on terminal portions of sympathetic postganglionic fibers or finally by drugs which act on alpha receptors at the myoneural junction of effector organs. It is this latter area which interests us because by altering the response of the receptor organs, we can block both the effect of increased sympathetic nerve activity and the effect of the increased catecholamines secreted by the adrenal.

Norepinephrine (Levophed), metaraminol (Aramine) and angiotensin (Hypertensin) are three drugs which will augment vasoconstriction by stimulating alpha receptors located in small vessels. In contrast, phenoxybenzamine (Dibenzyline) and, we believe, hydrocortisone (Solu-Cortef) in pharmacologic doses will cause

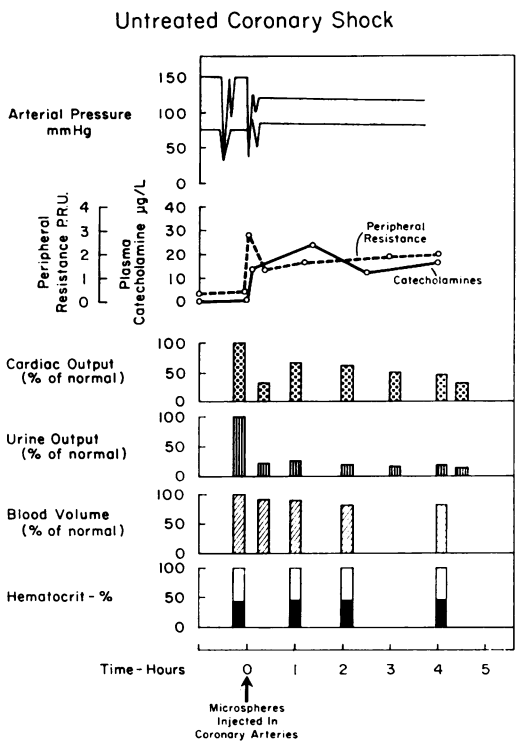

FIG. 10. Typical shock in the dog resulting from embolization of the coronary arteries with microspheres.

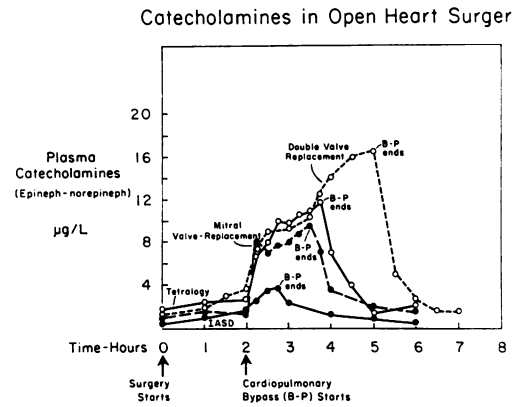

FIG. 11. The response of plasma catecholamines of patients to cardiopulmonary bypass of varying durations. The elevation of catecholamines is directly proportional to the length of the bypass. In patients with cyanotic heart disease, the catecholamines are also high even though the bypass may not be prolonged.

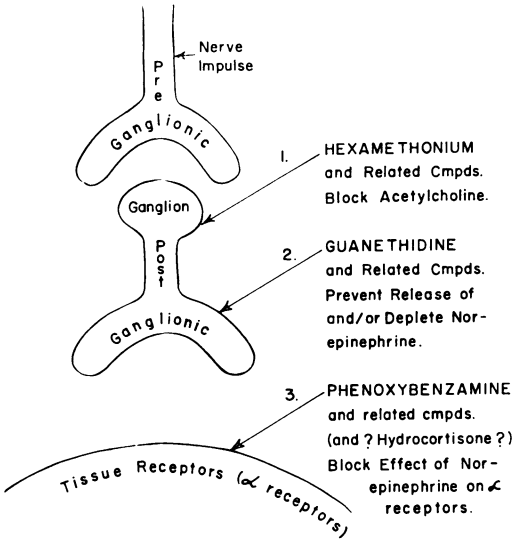

FIG. 12. The various sites of nerve transmission which can be affected by drug therapy. It is important to distinguish between adrenergic and ganglionic blocking agents. It is our opinion that adrenergic blocking agents are more specific and hence more effective in treating the hemodynamic capillary disturbances of shock than ganglionic blocking agents.

vasodilatation by blocking these same receptors.

Treatment of Hemorrhagic Shock. In Figure 13 are illustrated hemodynamic effects of norepinephrine administered during hemorrhagic shock experiments. When one of these vasopressor drugs is given early in shock after maximal bleed-out has occurred, and the bleed-out cannula is clamped, a prompt return of blood pressure to normal can be obtained. However, pulse pressures are narrowed even more than in untreated dogs as peripheral constriction of small vessels becomes more intense. Cardiac output which is transiently increased by these agents is subsequently further depressed in spite of elevation of systemic pressure to normal. This is because the effect of these agents is to reverse the process of fluid passage into the vascular system during the early phases of shock and, instead, drive fluid out of the vascular system and speed the progression of ischemic anoxia to stagnant anoxia in the viscera. Further proof of the ability of these agents to accelerate the onset of irreversible shock is obtained by retransfusing dogs treated with norepinephrine or metaraminol at 3 hours. About 50 per cent of untreated dogs will survive this period of hemorrhagic shock, but all dogs will die after this same period of hemorrhagic shock if treated with vasopressor agents (Table 7). At autopsy, the tissue damage in dogs treated with vasopressors is considerably worse than in untreated animals.

A word about angiotensin; this vasopressor agent apparently acts mainly on alpha receptors in the arteriolar sphincters and has little effect on the venular sphincters. Therefore its ability to induce profound vasoconstriction is less than with norepinephrine or metaraminol. Nevertheless, in our hands it ultimately causes the same tissue damage as norepinephrine and

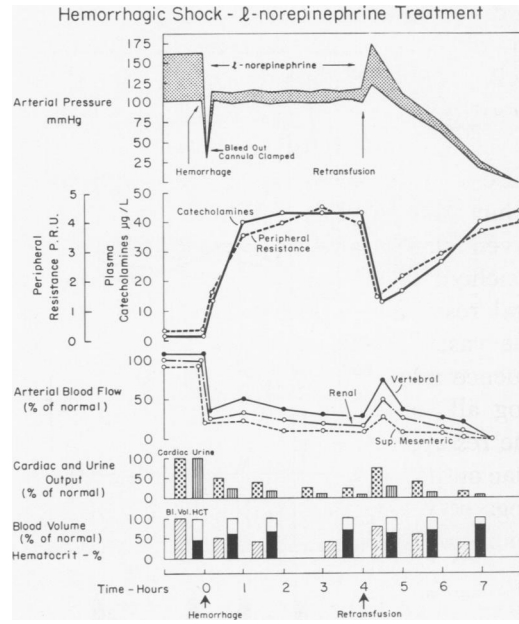

FIG. 13. Typical hemorrhagic shock in the dog treated with l-norepinephrine (Levophed). It is important to note that systemic pressure can be raised to normal levels only at the expense of further decreases in blood flow to the viscera. The accelerated stagnation caused by this drug inevitably further reduces venous return and cardiac output.

TABLE 7. *Treatment of Hemorrhagic Shock*

Therapy	No. Dogs	Level of Hypotension mm. Hg	Retransfusion Hours	No. Survivors[1]
None	10	35	4–4.5	1
None	10	35	3	5
L-norepinephrine[2] with or without added blood or blood substitute	10	35	3	0
Phenoxybenzamine 1 mg./Kg. i.v. 2–12 hours prior to hemorrhage	10	35	4.5	8
Phenoxybenzamine 1 hour after start of hemorrhage[3]	10	35	4.5	7

[1] Alive 72 hours following an experiment.
[2] Systemic arterial pressure supported at 100 mm. Hg after maximal bleeding volume reached. Bleed-out cannula clamped.
[3] Bleed-out cannula clamped and mean systemic arterial pressure supported at 35 mm. Hg with blood or blood substitute.

metaraminol, although it takes somewhat longer to do so.

Finally, the administration of additional blood or blood substitutes to the dog, over and above that removed, does not enhance the effect of vasopressor agents, but fluids will, temporarily, delay the death of the dogs.

In Figure 14 is depicted the use of the adrenergic blocking agent, phenoxybenzamine (Dibenzyline). When this drug is given slowly after maximal bleed-out is reached, the effect is quite different. Peripheral resistance is lowered and the size of the vascular space increased. As a consequence added fluids must be given or the dog allowed to take up shed blood from the reservoir. This results in increased cardiac outputs and visceral blood flows. When dogs so treated are retransferred after 4.5 hours with remaining shed blood in the reservoir, over half the dogs will survive this usually lethal procedure. If the phenoxybenzamine is given prior to the start of hemorrhagic shock, then almost all dogs (80%) will survive following retransfusion (Table 7). Comparison of hemorrhagic shock studies in which adrenergic blocking drugs or vasopressor drugs are used as pretreatment is complicated by the fact that dogs pretreated with adrenergic blocking agents do not reach the same maximal bleed-out volume as untreated dogs. Nevertheless, the beneficial effects of using adrenergic blocking agents before or early in the

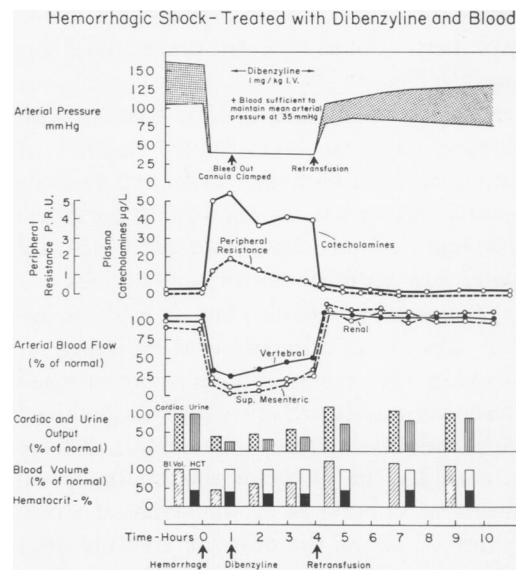

FIG. 14. Typical hemorrhagic shock in the dog treated with phenoxybenzamine (Dibenzyline). The effect of this drug is to increase the size of the vascular space, therefore it is imperative that the blood volume be increased by some means to prevent further falls in systemic arterial pressure.

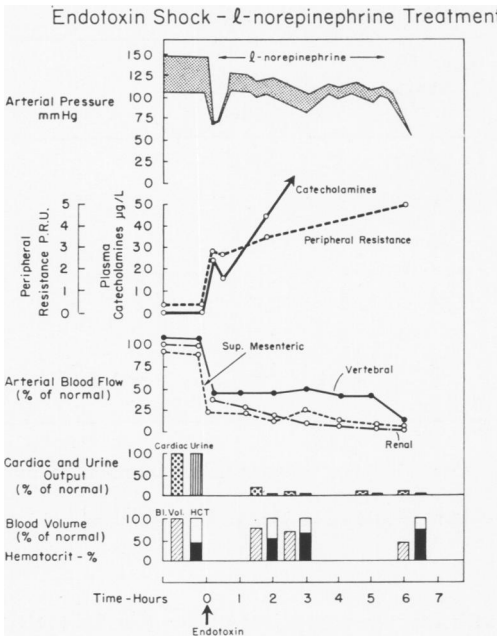

FIG. 15. Typical endotoxin shock in the dog treated with l-norepinephrine. The effects here are similar to those seen in hemorrhagic shock. The specious effect of this drug on the systemic arterial pressure masks its destructive effect on the microcirculation.

course of hemorrhagic shock experiments have been also shown by other investigators.[6, 17, 28]

Sacrifice of surviving dogs treated with phenoxybenzamine or related agents at varied times following these experiments reveals normal viscera, confirming the measurements which show increased visceral blood flow with the use of such agents.

Treatment of Shock Due to Endotoxins. The effects of adrenergic stimulating or blocking drugs can probably be assessed more accurately when shock is induced with endotoxins, since one does not have to consider the effect of the treatment on bleed-out volume as in hemorrhagic shock. Figure 15 shows the effect of treating dogs with norepinephrine 30 to 60 minutes after shock is induced with endotoxin. Again, the use of norepinephrine or related agents merely intensifies the peripheral circulatory disturbances already caused by the endotoxin and hastens death. Prior to death, cardiac output and visceral organ blood flows are decreased almost to zero, even while mean systemic pressure is supported at normal levels by great increase in peripheral resistance. The addition of fluids to vasopressor therapy will ameliorate somewhat the deleterious effects of the vasopressor agents, but eventually these additional fluids are also driven from the circulatory system or stagnate in peripheral pools (Table 8).

Contrasting results are obtained using phenoxybenzamine for pretreatment or treatment in the first hour following the endotoxin injection (Fig. 16, 17). The best results are obtained when blood volume is replenished with plasma or low molecular weight dextran prior to or simultaneously with the phenoxybenzamine administration (Table 8). Peripheral resistance and plasma catecholamines are returned towards normal levels. As a result, venous return is increased with resultant

TABLE 8. *Treatment of Endotoxin Shock 30–60 Minutes After Induction of Shock*

Therapy	No. Dogs	No. Survivors[1]
Normal saline (25–50 ml./Kg.)	10	1
Low molecular (40,000) dextran 2.5–7.5 gm./Kg. (Rheomacrodex)	10	0[2]
L-norepinephrine with or without plasma	10	1
Phenoxybenzamine 0.5–1 mg./Kg. i.v.	5	0
Phenoxybenzamine 0.5–1 mg./Kg. i.v. with 25 ml./Kg. plasma	10	6
Hydrocortisone 50 mg./Kg. i.v.	10	5
Hydrocortisone 50 mg./Kg. i.v. with 25 ml./Kg. plasma	10	7
Hydrocortisone 50 mg./Kg. i.v. with 2 gm./Kg. low molecular dextran	10	8

[1] Survived 72 hours or more.
[2] Significant increase in duration of survival but dogs died of a bleeding diathesis.

increases in cardiac output and organ blood flows. An interesting finding is the volume of plasma or dextran used in these experiments. While it would initially seem to be excessive (25 ml./Kg. or more) central venous pressure does not increase, indicating the extent of pooling and loss of circulating blood volume in the peripheral tissues in endotoxin shock (Fig. 18).

Hydrocortisone in Endotoxin Shock. In searching for methods to ameliorate the effects of experimental epinephrine shock, we found that pretreatment with intravenous hydrocortisone in doses of 15 to 25 mg./Kg. would protect 80 per cent of dogs from a lethal dose of epinephrine (Table 6).[15] After a period of trial and error, we found that hydrocortisone in doses of 50 mg./Kg. administered after epinephrine shock was induced would have similar effects. This same dosage schedule was then used in treating endotoxin shock, and we found that 50 per cent of dogs survived a usually lethal dose of endotoxin when treated with 50 mg./Kg. of hydrocortisone alone (Table 8). If plasma or low molecular weight dextran is used in conjunction with this pharmacological dose of hydrocortisone, then survival is increased to 80 per cent (Fig. 19). The reason for these salutary effects is apparently explained by

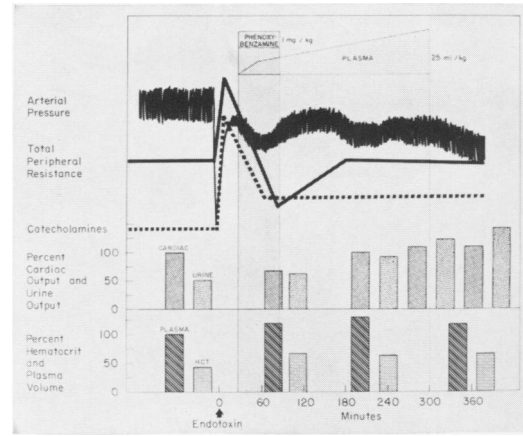

FIG. 17. When phenoxybenzamine is used to treat dogs already in shock from the injection of endotoxin, then it is imperative that its administration be accompanied by copious amounts of plasma or low molecular weight dextran. This is because the rapid action of the phenoxybenzamine expands the size of the vascular space at a time when there already is a deficit in the circulating blood volume.

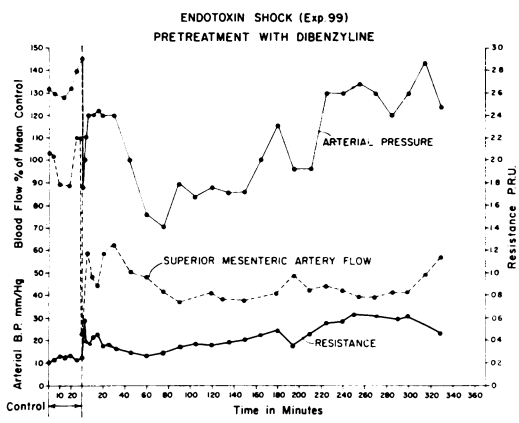

FIG. 16. Dogs given 1 mg./Kg. of phenoxybenzamine intravenously, 2 to 24 hours prior to the injection of a lethal dose of endotoxin, are protected in most instances (90% survival). There is some drop in arterial pressure after injection of the endotoxin, but not to the low levels seen in control animals. Plasma losses are minimal and resistance is only moderately increased. Within three hours there is a gradual recovery to normal of all measured values.

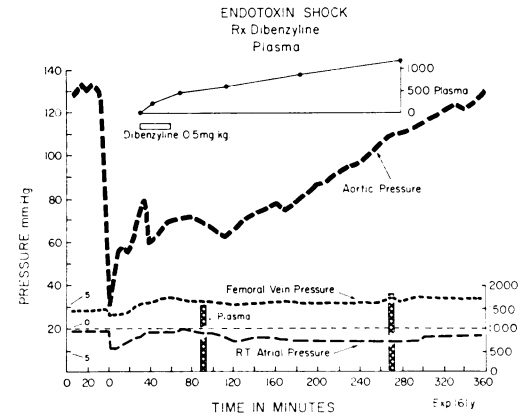

FIG. 18. The need for large volumes of plasma or other suitable substitute in endotoxin shock is seen in this experiment where 25 ml./Kg. of plasma is given to the dog along with phenoxybenzamine. Note that the central venous (right atrial) pressure has actually decreased slightly. These and similar studies clearly indicate that endotoxin shock is hypovolemic, *not* normovolemic, shock; thus it resembles the shock seen after a prolonged period of hemorrhage followed by retransfusion.

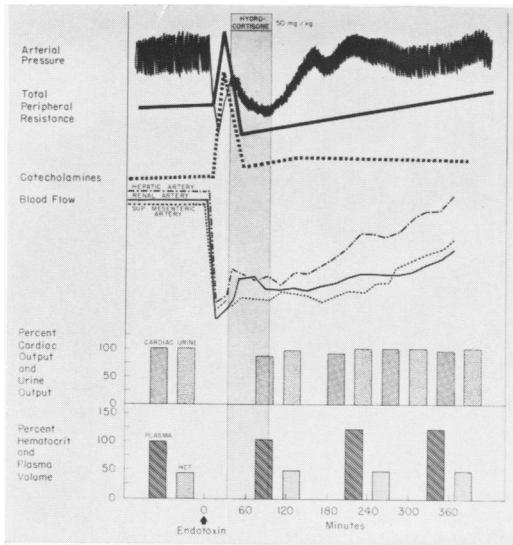

FIG. 19. When 50 mg./Kg. of hydrocortisone is given intravenously to dogs already suffering endotoxin shock, there is a striking beneficial effect and 50 per cent of dogs will recover without any other treatment. This is in contrast to the use of phenoxybenzamine in existing shock where it is imperative to administer blood or substitutes in order to prevent further hypotension. These contrasting results are likely due to the more subtle action of hydrocortisone in reducing peripheral resistance as well as to its probable direct protective effect on cells.

the ability of this therapeutic regimen to lower catecholamine levels and peripheral resistance, and to increase venous return, cardiac output and visceral organ blood flow (Fig. 20). These beneficial effects apparently come about as the result of restoration by hydrocortisone of the normal relationships between arteriolar and venular sphincters in the peripheral circulation. Hence, we believe that, in such doses, hydrocortisone acts as an adrenergic blocking agent similar to phenoxybenzamine. It should be noted that others have also found pharmacological doses of hydrocortisone to be beneficial in hemorrhagic shock.[22]

Low Molecular Weight Dextran (Rheomacrodex). In endotoxin shock, as well as in other types of shock included in this study, we have found that low molecular weight dextran (40,000 average weight) surpasses plasma in its efficiency in restoring blood volume and blood flow in the peripheral circulation. Yet, while it will prolong survival in endotoxin shock in dogs when used alone, it will not prevent the ultimate death of the animals unless combined with phenoxybenzamine or hydrocortisone. When using low molecular weight dextran in endotoxin shock experiments, we have found that the optimal dose of this dextran is about 2 Gm./Kg. dissolved in normal saline or 5 per cent dextrose. Larger amounts of the low molecular dextran will decrease fibrinogen levels, which are already depleted by endotoxin, with the result that a bleeding diathesis may occur in the dog. The significance of these findings for the human has not been determined; therefore, low molecular weight dextran should be used cautiously in the treatment of bacterial shock in man.

Treatment of Shock Associated With Myocardial Failure

Preliminary studies in the treatment of shock following coronary embolization in the dog indicate that vasopressor therapy is, again, either without benefit or associated with an accelerated course leading to death of dogs so treated.

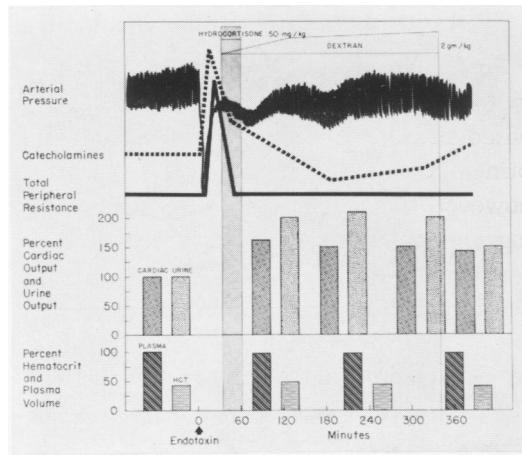

FIG. 20. When plasma or low molecular weight dextran is added to the hydrocortisone therapy, 80 per cent of dogs will recover from the lethal dose of endotoxin.

In contrast, substances which reduce peripheral resistance, such as phenoxybenzamine, are effective in reducing the mortality of dogs suffering coronary shock. Out of these studies also has emerged the concept that it is possible to utilize the positive ionotropic effect of l-norepinephrine on the heart, which is beneficial, while blocking its deleterious effects on the peripheral circulation (Fig. 21). This is done by combining phenoxybenzamine with l-norepinephrine, whereby it is possible to decrease peripheral resistance, while at the same time increasing cardiac output. This results not only from the increased venous return as a result of reduced peripheral resistance, but also from an increased force of contraction of the myocardium. Isoproterenol (Isuprel) has an action similar to the combined effect of phenoxybenzamine and l-norepinephrine. This drug stimulates beta receptors in the heart to increase cardiac output, mainly through increased rate, while at the same time activating beta receptors located principally in the peripheral circulation of the striated muscles to cause vasodilatation and decreased peripheral resistance.

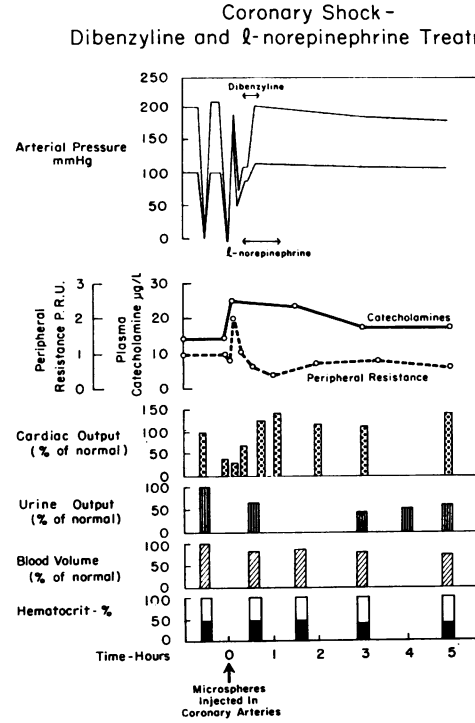

FIG. 21. In coronary shock in dogs resulting from embolization of the coronary arteries, a combination of phenoxybenzamine and l-norepinephrine is an effective treatment. In this pairing of drugs, peripheral resistance is lowered by the phenoxybenzamine which also blocks the peripheral adrenergic stimulating effects of the l-norepinephrine on alpha receptors in the tissues. The stimulating effect on the heart of l-norepinephrine (ionotropic effect) is apparently medicated by beta receptors which are not blocked by phenoxybenzamine. Thus, this appears to be an ideal combination in those conditions where there is a damaged heart, since cardiac output is increased and peripheral resistance is decreased.

Clinical Studies in the Treatment of Myocardial Failure and Shock

So far we have not had the opportunity to treat patients with shock due to diagnosed myocardial infarct according to the principles put forth in this study. We have, however, for the past two years been treating and pretreating patients who undergo cardiopulmonary bypass for repair of difficult congenital or acquired defects which will require more than one hour of bypass for correction. This has been done because of the frequent occurrence of myocardial failure and consequent low output syndrome which may follow a prolonged period of bypass. These problems arise, we believe, when a high peripheral resistance due to high levels of plasma catecholamines is imposed upon an already weakened heart.[16, 25]

For pretreatment, patients have received 1 mg./Kg. of phenoxybenzamine given intravenously one to two hours before going on cardiopulmonary bypass. This dosage has usually been given after the chest has been opened, but it is also possible to give this same dosage the night prior to operation, since the duration of action of phenoxybenzamine is about 24 hours. If administered the night prior to operation, it is

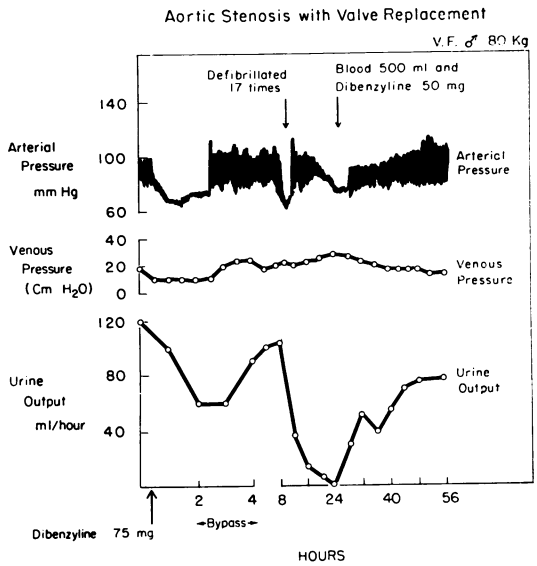

FIG. 22. This patient was pretreated prior to cardiopulmonary bypass with phenoxybenzamine. He did quite nicely for a few hours after surgery and then fibrillated repeatedly, but was successfully defibrillated each time. Despite the repeated fibrillations which are usually associated with oliguria or anuria, the patient's urine output remained good. About 24 hours after surgery, when the effects of the phenoxybenzamine had worn off, the patient went into congestive failure and shock. A repeat dose of phenoxybenzamine and added blood lowered central venous pressure and increased urine output, while also effectively treating the congestive failure and shock.

important to keep such patients in bed until operation to avoid orthostatic hypotension.

This form of pretreatment has been used in over 200 patients so far and, while controls for this type of clinical study can never be as rigid as in the laboratory, the results of such prophylaxis have been good. Similar to our experimental studies, we have found that phenoxybenzamine does not prevent the rise of plasma catecholamines associated with cardiopulmonary bypass, but it does reduce or prevent the adverse effects of these vasoactive substances on the peripheral circulation. With excessive vasoconstriction eliminated, better perfusions are obtained. Such patients continue to secrete urine during bypass at an average rate of 1 ml./Kg./hr. of bypass. The continued renal function gives evidence of improved visceral organ blood flow, since our previous experience has been that patients are usually oliguric or anuric during a prolonged bypass. At the end of the bypass in pretreated patients, the surgeon can instruct the anesthesiologist to continue transfusion until arterial pressure is normal, since low arterial pressure means low blood volume in the face of adrenergic blockade.

In the recovery room, the patient appears warm and pink, with a wide arterial pulse pressure and normal or low venous pressure. Postoperative blood volumes are often identical with preoperative measurements and urine output continues adequate. In fact, postoperative anuria has not occurred, since phenoxybenzamine has been utilized in this fashion.

In following patients after open-heart surgery who have been pretreated with phenoxybenzamine, an interesting observation has been made. A few patients, who have initially done well, have then manifested signs of myocardial failure and shock 24 to 36 hours after open-heart surgery. This is coincident with the waning effect of the phenoxybenzamine. In these patients, the adrenergic blockade with phenoxybenzamine has been renewed (1 mg./Kg. intravenously) and this has coincided with recovery from the myocardial failure and shock. Often additional blood or plasma has been found necessary in these patients who, prior to renewal of the blockade, were in congestive heart failure, with excessive elevations of central venous pressure in the face of blood volume deficits (Fig. 22). If an attempt was made to expand the blood volume without adrenergic blockade, the congestive failure worsened in such patients. From these observations, we believe that reduction of excessive peripheral resistance is of value not only as a form of prophylaxis, but also as treatment for patients suffering myocardial failure not responding to the usual methods of treating this condition.

A Unified Concept of Shock

In the foregoing discussion, we have indicted excessive peripheral resistances as a constant concomitant as well as a probable cause of irreversible shock due to a variety of causes. Both experimental and clinical evidence has been presented to support this indictment, but we do not imply here that the death of all patients suffering prolonged shock is a result of damage to the splanchnic viscera, although gastro-intestinal changes may have more consequences than we usually accord to them. We definitely believe, however, that the basic hemodynamic disturbances caused by prolonged shock, whatever the cause, are similar in dog and man or in any of the mammalian species. The differences among the various animals and man appear to be in the susceptibility of the various organs to the hemodynamic disturbances of shock, a hierarchy of sensitivity occurring through evolutionary changes. In the dog, the gut is unusually sensitive to the effects of anoxia and this apparently is related to the architecture of the vascular system of the canine bowel as described by Spanner.[29] In his studies, Spanner found that the end arteries of the small intestine of the dog were in the mucosa which placed it as the layer of bowel farthest from the heart. Moreover, arteriovenous shunts in the submucosa divert blood from the mucosa during periods of low flow, which leads to the early appearance of mucosal damage in the dog. In contrast, the end arteries of the human intestine are in the submucosa and it is this layer in the bowel which suffers the first ravages of ischemia. This anatomical pattern may explain the appearance of pseudomembranes of the small bowel which may follow shock in the human. It should also be noted here that there are an increasing number of reports of intestinal infarction occurring in patients in congestive heart failure. At autopsy these patients show no organic obstruction in the superior mesenteric vasculature; the infarction apparently being a result of splanchnic vasoconstriction intensifying the anoxia accompanying low cardiac output.

There are other species differences as well. The lungs of the rabbit and cat are especially susceptible to the effects of the profound vasospasm resulting from endotoxins. Here again, the human findings are similar for it is unexplained tachypnea, dyspnea and cyanosis which often herald gram-negative bacterial shock in the human. When such patients die, we find that the endotoxin has damaged the lungs in a manner similar to that described above for the gut of the dog. The lungs of the dog are also damaged by endotoxin but the changes are not as striking as those in the bowel unless the dog lives beyond 18 hours.

In man, again, obvious pathologic signs of shock are seen in the kidneys. The failure of this organ is often a cause of late death in patients suffering gram-negative septicemia who survive the initial shock. Despite these differences in the target organs of shock in various species of mammals, it is encouraging that treatment with pharmacologic doses of hydrocortisone or with phenoxybenzamine results in increased survival rates in a variety of animals, as well as in man in our own experience and in the experience of others.[23, 24, 27, 32]

The Heart in Shock

One should not interpret these remarks as indicating that we believe there is no cardiac factor in the genesis of irreversible shock. Still, the available evidence from experimental studies and clinical observations clearly shows that the normal heart is more resistant than the other viscera to the hemodynamic disturbances of shock. Yet even the most normal heart will eventually succumb to the increased peripheral resistance, decreased venous return and acidosis attendant on shock. The heart which is not normal to start with will fail even earlier.

TABLE 9. *Interrelationship Between Shock Due to Epinephrine, Endotoxin and Hemorrhage*

Group	No. Dogs	No. Survivors[1]
Hemorrhagic shock "controls"	41	2
Hemorrhagic shock in endotoxin tolerant dogs	10	9
Hemorrhagic shock in epinephrine tolerant dogs	10	8
Endotoxin shock "controls"	90	6
Endotoxin shock in epinephrine tolerant dogs	10	7
Epinephrine shock "controls"	10	1
Epinephrine shock in endotoxin tolerant dogs	10	9

[1] Survived 72 hours or more.

Hence, it appears to us that cardiac function is enhanced more by reducing peripheral resistance, which insures a more normal peripheral tissue blood flow with all that this implies, than by raising peripheral resistance artificially in an effort to enhance coronary perfusion. The salutary effects of reducing peripheral resistance in man to improve cardiac function after open-heart surgery have already been cited. In contrast, there are few instances in the same situation where prolonged vasopressor therapy has salvaged the patient.

Since there appears to be no basic difference between myocardial failure following open-heart surgery and that following myocardial infarction (both are caused by a damaged myocardium) we believe that these principles of treatment cited above should be considered for those patients suffering shock due to myocardial infarcts who do not respond to the conventional treatment. Indeed, it would appear that vasopressors unaccompanied by some form of adrenergic blockade may also be harmful in these patients.[9, 19] The reader should be reminded that the mortality of coronary shock in humans is still 60 per cent.[1] The mortality rate for bacterial shock in patients with positive blood cultures is also over 50 per cent.[20, 31] Hence, we have no reason to feel complacent about our current methods for treating these conditions.

Treatment of Shock by Induced Tolerance

Another method to demonstrate that there is a basic hemodynamic peripheral vascular disturbance in shock from varied causes is by producing cross-resistance or tolerance to shock, Table 9.[11, 14] For example, if dogs are injected with gradually increasing amounts of epinephrine intravenously over a several-week period, they eventually become tolerant to a lethal dose of epinephrine. Once having reached this state, these dogs are also able to withstand lethal doses of endotoxins or lethal periods of hemorrhagic shock. This same cross-resistance to shock is seen in dogs which are gradually made tolerant to increasing doses of intravenous endotoxin over a period of weeks. These endotoxin-tolerant dogs are then resistant to lethal doses of epinephrine or lethal periods of hemorrhagic shock. In tolerant dogs, the endogenous catecholamine response to shock is less than is usually seen. As a result, blood volume, peripheral resistance and organ blood flows also remain at more normal levels (Fig. 23). Studies are continuing to produce tolerance to coronary shock with endotoxins or epinephrine.

Philosophy, Evolution and Shock

A frequent question during such discussions concerns the philosophy of this theory of irreversible shock. Why in the evolution of man did this vasoconstrictive response to stress survive if it is harmful? It is our opinion that the endogenous vasoconstrictive response of the organism is a beneficial one in the short run, and this is especially true when no treatment of any kind is available. After all, in our evolutionary ascent up from the ocean mud there were no physicians available to give any treat-

ment, good or bad. This endogenous vasoconstrictive response alone will spare us problems from many lesser traumas, as witnessed by the ease of the 500 ml. blood donation which make our blood banks possible. What we are dealing with now, however, is the long run. Nature never dreamed of the trifling that men would do with her product in prolonging life, where "survival of the fittest," if allowed to operate at will, would have eliminated the problem altogether. There is no real harm in this natural vasoconstrictive response for a short period, but we clearly should not add to it by giving those substances which cause additional and excessive vasoconstriction. Instead, we should consider Nature's reaction as first aid until the doctor arrives and then institute a regimen such as that described below.

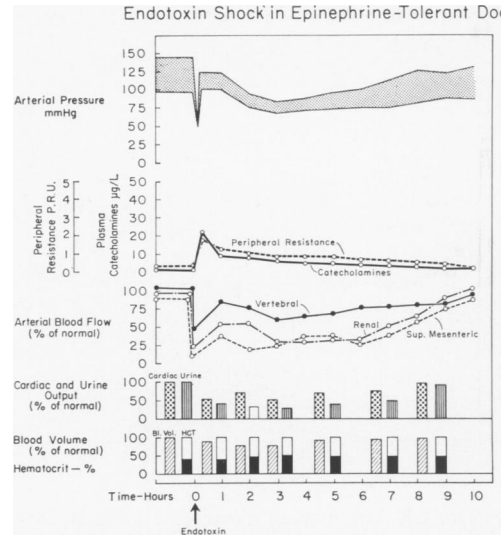

FIG. 23. Dogs made tolerant to large doses of intravenous epinephrine are able to survive lethal doses of endotoxin. This apparently results from the ability of the tolerant dogs to react less violently to the sympathomimetic effects of the endotoxin. Epinephrine-tolerant dogs are also able to survive usually lethal periods of hemorrhagic shock, probably for the same reason. Tolerance to lethal epinephrine or hemorrhagic shock can also be induced in dogs with endotoxin.

A Program for Man

There seems little reason to doubt that the physiologic disturbances of shock in man differ in any significant manner from that described for the dog. The problem in clinical studies of shock is to define irreversible shock in man with the same preciseness that it can be done in the experimental laboratory. Our preference is to designate patients as suffering from irreversible shock when they either respond only temporarily or fail completely to respond to the administration of blood, plasma or plasma substitutes. With this as a working definition, the following protocol is used in the treatment of shock in man.

Our initial efforts are directed at getting an intravenous catheter advanced into the superior or inferior vena cava via a puncture or cutdown in the neck or groin. This catheter is used to take blood cultures, measure central venous pressure and administer fluids. Perhaps 80 per cent of patients thought to be suffering from irreversible shock have merely been undertransfused. Often, if there is no obvious trauma or blood loss, the patient is assumed to have a normal blood volume. Perhaps a blood volume has been determined and is found to be in the normal range, yet the patient may still have a significant deficit in the circulating blood volume. The best measure of the adequacy of the circulating blood volume, in our estimation, is observation of changes in the central venous pressure with transfusion. If this determination is below 12 cm. of saline, blood or plasma should be administered as long as the central venous pressure stays within this limit. Often a liter or more of plasma or blood may be needed despite the fact that there have been no apparent losses.

When one is satisfied that the circulating blood volume is adequate, and there is still little or no response of the patient, our preference is then to give the adult patient 2 Gm. of hydrocortisone (Solu-Cortef) intravenously over a period of a few minutes. This dose is repeated in 1–2 hours. Additional amounts of plasma are then also

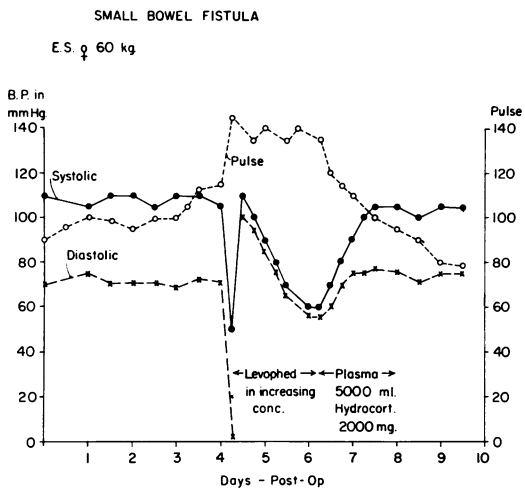

FIG. 24. This patient developed a small bowel fistula and shock a few days following intestinal surgery. L-norepinephrine in increasing concentrations failed to resuscitate the patient and she was then given 2 Gm. of hydrocortisone in a single dose followed by 5 liters of plasma. A blood culture taken during the initial shock subsequently grew out Pseudomonas. The patient recovered after a prolonged period of dependent drainage on a Foster frame.

given as this pharmacologic dose of hydrocortisone gradually reduces peripheral resistance and expands the size of the vascular space. With this combination of fluids to restore losses, and corticosteroids to correct disturbances in the hemodynamics of the peripheral circulation, most patients are resuscitated from their shock (Fig. 24). The cortisone therapy is usually stopped abruptly after resuscitation of the patient, without tapering off the dosage.

The problem is not yet solved, however, for the physician must be persistent in finding the cause of the shock where it is not evident. If bacterial shock with gram-negative organisms is suspected, then the source of the infection must be found, for even the most effective therapeutic regimen will ultimately fail if there is a continuing seeding of the blood with endotoxin from a reservoir of infection.

Recognition of Bacterial Shock

Infection with gram-negative bacteria is so often either a primary, or at least contributory, cause of the development of irreversible shock in man that this condition is suspected in all patients who have not responded to volume replacement. There is no better start in the recognition of bacterial shock than to have a high index of suspicion. Usually a careful history will lead one to suspect this dread complication. Often the patient has had recent operation, or urological instrumentation, or a history of urinary tract infection. Several physical signs need emphasizing which also lead one to suspect gram-negative bacteria as causing or abetting the shock. Unexplained tachypnea and/or dyspnea frequently herald impending bacterial shock. These respiratory signs in man apparently reflect, in part, a profound metabolic acidosis resulting from the disturbances in the peripheral circulation caused by endotoxins. While the blood pH is usually low, carbon dioxide tensions in the blood are also low or normal indicating that a CO_2 diffusion problem is not at fault. There may, in addition, be evidence of cyanosis which can be confirmed by determination of arterial saturation. This low saturation likely reflects both a depressed cardiac output and a disturbance in oxygen uptake in stagnant pulmonary capillary beds which are affected by endotoxin in a manner similar to that described for the splanchnic circulation.

Another harbinger of septicemia is unexplained jaundice. This, in the presence of tachypnea, indicates a process which can end in death in a few hours. All of these ominous signs of septicemia are usually ushered in by temperatures often exceeding 39.4° C., although this is not always the case, exceptions being especially common in the aged patient where hypothermia can occur. Any or all of these signs indicate that therapy for the shock must be carried out with dispatch.

Use of Antibiotics

If there is even a remote possibility that infection is involved in the genesis of the

shock, wide spectrum antibiotics should be started at once, but only after cultures of blood and urine and other suspected sources of infection are taken. Our preference is to give adults 1 Gm. of chloramphenicol, 500 mg. of tetracycline and one million units of penicillin, all intravenously initially and then at 4 to 6-hour intervals. Streptomycin, 0.5 Gm. intramuscularly, can also be given twice daily. When culture and sensitivity results are available, this wide spectrum of antibiotics can be narrowed. If, however, one waits for culture results before starting antibiotics in a patient with septicemia, he will rarely have a live patient available for antibiotic treatment. A word also about blood and other culture results. Such cultures may frequently be sterile in the face of septicemia, because antibiotics have so often been used prior to the shock. Even though the bacteria are resistant to the antibiotics previously used, these antibiotics will frequently prevent the *in vitro* growth of the offending bacteria on culture media.

Use of Phenoxybenzamine

The regimen outlined above will in most cases bring the patient out of shock and restore urine output, allowing time for the physician to discover and treat the cause of shock. In patients who do not respond to the above protocol, we have added 1 mg./Kg. of phenoxybenzamine (Dibenzyline) intravenously. There are two good reasons for advocating the use of hydrocortisone initially, instead of phenoxybenzamine. First and most practical, phenoxybenzamine is not available for general use because it has not been approved by the Federal Drug Administration. Secondly, phenoxybenzamine acts within minutes to decrease peripheral resistance and increase the size of the vascular space in contrast to the similar, but more subtle action of pharmacologic doses of hydrocortisone. Thus, a patient in shock may have a further depression in blood pressure if phenoxybenzamine administration is not accompanied by simultaneous volume replacement; hence, we believe that until physicians develop a wider experience with rapid-acting adrenergic blocking agents, it is safer to use hydrocortisone as the initial treatment of apparent irreversible shock in patients. However, when cardiac failure is a primary concern, the use of phenoxybenzamine is to be preferred to hydrocortisone because of this rapidity of action. A further delineation of the use of this drug is given immediately below.

Cardiac Problems and Shock

A recurring problem in the treatment of shock in the older patient is the finding of an elevated central venous pressure in the face of hypovolemia. Such a finding requires rapid digitalization before the hypovolemia can be fully corrected. Few would quarrel with the use of digitalis where overt failure is obvious; however, there are good reasons to use digitalis in any situation where the heart is laboring under adverse conditions such as in shock. Crowell has shown that prophylactic digitalization of dogs with normal hearts protects them from the myocardial depression consequent to hemorrhagic shock and also allows the dogs to survive longer periods of shock at higher oxygen debts.[4]

Even more pertinent in this discussion are the findings of Braunwald in his human studies.[2] Here, digitalis was shown to increase the force of the non-failing heart as well as lower the oxygen debt of nonfailing human hearts. It is our belief that digitalization is indicated in almost all patients, beyond the age of 50, suffering shock not immediately responding to treatment. Such a statement may shock some physicians, but with proper assessment of serum potassium levels, there is much to be gained by such therapy. Still, congestive failure may persist in a small group of patients in shock, despite digitalization and other usual meth-

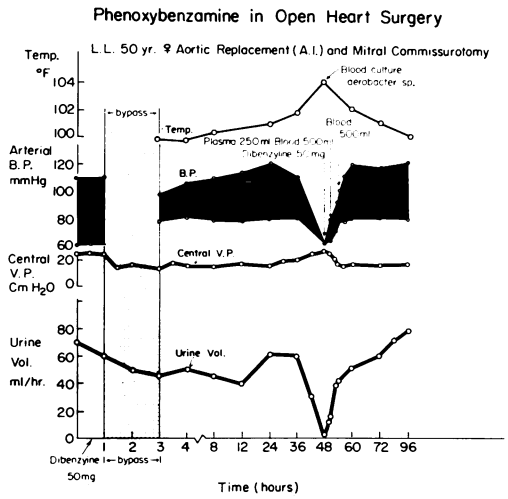

FIG. 25. This patient was pretreated with phenoxybenzamine prior to her open-heart operation and did nicely until the second postoperative day when she suffered septicemia and shock, further complicated by congestive failure. By this time, the initial phenoxybenzamine therapy had worn off and so she was given a repeat dose of this substance along with added blood and plasma. This treatment effectively restored her disturbed central and peripheral hemodynamics. The source of the Aerobacter was a pneumonitis.

ods for treating the cardiac problem. It is here that the rapid action of phenoxybenzamine is lifesaving, because it will expand the size of the vascular space, shift blood out of the pulmonary circulation and reverse pulmonary congestion, reduce the work of the heart and allow needed replacement of blood volume to insure adequate peripheral circulation (Fig. 25, 26). With such an adrenergic blockade, it may now be proper to administer a drug such as l-norepinephrine for its central cardiac stimulating effects without fear of disrupting the peripheral circulation and increasing the work load of the heart.

Summary and Conclusions

When patients in shock respond temporarily or not at all to blood, plasma or plasma substitutes, they are thought to be in irreversible shock. Our studies in the dog indicate that whether shock is induced by hemorrhage, bacterial endotoxins, epinephrine, or myocardial failure, there is a final common hemodynamic disturbance in the peripheral vascular bed. This disturbance is characterized at first by *ischemic anoxia* in which both the precapillary arterial sphincters (resistance vessels) and postcapillary venular sphincters (capacitance vessels) are tightly constricted, thus allowing little blood to enter the splanchnic bed. This is the period of reversible shock and lasts about 2–3 hours in the dog, regardless of the original insult. Within 4–5 hours, irreversible shock supervenes and is characterized by *stagnant anoxia* in which the precapillary arterial sphincters have lost their tone while the postcapillary sphincters are still constricted. Now blood can get into the splanchnic bed but exits with difficulty, and hydrostatic capillary pressure

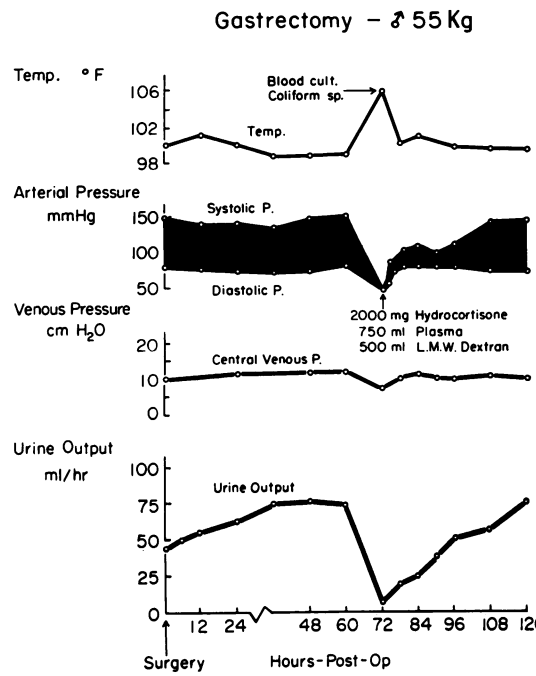

FIG. 26. This man was successfully resuscitated from profound shock due to a Coliform species. The endotoxin of this organism initially caused such an intense peripheral vasoconstriction that the patient developed gangrene of fingers, toes and nose following recovery from the shock. The source of the septicemia was probably from atelectatic lung.

increases. As a result, plasma begins to leave the vascular system at the venous end of the capillaries and circulating blood volume is progressively decreased. As shock is further prolonged, the capillary beds lose their integrity and slough, allowing whole blood to sequester outside of, as well as inside, the vascular system. During this period, myocardial function, which already is suffering from decreased venous return, is even more severely depressed by the acidosis attendant on the peripheral circulatory stagnation. It is clear now why fluids added at this time are of only temporary benefit, for what is needed in addition to fluid replacement is some means of correcting the imbalance between the arterial and venular sphincters to prevent further stagnation. In numerous animal experiments, we have found that the combination of the adrenergic blocking agent phenoxybenzamine (Dibenzyline), 1 mg./Kg. intravenously, and plasma or low-molecular-weight dextran is an effective means for salvaging dogs from irreversible shock induced by various methods. Hydrocortisone when given intravenously in doses of 50 mg./Kg. acts also as an adrenergic blocking agent and restores normal relationships in the capillary bed even more effectively than Dibenzyline. The volume of plasma or dextran given, over and above replacement of known losses, often exceeds 25 ml./Kg. and is determined solely by the central venous pressure rather than by the blood volume. This is because measurements of blood volume in shock do not accurately reflect effective circulating volume. The adequacy of the circulating blood volume is best judged by observations of changes in central venous pressure. The effectiveness of this therapy is assessed by its influence on cardiac output, organ blood flow, selective and total peripheral resistance, central venous pressure, catecholamines, acid-base balance and renal function, as well as upon survival of the animal.

With this background as our guide, we are now treating patients suffering shock from trauma, infection, myocardial failure or combinations of these insults, with a regimen including pharmacologic doses of hydrocortisone or phenoxybenzamine in combination with blood, plasma, or dextran. The salutary results in these patients give added support to our belief that shock in man and animals is similar. This is not to say that all aspects of shock are identical, for we know that the visceral organs which suffer the ravages of shock may vary among the species. Rather, these findings support our concept that the basis for irreversible shock resides in a disturbed peripheral circulation and we should make use of this knowledge to improve our results in treating patients.

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