CLINICAL PROGRESS

Current Concepts on the Management of Shock

By Max H. Weil, M.D., Ph.D.

SHOCK is a descriptive term used by clinicians to denote a syndrome that is characterized by protracted prostration and hypotension and usually is accompanied by pallor, coldness and moistness of the skin, collapse of superficial veins, alteration of mental status, and suppression of the formation of urine. A voluminous literature reflects intense disagreement over the meaning and the significance of the term. Most of this, however, results from the use of a single name to describe a condition produced by many unrelated causes; occasion for disagreement disappears if the term shock is used within the limits of its definition—namely, to indicate the clinical state of the patient without specific implication as to the underlying cause.

"Vasomotor collapse" and "peripheral vascular failure" are frequently employed by authors to circumvent the dispute aroused by use of the term shock. These names are subject to the same misunderstanding and add hemodynamic implications that may be misleading. Shock simply refers to the presenting signs of the patient, and within this limit the term is valid and meaningful.

Hemodynamic Mechanisms in Shock

In order to give a patient the advantage of rational and effective treatment, it is essential to determine in each case the specific cause of shock. Yet, at the same time, it is possible and helpful to think of a general mechanism that is involved. To illustrate the relationship between a specific mechanism and the general mechanism, the results of some recent investigative studies may be cited.

From Overwhelming Infection. The cause of shock that occurs during overwhelming infections due to gram-negative bacteria has been studied in laboratory dogs after intravenous injection of endotoxins derived from Brucella melitensis or Escherichia coli. Within 1 minute following such an injection, arterial pressure falls sharply and portal venous pressure increases pronouncedly. The liver and intestines become engorged with blood, suggesting that the fall in arterial pressure and the elevation of the portal venous pressure result from pooling the blood in the splanchnic venous bed. Direct measurements of the change of weight of the liver and intestines indicate that large amounts of blood are pooled in these organs. Measurement of venous flow into the heart demonstrates that the volume of blood returned to the heart is correspondingly decreased. When the cardiac output is determined, a quantitatively similar decline is observed which is the direct cause of the sharp fall in arterial pressure. A secondary and late feature involves electrocardiographic evidence of myocardial ischemia. This is attributed to reduction in blood flow through the coronary arteries because of the sharp decline in arterial pressure. The resulting reduction in coronary flow, if sufficiently prolonged, leads to defective myocardial contractility. Thus cardiac output declines further and arterial pressure falls even lower. These hemodynamic features, beginning with the reduction in effective volume of circulating blood caused by pooling, are presented schematically in figure 1. It is apparent that 2 vicious circles are established. One is related to pooling and the other to coronary insufficiency. These factors may intensify and propagate the state of shock long after the initiating disturbance has taken place.
Fig. 1. A model of the circulatory system illustrating the relationship of clinical conditions to hemodynamic disturbances that may lead to shock. The 6 numbers in this figure refer to the 6 causes of shock listed in Table 1.

From Other Causes. The schema serves equally well as a general outline of the mechanism involved in the development of shock from various causes. Table 1 provides a tentative classification of the various types of shock encountered in clinical practice. Six different mechanisms are listed, and each of them may be related to the general mechanism indicated in the figure.

Hypovolemia results from hemorrhage, dehydration, loss of protein, or capillary leakage. When one third of total blood fluid is lost, a critical point is reached at which the volume of blood is no longer sufficient to fill the vascular bed. The venous return and cardiac output are reduced to a level where compensatory vasoconstriction is insufficient to maintain the arterial pressure.

Cardiac failure may be caused by myocardial infarction or cardiac dysrhythmia. Failure of the cardiac pump reduces the cardiac output, sometimes severely enough to produce shock. Hypersensitivity and, particularly, anaphylactic reactions are not completely understood. Present evidence, which is also based on studies in dogs, indicates that shock associated with these phenomena is mainly the result of sudden constriction of small hepatic veins followed by pooling of large quantities of blood in the portal venous bed, which leads to sudden reduction in venous return and cardiac output. Thus the initial hemodynamic disturbance is similar to that of shock associated with bacteremia, already described in some detail.

In the absence of normal vasoconstrictive impulses that follow transection of the spinal cord, sympathectomy, administration of certain anesthetic agents, or drug-induced ganglionic blockade, normal neurogenic control of the caliber of blood vessels is lost. Vasodilation may increase the capacity of the peripheral vascular bed, and especially the venous bed, to such an extent that the volume of blood is inadequate to fill this large space. The condition results in critical reduction of the venous return and cardiac output. Contrary to earlier concepts, loss of venomotor tone rather than decrease of arteriolar resistance appears to be the major defect in this type of shock.

Finally, there is a type of shock that is brought about by physical obstruction of a main thoroughfare, so that the total blood flow is inadequate to maintain circulation, and therefore venous return and cardiac output are insufficient. The basic mechanism is analogous to the chain of effects from stepping on a garden hose. Pulmonary embolism and dissecting aneurysm are examples.

### Table 1—Classification of Specific Causes of Shock

<table>
<thead>
<tr>
<th>No.</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Hypovolemia</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage, dehydration, loss of protein</td>
</tr>
<tr>
<td>2.</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction, cardiac dysrhythmia</td>
</tr>
<tr>
<td>3.</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis, reaction to drugs</td>
</tr>
<tr>
<td>4.</td>
<td>Bacteremia</td>
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<tr>
<td></td>
<td>Bacterial toxins (endotoxin)</td>
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<tr>
<td>5.</td>
<td>Neurogenic factors</td>
</tr>
<tr>
<td></td>
<td>Vasomotor paralysis, spinal shock, ganglionic blockade</td>
</tr>
<tr>
<td>6.</td>
<td>Impediment to blood flow</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism, dissecting aneurysm</td>
</tr>
</tbody>
</table>

Vasopressor Agents

The value of vasopressor agents in the treatment of some patients with shock has been widely recognized. Important considerations are the selection of a suitable pressor amine and the definition of the specific circumstances in which this type of drug is indicated.

The most potent vasopressor agents presently available are norepinephrine, or levartenol (Levophed), and metaraminol (Aramine). Less potent drugs such as methoxamine (Vasoxyll, phenylephrine (Neosynephrine) and
mephentermine (Wyamine), which are available for the treatment of more transient forms of hypotension, will not be discussed here.

Effects of Levarterenol and Metaraminol. Levarterenol and metaraminol are useful allies in the treatment of shock caused by myocardial infarction, bacteremia, or hypersensitivity reactions, and usually provide a favorable effect against neurogenic shock. The beneficial effects in cardiogenic shock are related only in part to the improvement of coronary blood flow that follows elevation of the systemic blood pressure. Recent studies have shown that both these drugs have a direct beneficial effect on the myocardium, increasing the contractility of the myocardial fibers and thereby increasing cardiac output.5, 10 In experiments with bacteremic shock in dogs, these drugs have been shown to remedy pooling by reducing obstruction to outflow from the splanchnic venous channels in which the large quantities of blood are pooled.11 Similar considerations pertain to the use of pressor amines in the treatment of shock caused by hypersensitivity to drugs or foreign proteins. For immediate treatment of acute anaphylactic shock, which sometimes is accompanied by bronchoconstriction and increased resistance to the flow of blood through the lungs, epinephrine rather than levarterenol or metaraminol appears to be the agent of choice. For neurogenic hypotension, levarterenol and metaraminol are particularly apt and helpful, as they produce vasoconstriction by substituting the sympathomimetic action of these drugs for the vasoconstrictive action that is normally supplied by the sympathetic nervous system.

Seldom Indicated in Hypovolemia and Circulatory Block. The use of vasopressor drugs in the treatment of hypovolemic shock is only occasionally justified. Treatment in these patients requires replacement of the fluid that is lost. Blood, plasma, and electrolytic fluids are used in amounts that are calculated to re-establish normal volumes and concentrations in the intravascular space. The clinician will be guided in his selection of fluids by the history of fluid loss and also by laboratory study of the relative volumes and concentrations of blood cells, plasma, and electrolytes. In spite of its antigenicity, dextran possesses most of the attributes of an ideal plasma expander.12 Used as a 6 per cent solution in isotonic saline, it is an expedient measure for treatment of hemorrhagic shock when whole blood or plasma is not immediately available. If shock persists after replacement of fluids, secondary pooling of blood and myocardial failure may be responsible in the vicious circles already described.13, 14 This situation, which is referred to as “irreversible shock” by some authors, is not unlike that which exists in bacteremic shock, a feature that has been stressed by Fine and his co-workers.15 In such instances, vasopressor agents may be helpful.

In the shock that results from physical impediment to blood flow, drugs that produce additional vasoconstriction are not ordinarily indicated.

Special Advantages of Metaraminol. Both levarterenol and metaraminol display the vasoconstrictive effects of epinephrine, but neither produces cardiac acceleration, stimulation of the central nervous system, or depression of the appetite.16 Levarterenol has the unfortunate disadvantage of injuring tissues at the site of injection. Deep ulceration involving the skin and subcutaneous tissues has been a disturbing complication of its use and on occasion has required subsequent skin grafting and even amputation.17, 18 In a recent report, Close and Kory19 have indicated that local infiltration of adrenergic blocking agents such as tolazoline hydrochloride (Priscoline) or phentolamine hydrochloride (Regitine) is an effective means of preventing this complication. Other undesirable features of the prolonged use of levarterenol include the transiency of its action, which necessitates administration under constant nursing supervision, and the need for large quantities of fluid vehicle when this may be undesirable because of inadequate excretion of urine. Metaraminol, on the other hand, causes no local injury to tissue. It may be injected by intravenous, intramuscular, or subcutaneous routes without additional fluid vehicle, and it manifests a prolonged period of action.16 In addition, metaraminol reportedly produces less constriction of the renal vessels than levarterenol for a dose that produces an equal
pressor response. This may be of particular advantage in patients in whom renal complications of shock cause the output of urine to be inadequate, even though vasopressor agents are used to maintain blood pressure at a satisfactory level.

Following intravenous administration, the pressor effect of metaraminol becomes manifest in 1 to 2 minutes, is maximal in 5 minutes, and persists for 20 to 25 minutes. After intramuscular or subcutaneous administration, a pressor response is observable in 5 to 12 minutes and maximal at approximately 30 minutes. The action of the intramuscular dose persists for only 50 minutes, but the action of the subcutaneous dose continues for 90 minutes. For this reason, the subcutaneous route has been favored for the treatment of patients whenever possible.

**Administration of Metaraminol.** The treatment of a patient with profound shock may be started with a single intravenous injection of 3 to 10 mg. of metaraminol, which usually produces a prompt elevation of blood pressure. When the peripheral veins are collapsed, the agent may be injected directly into the femoral vein, whereupon the arterial pressure is elevated and the peripheral veins become more normally distended. An intravenous infusion can be started then without difficulty, and thus a time-consuming and traumatic cut-down procedure is avoided. In most patients, the blood pressure is well maintained by the subcutaneous administration of 3 to 25 mg. of metaraminol with injection repeated every 1 1/2 to 2 hours. In patients who respond poorly, a continuous intravenous infusion of metaraminol in a dosage up to 500 mg. per L. may be administered. After satisfactory control has been achieved, the subcutaneous route is preferable. With improvement, the pressor response to metaraminol becomes more intense and requires reduction in dosage. My colleagues and I have found it more practical to reduce the amount of injections rather than their frequency until use of the agent is entirely discontinued.

**Review of Considerations.** The use of vasopressor agents has been criticized on the ground that they reduce blood flow by excessive vasocostriction. Brunson, Eckman, and Campbell have reported a high correlation between the administration of sympathomimetic amines to patients with shock and the finding of hepatic necrosis at postmortem examination. When these drugs are given to normotensive animals, vascular injury and extensive tissue damage may result. Nevertheless, there is now abundant evidence that the correct use of these drugs in selected patients with profound shock is not accompanied by undue risk of damage to vital organs. In the presence of severe hypotension and the absence of hypovolemia or physical obstruction to blood flow, a point is reached beyond which administration of these agents results in an increase rather than a reduction in blood flow to vital organs.

**Influence of Acidosis on Vasopressor Response**

Clinical observations have indicated repeatedly that patients with co-existent shock and acidosis respond poorly to vasopressor agents. In this connection Burget and Visscher noted in 1927 that the response of the vascular system of the pithed cat could be altered by changing the pH of the blood, and that the response to epinephrine progressively increased as the pH was increased from 6.9 to 8.0. More recently, Page and Olmsted demonstrated that the pressor action of epinephrine and levarterenol was diminished in dogs with respiratory acidosis. These facts suggested that similar considerations would pertain to patients with shock and acidosis.

**Findings in Dogs.** To test this idea, epinephrine, levarterenol, and metaraminol were administered to dogs under conditions of respiratory acidosis produced by the inhalation of 30 per cent carbon dioxide, and their reactions were contrasted to the response obtained when the pH was normal. The pressure and pH of arterial blood were recorded, and an electrocardiogram was obtained. It was found that in the presence of acidosis the pressor responses to each of the sympathomimetic drugs was somewhat diminished. Ventricular rhythm was not affected during acidosis, although marked dysrhythmia followed administration of these agents to dogs in the control.
state. Pressor responses and cardiac dysrhythmias produced by epinephrine, norepinephrine, and metaraminol were also diminished in a similar group of test animals under conditions of metabolic acidosis produced by intravenous infusion of a dilute solution of hydrochloric acid.28

These coincident findings with respect to cardiac rhythm were interesting in themselves, and especially so in relation to the recent studies by Bellet, Wasserman, and Brody.29 These authors reported that molar solution of sodium lactate increases the ventricular rate in patients with Stokes-Adams disease and proposed it for the treatment of this condition. It seems likely that the effectiveness of molar solutions of lactate is due, at least in part, to the increased activity of endogenous epinephrine and norepinephrine which is brought about by elevation of blood pH.

In order to separate the effect on cardiac rhythm from vasopressor effect, these same agents were administered to dogs subjected to total cardiac bypass. After the heart was excluded from the circulation, pressor responses under conditions of respiratory acidosis were uniformly much less than those obtained in the same animal after the pH was returned to or near normal levels.28

Effect of Molar Lactate in Patients. It was decided then to study at the bedside the value of correcting the acidosis by infusion of a molar solution of lactate. Six patients who had co-existing bacteremic shock and acidosis were treated. All six had received large doses of levaterenol or metaraminol before the studies, but in spite of this the mean arterial blood pressure was rarely more than 40 to 60 mm. Hg. The pH of arterial blood prior to treatment was as low as 7.06; following administration of 300 to 1,000 ml. of molar solution of sodium lactate, the pH was elevated to a maximal value of 7.51. During and after the intravenous administration of sodium lactate the blood pressure returned to near the normal range even though the infusion of vasopressor agents was decreased or discontinued. None of the patients survived for more than 7 days in spite of this treatment. However, it was significant that response to the vasopressor agents was restored by sodium lactate after the usual measures had failed.20

In view of the limited accumulation of clinical experience on the use of sodium lactate in the treatment of shock, conclusions regarding its value and the possible dangers involved in its use must await additional observations. For the present, it seems worthy of trial when all else has failed. Molar solution of sodium lactate is administered by continuous intravenous infusion at a rate of 5 ml. per Kg. of body weight per hour until a pH of approximately 7.50 is achieved. The average total dose in patients with moderately severe acidosis is believed to be approximately 10 ml. per Kg. of body weight.

**Adrenocortical Hormones**

*Insufficiency and Shock.* The ease with which shock may be precipitated in adrenalectomized animals is well documented. Their extreme susceptibility is diminished but not removed when these animals are sustained through treatment with saline. When they are optimally treated with adrenocortical hormones, normal susceptibility is re-established.31 Similar considerations pertain to human patients with adrenocortical insufficiency. Thus the appearance of shock during an acute illness or following a minor injury may be the presenting sign of previously unrecognized Addison’s disease. The administration of adrenal steroids is specific treatment. Clinicians recently have become aware of adrenocortical insufficiency in patients who have been treated with lengthy courses of cortisone or one of its analogs. Fatal circulatory failure has followed even minor surgical procedures on such patients when steroid therapy was withheld in the post-operative period.32-34 Special precautions are necessary to assure preoperative and postoperative administration of these hormones, and such patients should be carefully observed and promptly treated if evidence of acute adrenal insufficiency becomes manifest.

These facts notwithstanding, there is no clear evidence that adrenal insufficiency usually is involved in the causation or progression of shock. Recent clinical reports have created doubt that adrenal insufficiency due to hemor-
rhage into the adrenal glands is a major factor in shock associated with acute meningococcal septicemia (Waterhouse-Friderichsen syndrome).35, 36

Use in Treatment of Shock. The corticosteroid drugs nevertheless have a definite place in the treatment of certain patients with shock. An important therapeutic action of these hormones is the suppression of inflammation, and particularly the suppression of the systemic reaction to inflammation. For this reason they have been employed in the treatment of patients with bacteremic shock or shock related to a severe hypersensitivity reaction, and, on occasion, surgical patients with shock related to extensive tissue injury.37-39 By suppression of the manifestations of inflammation in a critically ill patient with high fever, rapid pulse, and hypotension, a period of grace is provided during which normal circulatory adjustment may be re-established and specific treatment instituted. These considerations apply only to instances of shock in which inflammation plays an important role.

Clinical and experimental evidence indicates that corticosteroids may potentiate the action of vasopressor agents.40-42 The steroid drugs have been used with some success to re-establish or increase response to vasopressor agents in patients with shock.

Spink39 has reviewed the indications for and the dangers involved in the use of corticotropin (ACTH) and the adrenal steroids in these critically ill patients. He has emphasized that the steroid drugs have profound metabolic effects that may be avoided by giving them for only brief periods. Although ACTH and the adrenal cortical hormones aggravate infection, the presence of infection should not deter from their use, provided that appropriate antibiotic therapy is given concomitantly.

For the treatment of these patients an initial intravenous injection of 50 to 100 mg. of hydrocortisone sodium succinate (Solu-cortef) is advised. Maintenance therapy for a period of from 1 1/2 to 5 days is provided by the continuous intravenous infusion of hydrocortisone (free alcohol) in proper dilution to supply 5 to 12 mg. per hour.

Indications for Use of Digitalis Glycosides and Atropine

Before vasopressor agents became available, digitalis was rather often employed in treatment of hypotensive states. It is apparent now, however, that digitalis is only occasionally of value and that it should be reserved for those instances in which specific indication exists—namely, congestive heart failure and cardiac dysrhythmia of supraventricular origin. Its use at other times may cause further decline in cardiac output and thereby intensify shock.

On occasion, severe hypotension may be caused in part by excessive vagal activity. This state actually may be worsened by the use of vasopressor agents, for they excite increased vagal activity with cardiac slowing.16 Electrocardiographic study of patients in this condition may indicate bradycardia with lack of impulse formation at the sinus node. The administration of 0.6 mg. (.01 gr.) of atropine sulfate has provided gratifying improvement in pulse rate and arterial pressure in such instances. Fortunately only the vagotonic and not the vasopressor action of levartenol and metaraminol is inhibited after such use of atropine. The effectiveness of the pressor amines is therefore not hampered. In selected instances atropine can be of remarkable benefit for the treatment of patients in shock.

Present Status of Chlorpromazine, Heparin, Hypothermia, and “Head-Down” Posture

Chlorpromazine hydrochloride is the principal ingredient of Laborit's lytic cocktail,43 which has been widely discussed, particularly in popular magazines and newspapers, as the “hibernation” treatment of shock. Pretreatment with chlorpromazine reduces the mortality of animals following hemorrhage or injection of endotoxin.44, 45 Despite its extensive use in France and Indochina and some enthusiastic reports from European centers, convincing proof of its clinical value in the treatment of patients with shock is lacking. Because chlorpromazine itself may markedly lower arterial pressure through a ganglion-ectomy-blocking effect, and because this drug reduces
the subsequent effectiveness of vasopressor agents, its use cannot be recommended at present.

On the basis of studies in dogs, development of "irreversibility" in shock has been attributed to the formation of minute thrombi that impede blood flow through vital capillary beds, especially in the lung. Increased fibrinolytic activity of plasma is observed during shock and is interpreted by some workers as a compensatory response to such intravascular clotting. The increased coagulability may be due to the release of thromboplastic agents in the blood stream from injured and ischemic tissue. Experimental proof of these explanations is incomplete. Griffith stated that heparinization of patients with shock increases their chance for survival, presumably by the prevention of thrombosis in small vessels. As yet, however, the value of this mode of treatment is unconfirmed.

Favorable results have been achieved with the use of hypothermia in the treatment of shock. The principle of its use in this situation is similar to that of its use in cardiac surgery, namely to minimize the injury caused by inadequate blood flow to vital organs. Hypothermia has been reported to increase the survival of dogs subjected to hemorrhagic shock. In treatment of 3 patients with bacteremic shock and high fever my colleagues at the University of Minnesota Hospitals and I have observed the use of a refrigerator blanket as described by Lewis, Ring, and Alden; it was our impression that the clinical course of these patients was favorably influenced, although only 1 of them recovered. This mode of treatment may have promise but also requires further evaluation.

The head-down or so-called Trendelenburg's position is routinely used in many hospitals for patients with hypotension. This posture may be effective in restoring consciousness after a syncopeal episode or during the initial period of shock that follows loss of blood or vasomotor paralysis. However, there is some doubt of its usefulness for prolonged periods after more specific treatment is started. Empirical observations in patients with protracted hypotension suggest that the head-down position may delay recovery, presumably by preventing return of normal postural vasomotor reflexes. For this reason as well as the comfort of the patient and the convenience of his nursing care, a 15-degree to 30-degree head-up position appears to be much more satisfactory, with reliance on more specific measures to maintain blood flow to the brain and other vital organs.

SUMMARY

In the handling of a patient with shock it is essential to identify the underlying cause in order to plan rational treatment. On the basis of information presently available, the specific causes of shock have been classified into 6 groups: hypovolemia, cardiac failure, bacteremia, hypersensitivity, neurogenic factors, and obstruction to blood flow. Treatment was discussed with reference to these groups.

Vasopressor agents are helpful in most instances of shock related to cardiac failure, bacteremia, and hypersensitivity. They usually are contraindicated in shock due to vascular obstruction and in hypovolemic shock until optimal replacement of fluid has been achieved. Recent studies have indicated that metaraminol may be the pressor amine of choice because it is therapeutically effective, simple to administer, without risk of injury to skin and subcutaneous tissues, and available for injection without additional fluid (thus especially suitable for patients with renal failure).

Rigorous attention to the fluid and electrolyte state is of special importance. In the presence of acidosis, the response to vasopressor agents is greatly diminished. The use of molar solution of sodium lactate to re-establish this responsiveness has met with limited success and seems worthy of trial in selected cases.

Adrenocortical hormones may be of striking benefit in shock due to bacteremia or hypersensitivity when an overwhelming response to inflammation threatens life. These drugs may be used also to augment the effectiveness of vasopressor drugs. Relatively little risk is involved, provided that the periods of employment are short and that antibiotics are used concurrently.

The indications for the use of digitalis glyco-
sides in shock are the same as at other times, and their routine use is of no proved benefit and may be injurious. Atropine is of value when excessive vagal activity with bradycardia produces or complicates the hypotensive state.

Chlorpromazine is of no proved worth in the treatment of shock, and possible benefits achieved with anticoagulants are not established as yet. Preliminary observations suggest that hypothermia may be of some value. The head-down position provides only transient benefit in patients with shock, and its prolonged or routine use may delay recovery.

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MAX H. WEIL

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