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RECENT PROGRESS AND PRESENT PROBLEMS IN THE FIELD OF SHOCK

Held at Walter Reed Army Institute of Research
Washington, D. C., December 14–17, 1960

Sponsored by

COMMITTEE ON SHOCK AND COMMITTEE ON TRAUMA OF THE
DIVISION OF MEDICAL SCIENCES
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Foreword

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TEN YEARS AGO, a Symposium on Shock was jointly sponsored by the Division of Medical Sciences of the Academy–Research Council and the Army Medical Service Graduate School. Its purpose was to consolidate and disseminate knowledge gained in the experiences of World War II and the Korean War and in the research that was stimulated by these national emergencies.

The present conference was organized on the initiative of the Committee on Shock and the Committee on Trauma to re-evaluate contemporary knowledge and practice and to stimulate wider interest in investigations of problems in a field which tends to be neglected in times of peace.

Acknowledgment is made to the National Institutes of Health and to the Department of Defense for the funds that made possible the conduct of the conference and the publication of its proceedings. The Division is also indebted to the Walter Reed Army Institute of Research for its hospitality in granting the use of its facilities for the conference and to the Television Division of the Walter Reed Army Medical Center for the television transmission of the proceedings to audiences in seven institutions in the area of Washington.

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Introduction

JOHN M. HOWARD

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A REVIEW OF EARLIER RESEARCH demonstrates that during and immediately following World War I there was an obvious increase in studies of traumatic shock. With the passing of the military stimulus, investigators turned to other areas. Again with World War II the spotlight of medical science reverted to studies of shock and transfusion. Again the investigative activities diminished with the passage of time, but not until the value of transfusion had been firmly established. By this time the syndrome of posttraumatic renal insufficiency had been described and hepatitis had been demonstrated as a sequel to transfusion, particularly of pooled plasma.

Attention then turned to the development of a plasma volume expander. With the advent of the Korean War investigative activities were intensified both in the combat area and in the civilian laboratory. Experience during Korea demonstrated that traumatic shock could be well treated in the young man with the skills and resuscitative tools then available. Few men died in Korea of hemorrhagic shock once therapy had been instituted. Whole blood was available in adequate quantities in the forward hospitals in that specific theatre. Albumin and dextran proved effective forward of the hospitals. Treatment of hemorrhagic shock in the young man had come a long way!

With the passage of time since 1953, research in this area has again tended to lapse.

The New Executive Order on The National Research Council issued 10 May 1956 by President Eisenhower outlined the functions of the Council as follows:

a) In general, to stimulate research in the . . . biological sciences, and in the application of these sciences to . . . medicine, and other useful arts, with the object of strengthening the national defense, and of contributing in other ways to the public welfare.

b) To survey the broad possibilities of science, to formulate comprehensive projects of research, and to develop effective means of utilizing the scientific and technical resources of the country for dealing with such projects.

c) To promote cooperation in research, at home and abroad, in order to secure concentration of effort, minimize duplication, and stimulate progress; but in all cooperative undertakings to give encouragement to individual initiative, as fundamentally important to the advancement of science.

d) To serve as a means of bringing American and foreign investigators into active cooperation with the scientific and technical services of the Department of Defense and of the civil branches of the Government.

e) To direct the attention of scientific and technical investigators to the importance of military and industrial problems in connection with national defense, and to aid in the solution of these problems by organizing specific researches.

f) To gather and collect scientific and technical information at home and abroad, in cooperation with governmental and other agencies, and to render such information available to duly accredited persons.

Several years ago a Subcommittee on Shock was established by the National Research Council. It has continued to function since that time in an advisory capacity to the Armed Forces and as a nidus of stimulation at the national level.

During the period of observation of this committee, its members have witnessed the increasing appreciation of the physiological changes and deficits associated with trauma and hemorrhage both in the military and in the civilian spheres. The treatment of hemorrhagic shock in the young man has been secured. Fluid replacement is better although we have little concept as to how imperfect it really is.

Because the primary problem, namely that of saving the life of men of military age from hemorrhage, has been largely solved, investigation of the problems of shock has again tended to diminish. This Congress on Shock has been planned by the Committee on Shock and its colleague, the Committee on Trauma, with the primary purpose of bringing the investigators up to date on the present research, thereby delineating the problems in research activities needed for the future.

Plasma volume expanders have been developed to a fairly satisfactory degree and great stockpiles exist for the treatment of mass casualties, but little work has been done on the effects of irradiations on the treatment of the shock in the military or civilian casualty. With the broadening frontiers of potential military and civilian exploration, few studies have been made of the treatment of men injured in frigid climates, subterranean conditions, or under conditions of outer space. Are the guide lines currently available?

Of paramount concern in civilian surgery is the refractory shock that all of us have repeatedly seen in the

geriatric patient during, and especially following, operation. The challenge of posttraumatic renal failure has not been accepted by many investigators. Septic shock remains essentially the problem that it was 10 years ago. Finally, although treatment of shock following burns has been improved, it would be an overstatement to say that it currently is satisfactory. The inadequacy of methods of determining blood and fluid compartments almost nullifies such studies to date.

In keeping with the Executive Order of the President, the reasons that this Congress is being held are: the definition of major problems at this time; the delineation of currently fruitful areas of exploration by the exchange of information at an international level; and the stimulation of continuing contribution toward the resuscitation after injury of men of all ages under any geographical condition.

It is a pleasure to have you join with us.

Some issues in the problem of shock[1]

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THE KEYNOTE OF THIS KEYNOTE ADDRESS is going to be "expression without inhibition." At the very outset, therefore, I want to say that I was immeasurably pleased to be asked to participate in this conference. To be sure, I was surprised by the invitation, because I had the feeling that I had reached, as one of my classmates has nicely put it, that pleasant stage of negative intellectual balance where the loss of information is greater than the intake. Be that as it may, this assignment has provided me a rare opportunity, namely that of publicly asking some questions without having to answer them. By definition, all I need to do is to raise some issues which are subject to debate. I have considerably more liberty than the political keynote speaker who has to discuss the issues which will appeal to the entire party; I need to mention only those problems in which I have been specially interested. And this is fortunate, for to outline still other debatable matters would take us far into the night.

Sixteen years ago, Richards (1944) ended his Harvey Lecture on "The Circulation in Traumatic Shock in Man" with the statement "The greatest mistake is to suggest, as some have done, that shock is a problem that has been solved." Much has been learned about shock since that lecture, and some previously amorphous ideas have become crystallized. Some progress has been made in the identification of certain metabolic intracellular derangements incident to shock and trauma, and there has been some clarification of the neuroendocrine basis for certain of the observed phenomena. But many of the questions asked four and five decades ago remain unanswered; new problems have been identified and much confusion has been generated by questions of interpretation of data. From among the various matters which could be debated, I have selected the following: *1*) the semantic problem, *2*) the role of the heart in shock, and *3*) the question of bacterial products in fatal shock.

SEMANTIC PROBLEM IN SHOCK

It would seem heretical to begin a conference on shock without discussing terminology. There is no denying that a problem of definition exists; the question is what can or should be done about it. Some conferences have recognized the problem, but have agreed at the outset not to discuss it for fear that nothing else would be accomplished during the entire time. There is justification in this attitude but, in all fairness, it is reasonable to wonder how much a conference can accomplish if each participant bases his remarks on something different from what everyone else has in mind. Little more could be achieved than at the tower of Babel. That progress has been made in past conferences on shock attests to the fact that in most instances the participants basically visualized the same disturbance in shock, albeit differing from one another in the details.

On the other hand, from their critical review of what had been written about clinical shock during and after World War I and from their own observations during the Battle of Britain and on the Italian front, Grant and Reeve (1951) came to the conclusion that the term shock is so lacking in precision as to be of little value. Quite rightly, they pointed out that whoever used the term had his own understanding of what he meant, which could be quite different from the understanding of others. They proposed in that publication and again at a Symposium on Shock, in this very auditorium (Grant, 1951), that since from the clinical point of view the outstanding feature of shock is the circulatory pattern presented by the patient, this pattern should be utilized for describing the patient precisely. Six patterns were suggested, utilizing four clinical indices of the state of the circulation. The circulatory patterns were: normal, cold tachycardia, warm tachycardia, hypertension, vasovagal, cold hypotension, and warm hypotension. The four clinical criteria were blood pressure, pulse rate, temperature of the extremities, and color of the face. These could easily be defined and in most instances the meaning would be clear to all. There would be no need for the word "shock." But surgical historians tell us that the word is two centuries old. Perusal of the sources indicates that one century old would be more nearly correct. Nevertheless, even a centenarian word would be difficult to dislodge from usage.

It is true that the understanding of any problem is hampered by lack of precise definition of important terms. However, one is equally justified in the thought that clear definition may not be possible when the phenomena involved are not entirely understood, or when

[1] Supported by U. S. Army Grant Number DA-49-193-MD-2022.

the term is a generic one and is used to define a group or class of conditions having a basic similarity but differing in important details. The term "shock" is a useful one if we can agree that it implies a situation in which the basic problem is an inadequate propulsion of blood into the aorta and, therefore, an inadequate flow of blood for perfusing the capillary beds of the skin and other organs. Cannon (1923) wrote "It seems to me that, in such a complex as shock, definition is not a prime requisite. The important matter is to obtain a careful description of the observed facts." Those of us who are worried that we differ among ourselves with regard to what is cause and what is effect in shock, may derive comfort from the words of Goethe: "The thinker makes a great mistake when he asks after cause and effect. They both together make up the individual phenomenon."

There is some evidence that investigators are not so terribly far apart in their understanding of what shock is. During the Second World War, I had the great privilege of being in charge of a Board of Officers appointed to study the severely wounded in the Mediterranean theater of war. The Board teemed with talent. It included Tracy Burr Mallory, Henry K. Beecher, Charles H. Burnett, Eugene R. Sullivan, Louis D. Smith, and Seymore Shapiro. A more discussion-minded group can hardly be imagined. I well remember the arguments regarding so-called "irreversibility," the criteria of clinical shock, and the question of whether shock was all-or-none or susceptible to grading. Nevertheless we did decide to evaluate on clinical grounds the severity of shock when we first saw the casualty and before the physiologic and biochemical data were available. At the end of the war in Europe we assembled the records of the casualties studied according to the degree of clinical shock, ranging in four categories between none and severe. We were surprised to see the close correlation between the degree of shock as evaluated on purely clinical grounds and the calculated deficit of circulating blood volume and other data. Of even greater interest is the close similarity between our classification and findings with those reported by Keith in 1919 from his studies of battle casualties in World War I. It is noteworthy that two groups working over 20 years apart, recognized three degrees of wound shock (Table 1). In addition there is similarity in the results of the two groups with regard to the extent of correlation between the degrees of severity and the changes in blood pressure (Table 2), the increases in pulse rate (Table 3), and the deficits of circulating blood volume (Table 4). At least when dealing with wound shock, therefore, the problem of terminology is not always a serious one.

TABLE 1. *Clinical Evaluation of Severity of Wound Shock in Battle Casualties*

World War I (Keith)	World War II (Board for Study of Severely Wounded)
	None
Compensated (group I)	Slight
Partially compensated (group II)	Moderately severe
Uncompensated (group III)	Severe

TABLE 2

CLINICAL EVALUATION OF WOUND SHOCK

	Systolic Blood Pressure	
Degree of Shock	World War I	World War II
None	-	126 ± 12
Slight	Over 100	109 ± 3
Moderate	Under 90	95 ± 5
Severe	Under 60	49 ± 8

TABLE 3

CLINICAL EVALUATION OF WOUND SHOCK

	Pulse Rate	
Degree of Shock	World War I	World War II
None	-	103 ± 7.2
Slight	90-110	111 ± 3.4
Moderate	120-140	113 ± 3.6
Severe	120-160	116 ± 3.3

TABLE 4

CLINICAL EVALUATION OF WOUND SHOCK

	Percent. of Blood Volume Lost	
Degree of Shock	World War I	World War II
None	-	15
Slight	Less than 20	20
Moderate	25 to 35	35
Severe	40 to 50	45

The clinical picture which we call shock is a resultant in common of many etiologic situations which ultimately cause inadequate perfusion of tissues and organs. This circulatory insufficiency can result through interference with any one or more of the components organized for circulatory homeostasis. Normal or adequate circulation is maintained through nice integration or modulation of the activities of these components, namely the heart, the vessels, and the blood propelled by the heart and by skeletal muscular activity and conducted under pressure by the vessels. The latter are locally modified by the accumulation or clearance of tissue metabolites. At the operational level these elements usually are selfsufficient, but a fourth agency is needed to permit the nice adjustments required when physiologic constancy is threatened. This is the neuroendocrine system which we might say functions at the policy level and by analogy with what goes on in society occasionally goes awry.

Viewed in this manner, circulatory insufficiency, which produces signs and symptoms collectively called shock, can have quite different causes which would be treated differently. But all in all, the basic problem is that what blood is contained within the arteries is under insufficient pressure to overcome the arteriolar and capillary resistances and to perfuse vital capillary beds. Clinically we recognize the condition because blood vessels of the skin and mucous membranes may be completely void of blood and because we have learned to recognize the signs and symptoms of physiologic compensatory reactions. Thus, because of this multiplicity of mechanisms

which are brought into play, we cannot expect to find a single word or a pair of words which would describe the ultimate clinical condition and at the same time be sufficiently discriminative to imply the responsible one of many possible etiologies.

We have two alternatives. The first is to abandon the word altogether This I think is unrealistic because the word is such a convenient one and has been in use in its present sense for over a century. Rather than abandon the word shock, I should prefer the second alternative, namely to teach that the word is indeed useless out of context and that in order to be meaningful must be understood in terms of the history of the condition in the particular patient or animal and in terms of the physical findings. The patient who has suffered a severe coronary thrombosis and the patient who has suffered massive bleeding into his gastrointestinal tract may both be in shock. In both, the heart and the compensatory reactions can reach the point where vital capillary beds are inadequately perfused. The two are in shock, but in each the antecedent history and the physical findings are different. The need for knowing what went on before is not uncommon in medical terminology.

Use of the term "wound shock" should be encouraged because this comprises a specific group of patients in which the wound and its treatment and the patient's neuroendocrine reaction contribute to the clinical effects of the underlying abnormality, namely a decrease in the effective circulating blood volume. However, even this phrase by itself does not tell us what part of the clinical picture is hematogenic, what part is vasogenic, and what part is neurogenic, to use Blalock's (1934) classical terminology. Monoverbal qualifications of the term shock are not sufficiently descriptive for application to all clinical situations. This conference may point the way to better terminology.

ROLE OF THE HEART IN FATAL SHOCK

Next let us turn to the question of what vital areas are responsible for decompensation in fatal shock. Impaired cardiac function in shock has been suspect and a matter of debate for some years. Opdyke and Wiggers (1946) reported the time course and characteristics of right intraventricular pressure changes in oligemic followed by normovolemic shock. From this and other evidence, Wiggers (1950) concluded that myocardial depression is a frequent complication of prolonged shock, but that one can expect considerable variability from one subject to the next. Furthermore, until immediately preceding death when right ventricular diastolic tension is slightly increased as is the systolic ventricular volume (Kohlstedt and Page, 1944), most of the changes could be attributed to changes in the venous return to the heart so that failure of the myocardium may not be the primary problem in fatal normovolemic shock.

The evidence for myocardial deterioration in shock stems from a number of sources, other than the study of intraventricular pressures and volumes. There is evidence

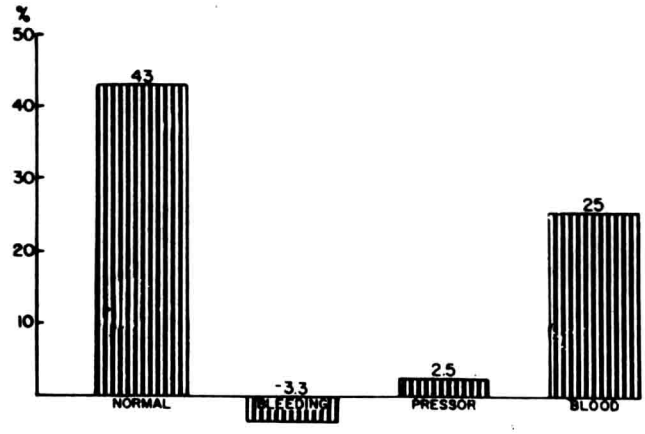

FIG. 1. Calculated pyruvate extractions (A-V/A × 100) from dogs before hemorrhage, during hemorrhagic hypotension, during oligemic normotension by means of an infusion of *l*-norepinephrine, and after reinfusion of reservoir blood (cf. Catchpole et al., 1955). Note the negative pyruvate balance during hypotension, failure of restoration with the vasopressor, and only partial restoration with transfusion.

from studies of the electrocardiograph, the coronary myocardial circulation, myocardial metabolism, and records of myocardial contractile force.

a) Electrocardiographic evidence for myocardial depression. In a study of the electrocardiographs of casualties in shock on the Italian front, Burnett, Bland and Beecher (1945) observed that diagnostic changes were rare. These were previously healthy young men. Under other circumstances, reversible electrocardiographic changes in the S-T segment and in the T-Wave have been described in human hemorrhagic shock (cf. Master et al., 1947). In carefully controlled experiments in which attention was paid to possible changes in heart size and position, Izquieta and Pasternack (1946) recorded similar changes in the electrocardiogram of the dog in early and late hemorrhagic shock.

b) Myocardial circulation in hemorrhagic hypotension. Corroboratory evidence for myocardial circulatory depression is provided from direct and indirect studies of the myocardial circulation (Opdyke and Foreman, 1947; Edwards, Siegel and Bing, 1954; Sarnoff et al., 1954; Catchpole et al., 1955). In general, there is a decrease in myocardial blood flow following hemorrhage. Reinfusion of blood after a period of oligemic hypotension temporarily restores the coronary arterial blood flow to above normal limits only to fall again to low levels in animals which fail to survive.

During oligemic hypotension, a decrease develops in the availability of oxygen to the myocardium (Simeone et al., 1959; Caliva et al., 1959). Despite the decrease in the work of the heart during the period of hypotension, the diminished coronary blood flow and the related lowering of the availability of oxygen to the myocardium and to other tissues result in cellular hypoxia and serious metabolic disturbances.

c) Myocardial metabolism in oligemic hypotension. There is clear evidence that the myocardial carbohydrate metabo-

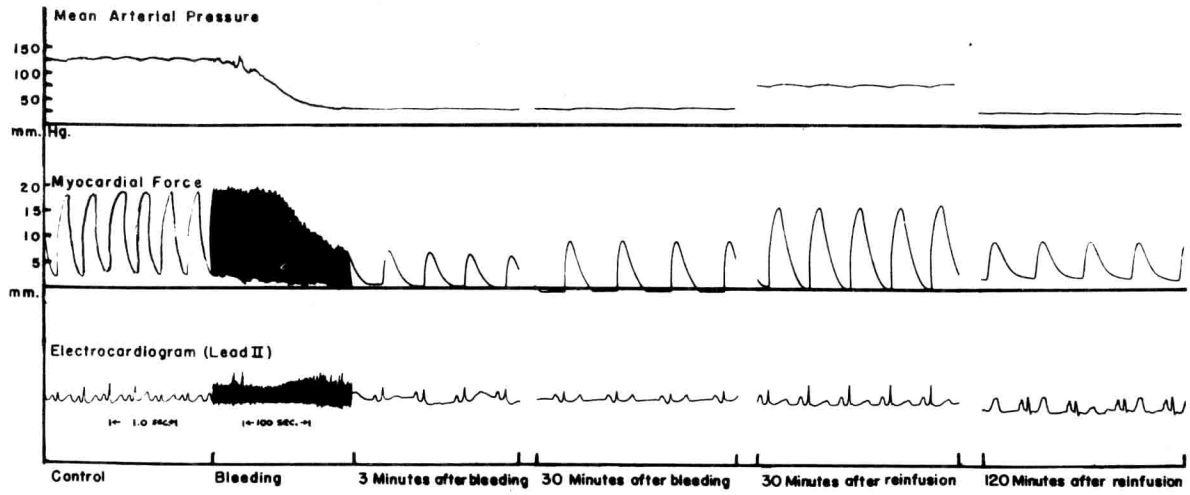

FIG. 2. Oscillographic tracings of arterial blood pressure, top record; electrocardiogram, lowermost record; and myocardial isometric contractile force as transduced by "force gauge," middle record. Chest open. Pentobarbital anesthesia. Note the prompt drop in myocardial force with onset of bleeding during oligemia. Cardiac output and myocardial oxygen availability low during this time. With reinfusion, myocardial force returns immediately to nearly normal, along with restoration of coronary blood flow and oxygen tension. Force then again deteriorates along with venous return and cardiac output.

lism is deranged during oligemic hypotension and fatal shock (Edwards et al., 1954; Hackel and Goodale, 1955). The extraction of dextrose from the coronary arterial blood is less than normal. Even more striking is a reversal of the normal pyruvate positive balance (Fig. 1) to a negative balance in which the myocardium contributes pyruvate to blood returning to the coronary sinus instead of extracting pyruvate from the arterial blood. The effect on dextrose metabolism is difficult to explain on the basis of the available data. The observation regarding pyruvate could be explained by a failure of cocarboxylase activity both in the myocardium and in other tissues as the result of hypoxia (Ochoa, 1939). Burdette and Wilhelmi (1946) showed, some years ago, that myocardial slices from rats in hemorrhagic hypotension could utilize pyruvate under appropriate conditions, but at best the utilization was not as great as by slices from control animals. Cocarboxylase is needed to permit pyruvate to enter the Krebs cycle. The relative hypoxia associated with poor tissue perfusion could lead to inactivation by dephosphorylation of cocarboxylase in the myocardium and even more so in other tissues (Greig, 1944 a and b). Of particular interest is the fact that this metabolic derangement in the heart is not corrected by restoring the myocardial circulation to normal or above normal by means of vasopressor agents and only partly toward normal by the transfusion of blood (Fig. 1).

Thus there is no doubt that the myocardium of the dog is adversely affected by oligemic hypotension. However, when provided with blood, even though the heart may be on the verge of failure, the myocardium will pump the blood into the aorta with nearly normal force (Fig. 2) until the very end. In man, the heart is known to withstand considerable insult. It frequently recovers normal function after major occlusions of its coronary blood supply. In approximately half the cases, it starts again after stopping for toxic, hypoxic, and for unknown reasons. It is reasonable to doubt that the heart plays a primary role in fatal hemorrhagic shock. Of greater immediate importance is the venous return to the heart. It would seem that other organs and tissues may fail before the heart. The small peripheral blood vessels, at least those of the skin, do not appear to fail. The response of the circulation of the dog's paw to intravenously injected l-norepinephrine is not impaired by prolonged oligemic hypotension (Catchpole, Hackel and Simeone, 1955). Especially suspect in the dog is the brain. In survival experiments in dogs under local anesthesia, we observed that those animals which died usually failed to regain consciousness after the stupor which always develops after the animals had been bled to severe hypotensive levels. The animals which survived usually awakened promptly or shortly after the predetermined period of oligemic hypotension.

ROLE OF BACTERIAL PRODUCTS IN FATAL SHOCK

A great body of evidence has been amassed to indicate that intestinal bacteria play a major role in the failure of animals to recover from prolonged oligemic hypotension (cf. Fine et al., 1959 for summary). Presumably, these bacteria elaborate endotoxins within the gastrointestinal tract or possibly in other tissues. The endotoxins reach the circulation, but under normal circumstances are very promptly removed by the reticuloendothelial system. The effect of hypotension, whether hemorrhagic or from other causes, is to depress the properdin system and the reticuloendothelial system to the extent that the endotoxins accumulate in the animal and in some way affect the circulation so that recovery is impossible.

It is not possible at this time to review the whole evidence for this concep , but it may be stimulating to

raise a question or two. We might state at the outset that, in recent years, attempts to demonstrate a role for infection in fatal wound shock in man have been unsuccessful. The data in support of the concept pertain to animals, but I hasten to add that this does not detract from the observations which have been made and recorded from the laboratory on this subject.

It is self evident that both insidious and fulminant infection can lead to eventual cardiovascular collapse and death both in animals and in man. But the concept that circulating exotoxins (Aub et al., 1947) or endotoxins are instrumental in the fatality of prolonged hemorrhagic shock, wound shock, or tourniquet shock is not so readily apparent. We may very briefly examine the evidence (Fine et al., 1959). First there is the point that the administration of liver pulp from animals long in shock is lethal to animals in otherwise still reversible shock (Fine, 1954). This would prove that such liver pulp is bad for dogs which have been oligemic and hypotensive for 2 hours, but does not necessarily imply the presence of a toxin. Could the extract of such a liver be charged with fixed acids and be so low in pH as to overwhelm the dog which already has been hypotensive for 2 hours and has undoubtedly developed a certain degree of metabolic acidosis? I should like to return to this point again in connection with the transfusion of "shock blood" to the "prepared dog."

Data have been provided to the effect that perfusion of the liver (Frank et al., 1946; Seligman et al., 1947) protects against the development of ineffectiveness of transfusion in oligemic hypotension. There are two questions in this connection. Can one be certain that some of the perfusing blood does not in fact reach the systemic circulation and remain in it? Although precautions were taken against the possibility, the same question can be asked of the recent experiments of Lillehei (1957) who showed improvement by arterial perfusion of the intestine during oligemic hypotension in the recipient. Can the perfusing blood serve as a dialyzer of a sort and thereby help to prevent the metabolic acidosis of shock? These questions may seem trivial at this time, but we shall refer to them again.

The injection of a small amount of endotoxin into the circulation of a dog which is on its way toward irreversibility has proved to be lethal. This is not surprising. Prolongation of the oligemia and the hypotension can accomplish the same end, but this does not prove that endotoxin is responsible for it. Hemorrhages are found in the intestine of dogs which die from the injection of endotoxin and in the intestine of those which die of prolonged oligemia and hypotension after the reinfusion of blood, but this is not necessarily a reaction specific to endotoxin. Could it, in some cases, be due to relative ischemia and the action of intestinal enzymes?

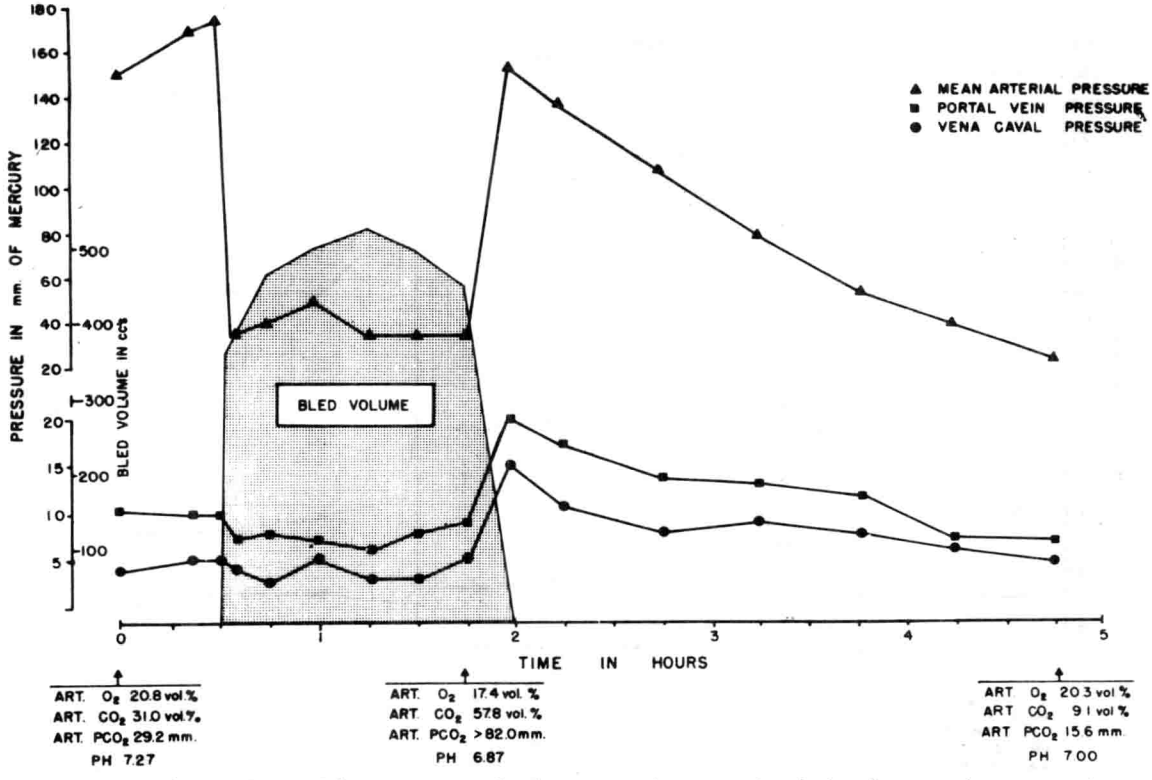

FIG. 3. Measurements of systemic arterial pressure, portal vein pressure (through catheter in splenic vein), and vena caval pressure before, during, and after severe hemorrhage. Note that portal pressure does not rise above normal during the period of oligemia. Nor does it rise after reinfusion to any great extent if the actual portal pressure is calculated as portal pressure minus vena caval pressure. Added along the abscissa are measurements of the respiratory gasses and the pH. Note the metabolic acidosis with added respiratory acidosis in the middle period and the severe acidosis in the late period.

The lesion does not develop in all animals. It has been observed in less than half of our animals which died (Hackel and Catchpole, 1958). Nor does it absolutely mean irreversibility, for it is found occasionally at autopsy in dogs which survived prolonged severe oligemia. Indeed, if it is true that the lesion invariably accompanies fatal endotoxin injection, this is one way in which the two conditions differ. Nor is the gastrointestinal tract the only target organ for hemorrhages. In our animals (Hackel and Catchpole, 1958), hemorrhages beneath the endocardium of the ventricles, particularly the left, were even more common than hemorrhages in the intestine. Therefore, it is reasonable to wonder about both the significance and the specificity of the hemorrhagic intestinal reaction.

There is further cause to question similarity between the animal dying of shock due to the injection of endotoxin and the animal dying of prolonged oligemic hypotension. Weil et al. (1956) demonstrated a temporary rise in portal vein pressure in animals injected with endotoxin and showed that it occurred for a matter of minutes regardless of whether the systemic arterial pressure fell or was maintained at a constant normal level by artificial perfusion. Recent work in our laboratories with Weidner and Tomin has shown very clearly, and Wiggers, Opdyke and Johnson (1946) reported similar findings in 1946, that the portal pressure falls abruptly with sudden hemorrhage along with a fall in the vena caval pressure (Fig. 3). Slowly the portal pressure returns toward normal and when the blood is reinfused after 90 minutes of severe hypotension both the portal and the systemic venous pressures rise, but if the vena caval pressure is subtracted from the portal, the latter shows no rise at all in about one fourth the cases.

Furthermore, a rise in portal pressure is not specific for endotoxin. Quintero et al. (1959) showed that it will rise when acidosis is produced in dogs by the injection of hydrochloric acid. With Weidner and Tomin we have recently shown a sharp rise in portal pressure with respiratory acidosis (Fig. 4) without hypoxia, and with hypoxia (Fig. 5) without acidosis.

The finding of lesions characteristic of a generalized Shwartzman phenomenon in animals dying of prolonged oligemic and normovolemic hypotension has been advanced as another similarity between this and the shock brought on by the injection of endotoxin. Hackel (Hackel and Catchpole, 1958) very carefully studied the histology of the heart, lungs, liver, intestine, stomach, and kidneys both in animals which died following prolonged oligemia and hypotension and in those which lived and later were autopsied. A Shwartzman phenomenon was not found. We have since studied more animals after the same general kind of experiments. In the kidney, we have observed submucosal hemorrhages in the renal pelvis, but nothing to suggest a generalized Shwartzman phenomenon.

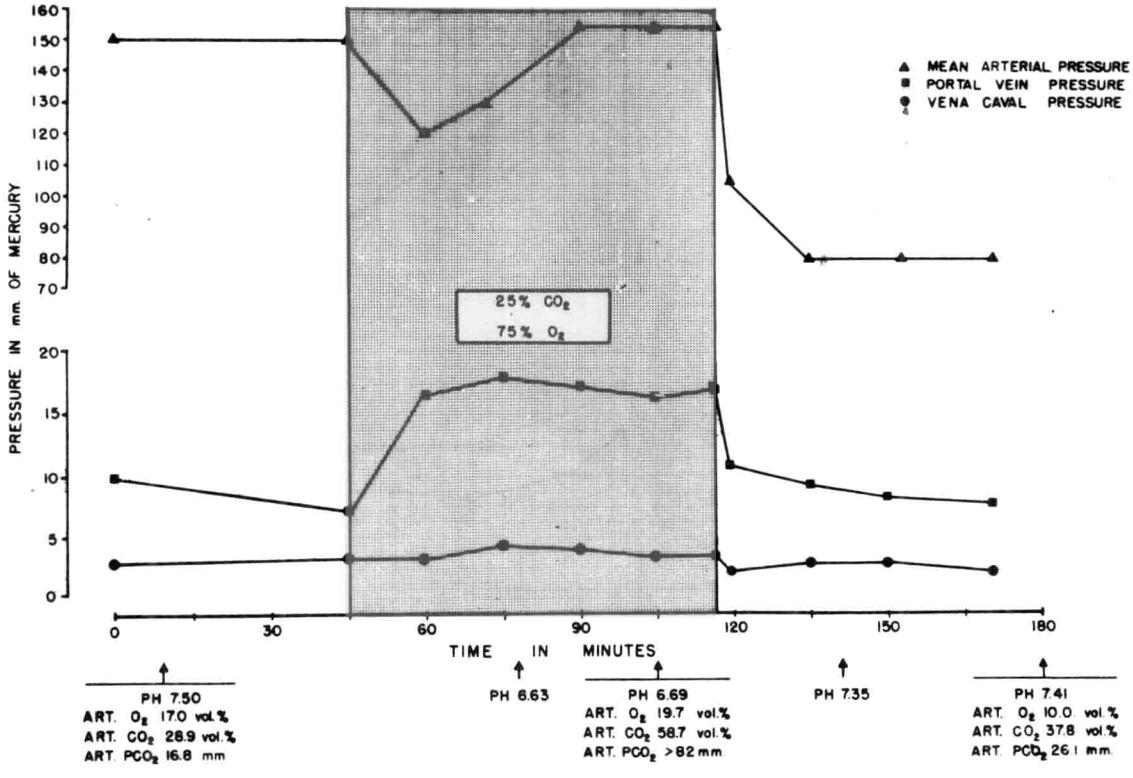

FIG. 4. Records of systemic arterial pressure, portal vein pressure, and vena caval pressure before, during, and after inhalation of 25% carbon dioxide. Measurements of the respiratory gasses and the pH are recorded along the abscissa and demonstrate the respiratory acidosis. Nembutal anesthesia; curarized.

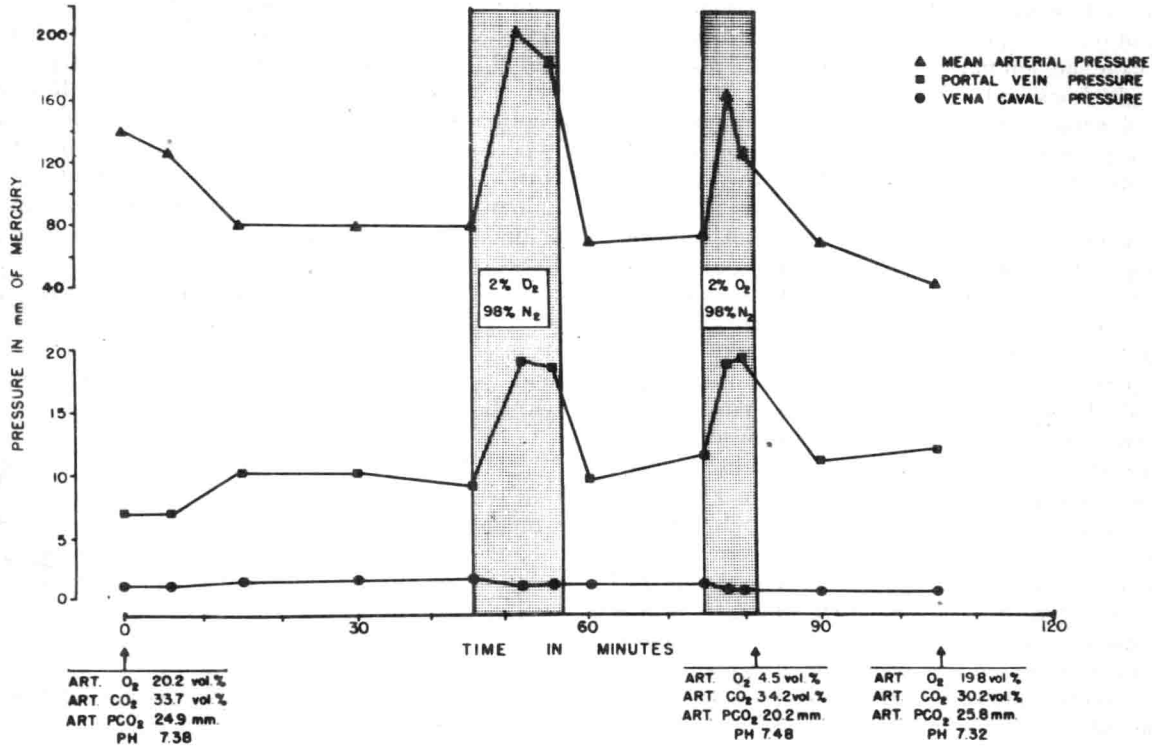

FIG. 5. Same preparation as in Fig. 4 but inhalation of 98% nitrogen instead of carbon dioxide. Figures along the abscissa show hypoxia without acidosis.

Of course these are negative observations in the dog and I must not imply that the Shwartzman phenomenon did not occur in the rabbit experiments cited by Fine et al. (1959). I merely want to state that it is possible for dogs to experience prolonged oligemic hypotension and either survive it or not without showing the Shwartzman phenomenon.

A word should be said about experiments on protection against prolonged oligemic hypotension by means of pretreatment with enteric antibiotics, even when these agents are not absorbed into the circulation. The data, at best, are not clear-cut with regard to statistical significance especially when one is dealing with prolongation of the time within which reversal is possible. The variables in a problem such as this are legion. For example, the establishment of a desired low level of hypotension may vary between 5 and 90 or more minutes depending upon the size of cannula used, the rate of hemodilution which starts with remarkable rapidity, and the level at which the collecting bottle is placed. The actual duration of severe hypotension in the animal, over a total period of 2 hours, could vary by as much as 25-50%. The rate at which blood is returned to the animal also must be carefully controlled, for it is well known that if an animal has been in severe oligemic hypotension for 90–120 or more minutes, the return of its blood intra-arterially within 5 minutes or so will precipitate heart failure and death. Thus the rate of transfusion can be an important variable with regard to survival.

The development of techniques for working with germfree animals had raised the hopes of those interested in this field that the role of endotoxins in hemorrhagic shock would be settled. This hope has not come to pass. However, although it is possible that germfree animals harbor heat-stable endotoxins in their intestines, having acquired these toxins from ingested food, the fact that in response to hemorrhage and trauma they behave very much as do the germ-laden animals (McNulty and Sinares, 1960) is evidence against the significance of toxins of bacterial origin in the progression of oligemic hypotension to fatal shock.

TABLE 5A, B

(A) WOUND SHOCK AND ALKALI RESERVE
(after Capt. Walter B. Cannon, M. O. R. C., 1919)

Number of Cases	Systolic Blood Pressure (in mm. Hg.)	Mean CO_2 Capacity (vol. percent.)
4	over 100	53
18	80-100	50
19	60-80	40
6	40-60	33

(B) ACIDOSIS IN WOUND SHOCK, HAEMORRHAGE AND GAS INFECTION
(Cannon, 1919)

Number of Cases	CO_2 Capacity (vol. percent.)		Mean Arterial Pressure (in mm. Hg.)
	Mean	Range	
6	24	20-29	49
8	35	30-39	59
26	44	40-49	61
7	53	50-59	69