AN INVITATION to formulate definitions and a classification of shock for an international symposium served as the impetus that led to a theoretical and experimental analysis of this subject. This initial experience with the field of shock research led us to the conclusion that clarification of semantic confusion is of prime importance for future progress in this area.

“Shock” is employed to designate certain patterns of signs or symptoms including lowered systemic arterial pressure, tachycardia, and cold, pale skin on the face and extremities. Since a variety of factors can initiate these signs, many of the current definitions of the condition are general and nonspecific. The following examples were encountered in reports of two major symposia presented during 1961: “Shock is a default in the transport mechanisms of the body, generally affecting vital cells”; or “a syndrome whose central feature is a precarious state of the circulation resulting in an over-all insufficiency of blood flow”; or “a general response to injury,” or “shock is an intricate dystrophic complex linked with over stimulation of the nervous system.” Moore concluded that a unified theory of shock exists in the words “prolonged deficiency of blood flow.” Reeves pointed out that confusion has arisen “first when the word is used in a single and consistent sense but the definition is so loose as to lack clarity, second when it has been assumed that because the same word has been used to describe both a clinical picture and some underlying disturbance the two are necessarily related, and third when the word ‘shock’ is used without clearly defined meaning.”

Attempting to classify shock on a functional basis, we were unable to arrive at a single unique definition. Instead, it appeared that a group of definitions would be required to identify precisely the many different functional conditions currently covered by the term. There is general recognition that the symptom complex commonly called “shock” stems from a wide assortment of causes (i.e., hemorrhage, trauma, myocardial infarction, peritonitis, anaphylaxis, etc.). Even if the patterns of resulting signs and symptoms have common features, the mechanisms may be significantly different in each instance. If the term “shock” is applied in practice to many different entities, then definition of the problems, understanding of the mechanisms, and appropriate therapies must relate to the individual causative factors.

In the traditional pattern, depressed systemic arterial blood pressure is accompanied by tachycardia, peripheral vasoconstriction,
Figure 1
Schematic representation of some of the factors that determine systemic arterial pressure. Since arterial hypotension is a common feature in shock, its various forms may be identified among these and similar factors. The tentative classification of types of hypotension in the right hand column is proposed as a basis for quantitative description of various mechanisms for more precise definition of the different entities. This diagram aids identification of initiating factors and compensatory mechanisms in the production of systemic arterial hypotension leading to "shock."

and sweating. These are obviously not completely independent variables. In fact, the baroreceptor reflexes would be expected to induce acceleration of the heart rate and peripheral vasoconstriction as an automatic response to systemic arterial hypotension from any cause. Although all the individual signs in the typical pattern need not appear in all instances, the basic causes of the shock-like states can be sought among the many different causes of lowered systemic arterial pressure.

Systemic Arterial Hypotension
Determining Factors
A very large number of factors influence the systemic arterial pressure; a few of the more obvious ones are illustrated in figure 1. The systemic arterial pressure is established
by the relationship between the cardiac output and the total peripheral resistance. An uncompensated reduction in either can lead to reduced pressure in the arterial system. The cardiac output is, in turn, determined by the product of the heart rate and the stroke volume. Since the left ventricle does not always fill completely during diastole nor empty completely during systole, the stroke volume must be regarded as the difference between the diastolic and systolic ventricular volumes.

Numerous factors influence the stroke volume, as indicated schematically in figure 1. Among the influences on diastolic ventricular volume are the effective ventricular filling pressure and the resistance of the ventricular walls to distention (distensibility). The ventricular filling pressure depends upon the total volume of blood in the cardiovascular system and the distribution of this blood as it is affected by the venous capacity in various channels and reservoirs. The distensibility, or compliance of the ventricular walls, is not a simple elastic relation between length and tension, but changes during the sequence of filling and is affected by the rate of filling. The sympathetic discharge to the ventricular myocardium affects the rate and degree of systolic ejection. The energy released by the contracting myocardium to expel the blood must be replenished continuously by processes dependent upon the continued flow of blood through the coronary arteries.

Control over heart rate can be readily traced to the balance of sympathetic and parasympathetic discharges into the region of the pacemaker. This balance is affected by a very wide variety of neural pathways. Reflexes initiated by distortion receptors in the carotid sinus and aortic arch are generally recognized as mechanisms for producing tachycardia in response to lowered systemic arterial pressure. Spontaneous variations in heart rate apparently stem from diverse central mechanisms acting through the autonomic system as final common pathways. For example, visual images, sounds, cold, pain, and cerebration can all affect heart rate. Our knowledge of these mechanisms is woefully inadequate.

General control over the peripheral resistance is exerted by the autonomic nervous system and circulating hormones, which are both predominantly constrictor in nature, except in skeletal muscles and glands. In addition, local accumulation of various chemicals (carbon dioxide acids, adenosine triphosphate, adenosine diphosphate, and histamine) have a predominantly vasodilator action.

Systemic arterial pressure could theoretically be reduced by an appropriate and uncompensated alteration in any of the controlling factors, as illustrated in figure 1. It is obvious, however, that the analysis could be readily extended further to include factors controlling the total blood volume, those affecting the venous capacity, the causes of changes in coronary blood flow, and so on. Even an oversimplified scheme like that in figure 1 inevitably leads to the conclusion that many mechanisms are potentially capable of causing a depression of systemic arterial pressure. With but a moderate stretching of the imagination, a clinical cause of arterial hypotension was listed for virtually every mechanism indicated in figure 1. Thus, either blood loss (hemorrhage) or reduced plasma volume (dehydremia) could lead to reduced blood pressure, reduced diastolic volume, diminished stroke volume, smaller cardiac output, and lower systemic arterial pressure. Similarly, venodilatation could reduce ventricular filling pressure by changing the distribution of blood and lowering central venous pressure, and so on down the list.

Compensatory Mechanisms

When factors that influence the systemic arterial pressure are represented schematically like the branchings of a tree, each fork in the arborization constitutes an opportunity for a functional compensation. For example, a reduction in cardiac output can be offset by a corresponding increase in total peripheral resistance, so that the systemic arterial pressure remains unchanged. Similarly, a reduction in total peripheral resistance can
be completely compensated by a corresponding increase in cardiac output (e.g., during exercise). A reduction in ventricular stroke volume can be balanced by an increase in heart rate, so that cardiac output is unchanged. A local vasodilatation can be compensated by a generalized vasoconstriction. If the ventricular diastolic volume is diminished, the stroke volume can be maintained by more complete systolic ejection. A reduction in the sympathetic discharge to the cardiac pacemaker can be balanced by a correspondingly effective reduction in the parasympathetic discharge to prevent a change in heart rate. The ventricular filling pressure is established by the relationship between total blood volume and the capacity of the cardiovascular system, with particular reference to the venous system. Thus a reduction in total blood volume can theoretically be compensated by a constriction of the venous capacity, maintaining the central venous pressure unchanged.

Etiologic Factors Producing Systemic Arterial Hypotension

In such a complex system, many different mechanisms capable of lowering the arterial pressure must be considered. These "primary" mechanisms can affect the systemic arterial pressure only by inducing changes that are not, or cannot be, balanced by the net effect of all the compensatory mechanisms in the chain extending from right to left in figure 1. Viewed in this light, a change in any item listed under "causes of hypotension" in figure 1 can theoretically call forth either additive or compensatory effects among virtually all interacting factors in the chart. This does not, however, preclude identification of the initiating factors primarily responsible for the final result. If primary mechanisms of the sort illustrated in figure 1 can ultimately be identified with specific clinical forms of shock, then the essential first step in solving this complex problem can be taken by providing a group of tentative definitions of discrete forms of shock. The classification of "shock" suggested on the right side of figure 1 is intended to be only a first approximation as a basis for a more definitive analysis of the various clinical disturbances.

Exsanguination

The average human adult can lose somewhat more than 500 ml. of blood without significant cardiovascular disturbance, as judged by widespread experience at blood banks. If exsanguination is of such magnitude that the neural and hormonal controls fail to compensate fully, then the systemic arterial blood pressure will fall. Simple loss of blood accompanied by low blood pressure is insufficient evidence, however, to delineate exsanguination hypotension, because many people faint merely from the sight of blood. Effective criteria for the presence of exsanguination hypotension should include evidence for each step in the functional chain of events leading from blood loss to systemic arterial hypotension in figure 1. In addition, evidence for appropriate compensatory reactions should be demonstrable. Thus, a functional definition of exsanguination hypotension should include specified diminution in blood volume, ventricular filling pressure, diastolic volume, stroke volume, and cardiac output. Evidence for compensatory peripheral vasoconstriction, tachycardia, and increased systolic ejection (smaller end-systolic volume) would indicate that appropriate compensatory mechanisms were active.

Patients and experimental animals can survive for many hours with a mean systemic arterial pressure of 40 to 50 mm. Hg and quickly respond to restoration of the blood volume without ill effects. The term "exsanguination hypotension" should be reserved for the above-described pattern in which the blood pressure is stabilized at a low level (i.e., below a mean value of 60 mm. Hg). If the compensatory reactions begin to fail and the systemic arterial pressure is not sustained even after full restoration of the blood volume, the term "decompensating exsanguination hypotension" would appear appropriate (see section below, "Vicious Circles in Terminal Circulatory Collapse").
If the problem were really this simple, further research on the subject would not be needed. There is no assurance whatever that the functional definition of "exsanguination hypotension" indicated in figure 1 is the correct or final one, but it is a more explicit and unique designation than is commonly employed. Some of the physiologic and semantic problems that appear during one form of experimentally induced exsanguination hypotension in unanesthetized experimental animals are described below (figs. 2 and 4).

Deshydreremia

The loss of large quantities of body fluids (i.e., due to cholera, burns, Addison's disease, water depletion, etc.), leads to a reduced plasma volume. Systemic arterial hypotension can also result from losses of plasma fluid into the tissues. Deshydreremic hypotension, characterized by increased blood viscosity and hematocrit level due to concentration of the blood cells and blood elements, theoretically can be distinguished from exsanguination hypotension with hemodilution by body fluids absorbed from the tissue spaces.
Sequestration

Nearly three fourths of the total blood volume is normally contained within the venules, venous channels, and venous reservoirs. If the capacity of some large portion of the venous system suddenly increased, a substantial part of the total blood volume could be sequestered, producing effects corresponding to external blood loss. (The term sequestration is used here to denote a net increase in the quantity of blood contained within vascular channels through which forward flow may or may not persist.) For example, when a man stands, a substantial quantity of blood is displaced into his legs from the heart, lungs, and upper portion of his body. During prolonged quiet standing (e.g., on parade ground) further accumulation of blood in the dependent vessels predisposes to a drop in systemic arterial pressure sufficient to cause fainting. However, sequestration of blood probably assumes far greater importance in the production of shock-like states by trauma, peritonitis, or the crush syndrome (fig. 1). In these conditions, sequestration occurs in capillaries and venules as well as in the veins and reservoirs. With the lack of suitable methods of determining the amount of blood contained in various regions of the body, information concerning the incidence, significance, and quantitative contribution of this mechanism is woefully inadequate.

Trauma

"Trauma" is a nonspecific term and the effects of injury are so widespread and diverse that no single functional mechanism could reasonably be labeled as an initiating cause of the resulting hypotension. If blood escapes from the vascular system into the tissues or outside the body, the blood volume is diminished. Damage to capillaries may lead to loss of plasma into the tissues. Vascular distention and hyperemia in injured parts lead to sequestration of blood. In addition, hemopericardium can produce ventricular compression in some instances. Autonomic controls to heart and peripheral vessels may be disturbed by massive discharge in somatic and visceral afferent nerve. Finally, vasodilatation in the injured tissues should tend to reduce peripheral resistance. These mechanisms could contribute in various degrees to systemic arterial hypotension following injury.

Cardiac Compression

Rapid collection of blood or fluid within the pericardial sac can be viewed as interfering with ventricular distention and preventing normal ventricular diastolic filling. Theoretically, extracardiac compression diminishes the diastolic and systolic ventricular volumes, reduces the stroke volume, and lowers the cardiac output in spite of tachycardia. Systemic arterial hypotension develops when the drop in cardiac output is not adequately compensated by increased total peripheral resistance. Although pericardial tamponade may exert its effects through the same final pathway as exsanguination and sequestration, the distinction can be readily made. The total blood volume is essentially normal and the central venous pressure should be elevated in the presence of extracardiac compression.

Coronary Insufficiency

Acute myocardial infarction may produce severe or fatal systemic arterial hypotension by mechanisms indicated in figure 1. Acute interference with the blood supply to a substantial area of the myocardium reduces ventricular ejection and the stroke volume. The infarcted myocardium not only fails to contribute to ejection, but actually expands during systole so that the effectiveness of the remaining myocardium is reduced. Under these conditions the cardiac output could be reduced in spite of increased ventricular volume and tachycardia. A full blown clinical picture of shock may then appear as compensatory mechanisms are activated in response to diminished systemic arterial blood pressure.

Autonomic Imbalances

The sympathetic division of the autonomic nervous system directly affects the stroke volume by acting on the myocardium; affects the heart rate by acting on the pacemaker; and affects the total peripheral resistance by acting on the peripheral vessels. Severe de-

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Quantitative measurements on human patients are required to define clinical entities and validate experimental models. Some technics currently available for exploring these mechanisms are indicated. C.O., cardiac output; H.R., heart rate; S.V., stroke volume; T.P.R., total peripheral resistance.

pression of arterial pressure resulting from autonomic imbalance is characterized by bradycardia and regional vasodilatation (e.g., in skeletal muscle), as though the normal baroreceptor reflexes were depressed or overridden. The well-known syncopal reactions to carotid sinus pressure, intense visceral afferent pain or unpleasant sights result from transient bradycardia with some peripheral vasodilatation. Transient autonomic imbalance frequently produces brief loss of consciousness but rarely leads to prolonged hypotension or the typical symptoms of shock. Severe disturbances of the central nervous system (e.g., head injury) may produce a shock-like state characterized by prolonged

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Peripheral Vasodilatation

A reduction in the total peripheral resistance could be the primary mechanism producing hypotension in a number of clinical conditions. For example, peritonitis, crush injury, and anaphylaxis are all characterized by extreme vasodilatation. The expected compensatory reaction to vasodilatation in one portion of the vascular system would be an appropriate increase in cardiac output, as in exercise, and vasoconstriction in other vascular areas. Severe arterial hypotension produced solely by net peripheral vasodilatation would signify that the level of cardiac output was insufficient to balance the vasodilatation. In other words, these clinical conditions should be accompanied by extreme tachycardia and increased cardiac output. Sustained reduction in arterial pressure from lowered total peripheral resistance indicates either massive vasodilatation, limited compensatory vasoconstriction, or interference with a full increase in cardiac output. For example, limited cardiac output could result from sequestration of blood in dilated capillaries, venules, and veins. Filtration of fluid from the blood in the distended capillaries may further reduce the volume of blood available to the point that stroke volume could not be increased.

Evaluation of Factors Initiating Shock

A plausible schematic representation of a complex physiologic problem can be an obstacle to scientific progress if it is accepted without critical appraisal. To illustrate this point let us consider a type of hypotension that can be consistently produced experimentally and see if the response conforms to expectations derived from figure 1.

Exsanguination hypotension was chosen for study because it is a standard model of shock and can be quantitatively reproduced. By cannulating a large artery and allowing blood to run into a reservoir adjusted so that the fluid level is maintained at 54 cm. above the heart, one can consistently lower the systemic arterial pressure to 40 mm. Hg. Since anesthesia can easily distort the cardiovascular control mechanisms, the study was carried out in seven healthy unanesthetized dogs, lying quietly under minimal restraint. One or two weeks before the study, pulsed ultrasonic flowmeters had been installed on various strategic arteries in the chest and abdomen. A femoral artery exposed under local anesthesia and cannulated with tubing was connected to a pressure recorder and to a sterile reservoir through a heat exchanger. As blood flowed out of the arterial system into the reservoir, it was cooled to 5 C. to retard bacterial growth. When returned to the dog minutes or hours later, the blood was rewarmed to body temperature. Arterial blood pressure was reduced to a mean of 40 mm. Hg when 900 ml of blood flowed into the reservoir.

The response to repeated periods of induced systemic arterial hypotension is indicated in figure 2 in terms of aortic pressure, heart rate, and instantaneous aortic flow (left ventricular output minus coronary flow). The integrated flow record was derived from instantaneous flow by an analogue computer that added increments of flow over each successive period of 2.5 seconds. Instantaneous and integrated flows were recorded from the superior mesenteric artery, renal artery, and terminal abdominal aorta to determine changes in blood flow and its distribution to the splanchnic bed, kidneys, and hindquarters.

The heart rate increased as the blood pressure gradually diminished, but returned toward control level when the arterial pressure leveled off at 40 mm. Hg. Thus the tachycardia was transient in spite of a sustained reduction in arterial pressure to low levels that should have activated powerful baroreceptor reflexes to accelerate the heart. This phenomenon was consistently observed during the initial period of hypotension in all seven dogs, but might be missed in experiments on anesthetized dogs with control heart rates elevated above 120 per minute.
Left ventricular ejection velocity and integrated output diminished as the blood flowed into the reservoir and remained depressed until the blood was reinfused. Blood flow through the superior mesenteric artery and terminal aorta was greatly diminished, but renal flow was well maintained. The reduction in flow through the splanchnic bed and hindquarters could result from reduced arterial pressure, compensating vasoconstriction, or both. Huvos et al. found either no change or a slight increase in total peripheral resistance and in the resistance in the mesenteric, renal, and iliac arterial beds during similar exsanguination hypotension in unanesthetized dogs. The sustained renal flow in the present experiment suggested vasodilatation in the face of reduced perfusion pressure.

The cardiovascular responses differed to some extent in each subsequent period of induced hypotension. For example, the heart rate accelerated on each successive bleeding and remained at a level of about 190 per minute between the third and fourth periods. The left ventricular output was affected to about the same degree in each of the four periods of hypotension, but the flow distribution varied. Superior mesenteric flow increased to different levels with each successive reinfusion, reaching very high levels after the third and fourth hypotensive intervals (see also ref. 12). Renal flow diminished to low levels late in the second period of hypotension and during the early part of the third period. Changes in terminal aortic flow were fairly similar during each period of hypotension.

In view of the different patterns of response in the same animal, several important questions arise. What accounts for the return of the heart rate to near the control values in the face of maintained arterial hypotension? What mechanisms are responsible for the variability in the flow through different vascular beds during successive bouts of induced hypotension? The answers to these questions can come only from an experimental analysis of such responses. Finally, if this analysis is productive, will the results be applicable to the problems of “shock” encountered in human patients? In other words, are these experiments being conducted on a model that is adequate to elucidate the response to exsanguination in humans?

There are many reasons for believing that data obtained from experimental animals cannot be applied directly to clinical problems. Of particular importance in this regard is the hepatic sphincter mechanism in dogs. This mechanism, which can produce splanchnic engorgement by increasing outflow resistance in the liver, has no functional counterpart in humans. This consideration led Selkurt and Rothe to turn to primates in their studies of shock. In addition, anesthesia may greatly influence the nature of the cardiovascular response. If cardiovascular performance can be continuously monitored in alert, healthy, unanesthetized dogs, (figs. 2 and 4) general anesthesia can be avoided during experiments on forms of shock that can be induced without inflicting pain. Finally, the experimental procedures employed to induce shock in animals are probably not strictly comparable to the conditions that lead to shock in patients. In the long run, the only way to validate an experimental model is to compare it, point by point, with the original problems. Thus, comparison of experimental with clinical exsanguination hypotension requires corresponding records from dogs and from patients carefully selected as uncomplicated examples of the condition.

Quantitative Evaluation of Shock in Man

The definition or identification of various types of shock must come from direct studies on affected patients, not from physiologic concepts or experimental models. The effects of exsanguination of an anesthetized dog, rotation of rats in a drum, application of tourniquets on extremities, and administration of “endotoxin” cannot be accepted as adequately corresponding to symptoms of “shock” in patients until these conditions have been precisely defined and quantitatively measured on carefully selected patients. Although most clinicians despair that such measurements can actually be achieved, much of the essential
Measurements during and after induction of exsanguination hypotension maintained for 2 hours in an unanesthetized dog. In the subsequent period, beginning at "auto-infuse," he was on the brink of death from three different causes (a) progressive fall of arterial pressure in spite of restoration of blood volume and vasoconstrictors, (b) respiratory arrest and (c) severe bradycardia. This experiment illustrates that terminal circulatory collapse can occur in many ways by different mechanisms like those indicated in figure 5. (Previously published in Shock: Pathogenesis and Therapy. An international symposium. Reproduced with the permission of Springer-Verlag, Berlin, Gottingen, Heidelberg.)

Information theoretically could be collected by techniques that are currently available (fig. 3). Although some of these techniques are far from ideal, they could provide clues regarding many of the mechanisms illustrated in figure 1.

Systemic arterial pressure can be recorded by sphygmomanometry or directly by puncture or catheterization. Cardiac output can be estimated by cardiac catheterization or by indicator-dilution techniques. Total peripheral resistance can be computed from cardiac output and mean aortic pressure. The heart rate can be counted or can be recorded by rate-meters triggered by arterial pulses or electrocardiograms. Heart rate serves as one indicator of the balance of autonomic discharges to the cardiac pacemaker. Tachycardia due to sympathetic discharge to the heart is typically associated with a more rapid rate of pressure rise (dP/dt) in the ventricle and a shortened systolic interval. Thus, an analysis of ventricular pressure pulses could indicate the nature of the autonomic influence being exerted on the heart. Stroke volume can be computed from the heart rate and the cardiac output. The systolic and diastolic volumes of the cardiac silhouette can be estimated from timed roentgenograms (see fig. 6 in ref. 14), angiograms, or roentgenograms. Ventricular filling pressure can be determined by catheterization. Ventricular distensibility could be estimated from changes in ventricular size and diastolic pressure.

The total blood volume can be estimated by indicator-dilution techniques, although this approach is fraught with potential error in patients with increased "capillary permeability" or extravascular collections of blood and plasma. The distribution of the blood flow.
through the various vascular beds can be estimated by numerous methods. For example, blood flow through samples of muscle and skin can be determined by venous occlusion plethysmography, Whitney gages, or thermal methods such as Hensel’s disks and needles. Blood flow through the kidney can be determined by clearance technics when urine is being formed. Splanchnic flow can be estimated by bromsulphthalein clearance in the liver. Indicator-dilution technics can give some indication of regional blood flow. Regional blood volume can also be estimated by indicator dilution although this method is not completely reliable, particularly under certain conditions in some patients with shock (e.g., local extravasation, edema, and capillary damage).

The methods listed above cover rather completely the factors illustrated in figure 1. Thus technics are available to give numerical values to many of the important variables, even though some of them are not quantitatively accurate. To make such measurements on patients who are critically ill would be extremely difficult at best. A special treatment station could be established, however, with specialized staff and equipment so that critical measurements could be obtained while the therapy was being prepared and instituted. The equipment would have to be specifically designed for prompt application and use. Clearly, if a substantial proportion of these measurements could be made on even a few patients with the same clinical condition, it should be possible to provide unique functional definitions of particular shock-like states. A fairly complete description of a few selected patients could equal the incomplete study of hundreds of patients by the few standard technics currently in use. By use of a scheme like that in figure 1, the initiating mechanisms and the compensatory reactions should be identified. If the characteristics of the condition are known, experimental models could then be devised and validated by quantitative measurements to compare with those on the patients.

Variations in the Course and Termination of Hypotension

To propose a single therapy to combat a particular form of shock implies that the clinical course of the condition is comparable in different individuals. Figure 2 demonstrates that the response to exsanguination differed in four successive experiences of the same unanesthetized dog on the same day. If different responses are produced by the same initiating event, we must anticipate even greater differences during a protracted period of hypotension.

Theoretically, effective elimination of the factor or factors that initiated the systemic arterial hypotension should be promptly followed by a return of the blood pressure to normal levels and restoration of good health. For example, exsanguination can produce an arterial hypotension lasting many hours and be followed by a prompt return of the blood pressure to normal by restoration of the shed blood. Experience has shown, however, that most types of hypotension listed in figure 1 may be of sufficient degree and duration that deterioration and death may occur even after the apparent initiating factors are removed. Thus the condition of patients or animals suffering from protracted exsanguination hypotension may improve only transiently following restoration of the blood volume. The blood pressure returns to normal briefly and then gradually falls despite all efforts to maintain blood volume, peripheral resistance and cardiac output. This condition has been called “irreversible” shock, but should probably be considered as a group of separate entities. Just as there are many different factors capable of initiating hypotension and shock, so there are many different terminal mechanisms or pathways leading to death.

If an animal has been rendered hypotensive by exsanguination, and hypotension remains or returns after restoration of the blood volume, a new set of mechanisms must be sought to explain this new abnormality of cardiovascular function. For example, the mean arterial pressure was reduced to 45 mm. Hg in a healthy alert dog by allowing blood to
flow from the femoral artery into a reservoir slowly at first and then more rapidly (fig. 4). After 2 hours about 300 ml. of blood had spontaneously returned into the dog at the same low arterial pressure. This autoinfusion was a signal of beginning cardiovascular deterioration. An additional 300 ml. of blood was forcefully reinfused, and the femoral catheter was clamped at the time indicated by the abrupt widening of the arterial pulse pressure. The arterial pressure fell progressively for 30 minutes, when the last (360 ml.) of the shed blood was reinfused. The decline persisted, but the pressure was transiently raised by the infusion of levarterenol (Levophed), without which the animal would have died from the progressive fall in pressure. Abruptly respiration ceased, but death of the animal was prevented by artificial respiration. After ventilation had been restored, the heart rate suddenly slowed, and death would surely have ensued from bradycardia had not the arterial pressure been rapidly elevated by a heroic dose of epinephrine.

The sequence of events illustrated in figure 4 is representative of the common observation that the terminal patterns and final causes of death are quite variable. Prompt remedial action postponed death from one mechanism only to be followed by a different threat. In effect the animal was on the brink of death from three different causes in rapid succession: (a) progressive fall in arterial pressure in spite of restoration of blood volume and vasopressor agents, (b) respiratory arrest, and (c) severe bradycardia. The progressive hypotension is attributed to spontaneous venodilatation, but such a concept should be verified by improved techinies. Since both renal and mesenteric flow were drastically reduced in this animal, the reduction in arterial pressure was not apparently due to vasodilatation in these vascular beds.

Respiratory arrest might result from severe cerebral depression as indicated by other manifestations of impaired function of the brain. The animals generally remained responsive and alert until they began to exhibit autoinfusion and other signs of circulatory deterioration. Then they became unresponsive, appeared to lose consciousness, and frequently exhibited depressed or absent corneal and pupillary reflexes. Severe bradycardia was a fairly common terminal event.

The state of deteriorating circulatory control illustrated in figure 4 is fundamentally different from the original condition of exsanguination hypotension. Kováich and Takács found that the responsiveness of the vascular system to autonomic activity and circulating hormones is progressively depressed during both hemorrhagic and tourniquet shock. Quite possibly a different set of variables must be measured to identify the underlying neural mechanisms both in such experimentally induced hypotension and in clinical ‘‘shock.’’ For example, the evidence for central neural depression suggests the need for critical measurements and useful signs of central autonomic control and cerebral function. More discrete and definitive measures of neural mechanisms of cardiovascular and respiratory control might be most valuable. Clearly, preoccupation with changes in the peripheral vascular system during the terminal phases of shock could easily retard progress toward understanding some of these mechanisms. Similarly, validation of the evidence for depression in the central nervous system must be sought in critical measurements on patients approaching death from shock.

**Depression of Central Nervous Systems in Terminal States**

Subnormal responsiveness or unconsciousness with sluggish reflexes have been regularly manifest when the animals began to display autoreinfusion, abrupt bradycardia, or respiratory arrest. In two dogs fully equipped with instruments, electrodes were chronically implanted at sites in the diencephalon where stimulation produced exorbitantly elevated heart rate and blood pressure. In these two dogs, the diencephalic sites were stimulated repeatedly during exsanguination hypotension produced in the standard manner. When autoinfusion and depression of reflexes developed, the same stimulus strength produced...
A. DIFFERENTIATION OF EARLY ARTERIAL HYPOTENSION AND SUBSEQUENT CIRCULATORY COLLAPSE

Systemic arterial hypotension leads to reduced peripheral blood flow because of reduced perfusion pressure and compensatory vasoconstriction. If systemic arterial hypotension is sufficiently severe and prolonged, terminal circulatory collapse can result from any of a number of vicious circles leading to progressively lower cardiac output or to reduced peripheral resistance. (Previously published in Shock: Pathogenesis and Therapy. An international symposium. Reproduced with the permission of Springer-Verlag, Berlin, Gottingen, Heidelberg.)

Vicious Circles in Terminal Circulatory Collapse

A reduction in blood flow through virtually all tissues is a natural result of a greatly lowered systemic arterial pressure (fig. 5A). The reduced arterial pressure correspondingly diminishes the arteriovenous perfusion gradient. Lower perfusion pressure tends to slow up vascular flow in every tissue, in some more than in others. The cerebral blood flow would be diminished by this mechanism primarily. In addition, a compensatory response to hypotension is a generalized vasoconstriction induced by baroreceptor reflexes. Thus, flow through the splanchnic bed, kidney, muscles,
and skin may be greatly curtailed (figs. 2 and 4). A compensatory tachycardia might also contribute to a reduction in coronary flow. No tissue would be fully spared from a diminu-
tion of blood flow.

The blood supply to the central nervous system should be adversely affected by a re-
duction in arterial pressure because the cere-
bral circulation is not very responsive to
diminished blood flow. Cerebral vasodilata-
tion is difficult to produce experimentally by
neural, hormonal, or chemical means except
for moderate effects from increased carbon
dioxide content of the blood. Thus, the cere-
bral blood flow is generally regarded as
dependent primarily upon the perfusion pres-
sure. A pronounced reduction in mean
arterial pressure should therefore produce a
corresponding reduction in cerebral blood
flow (fig. 5).

Respiratory arrest might result from cumu-
lative effects of inadequate cerebral blood flow
producing failure of the respiratory control
centers (fig. 5). On the other hand, the auto-
reinfusion may represent a release of the
venoconstrictor tone that had caused compen-
satory shrinkage of venous channels and res-
ervoirs. The relaxation of these channels
could increase the capacity of the venous sys-
tem and thus further diminish ventricular
filling pressure and cardiac output. Abrupt
appearance of bradycardia (fig. 4) might sig-
nal serious autonomic imbalance from depres-
sion of the nervous system. The combined
effect of lowered perfusion pressure and tachy-
cardia could lead to acute myocardial failure
with a further drop in cardiac output and
lower arterial pressure.

Loss of neural controls could be expressed
as a release of compensatory vasoconstric-
tion. The resulting reduction in peripheral resis-
tance would directly diminish arterial pressure
without a further reduction in cardiac out-
put. The compensatory constriction in peri-
pheral vessels could be sufficiently severe
and prolonged to curtail drastically flow
through many vascular beds. Chemical vasodilators
could accumulate and finally reach
levels high enough to overcome the constrictor
tone by a mechanism resembling reactive hy-
peremia. Selkurt18 postulated an unidentified
vasotoxic substance that might be elaborated
in the intestine and might enter the systemic
circulation when liver function is depressed.
Vasodilatation from any of these causes could
increase a loss of fluid from plasma into the
tissues, and the resulting reduction in blood
volume could lead to reduced stroke volume
and cardiac output.

The cardiovascular control could deteriorate
by mechanisms like those illustrated in figure
5 despite efforts at combating them. Deter-
mination of the pathways of circulatory col-
lapse would depend upon appropriate meas-
urements on patients in these final stages of
shock. Although the difficulties involved in
collecting such data are extremely severe,
they must be circumvented before rational
methods of therapy can be based on a full
understanding of appropriate physiologic
mechanisms.

Summary

The first step in analyzing any clinical
problem must be the identification and pre-
cise definition of the entity. An adequate
definition must be based on accurate and
quantitative description in terms of crucial
variables. Since many of the essential vari-
bles can be measured or estimated on patients,
shock can be approached in a series of logical
steps for each type:

1. A discrete clinical condition currently
classified under the term "shock" could be
identified.

2. A specific and unique name and defini-
tion of this condition could be derived by di-
rect and quantitative measurements of vari-
bles such as those represented in figure 1.

3. The initiating factors would become
apparent from these measurements.

4. The compensatory reactions that are in-
adquate should be distinguished from re-
sponses that are inappropriate.

5. With this knowledge at hand, a suitable
model of the circulatory disturbance could be
evolved and validated by quantitative meas-
urements in experimental analysis.

6. Appropriate therapy of the defined con-
dition could then be based on knowledge of the nature of the basic disturbance. Obviously, treatment that would effectively correct the fundamental defect from extravasation or anaphylaxis might be dangerous if applied to a patient with myocardial infarction.

7. The terminal events in fatal shock-like states can be regarded as a group of potential vicious circles that may have no obvious connection with the original cause of the systemic arterial hypotension. Effective therapy during the final stages of circulatory deterioration requires a great deal more knowledge regarding the various mechanisms of circulatory collapse than we now possess.

References