SHOCK

EDITED BY S. G. HERSHEY, M.D., *Professor of Anesthesiology, New York University Medical Center,* WITH 27 CONTRIBUTORS

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CONTRIBUTORS

S. G. Hershey, M.D., Editor
Professor of Anesthesiology, New York University Medical Center

Silvio Baez, M.D.
Associate Professor of Anesthesiology and Physiology, Albert Einstein College of Medicine of Yeshiva University

Benjamin Blattberg, M.A.
Associate, Research Division, St. Vincent Charity Hospital (Cleveland)

Jack H. Bloch, M.D.
Medical Fellow in Surgery, University of Minnesota Medical School

C. James Carrico, M.D.
Fellow in Surgery, University of Texas, Southwestern Medical School

Dale Coln, M.D.
Fellow in Surgery, University of Texas, Southwestern Medical School

J. W. Crowell, Ph.D.
Associate Professor of Physiology, University of Mississippi School of Medicine

Albert Einheber, Ph.D.
Chief, Department of Germfree Research, Division of Basic Surgical Research, Walter Reed Army Institute of Research, Walter Reed Medical Center

Edward D. Frank, M.D.
Associate Visiting Surgeon, Beth Israel Hospital (Boston)
Assistant Professor of Surgery, Harvard Medical School

A. C. Guyton, M.D.
Professor and Chairman, Department of Physiology and Biophysics, University of Mississippi School of Medicine

Aaron Janoff, Ph.D.
Assistant Professor of Pathology, New York University School of Medicine

Stanley M. Levenson, M.D.
Professor of Surgery, Albert Einstein College of Medicine of Yeshiva University

Matthew N. Levy, M.D.
Director, Research Division, St. Vincent Charity Hospital (Cleveland)
Associate Professor of Physiology, Western Reserve University

Richard C. Lillehei, M.D., Ph.D.
Associate Professor of Surgery, University of Minnesota Medical School

Jerrold K. Longerbeam, M.D.
USPHS Special Research Fellow, University of Minnesota Medical School

William G. Manax, M.D.
Medical Fellow in Surgery, University of Minnesota Medical School

V. D. B. Mazzia, M.D.
Professor and Chairman, Department of Anesthesiology, New York University School of Medicine

Arnold L. Nagler, Ph.D.
Associate, Departments of Surgery and Pathology, Albert Einstein College of Medicine of Yeshiva University

Mark Nickerson, Ph.D., M.D.
Professor and Head of Department of Pharmacology and Therapeutics, Faculty of Medicine, University of Manitoba

Louis R. Orkin, M.D.
Professor and Chairman, Department of Anesthesiology, Albert Einstein College of Medicine of Yeshiva University

Felix T. Rapaport, M.D.
Assistant Professor of Surgery, New York University School of Medicine

Mohinder P. Sambhi, M.B., B.S., M.Sc.
Research Associate, Department of Medicine, University of Southern California School of Medicine
Established Investigator, Los Angeles County Heart Association

Ewald E. Selkurt, Ph.D.
Professor and Chairman, Department of Physiology, Indiana University School of Medicine

G. Tom Shires, M.D.
Professor and Chairman, Department of Surgery, University of Texas, Southwestern Medical School

Herbert Shubin, M.D.
Instructor in Medicine, University of Southern California School of Medicine
Attending Physician, Los Angeles County Hospital

Vasant N. Udhoji, M.B., B.S.
Research Associate, Department of Medicine, University of Southern California School of Medicine

Max Harry Weil, M.D.
Associate Professor of Medicine and Director of the Shock Research Unit, University of Southern California School of Medicine
Attending Physician, Los Angeles County Hospital

Benjamin W. Zweifach, Ph.D.
Professor of Pathology, New York University School of Medicine

PREFACE

Active research interest in shock dates back to the early years of this century. Awareness of the clinical problem of shock existed much before this. The history of this long effort to determine the true nature of the syndrome provides eloquent testimony to its inherent complexity. For at this moment, the critical shock mechanism still remains an elusive entity. Yet much of great importance has undoubtedly been learned about this subject over the years. But this great mass of information looms as a poorly defined, amorphous body of accumulated data, in that no one can say which, if any, of its features reliably point to the path of a precise, complete solution to the fundamental problem posed by shock. In recognition of this uncertain situation, many people directly interested in shock have recently expressed the need to bring more form and shape to current and future study of the syndrome. As a result, we are now in what might be called a period of reassessment of the subject to formulate research criteria and to direct attention to those facets of the problem to further the above need. In a sense, this volume is an expression in this direction. This symposium provides no clear-cut, final answers, but it does carry us to those areas in which some of these answers may be found, or perhaps already have been found.

For the most part shock research has been synonymous with animal research. Clinical investigation of the syndrome has, by comparison, been very limited and much less incisive. The fundamentally lethal nature of the disturbance makes this situation understandable. But herein probably lie the two most serious criticisms and weaknesses of what has been, up to now, the overall approach to the study of shock. Even though the products of shock research are for human consumption, the vital process of feedback between clinic and animal laboratory, to the advantage of each, has been limited. Thus meaningful traffic and transfer of information from the animal laboratory, where it exists for the most part, to the clinic, for which the information is intended, have not occurred to any great extent. As a corollary of this weakness in feedback, the characteristics of shock in patients, in whom it occurs in its natural form, have not sufficiently shaped the conditions during which experimental shock is studied. Because of this, no one can reliably identify which of the experimental data are valid for man. Shock is a protean entity; and each experimental study, carefully circumscribed and controlled, is, by experience, not a microcosm of the multifaceted natural phenomenon. Caution, perhaps even beyond our ability to exercise it, is required to extrapolate animal data to humans. The reverse situation also exists.

The basic differences between shock studied in many species of laboratory animals and shock as it occurs "spontaneously" in man comprise a subject of considerable scope and major importance. Details of this subject cannot and need not be dealt with here. But the realization of its significance toward furthering the common objective of treating patients more skillfully has been developing. The beginnings of organized studies of the comparative physiology of shock already exist. Investigations of shock in man are expanding in frequency and scope. The walls between the clinic and laboratory are beginning to come down. Undoubtedly, a most productive period in the study of shock is being ushered in. The various sections of this volume already show this to an extent not possible even a few years ago.

Having exercised an editor's prerogative of personal expression in this introduction, I would wish to add one other remark. I consider that I was most fortunate in being able to convince each of the authors to contribute to this volume. Anesthesiologists and others familiar with the confusing current status of shock will immediately recognize the singular value of each participant's contribution. The collective effort, with all due modesty, affords a most valuable, comprehensive, and updated source of information on the subject. To each of the authors, may I express my deep, personal gratitude.

S. G. HERSHEY

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CARDIAC DETERIORATION IN SHOCK: I. ITS PROGRESSIVE NATURE

A. C. Guyton and J. W. Crowell

FROM THE EARLIEST RECOGNITION of shock as an entity, attempts to define it have been almost as difficult as attempts to determine its mechanisms. The definition by Gross in 1872, commented on by Davis (3), of shock as "a manifestation of a rude unhinging of the machinery of life," offers some idea of the difficulties involved. Yet, for discussion in this and the following section, another definition of shock will be used: Circulatory shock is a state of the circulation in which the cardiac output is too low to supply normal nutritional needs of the body's tissues even when the subject is at rest. Also, the definition which will be used for *progressive shock* is shock that is becoming progressively more severe even though the initial cause of the shock is not itself becoming more severe. In other words, intrinsic factors in the animal, aside from the original cause of the shock, are causing the animal's condition to deteriorate. And, *irreversible* shock is a final stage of shock in which *no* type of therapy can cause the animal to recover from the shock.

Our studies on hemorrhagic shock have demonstrated that the heart deteriorates severely as shock progresses and that this deterioration is one of the major causes of death. This chapter will discuss the events that lead up to cardiac deterioration, and the subsequent chapter will present evidence that irreversibility of shock occurs when the heart has deteriorated beyond a certain critical level.

Our view that deterioration of the heart is one of the most important causes of progression and irreversibility in shock contrasts markedly with views of many other workers in the field of shock; but even so, there is a growing list of research workers who have come to many of the same conclusions as we, including Wiggers (10), Edwards, Siegel, and Bing (4), Sarnoff, Case, Waithe, and Isaacs (8), and Gomez (5), all of whom have demonstrated either minor or major degrees of cardiac damage in experimental shock.

The role of the heart in shock has been neglected by many research workers, probably because cardiac deterioration is masked by the tremendous cardiac reserve which all animals have. This reserve is 300 per cent to 400 per cent in the normal nonathletically trained human being, and it may be as great as 600 per cent to 700 per cent in a greyhound dog. Because of the reserve, the heart can deteriorate to less than one-third or sometimes less than one-fifth its normal pumping strength without any measurable evidence of cardiac failure. Therefore, experiments on shock would not be expected to detect cardiac deterioration until almost terminal conditions had ensued. This, indeed, is what has been found in our experiments which have been almost exactly duplicated by Gomez (1962).

Vicious Cycles that Cause Progression of Shock

Once the severity of shock has reached a certain critical level, the shock will thereafter progress until the person dies, even though the initiating cause of the shock does not become more serious. That is, a vicious cycle develops in which the shock "breeds" more shock. Some of these vicious cycles are represented in Figure 1. From this figure six separate known types of "feedback" that further depress the cardiac output in shock can be discerned. These are (1) decreased coronary flow which causes a weakened heart with consequent further decrease in cardiac output; (2) decreased blood flow to the brain which depresses the sympathetic nervous system, followed by vascular dilatation, pooling of blood, and decreased output; (3) decreased nutrition of the vascular system which also causes vascular dilatation, resulting in pooling of blood and decreased

output; (4) increased capillary permeability resulting after many hours of capillary anoxia; this allows decreased blood volume, decreased venous return, and further decrease in cardiac output; (5) ischemia of many different tissues, such as of the liver, intestines, and perhaps others, causing release of toxins or metabolic substrates that in turn cause cardiac depression, increased capillary permeability, vascular dilatation, and other effects that eventuate in decreased cardiac output; and (6) intravascular clotting results from sluggish blood flow, which further decreases the venous return and cardiac output.

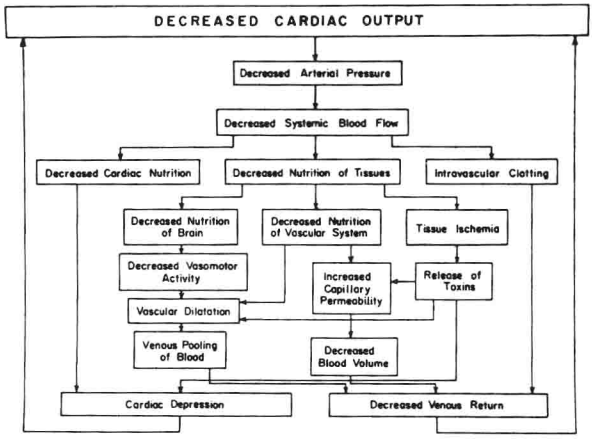

FIGURE 1. Feedback cycles that can lead to progression of shock.

INITIATING CAUSES OF PROGRESSIVE SHOCK

It is evident from Figure 1 that the only requirement for initiating the separate types of feedback is for the cardiac output to fall below a critical level. Therefore, any circulatory change that can initially decrease the cardiac output can lead to progressive shock. This may be any one of the well-known initiating causes of shock such as hemorrhage, septicemia, toxemia, anaphylaxis, dehydration, and many others.

MATHEMATICAL BASIS OF VICIOUS CYCLES

Figure 1 might indicate to some readers that even the slightest decrease in cardiac output would lead to vicious cycles

that would eventuate in death. However, this is farthest from the truth, because a vicious cycle will not develop until the intensity of feedback surpasses a certain critical value. Vicious cycles develop only because of *positive feedback* and never because of *negative feedback*. To explain this, one of the feedback cycles of Figure 1 can serve to illustrate: Decreased cardiac output → decreased arterial pressure → decreased systemic blood flow → decreased cardiac nutrition → cardiac depression → decreased cardiac output; and the cycle continues again and again. On close study of this cycle it is evident that the initial decrease in cardiac output causes further decrease in cardiac output. This is called *positive* feedback because the secondary effect on cardiac output is in the same direction as the initial effect on cardiac output.

However, positive feedback will not cause a vicious cycle unless the gain of the feedback is greater than 1.0; that is, unless the secondary decrease in cardiac output in the above example is greater than the initiating decrease in cardiac output. This effect can be explained by referring to Figure 2. The solid curve shows an initial decrease in cardiac output followed by a secondary decrease in output three-quarters as great as the initial decrease. Thus, the gain of the feedback is three-quarters.

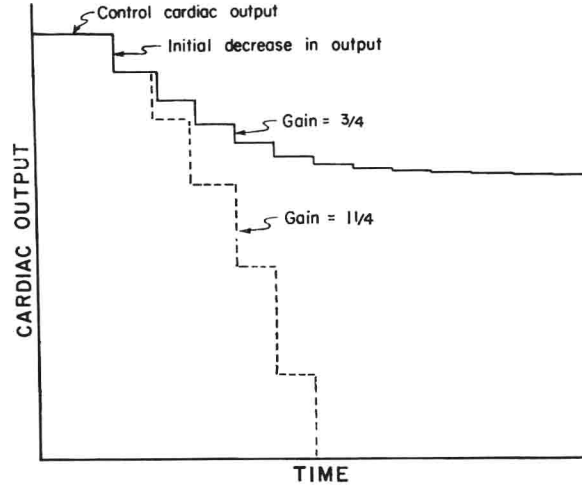

FIGURE 2. Basic principles of positive feedback and vicious cycles.

The secondary decrease in output in turn causes further feedback that leads to a tertiary decrease three-quarters as great as the secondary decrease, and this cycle continues indefinitely. Eventually, the cardiac output falls to a stable level because the successive effects of the feedback become less and less. On the other hand, the dashed curve shows a secondary fall in cardiac output equal to one and one-quarter times the initial decrease in output. Thus, the gain this time is one and one-quarter. The secondary decrease in turn causes a tertiary decrease one and one-quarter times as great as the secondary decrease, and the cycle continues; each additional decrease in cardiac output becomes progressively greater until eventually the output reaches zero.

Algebraically, the total change in cardiac output caused by an initial change can be represented by the following formula:

$$\text{Total change} = I + IG + IG^2 + \ldots\ldots + IG^n \qquad (1)$$

in which I is the initiating decrease in cardiac output, and G is the gain of the feedback. When the gain is less than 1, this formula reduces to

$$\text{Total change} = \frac{I}{1 - G} \qquad (2)$$

which shows that the cardiac output falls only a finite amount and stabilizes at a new level.

However, when the gain (G) becomes greater than 1.0, Formula 1 can be reduced to

$$\text{Total change} = \frac{I\,(\infty - 1)}{G - 1} = \infty \qquad (3)$$

which shows that once the cardiac output begins to change even the slightest amount, the change becomes infinite.

Thus, the positive feedbacks of Figure 1 will develop into a vicious cycle if the overall positive feedback gain becomes greater than 1.0. When such occurs, the shock will progress; but when the gain is less than 1.0, the shock will not progress of its own accord.

NEGATIVE FEEDBACK THAT OPPOSES POSITIVE FEEDBACK

Progression of shock is opposed by the many negative feedback control mechanisms which normally help to stabilize circu-

latory function. For instance, when the arterial pressure falls in shock, pressoreceptor reflexes are initiated and return the arterial pressure back toward normal. Similarly, a decrease in capillary pressure in shock causes fluid to be absorbed into the circulatory system (at least in the early stages of shock) to increase the blood volume, increase the cardiac output, and therefore, raise the capillary pressure back toward normal. Both of these are instances of *negative feedback* in that the initiating stimulus results in feedback that causes the initiating stimulus to become less severe.

Some of the negative feedback mechanisms that undoubtedly help to oppose progression of shock are (1) the pressoreceptor reflexes, (2) fluid absorption into the capillaries from the tissues, (3) stress relaxation recovery of many of the peripheral vessels and blood reservoirs, and (4) the central nervous system ischemic reflex.

Negative feedback, like positive feedback, is expressed quantitatively in terms of gain. A negative feedback gain of -1.0 decreases the initiating stimulus to exactly one-half its initial value, whereas a negative feedback gain of $-\infty$ decreases the initiating stimulus all the way back to its original starting point.

A negative feedback gain of -4 exactly opposes a positive feedback gain of $+4$, and a negative feedback gain of -10 combined with a positive feedback gain of $+2$ will give a negative feedback gain of -8.

In the above discussion of vicious cycles, it was noted that a positive feedback gain of at least $+1.0$ is required for a vicious cycle to develop. Therefore, before shock will progress as a result of the feedback cycles shown in Figure 1, the overall positive feedback gain of all these cycles must be at least $+1.0$ greater than the negative feedback gain of all the stabilizing control systems of the circulation. For instance, at normal arterial pressures, the gain of the pressoreceptor control system is approximately -2, whereas the positive feedback gain that results from depressed cardiac nutrition when the cardiac output falls is somewhere in the order of 0.1. Thus, the net gain is -1.9. Under these conditions the circulation will be very stable.