CLINICAL PROGRESS

Nature and Treatment of Shock

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INTEREST in the practical problems of traumatic or wound shock in man, which was somewhat dormant after World War II, was reawakened by the military action in Korea, and has continued actively since. This has included both the analysis of various shock states, and their management; the study of problems of whole blood and plasma preservation and sterilization; the further development of plasma substitutes or plasma volume expanders; the use of arterial transfusions; the use of induced hypotension, especially in certain forms of surgery; and most recently, the use of induced hypothermia.

Experimental investigations in basic mechanisms of shock, on the other hand, have been in progress continuously since the end of World War II. In the medical field there has been recent interest in the question of infection in shock, and in the difficult problem of shock associated with myocardial infarction.

The present brief review will consider these subjects in turn.

TRAUMATIC SHOCK

Recent Reviews. A number of review articles covering various aspects of shock have appeared recently. Among these may be mentioned those by Wilhelmi, Davis, Evans, and Page. Symposia have been published by the Army Medical Service Graduate School, and the New York Academy of Sciences.

An important contribution describing problems encountered in civilian disasters is that of Blocker and Blocker on the Texas City explosion of 1949. Emphasis upon the predominant damage caused by flying glass fragments is one of the features of this report.

In a comprehensive monograph, "Observations on the General Effects of Injury in Man, with Special Reference to Wound Shock," Grant and Reeve have analyzed their own large experience in World War II, and compared it with other published work. One of the chief concerns of these authors was to establish a satisfactory definition of the shock state. They have arrived at a somewhat complex description, consisting of six different circulatory patterns: (1) cold tachycardia: normal blood pressure, fast pulse, cold extremities, pale face; encountered only after injury, associated with moderate blood loss; (2) warm tachycardia: normal blood pressure, fast bounding pulse, warm extremities, well colored face; found with 70 per cent blood volume or in patients with very low hemoglobin; (3) hypertensive pattern: encountered soon after injury, and with but slight blood loss; (4) vasovagal pattern: low blood pressure, slow pulse, cold extremities, pale face; usually seen early, with emotional disturbance, occasionally terminally in patients dying of hemorrhage; (5) cold hypotension: low blood pressure, fast pulse, cold extremities, pale face; seen in advanced shock, with severe blood loss, also in advanced sepsis; (6) warm hypotension: low blood pressure, fast pulse rate, warm extremities; usually a transient state, with moderate blood loss, encountered in warm surroundings, often after operation.

So far as depth of shock is concerned, Grant and Reeve agree with most other authorities that except in cases of severe hemorrhage from local vascular injury, shock is best cor-
related with the actual size of the injuries sustained.

**Experience with Battle Casualties in Korea.** Many problems arose due to the special circumstances of military action in Korea. These were under constant study; a special medical and surgical research unit, under the immediate direction of Major John O. Howard, was functioning during the last year of the war. Only preliminary reports of their investigations have as yet been made.9

With the widely scattered, entrenched positions that existed at the front, one of the difficulties was that of location and evacuation of wounded men. This sometimes resulted in long exposure after injury. Such cases later developed renal failure with anuria. The artificial kidney was used in a number of these cases, with some drop in blood nitrogen and plasma potassium, and at least temporary improvement.

If a wounded man is treated within three to four hours of his injury, he can be brought out of shock with sufficient blood in practically all instances except those of continuing rapid bleeding. Secondary shock may, however, develop later, especially during or after major corrective surgery.

Another genuine advance in treatment of the wounded has been the extension of reparative vascular surgery as an emergency measure.10

**Practical Therapy**

The Committee on Surgery of the National Research Council has recently prepared a brochure entitled "Emergency Treatment in Major Disasters."11 This is designed as a practical handbook, for use by the Federal Civil Defense Administration and similar agencies. It is presented in seven sections: I. Collection and Disposition of the Injured; II. Wounds; III. Wound Shock; IV. Burns; V. Fractures; VI. Acute Radiation Syndrome after Atomic Bombing; VII. Blood Transfusions. A few excerpts may be given from this excellent brief manual. It is noted that "burns, trauma, shock, and hysterical reactions are the major problems in the first hours after bombing." "In general, atomic casualties should be treated like any other injuries. Except with overwhelming dosage, symptoms of radiation injury appear late."

In the emergency treatment of the wounded, the principles are: "1. Arrest hemorrhage. 2. Check airway and respiration. 3. Treat shock immediately. 4. Diagnose extent of injury. 5. Relieve pain and anxiety. 6. Administer tetanus prophylaxis promptly. 7. Splint fractures. 8. Give first aid for eye injuries. 9. Evacuate first the wounded requiring surgery for resuscitation. These are: (a) intra-abdominal injuries, (b) extremity wounds requiring tourniquet, (c) intrathoracic injuries, (d) injuries with severe crush or laceration of muscle, (e) head and spinal cord injuries."

"Shock is expected after crushing injuries, traumatic amputations, major fractures, serious burns, large hemorrhages, chest and abdominal trauma. Severe extremity wounds are especially likely to cause rapidly developing shock. Except after massive hemorrhage, the fully developed picture of peripheral collapse associated with a fall of circulating blood volume may not appear for several hours. Shock may be recognized by: cool moist skin, pale or cyanotic lips, increasingly weak pulse, falling blood pressure, thirst and restlessness, collapsed peripheral veins, suppression of urine formation."

In treatment, "the most urgent duty of the physician is to restore blood volume," which will be reduced 15 to 20 per cent in mild cases, 40 per cent or more in severe cases. If the systolic blood pressure, after initial measures have been taken, remains below 80 mm. Hg, 1500 cc. to 2500 cc. of whole blood will usually be needed. Further details are given for treatment with plasma, plasma expanders, saline or glucose solutions, if whole blood is not available.

"If recovery from shock is not evident after adequate whole blood replacement (1500 cc. to 2500 cc.), the following possibilities arise: bleeding or plasma loss into injured areas is continuing, or blood loss is not responsible for the shock state."

**Blood, Plasma, Plasma Volume Expanders**

**Whole Blood.** All experience continues to support the position that whole blood transfusion is the best treatment for shock. Pro-
curement of blood by local agencies suffices for most civilian needs at present. For military needs the Red Cross program continues to be a basic necessity.

The primary efforts in research are being directed to (a) the preservation of blood for longer periods than the present three weeks provided by reduced temperature, with ACD solution (acid-citrate-dextrose) as an anticoagulant; and (b) sterilization of blood from hepatitis virus.

Deterioration of blood with time is progressive, even when kept at low temperatures. Blood 10 days to two weeks old may contain appreciable amounts of potassium and pigment in the plasma. With the multiple transfusions often given in severe shock, it is thought that hemoglobinemia and hyperpotassemia from this cause may be harmful, especially on renal function.

Of the many investigations in progress to prolong the useful life of whole blood, the mixture of red cells with glycerol followed by freezing at very low temperature, as developed in Great Britain by Mollison, Sloviter, and others, is perhaps the most interesting.

**Plasma.** Pooled plasma, either as whole plasma or as dried plasma, which made so outstanding a contribution in the treatment of the injured in World War II, now carries so high an incidence of transmission of infectious hepatitis, that its present use by the Armed Forces has recently been prohibited by the Department of Defense. Sterilization of plasma is now the subject of extensive investigation. Ultraviolet irradiation has been shown to be ineffective. The chemical beta-propiolactone has shown some sterilizing action against the hepatitis virus, but its practical usefulness has yet to be demonstrated.

Human albumin solutions, produced by plasma fractionation, using cold ethanol followed by heating at 60°C, have been shown to be free of hepatitis virus, and this preparation is an excellent plasma expander. Other products of plasma fractionation are under study.

**Plasma Volume Expanders.** The onset of hostilities in Korea, and realization of the need for large volumes of fluid for blood volume replacement in the event of attack on civilian areas, have led to an extensive program of development of plasma substitutes or plasma volume expanders. An excellent recent review, with a large bibliography, is that of Gropper, Raisz, and Amspacher.13

The effort has been to obtain a material which on injection will sustain plasma volume to the extent of about half the volume infused, for a period of 8 to 12 hours; such material to be nontoxic, not stored in the body to an appreciable extent, either largely excreted or metabolized in the course of 48 to 72 hours.

**Dextran.** This material, a polymerized carbohydrate, is made by the action of the bacterial organism *Leuconostoc mesenteroides* on sucrose. The resulting polymer, of very high molecular weight, is then broken down by hydrolysis to an average molecular size of 75,000. Dextran was first suggested as a plasma expander in Germany, later developed on a large scale in Sweden.14

Initial clinical studies in this country showed that while the dextran used was effective, there was a considerable incidence of toxic reactions of an anaphylactoid type. It was later found that these products also produced skin reactions and specific agglutinins in normal subjects. This reactivity was associated with the high molecular fractions. Reduction in molecular size of the dextran has largely eliminated these reactions.

In further studies, it has been shown that dextran is about 63 per cent excreted in 24 hours, and that the fraction retained is at least in part metabolized. No significant toxic effects on renal, hepatic or other systems have been demonstrated, except for a recent finding of increased bleeding time following infusion. This is now being further investigated.

At present dextran of approved American manufacture has been released by the Food and Drug Administration, and passed by the Council on Pharmacy and Chemistry of the American Medical Association. It received extensive field trial in the Armed Forces.

**Polyvinylpyrrolidone (PVP).** This synthetic chemical, basically a polymerization of acetylene, was developed in Germany during World War II, used extensively in the German army, and is still widely employed as a plasma...
expander in Europe, particularly in France.\textsuperscript{13} It is an effective expander and has essentially no immediate toxic effects. Its chief disadvantage is that it is not metabolized at all, and 20 to 40 per cent of the injected dose remains stored, especially in the cells of the reticuloendothelial system, for protracted periods, perhaps indefinitely. The possible consequences of such storage not being fully known, there has been a reluctance to accept this product for general use. The analogy that comes to mind is that of gum acacia, which was shown in some instances with large doses, to produce liver enlargement due to deposited acacia. There has been no evidence to date of any such change produced by PVP.

The gelatins. During World War II a purified gelatin, lightly degraded or hydrolyzed, was found to be an adequate plasma expander. The chief disadvantage of this product was that it was viscous or semi-solid at room temperature and required warming before administration. In recent years there has been a considerable effort devoted to producing a gelatin which would remain in the circulation long enough to serve as a plasma expander and yet remain fluid down to freezing temperatures. Chief among these products are oxy-polygelatin and "modified fluid gelatin."\textsuperscript{13} Developmental work on these products is still in progress.

Other products, still in an experimental stage, are mentioned in the review of Gropper, Raisz, and Amspacher.\textsuperscript{13}

**Saline and Alkaline Salt Solutions**

The question is still raised from time to time, whether these solutions will not be adequate in treatment of shock, and can replace plasma, plasma expanders, or even blood. The majority of opinion at the end of World War II was that, while added amounts of saline (sodium chloride or sodium lactate) might be useful early in the treatment of burns, these solutions were not generally adequate for treatment of severe injury with shock.\textsuperscript{21} Saline can sustain the circulation for short periods while blood is being obtained. The prime objective in the use of salt or glucose solutions in conditions associated with shock might be said to be the maintenance of urine volume, rather than the restoration of blood volume.

**Hypotension as a Procedure in Surgery.** Hypotensive agents, such as the hexamethonium compounds, have been used to reduce blood pressure and aid in the control of bleeding, in extensive surgical operations. This has received much attention recently.\textsuperscript{40, 41, 42} Systolic pressure is reduced to 50 mm. or 70 mm. Hg, restored again before the operation is over, by Neo-Synephrine infusion. High spinal anesthesia has also been used.\textsuperscript{43} These procedures have to be used with great care; over-prolonged hypotension has resulted in blindness, hemiplegia, coronary occlusion, and cardiac arrest.

**Arterial Infusion.** This technic, originally suggested by Seeley,\textsuperscript{44} and developed by Kohlstaedt and Page,\textsuperscript{45} has a place, somewhat more limited than at first anticipated, in the rapid restoration of the circulation in cases of extreme shock. Blood is infused into a peripheral artery, usually in amounts from 250 to 500 cc., at inflow pressures around 100 to 120 mm. Hg, sometimes rapidly (75 to 100 cc. per min.), sometimes slowly (250 cc. in 30 minutes). Results in both acute surgical or operative emergencies, and in medical shock, such as that with myocardial infarction, have been quite variable.\textsuperscript{45, 46, 47} The general purpose is to restore the circulation of vital organs, such as heart and brain, rapidly, hoping that the myocardium itself will then take over.

**Hypothermia.** While induced hypothermia has been tried in various clinical conditions for a number of years, its systematic use in surgery is quite recent. It has been developed particularly in France.\textsuperscript{59, 60, 61} The essential features include: (1) The use of a combination of pharmacologic agents to provide sedation, vasodilatation, and "stabilization" of the circulation. The phenothiazine derivatives Phenergan and Largactil are among key agents used. (2) Body cooling to maintain central body temperature around 30 to 32 C. The surgery is performed at this temperature. (3) Very gradual rewarming over a period of many hours. The procedure is difficult and
complicated; the details cannot be included in this review.

These same principles have been applied in the treatment of shock. Here the drugs used often result in a hypothermia, and little additional cooling is needed. Blood and other fluid is of course given as required. Extensive experience has now been obtained in the French military theatre in Indo-China. Injured men are maintained for two and three days in the hypothermic state, semiconscious or unconscious, are transported from the front to hospitals, receive the necessary surgery, and are then returned slowly to normal temperature. Although the full value of such treatment is still under study, it is certainly a significant and interesting development.

**Fundamental Mechanisms of Shock**

In a clinical review, no adequate account can be given of the many and complex studies that have been in progress in recent years, on various fundamental mechanisms related to the shock state. A few of the notable contributions will be outlined briefly. Summaries of current work are given by Wilhelmi, Page, and in the Macy monographs on Shock and Circulatory Homeostasis.

**Irreversible Shock**

To the experimental physiologist and the clinician alike, the greatest interest has centered around the phenomena of “irreversible shock,” the condition developing after a more or less protracted period in moderate or severe shock, when the organism no longer responds to fluid replacement or other measures, and steadily fails and dies in a hypotensive state. In the experimental animal, irreversible shock can be produced by a variety of techniques: such as graded hemorrhage with protracted maintenance of hypotension, crushing or pounding a limb, or revolving the animal a certain number of times in the “Noble-Collip” drum.

**Vasomotor Factors.** One of the significant advances in physiology in recent years has been the elucidation of the relative roles played by adrenaline and noradrenaline in the animal body, through the work of von Euler and his collaborators, Goldenberg and co-workers, and others: noradrenaline the actual chemical transmitter liberated at the sympathetic or adrenergic nerve endings, constricting blood vessels without altering cardiac output; adrenaline, liberated only by the chromaffin cells of the adrenal medulla, raising blood pressure only secondarily through increased cardiac output, having actually an over-all vasodilator effect in physiologic concentrations, and with many metabolic and hormonal actions. Von Euler has recently postulated that noradrenaline may play a further role in relieving shock, by narrowing the venous vascular bed where pooling has taken place.

There is evidence that the action of noradrenaline may be potentiated by adrenocortical steroids. Clinical results with the use of this and related agents will be referred to later.

In 1944, Chambers and Zweifach, studying the action of the smaller blood vessels in the mesoappendix of the rat, found changes in the appearance and action of these vessels when perfused with blood from animals in severe shock. The actual form of vasomotion used was the increase or decrease in the vasoconstrictor action of epinephrine. On the basis of this finding, Shorr and Zweifach and their associates have since carried out extensive studies. Briefly summarized, it has been shown that in several forms of experimentally produced shock, there occurs at first a hyper-reactive, vasoconstrictor state, caused by the formation in the (anoxic) kidney, and appearance in the blood, of a vasoconstrictor principle, termed VEM. At this time, a vasodilator principle, VDM, is being formed by the liver, but also inactivated by the liver. Later, during the stage of profound hypotensive and irreversible shock, the (anoxic) liver no longer inactivates VDM, which then appears in the blood in increasing amounts, and is considered by these investigators to be largely responsible for the irreversible hypotensive state.

VDM has been shown to be the iron-containing protein ferritin. It is activated, as the sulphydryl form, by anaerobic liver tissue; it is inactivated, as the disulfide form, by
aerobic liver tissue. The chemical nature of VEM has not been worked out; it is activated by anaerobic kidney tissue, inactivated by aerobic. One of the interesting recent developments in these studies has been the correlation between VDM and the resistance developed in rats when subjected repeatedly to the Noble-Colip drum. As is well known, by repeated sublethal rotations in this apparatus, rats become relatively resistant and can tolerate "drumming" lethal to unpracticed rats. Shorr and Zweifach\textsuperscript{28, 29} have found that in resistant rats there is a corresponding decrease in blood VDM, and increase in the ability of liver slices from these rats to inactivate VDM.

Shorr and Zweifach believe that this mechanism plays an important role in the cause of irreversible shock. Question has been raised in regard to their findings because all the results are based upon observations of a particular reaction in one specialized tissue. Recently Fine\textsuperscript{30} has given large doses of activated ferritin to a hepatectomized, renalec-tomized dog and no fall in blood pressure or other circulatory change occurred. Shorr and Zweifach\textsuperscript{4} claim that the VDM, VEM mechanism concerns the smaller vessels only, and should not be expected of itself to cause hypotension.

Physiologists have been much interested recently in certain vasodilator agents, especially Dibenamine, which, while producing a profound hypotensive state, still permits severe hemorrhage to take place without the development of irreversible shock.\textsuperscript{4, 22, 23} It suggests that some of the body's reflex or "compensatory" vasoconstrictor reactions may actually be harmful. The relation of Dibenamine hypotension to that recognized in the vasovagal reaction of clinical syncope, or fainting, is also of interest, syncope being a reaction in which arterial blood pressure falls with but little alteration either in blood volume, cardiac output, or the pressure of venous return flow to the heart,\textsuperscript{23} apparently a direct collapse of arteriolar tone. These experimental studies are somewhat complex, and further clarification is needed. The use of vasodilator agents in clinical surgery will be referred to later.

Factor of Infection. Clinically, while irreversible shock may be precipitated immediately after massive injury, it is more likely to come on progressively, when after initial resuscitation, the patient suffers some additional strain such as operation, or infection. In this condition, massive replacement with blood, bringing blood volume, and venous pressure also, to or even well above normal values, is associated with less and less response by the heart and arterial pressure; the latter finally fails progressively, the patient passes into coma, and expires. Among nontraumatic medical conditions, a not dissimilar picture may be seen in severe septic states, except that here the blood volume may be normal throughout.\textsuperscript{30}

"Toxic" substances of infectious origin have long been searched for, as causative agents in both medical and surgical shock. During the war, Aub and his colleagues,\textsuperscript{31} studying the shock that developed in dogs with gastrocnemius muscles tied off, found that the hypotensive collapse occurring after release of the ligatures was due to a toxin elaborated by clostridial organisms in the muscles during the period of ligation. Fine and his associates made similar observations at about the same time. Frank, Seligman, and Fine\textsuperscript{32} also demonstrated that irreversible hemorrhagic shock in dogs could be prevented either by cutting the liver out of the circulation, or by perfusing the liver with oxygenated blood from another animal, while the first dog was bled. Coming back to this problem again, Fine and his associates have recently made further observations on the infectious factor in shock.\textsuperscript{6, 22, 23, 33} Dogs normally harbor intestinal bacteria in their livers, in a large percentage of animals, particularly Clostridia. During shock these organisms grow rapidly. If the animals have been pretreated with Aureomycin, orally or by portal injection, or with Neomycin orally, then they are able to survive the standard lethal bleeding procedure, in most instances. This is evidence suggesting that infection plays an important role in the irreversibility of acute shock in
dogs. The nature of the substance or bacterial agent causing the irreversible state has not been identified. It has been shown, for example, that the number of clostridial organisms in the dogs' livers is the same in treated and in control groups. This work is still in progress.

Metabolic Factors. Studies during World War II24 showed that in severe progressing traumatic shock, the tissues generally appear to be much more severely affected than would be expected from the depression of the circulation as a whole. Cardiac output may be decreased by about one-half, a situation frequently encountered in ambulatory cardiac patients, and yet there develops in the shock state a profound acidosis, presumably on the basis of tissue anoxia. It would appear that blood circulation through capillaries may be more seriously deranged than the total blood flow.

Investigation of the metabolism in shock in experimental animals, also going back to the early years of World War II, has indicated that following the early responses to injury, such as hyperglycemia and increased protein catabolism, there occur progressing evidences of tissue anoxia, anaerobic glycolysis, increased blood lactate and pyruvate, increased blood amino acids, etc. It is now generally agreed that while the adrenal cortex participates in these changes, its activity is in no way causative in traumatic shock.6, 55

The metabolism of individual organs in shock has been under study for many years. The depression of renal function, with marked decrease in renal blood flow progressing, if unchecked, to ultimate renal failure in the syndrome of lower nephron nephrosis, was fully worked out in World War II.56, 57, 38 The depression of hepatic function appears also to proceed largely from progressive anoxia, with recovery when the circulation is restored.23

In classic traumatic shock, the chief difficulty suffered by the heart is insufficient return of blood to the right auricle. In irreversible shock in dogs, Wiggers89 has produced evidence, over a period of some years, that there is a true failure of the myocardium. In his experimental animals, during the state of irreversible shock, venous return is adequate, while cardiac output remains diminished. Heart size may be increased. Whether this occurs in human irreversible shock is not known. Sharpey-Schafer suspects that there may be a cardiac element in syncope, or late in hemorrhagic shock.25

The shock occurring in myocardial infarction is a different entity. This will be discussed further presently.

MEDICAL SHOCK

Overwhelming Infection

Vigorous antibiotic therapy is the mainstay in overwhelming bacterial infection with shock developing in the presence of normal blood volume. Whole blood transfusions are often of temporary aid. The use of cortisone or corticotropin has apparently been effective in some cases of Waterhouse-Friderichsen syndrome.48-52

Shock in Myocardial Infarction

Sustained shock in myocardial infarction is attended by very high mortality, usually reported as about 80 per cent, but varying somewhat with the definition of "shock." Transitory fall of blood pressure is of course one of the common events in acute myocardial infarction of moderate or even mild degree. When, however, at any time in the course of an acute infarction, the blood pressure and pulse pressure drop to shock levels, remain there for several hours, and, even more important, are associated with the clinical evidences of the shock state, the clinical picture is easily recognized. Granting that the primary event is myocardial failure, and that there frequently are associated signs of congestive failure as well—pulmonary edema, and elevated venous pressure—nonetheless there are present also all the evidences of true peripheral circulatory failure,56 with all the consequences of the progressing anoxia of shock.

The usual therapy for acute myocardial infarction is administered: morphine, oxygen (by positive pressure mask if there is frank pulmonary edema), intravenous digitalis.
Ethyl alcohol inhalation has been recommended for the pulmonary edema. The basic controversial question is whether the above are all that should be done, or whether the "tired horse" should be "whipped," that is, blood pressure elevated by drugs, and blood flow forced by infusion or transfusion, in the hope that the temporary dynamic improvement so achieved can thereafter be sustained.

Most recent writers appear to favor the use of a vasopressor agent to maintain arterial pressure for 12 to 48 hours: such as Paredrine, Neo-Synephrine, or norepinephrine. Many cases, of course, fail to respond adequately, some do not respond at all.

Opinion is more divided on the use of infusions or transfusions. This has been a controversial question for a number of years. Cochran, Wallace, and Griffith advocate intravenous fluid, plasma, or blood, unless there is frank pulmonary edema, in amounts up to 1500 cc. after periods of 7 to 48 hours. Intraarterial transfusions have been reported by Silber and co-workers and Berman and Akman. It is difficult to evaluate these various results; mortality usually appears to be less with the procedures used, but remains 50 per cent or higher.

Intravenous cholinesterase and intravenous and intramuscular cortisone gave results "suggesting a beneficial role" in preliminary studies by Cochran, Wallace, and Griffith. Physiologic theory will hardly be able to give the answers on these therapeutic questions; they will have to await the accumulation of much careful clinical trial.

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