1965

Current concepts in the pathogenesis and therapy of shock

Barry Richard Hillmer
University of Nebraska Medical Center

CURRENT CONCEPTS IN THE PATHOGENESIS AND THERAPY OF SHOCK

Barry Hillmer

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

February 1, 1965

Omaha, Nebraska

TABLE OF CONTENTS

Introduction: In regard to the treatment of shock, a conflict is raging today among clinicians. This conflict centers around controversy concerning the pathophysiology of the development of the shock syndrome, and ultimately, one area of great concern is whether vasopressors, vasodilators, neither or both are advisable treatment for different forms of shock. It will be the purpose of this treatise to explore the pathophysiological development of shock and to draw certain conclusions from this discussion as a basis for the treatment of shock. But first it will be necessary to define the subject.

Definition of Shock: Shock has evolved to be a very broad term that almost defied an accurate definition. It is hardly an exaggeration to say that there are as many definitions of shock as there are investigators in this field. Attempts at defining shock run from this rather complete and but nebulous definition: "shock is a failure to adequately perfuse the vital organs" (31), to this tongue-twisting but more sophisticated definition: "Shock is a syndrome with reduction of effective circulating volume accompanied by depression

of many systems which become self-sustaining and progressively impairs the peripheral circulation until it is climaxed in a state of irreversible failure; a dynamic picture, with multiple causes, and interrelated consequences". (4) This latter definition is untrue in that shock does not always become "progressive and irreversible". The above two definitions are two of the best found in the literature. Others such as: "shock is a general response to injury" (50) or "shock is an intricate dystrophic complex linked with over stimulation of the nervous system", (41) are even less clear in their meaning. As Reeve has pointed out the 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 clincial picture and some underlying disturbance the two are necessarily related, and third when the word 'shock' is used without clearly defined meaning". (42)

Various attempts have been made to narrow the definition of shock. One such approach has been to divide shock into vasodilatory and vasoconstrictive shock. Under this classification such initiating

factors as peritonitis, crush syndrome and anaphylaxis would fall under the vasodilatory shock category while most other common causes would be categorized as vasoconstrictive shock. This classification fails when it is realized that almost always both processes are interacting during the shock syndrome to varying degrees at varying times, even in the same person. (44) This attempt at a classification of shock does however suggest the importance of the Autonomic Nervous System and will deserve consideration later.

Another twist in the possible meanings of shock occurs when terms are added to describe the progression of shock. Guyton (17) would classify shock as:

1. Circulating shock: a state of the circulation in which cardiac output is too low to supply normal nutritional needs of the body's tissues even when the body is at rest.

2. Progressive shock: shock that is becoming progressively more severe even though the initial cause of the shock is not itself becoming more severe.

3. Irreversible shock: condition whereby no therapy whatsoever can reverse shock.

Others use the terms compensated or reversible for circulating shock, and would call irreversible shock uncompensated. (19)

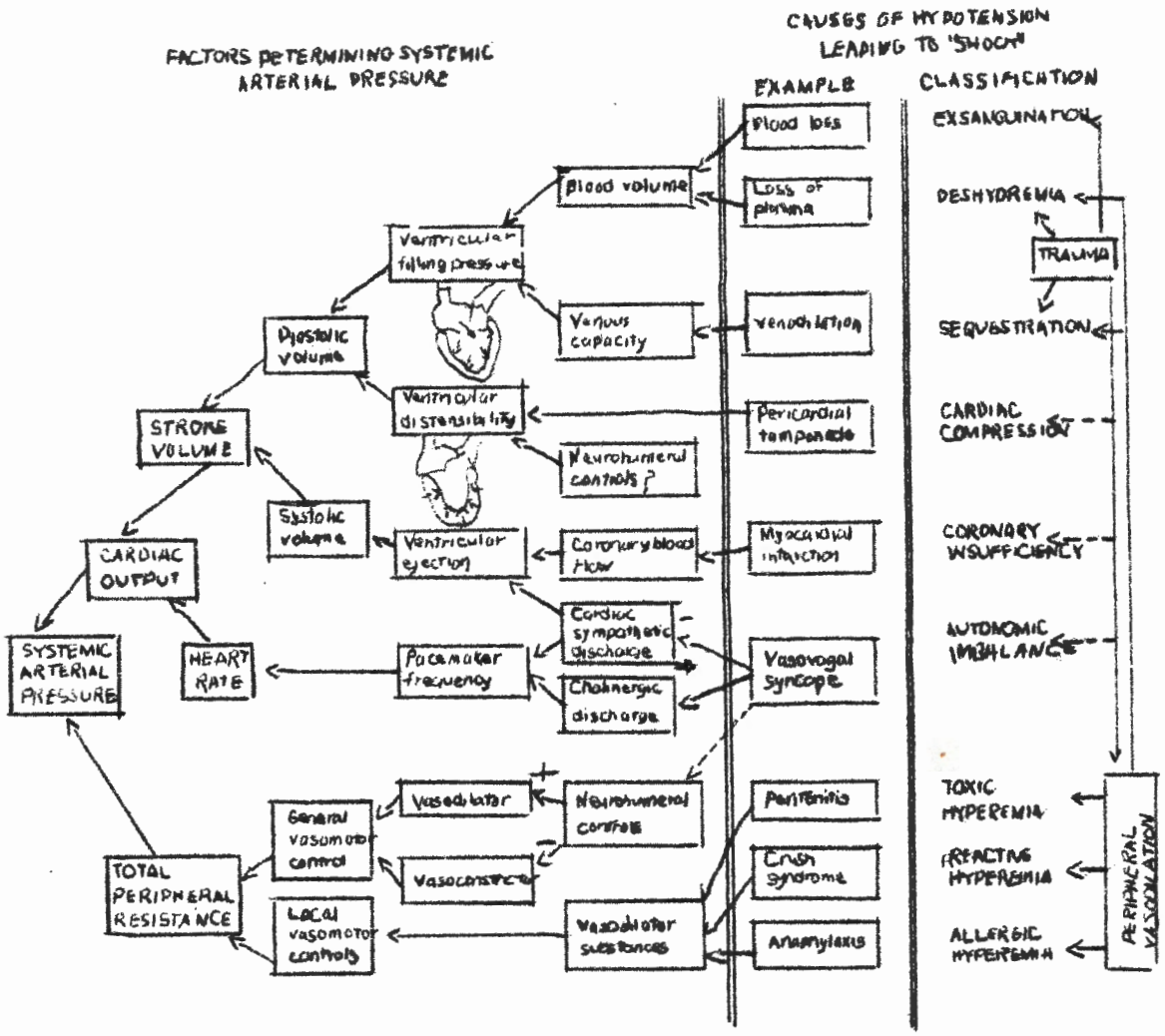

Figure 1.

Schematic representation of some of the factors that determine systemic arterial pressure. (From Rushmer, p. 446) The tentative classification of types of hypotension in the right hand column is proposed as basis for quantitative description of various mechanisms for more precise definitions of the different entities. This diagram aids identification of initiating factors and compensatory mechanisms in the production of systemic arterial hypotension.

Most likely the best approach in defining shock will be according to initiating mechanisms. One author would do this by using terms cardiogenic shock, vasogenic shock, neurogenic shock and hemorrhagic shock. (38) This would seem a step in the right direction but lacks exactitude. For example many different factors can initiate cardiogenic shock. Rushmer has established an approach for defining shock that has warranted the approval of many thoughtful clinicians. He centers his discussion on hypotension (see figure 1), long recognized as the sine qua non of manifold signs of shock, and proposes some of the most common mechanisms leading toward hypotensive shock. He then advocates using a mechanistic approach toward defining the cause of shock, for example myocardial infarction leads to decreased coronary blood flow which leads to decreased ventricular ejection which leads to decreased systolic volume which leads to decreased stroke volume which leads to decreased cardiac output which leads to systemic hypotension which leads to the shock syndrome. This approach is clumsy syntactically, but very helpful in its exactness.

The use of the term "shock syndrome" deserves comment. The entity which is recognized as shock

involves a protean group of symptoms, i.e. a syndrome, no one of which absolutely must be present in order to say that the shock syndrome exists. For example a twenty-five year old man may be exsanguinating while maintaining a "sound" blood pressure of 120/80, thanks to a compensating sympathetic nervous system overflow. However in this case the other "classical" signs and symptoms of the shock syndrome, pale, cold sweaty extremities, tachicardia, restlessness, decreased urine output, would likely be present. Thus, the important principle to be remembered is that shock is a syndrome indicative of poor p r-fusion of vital organs; it can manifest itself in a number of ways because it can be initiated by innumerable different factors whose interactions become exceedingly complex.

Basic Cardio-Vascular Physiology in Shock: The systemic blood pressure is dependent upon the ratio between cardiac output and peripheral resistance. B. P. = C. O. x P. R. However, since the shock syndrome is basically a failure to perfuse vital organs, and not hypotension per se, our concern must be centered around blood flow, not blood pressure. Blood flow is determined by a ratio between perfusion pressure (B.P.) to peripheral resistance.

F = B. P./ P. R. The similarity between these two formulas can easily be seen and lead to the conclusion that blood flow is equal to cardiac output when blood pressure and peripheral resistance are stable. The importance of blood flow rather than blood pressure per se can hardly be overemphasized. Even with a drop in blood pressure, a corresponding drop in peripheral resistance will theoretically lead to unchanged blood flow; but on the other hand a momentous drop in cardiac output with a compensatory increase in peripheral resistance maintains a normal systemic blood pressure in the face of a marked decrease in cardiac output and thereby decreased blood flow. These principles will have important bearing when treatment is considered.

Cardiac output is determined by stroke volume times heart rate. Since complete filling of the left ventricle does not always occur during diastole, the stroke volume is dependent on the difference between diastolic and systolic volumes. The greater the diastolic volume and the less the systolic volume, the greater is the cardiac output. The amount of blood remaining following systole depends onthe efficiency and the completeness of myocardial contraction; which is respectively dependent on coronary

blood flow. Among the factors influencing diastolic volume, as seen in figure 1, are ventricular filling pressure and ventricular distensibility. Ventricular filling pressure, in turn, is controlled by the blood volume in relationship to the venous capacity. Thus up to a certain point an increase in blood volume with a decreasing venous capacity leads to an increased ventricular filling pressure, and up to a point of diminishing returns an increase in cardiac output, whereas blood or plasma loss and venodilatation have an opposite effect. The distensibility, or compliance of the ventricular walls, is not a simple elastic relationship 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 control over the heart rate can be readily traced to the balance of sympathetic and parasympathetic discharges into the region of the pacemaker. (44) Several reflex mechanisms, which profoundly influence the heart rate as well as the peripheral resistance, and involving the Autonomic and Central Nervous Systems, are stimulated by the changes occurring during shock. They are as follows:

1. The stretch receptors or mechanoreceptors, as they are also known, are responsive to changes in the mean perfusion pressure. (39), (44) The carotid sinus or baroreceptors have been most intensely studied and are believed to be representative of similar autonomic afferent intervation occurring in the adventicia in most of the large and medium-sized blood vessels throughout the body as well as the heart. A drop in systemic blood pressure, through afferent nerve stimulation to the medullary vasomotor center from the stretch receptors, leads to (1) increase in heart rate, (2) increase in stroke volume, (3) increase in peripheral resistance in venous and arteriole capillary beds. All these effects combine to increase the systemic blood pressure via sympathetic fibers supplying both the heart and the systemic arterioles and veins. On the other hand, an increase in systemic blood has the exact opposite effect mediated by the cardio-inhibitory center, or as it is also known, the dorsal motor nucleus of the vagus. It too is located in the medulla.

The stretch receptors give off a salvo of impulses with each heart beat. The frequency, pattern and duration of these bursts depend not only on the

on the mean blood pressure level but also on the rate and amplitude of the pulse pressure. The reduction in pulse pressure which inevitably results from even mild bleeding or from a decreasing cardiac output leads to a more sparse discharge from the stretch receptors; this in turn causes a reflex tachicardia which further reduces the pulse pressure. Even while the systemic blood pressure remains elevated by this reflex mechanism, the ever-accelerating heart rate and the deepening pallor secondary to sympathetic stimulation to the skin warn the experienced clinician of impending shock. When the hemorrhage is more profound these reflex mechanisms are intensified.

The baroreceptors also innervate the ascending reticular system; whose stimulation might well explain the feeling of restlessness which often is evidenced by persons in shock.

2. Higher centers out on the medullary centers. For example, visual images, sounds, cold, pain, and cerebration all affect heart rate. There are, after all, few things more emotionally disturbing than to see ones blood distributed over a wide area, particularly when this experience is accompanied by the sight of widespread tissue injury and the conscious

and unconscious acknowledgement by the central nervous system of the receipt of nociceptive stimuli. Cortico-hypothalamicofugal barrages presumably reinforce sympathetic activity and indeed in the early stages of injury probably outweigh the reflex effects described above. (39)

3. Cardiac receptors, other than those acting as stretch receptors, are believed to exist. Left atrial receptors have been identified during oligemia which appear to influence the increased secretion of anti-diuretic hormone. However, the mechanism appears to be of little importance in kidney conservation of fluid in comparison to greatly curtailed glomerular filtration rate and renal filtration pressure occurring during shock. Right atrial receptors may be involved with the reflex regulation of aldosterone secretion, but do not seem to be as important as the reflex increase in aldosterone secretion which during oliguria results from a diminution in the afferent impulse activity of vagal mechanoreceptors situated in the thyrocarotid area. Cardio-sensory nerve endings remain to be investigated, for example, the possibility exists that myocardial ischemia may lead to potent reflex mechanisms. (39)

4. The Chemoreceptors of the carotid and aortic bodies are profoundly stimulated by reduced oxygen,

increased carbon dioxide and lowered pH in the arterial blood perfusing them. These areas have one of the most active blood supplies in the body, three times the mean brain blood flow via weight. (39) Stagnant anoxia leads to a thunderous discharge of afferent impulses, resulting in reflex vasoconstriction and hyperpnea. This response is sensitized by acidemia (39).

Via these mechanisms an intense vasoconstrictive and cardiac response are manifest following a decrease in the systemic blood pressure. This intensive vasoconstrictive response results in a marked increase in peripheral resistance in these arterioles and venules which are responsive to sympathetic outflow and secondarily lead to a marked decrease in blood flow in these organs. Thus it is that blood flow tends to shift from constricted splanchnic, skin and renal capillary beds in favor of unaffected coronary, cerebral and pulmonary capillary beds early in shock. This primary response thus favors maintenance of function in these three vital organs as long as necessary, but nevertheless brings in its train the results accruing from splanchnic asphyxia, which are so important in the development of irreversible or uncompensated shock. Before beginning discussion of this vital subject it

will be necessary to expand on the family of sympathomimetic-amine drugs which mediate this intense vasoconstrictive reaction and on the tissues which are responsive to them.

As discussed earlier, the peripheral resistance as well as the cardiac output, are the major regulators of systemic blood pressure. It is currently widely accepted that the Sympathetic Nervous System contributes markedly to the regulation of peripheral resistance by the interactions of receptors, designated as $\alpha, \beta,$ AND γ.(43) The development of the receptor theory has greatly increased understanding of the mode of action of sympathomimetic amines, (47), (33), (54), (7), (14), although it isa more convenient means of explanation than a proven anatomical reality. The α-receptors are located in the smooth muscle of arteries, arterioles and veins. They exert their maximum effect in skin, splanchnic and renal vessels. Upon stimulation by post-ganglionic adrenergic nerve fibers, intense vaso-constriction will occur. In diminishing order of potency, this action will be mediate by nor-epinephrine (Levophed), epinephrine, metaraminol (Aramine), methoxamine (Vasoxyl) and phenylephrine (Neo-Synephrine). The Beta receptors have the opposite effect, that of vasodilitation of

arterial and arteriolar beds. Isopropylnor-Epinephrine (isoproterinol, Isuprel) is the most potent stimulator of the beta-receptors, epinephrine has considerable potency, while nor-epinephrine, metaraminol, methoxamine and phenylephrine have little or no effect. The gamma receptors appear to be a sympathetic cholinergic vasodilator system confined to skeletal muscle and mediate by release of acetylcholine.

Receptors in the heart are apparently less well differentiated. Beta receptor stimulators (isoproterinol, epinephrine) are the most powerful stimulators of myocardial contraction (positive inotropic effect) and heart rate (positive chronotropic effect). However, nor-epinephrine and metaraminol also have strong inotropic and chronotropic effects, although the latter isoften cancelled in the intact heart by stretch receptor reflex vagal slowing secondary to the rise in systemic arterial blood pressure that results from increased systemic vascular resistance. (39), (43). Methoxamine and phenylephrine do not stimulate the heart nor will they induce cardiac arrhythmias.

Epinephrine is one of the two naturally occurring sympathomimetic amines and physiologically appears to be an "emergency" hormone released by the

adrenal medulla in large quantities in times of stress. (24) Its actions result in the typical "fight or flight" reaction mediated by the alpha and beta receptors. During shock blood concentrations of epinephrine increase momentarily (24) (et al), and suggest that the increased levels of circulatory epinephrine are sufficient to account for the intense vasoconstriction of early shock.

Epinephrine causes a marked rise in systemic blood pressure secondary to increases in both peripheral resistance and cardiac output. The systolic blood pressure increases markedly while diastolic blood pressure rises slightly or not at all, suggesting that the cardiac effect dominates over the increase in peripheral resistance in bringing about increased blood pressure.

Epinephrine increases cardiac output by both an inotropic and chronotropic response, although the vagal effect may actually lead to a slowing in rate. An increase in venous pressure on the atria increases ventricular filling, thereby aiding stroke output. The beats become strong and forceful. However the myocardial oxygen consumption is increased to a greater degree than is the coronary flow of blood. (24) This suggest that epinephrine would tend to increase any myocardial ischemia which might already

be present. Certainly this would coincide with the effect of epinephrine on anginal pain. Also in large doses the direct action of epinephrine on the myocardium may produce cardiac dilitation and ventricular fibrillation.

Epinephrine produces maximal constriction in the splanchnic area; peristalsis ceases; mesenteric vessels constrict; and the mesentery appears blanched. Kidney vessels are at first constricted and little urine is secreted. They dilate, however, more promptly than do many of the other vessels and overall an increase in urine output occurs as a result of the increase in blood pressure which leads to a more effective glomerular filtration pressure. Constriction is also marked in the skin and mucous membranes.

Nor-epinephrine (Levarterenol, Levophed) also occurs naturally and is released from its storage sites upon stimulation by the post-ganglionic sympathetic nerve fibers, and acts on the gamma-receptors only. It also represents about twenty percent of the combined total of epinephrine and nor-epinephrine located in the adrenal medulla. The primary response to nor-epinephrine is an increase in peripheral resistance with marked constriction in splanchnic, renal, and skin and mucous membrane vessels.

The heart rate decreases due to marked vagal effect, while the inotropic effect of the heartincreases, and cardiac output decreases or remains steady. Coronary, cerebral and pulmonary vessels do not respond well to nor-epinephrine and little if any vasoconstriction occurs. (7) Nor-epinephrine has been widely used therapeutically in the past because of marked increase it brings about in systemic blood pressure while favoring coronary, cerebral andpulmonary blood flow. However overall blood flow decreases, and the therapeutic role of this drug is changing, as we shall see.

Sympathomimetric amines which act on receptor sites are called "direct", those which act on receptor sites only by causing release of nor-epinephrine are called "indirect". This becomes important when non-epinephrine storage sites are depleted, as occurs after the use of ganglionic blockers such as guamethidine and brytylium or prolonged treatment with reserpine. In these instances the effectiveness of the indirectly acting sympathomimetric amines is greatly decreased, while on the other hand, the receptors show definite high sensitivity to those drugs exerting a direct effect. Brief mention of several of these synthetic sympathomimetic amines will prove helpful in later discussion.

Metaraminol (Aramine) has had widespread clinical use. It acts both directly and indirectly on gamma effector sites, but its indirect effect dominates. Its action is very similar to nor-epinephrine but carries less danger of tissue sloughing; has a more sustained action, but slower onset; and seems to cause a steadier response, especially in patients with coronary insufficiency. (7) Phenylephrine (Neo-Synephrine) and Methoxamine (Vasoxyl) are synthetic sympathomimetic amines which act directly, have little or no effect onthe heart, but cause an intense rise in peripheral resistance through stimulation of gamma-effectors. Mephentermine (Wyamine), Ephedrine, and methanphetamine (Methedrine) all act indirectly and cause dual increase in cardiac output and peripheral resistance, with the cardiac effects dominating. (7) Methamphetamine is a potent CNS stimulant.

Isoproterenol (Isuprel) and mylidrin (Arlidin) stimulate only the beta-receptors and lead to productive increase in cardiac output, while peripheral resistance is diminished. The blood pressure may remain unchanged but blood flow is substantially increased. Isoproterenol is much more the potent of the two drugs, but mylidrin has a longer duration of action. The qualities of these twodrugs will merit further discussion in regard to the treatment of the

of the shock syndrome.

Evidence indicates that the sympathomimetic amines do not directly influence the microcirculation (i.e. capillary beds located between arterioles and venules). As the arterioles are studied by newer techniques which allow visualization of the finest ramifications of adrenergic nerve fibers, Falck (10) has observed that the adrenergic nerve endings merely seemed to reach the inner surface of the smooth muscle layer without penetrating to the cells situated closer to the lumen. The inner smooth muscle cells appear to maintain normal tone regulated by local autoregulation. Because of the anatomical arrangement of a cylinder of outer smooth muscle over a cylinder of inner smooth muscle a constriction of the outer ring also forces the inner ring to constrict, but the inner ring apparently does not have the reverse capacity. (24) If this be so, the constrictor fibers can take precedence and centralize the control of regional flow whenever the sympathetic discharge is increased. (10)

As emphasized earlier, shock in its broadest definition is a failure to perfuse the vital organs. The capillary beds, because of their fundamental importance in maintaining tissue perfusion, become the

final common pathway through which the basic etiologic mechanism(s) in shock must operate (12). The regulation of this portion of the cardiovascular system is not completely understood, but is being intensely investigated at the present time.

The microcirculation, also known as the terminal vascular bed, the capillary circulation and the peripheral circulation, is the largest organic unit in the body (19). It is double the bulk of the liver and the total blood volume can be comfortably contained in the capillaries of the liver alone. No cell in the body is more than 25-30 micra from a capillary. Although it represents greater than 90 % of the blood vessels in the body, the microcirculation utilizes for its ownpurposes only six to seven per cent of the oxygen consumed. A common representation of the microcirculation and its vessels is seen below. (19)

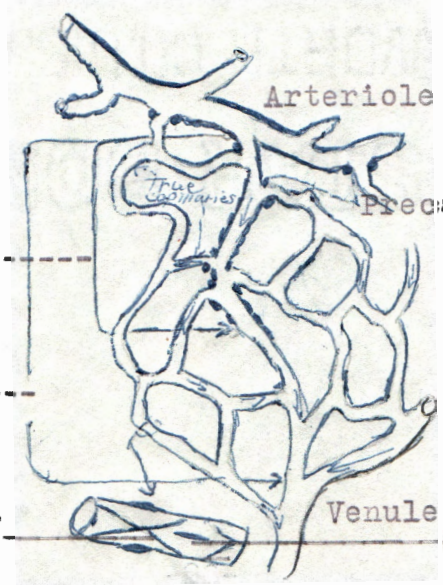

Figure 2. Basic module of capillary unit.

Johnson presents three major hypotheses which he feels best explain the r gulation of the microcirculation. (1) The tissue pressure hypothesis stat s that as the blood pressure rises, increased fluid is forced from the capillary circulation. The extravascular fluid increases and, in turn, exerts an increased pressure which affects the more thin-walled venules first and leads to their compression, and eventually an increase in peripheral resistance. Control in such a system would be centered in the venules. This explanation seems similar to Starling's law of the capillaries which explained the microcirculation on the basis of changes in blood pressure occuring from the beginning to the end of the capillary unit, although under Starling's Law, control would be within the capillaries.

2. The myogenic hypothesis supposes that there is an intrinsic mechanism on the smooth muscle cells of the arteries or arterioles which responds to an increase in internal pressure or tension in the wall by contraction. When the transmural pressure across the vascular wall is increased, by increasing arterial or venous pressure or by decreasing pressure around the organ, it follows from the myogenic hypothesis that these vessels should constrict. In contrast to

the tissue pressure hypothesis, autoregulation should occur in the precapillary vessels, rather than the venous vessels.

3. The various metabolic hypotheses are primarily based on the supposition that a decrease in blood flow causes vascular relaxation by the accumulationof vasodilator metabolites in the tissue. The relaxation leads to increased blood flow across the capillaries; improved circulation, resulting in transport of metabolites and a tendency for relaxation to decrease. Regulation in this case would be within the microcirculation itself.

Hershey, (19) Rushmer (43) and most others writing in the field of shock accept the metabolic hypothesis as being the most likely. They emphasize the role of the precapillary sphincters sensitive to these local metabolites as central controls of the amount of blood allowed into the capillary beds. Regulation would then occur as pictured in figure 3 below. During rest and normal metabolism, little blood goes through the true capillaries. Flow is ischemic with only a few units active at any one moment. Integrated activity of this system determines the pathway of blood flow through the capillary bed: (1) through the A-V anastomoses to bypass the capillary unit with no blood tissue exchange,

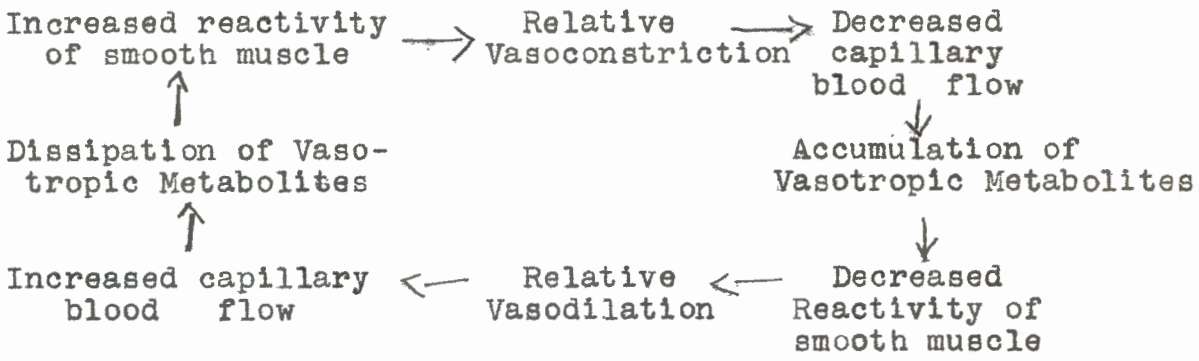

Figure 3
Local Regulation of
Blood Flow

(2) confined to thoroughfare (metarteriolar) channels with minimal blood-tissue exchange or (3) enter the true capillaries intermittently via the pre-capillary sphincters with optimal blood exchange. This theory results in the concept of vasomotion. Vasomotion refers to a coordinate, cyclic pattern of contraction and relaxation phases observed in metarterioles and precapillaries. (19) Increased vasomotion leads to predominance of constrictor phase, to hemodilution, to improved venous return. Decreased vasomotion leads to predominance of the dilator phase, to oligemia, and to tissue congestion.

Hershey feels initially with the onset of decreased blood flow and shock, both the systemic and microcirculation coordinate toward preserving the hydraulic integrity of the entire system. (19) The heart increases its rate and stroke output. The large vessels, arterioles and venules constrict. Blood flow is shunted

through the metarterioles and shock is compensated. But in time, when the blood flow to the tissues can no longer support their minimum needs, the compensatory phase gives way to a decompensatory phase which is esesntially a peripheral vascular phenomon. During the decompensatory phase the systemic bed sustains its initial compensatory readjustment. The micro-bed does not. The capillary unit activates its intrinsic functional autonomy to reverse its adjustment from that of a curtailment of blood flow toward securing for itself more of the limited volume of available blood. In effect, the purposive response of the circulation as a whole is no longer coordinated, and the systemic and terminal circulations literally function in opposite directions. As a result, blood is sequestered progressively in the capillary beds. (See figure 4).

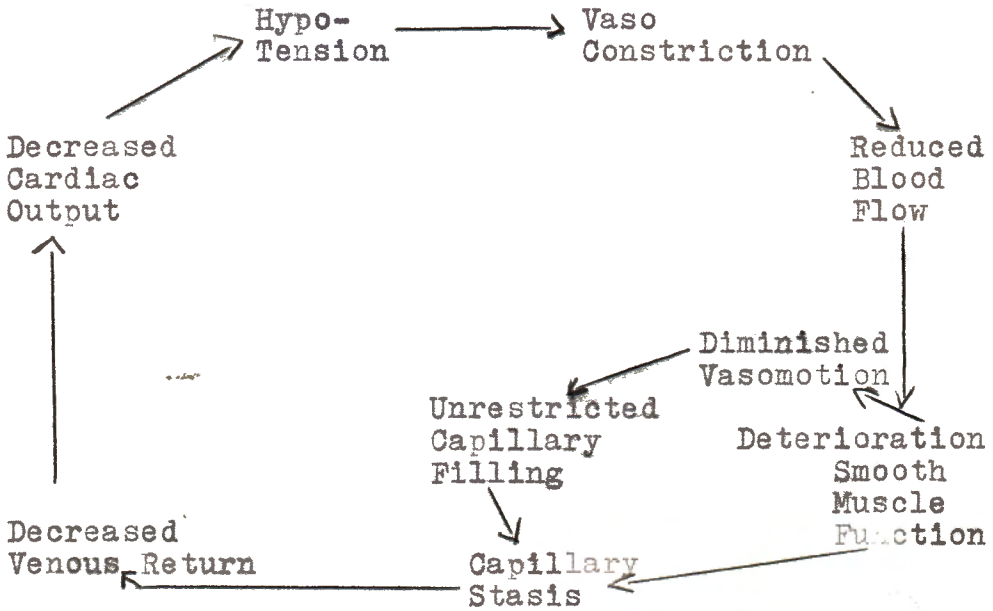

Figure 4. Decompensating shock secondary to Failure of the microcirculation.

The entire process, in the absence of modulating feedback mechanisms, is unremittant and eventuates in total circulatory disruption. In a sense the phylogenetically oldest portion of the circulation secedes from the system to function as it did in earlier living forms. The result is self-defeating in that it is totally incompatible with the survival of the complex organism in which it now exists. (19)

Hershey's hypothesis is supported in its broadest sense by the work of Lillehei, (29) (30), Fine (9), Selpert and Levenson (27), with much difference of opinion regarding possible causative factors. The dysfunction of the microcirculation appears to be especially prominent in the splanchnic areas, involving the gastro-intestinal tract and the liver. The kidney remains intensely ischemic throughout the course of the lethal stages of the syndrome without evidence of decompensatory vascular changes. Hershey emphasizes that dysfunction of the microcirculation as such leads to the dysfunction of the tissues dependent on the microcirculation and a positive feedback mechanism results. For example, one proposal is that the failure of the liver cells to receive oxygen leads to an inability of the liver to deactivate various cellular metabolic waste products leading to further failure of

microcirculation and so on in a vicious cycle (47).

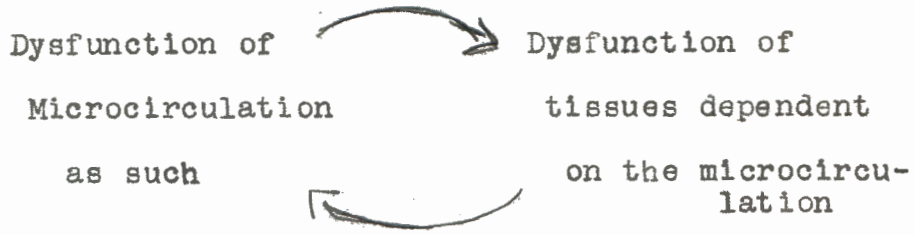

Figure 5
One important positive feedback
mechanism active in uncompensated shock

Furthermore Hershey feels that the failure of tissue function dependent on the microcirculation is the key to perpetuation of decompensated shock and eventual death, rather than the failure of the microcirculation per se (see Figure 5). For evaluation of this hypothesis, and the many different mechanisms which may be involved in the pathogenesis of uncompensated or irreversible shock it will be essential to systematically consider the role of many diverse factors within the gastro-intestinal tract and liver. The role of the heart, respiratory and central nervous system also warrant consideration.

The Pathogenesis of Irreversible (Decompensated) Shock. Irreversible shock was earlier defined as shock which is resistant to all treatment and results in death. The term is of no meaning clinically because only after death can it be absolutely stated that "the patient was in 'irreversible' shock". Most clinicians

feel that many cases of irreversible shock would be reversible if greater understanding, leading to enlightened treatment, could be gathered. The term is being replaced by usage of the term decompensated shock, which still suggests thatthe shock syndrome is progressing, but does not imply dogmatically that enlightened therapy will not be effective.

In some circumstances decompensated shock may result solely from the initiating cause. Death may be rapid; the treatment may be obvious, but limited by the severity of the injury. Exsanguination from a ruptured aortic aneurysin and massive myocardial infarct are two such examples. More difficult to treat are the cases in which multiple causes and perpetuating factors are involved. In the past it has been especially perplexing to clinicians to treat the causative factor with at least some success, watch the patient improve briefly, only to later decompensate and eventually die. This type of a clincial course occurs commonly in endotoxin shock and has stimulated recent interest in the study of decompensating shock.

The role of the heart in particular in decompensating shock is a controversial subject. The great increase in blood levels of epinephrine and to a lesser extent, nor-epinephrine, typically occurs early during the shock

syndrome and brings about a marked inotropic and chemotropic effect leading to some increase in cardiac output. The coronary vessels are little affected by the sympathomimetic amines, the increase in peripheral resistance, improved cardiac output and the coronary vessels' lack of constriction produce an increase in coronary blood flow. Thus blood flow to the heart is favored during early shock. However slightly more oxygen is consumed in proportion to the work accomplished under epinephrine stimulation. As peripheral resistance increases under adrenalin stimulation, the cardiac work load increases. Guyton (17) emphasizes the three to four hundred per cent reserve capacity of the heart disguises heart failure until very late stages of shock. He proposes several vicious cycles active in decompensated shock, all of which are initiated by a decrease in cardiac output and may lead to a further decrease in cardiac output: (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 dilitation, pooling of blood, and decreased output; (3) decreased nutrition of the vascular system which also causes vascular dilitation, 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 the liver, intestines, and perhaps others, causing release of toxins or metabolic substrates that in turn cause cardiac depression, incapillary permeability, vascular dilitation, 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. (See Figure 6) Arrhythmia and acidosis also have an adverse effect on cardiac output.

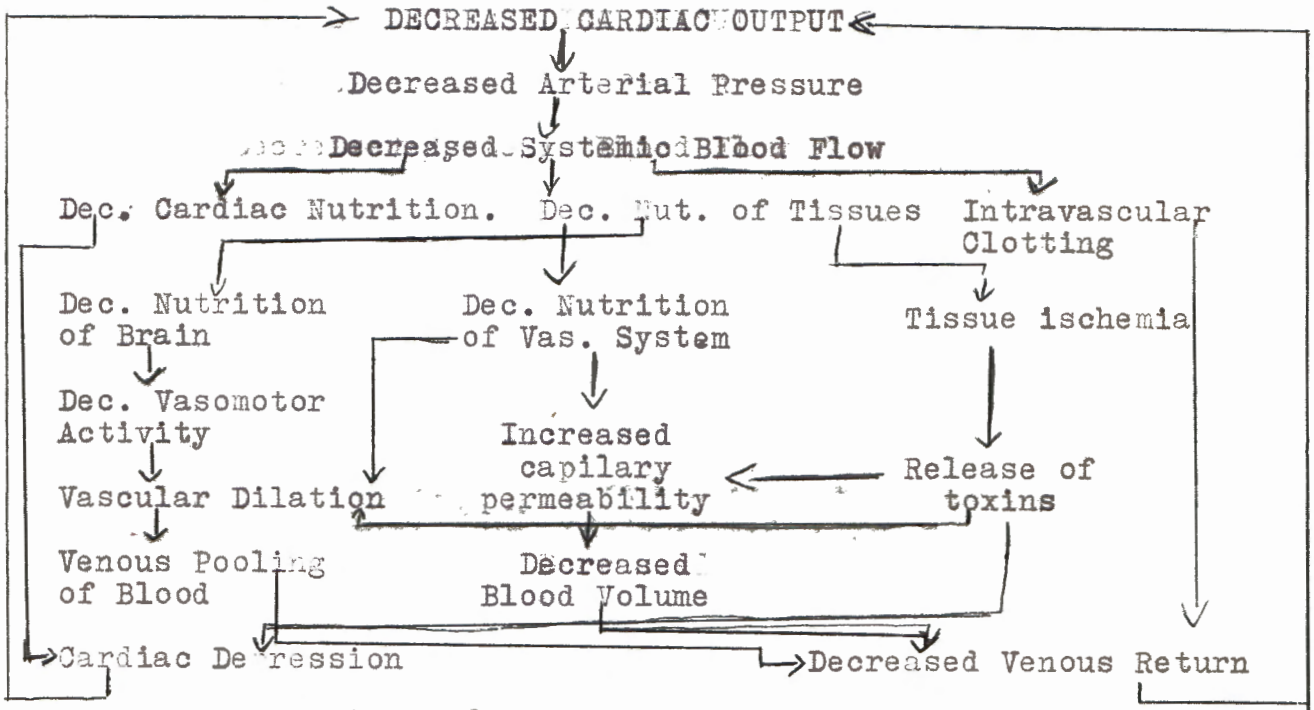

Figure 6. Feedback cycle that can lead to progression of shock. (17) page 3.

Both Guyton and Crawell present experimental data which shows that decompensated shock can be produced in the dog by several different cardiac mechanisms, but do not prove that they actually do occur in clincial situations. They conclude the "irreversible shock is commonly associated with myocardial dysfunction". (6)

In an excellently monitored study of twenty patients in severe shock, MacLean and all were surprised to find varying degrees of cardiac failure in ten cases; only three of whom were suspected clinically. (31) The diagnosis was based on occurrence of rising central nervous pressure, decreasing cardiac output, which were reversed following Isuprel therapy. They concluded that myocardial dysfunction frequently is involved in the shock syndrome.

Many clinicians do not believe the heart plays a central role so often in decompensating shock. Lillehei relates in experiments utilizing gradual exsanguination of dogs that even after prolonged shock in which bowel has become necrotic, the heart continues to function well. (18) He, along with Nickerson, (40) conclude that relative insensibility of coronary vessels to the sympathomimetic amines greatly favors maintenance of heart function. Nickerson further notes that coronary blood flow decreases less than the myocardial work load during periods of decreased blood flow, thus providing a

built-in safety mechanism preventing heart failure. He concludes that myocardial decompensation undoubtedly contributes to terminal events in shock, but ultimate survival depends on earlier mechanisms.

The respiratory system, as pictured in figure 7 below, may contribute to decompensated shock through a number of mechanisms. Most of these causes can be readily recognized early in the shock syndrome and treated

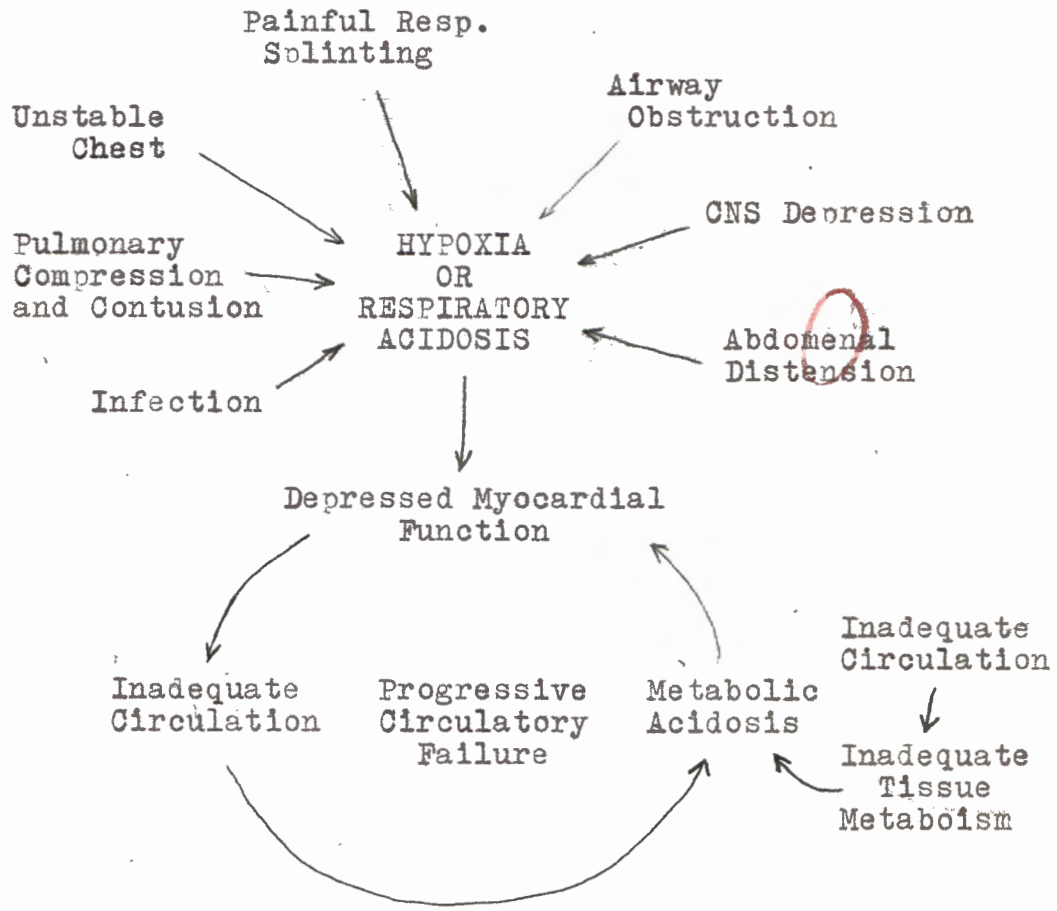

Figure 7. Role of the lungs in decompensating shock. (57)

effectively. As with the heart, the failure of respiratory arterioles and venules to respond to the sympathomimetic amines, protects the lung beds from ischemic anoxia.

The Central Nervous System (CNS) is a third vital organ which is favored by adrenalin outflow. Neither cerebral vasoconstriction nor vasodilitation can be easily produced experimentally by neural, hormonal or chemical means except for moderate effects from increased carbon dioxide of the blood (44). Thus, the cerebral blood flow is generally regarded as dependent primarily upon the perfusion pressure. So long as adrenalin levels maintain high blood pressure the CNS should function adequately. Whether a drop in blood pressure actually does bring about significant decompensation of the cerebral controlling mechanisms remains open to question. The problem is that controlled studies have not been accomplished in regard to the role ofthe CNS as an etiological factor in decompensating shock. It is all too understandable that CNS depression could lead to depression of the cardio-vasculative and respiratory control centers. Rushmer (44) found this to be so during exsanguination of dogs in which diencephalic activity was monitored.

Following decompensated hemorrhagic or endotoxic shock leading to death in experimental dogs, autopsy

findings consistently reveal marked pathology within the gastro-intestinal tract and liver. In the largest clinical study to date on endotoxic shock similar autopsy changes were found to exist although not as marked. (55) In both man and dogs changes occurring within the gastro-intestinal tract and liver ware sufficiently severe to explain death of the organism. The intestinal mucosa becomes congested and hemorrhagic necrosis becomes manifest. Micro thrombi often dominate the microscopic picture.

Numerous hypotheses have been proposed to explain these changes. All are based on the well-documented and intense vasoconstriction which occurs within the splanchnic circulation during early shock, secondarily to great outpouring of epinephrine and nor-epinephrine which occur at that time. (30), (29), (60). As reviewed earlier, Hershey believes that intense splanchnic ischemia anoxia results, later giving way to stagnant anoxia when pre-capillary sphincters (resistance vessels) relax. Lillehei emphasizes his belief that the resistance vessles respond to a milder state of local acidosis sooner than the postcapillary sphincters (capacitance vessels) on the venous side, which are more resistant to anoxia and acidosis of shock even when resistant vessels fail. The end result in either case would be loss of fluid extravascularly, and conceivably the

the pathological changes described earlier. The very simplicity of these two hypotheses is most appealing, but difficult to prove.

Other investigators have turned to more complicated explanations. Zweifoch emphasizes the role of the Reticulo-Endothelium System (RES) in initiating changes predisposing to decompensating shock. The RES is composed of cells which form an integral part of the endothelium barrier separating the blood and the parenchyma in such organs as the liver, spleen, lymph nodes and bone marrow. These cells have a complex function, including the inherent capacity, under proper stimulation to phagocytize materials from the blood stream. Zweiboch based his experimental studies on the ability of the RES to undergo hypertrophy when challenged by different agents, organs such as the liver and spleen may double in size, leading to a state of increased tolerance. He found that other agents blocked RES function with devastating effect. Following blockage of the RES, endotoxin or hemorrhagic shock was particularly devastating. He hypothesized from his data that such a blockage actually occurs in shock, most likely as a direct consequence of reduced blood flow through the tissues and secondary anoxic depression of RES. Depression of the RES appeared to bring the following mechanisms into play: (1) failure of RES to phagocytize endotoxic bacteria appearing in

blood vessels following invasion through ischemic bowel wall; (2) vasotoxic effect of pressor amines may be normally counteracted by some factor produced by the RES; (3) increased reactivity of small blood vessels to vasoconstrictor substances, which depend on RES for removal; later the opposite effect appears to occur, (4) failure in ferritin transport and metabolism (Frank (17) et al, have investigated ferritin and found it to be relatively non-reactive as a vasoactive factor), (5) failure to remove fibrin from blood leading to initial state of hypercoagulability, (6) with blockage of RES closely related endothelial cells attempt to take over function of RES, later die, vessel walls secondarily break down. In short, Zweifoch proposes that RES breakdown results in stasis, sludging, increased thrombosis, increased capillary permeability and frequent death. He maintains the hope of finding clinical means to make RES resistant during shock. Most of his theories are unopposed, but the question is not so much the feasibility of his hypotheses, as whether they actually occur.

Fine and associates believe the key mechanism leading to decompensating shock is an overwhelming blockage of the RES caused by leakage of bacteria from the ischemic gut lumen. Others, including Zweifoch and Hershey would discount this thesis because of failure of prophylactic antibiotics to protect organisms from fatal shock. Dr. Fine

however found that non-absorbable anti-biotics did protect and prevent the appearance of toxin. Figure 8 summarizes the hypotheses of the Harvard group.

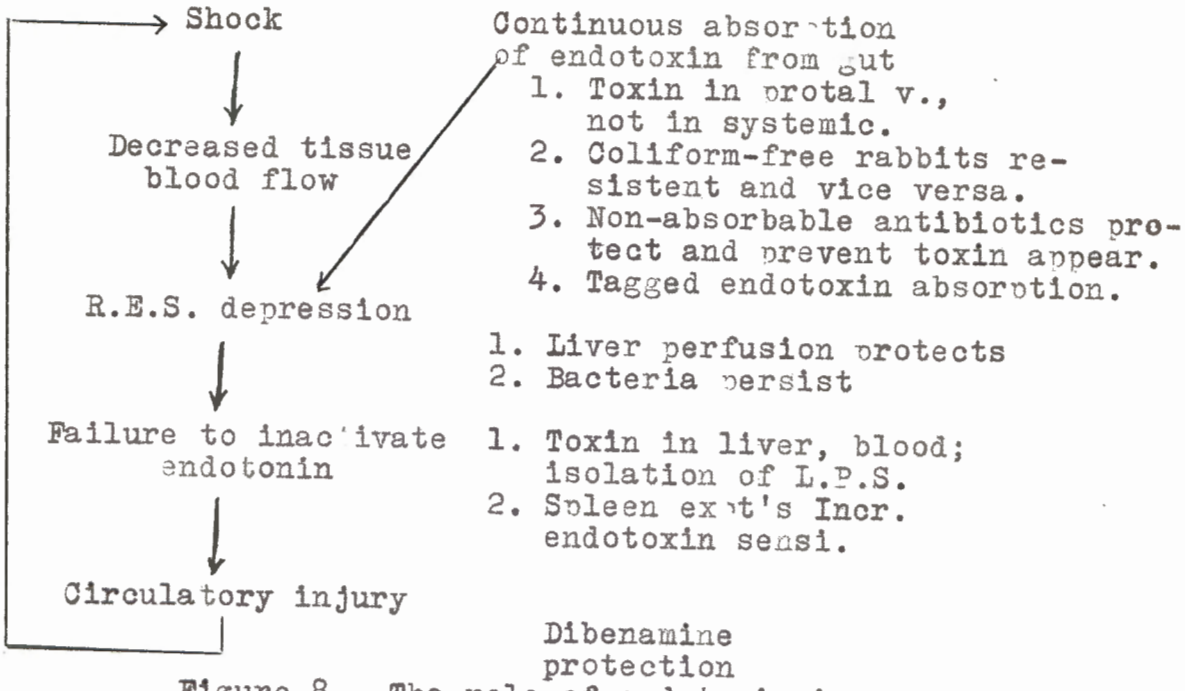

Figure 8. The role of endotoxin in the perpetuation of Shock. (12)

Dr. Fine further emphasizes that endotoxin either acts as a vasoconstrictor itself or sensitizes the tissue to vasoconstrictive drugs.

The role of the liver in decompensating shock is uncertain (47). Two-thirds to three-fourths of its blood supply is dependent on the portal vein, and hence conditions in the prehepatic splanchnic bed will have an important bearing on blood flow through the liver. In contrast to the portal vein, the hepatic artery dissipates its pressure wholly in passage through the liver, and hence should be regulated principally by intrahepatic

splanchnic nerve vasomotor control, probably at the local end-arterioles draining into the sinusoidal bed. Proposals have been made that the congestion known to occur during decompensating shock are due to (1) loss of activity of inflow sphincters, (2) loss of activity of outflow sphincters, (3) plugging to small sinusoids with agglutinated blood (47). It is doubtful that the outflow phincters so important in decompensating shock in the dog are present in man (47).

Impaired utilization of oxygen occurs in the liver during shock; Brauer's work in the rat liver would indicate that zones of sever hypoxia coexist with zones receiving fairly adequate oxygen (47). It is of interest that hepatic utilization of oxygen appears to be rapidly restored on transfusion and this fact certainly speaks against the occurrence of an oxygen debt in the liver.

The expectation that the liver should play a key role in shock is based importantly on the fatal outcome of hepatectomy. The manifold functional aberrations which occur in the liver as the result of shock have been thoroughly documented (47). The liver (1) has a central role in protein, carbohydrate and fat metabolism; (2) produces plasma protein, fibrinogen, prothrombin and heparin; (3) forms and destroys red blood cells, (4) synthesizes bile acids and bile secretions; (5) detoxifies by conjugation, oxidation, reduction and hydrolysis

(6) forms ammonia from NH_2 groups and from ammonia makes urea. After hepatectomy blood sugar falls rapidly and the animal dies in convulsions. Protein and lipid metabolism cease. Blood amino acid and ammonia levels rise, while urea and uric acid levels rapidly fall. Jaundice develops. Even though blood sugar levels are kept up by glucose infusion, the animal dies in 18 to 24 hours, presumably of ammonia intoxication.

Hift and Strawitz look upon the blood glucose curve as a significant "turning point" in the prognostication of irreversibility. (47) Although rising at first in early hypotension, it begins to fall approximately coincidental with first uptake of blood, and with the first indications of changes in the liver mitachondria. They attach particular significance to the metabolic need for glucose at this time in other organs and tissues, e. g., the heart and brain.

Selbert points out loss of the liver's ability to detoxify certain intestinal toxins, which presently are not well identified, and may be diverse, may prove to be important. The liver itself may be a source of toxic material in shock. Janoff (21) found that disruption of lysosomes--subcellular particles containing a variety of hydrolytic enzymes--and release of their enzymes in free, active form occurs in the liver of shocked animals. He found evidence that activation of

of lysosomal hydrolases within cells and their release into circulation may play an important role in execerbating tissue injury and accelerating the development of irreversibility at the cellular levels during shock. However, rendering animals tolerant or pretreating them with cortisone seemed to stabilize the lysosomes.

In summing, critical examination of available evidence, while suggesting a contribution to irreversibility in shock in terms of metabolic derangements, loss of detoxifying ability, as well as in hemodynamic irregularities (pooling), nevertheless appears to put the liver in a role secondary to failure of the peripheral vascular bed and/or myocardium. This may be because the stress to the liver in most shock procedures may not be great enough to impair seriously its function. Alternately, the influence of hepatic impairment may be of a more subtle nature than heretofore anticipated, so that further refinement of techniques and experimental approaches will be required to show a more pervasive influence, not only on immediate metabolic events, but more indirectly on the heart and vascular bed through the liver's role in handling vasotoxic substances. (47)

Harding (18), Levy (28), Blattberg (28) and Collins (4) among others, feel the disturbances in blood clotting in shock are of great significance. In experimental endotoxin and hemorrhagic shock a biphasic reaction

occurs manifested by early hypercoaguability, followed by reversal to hypocoaguability late in decompensating shock. See Figure 10.

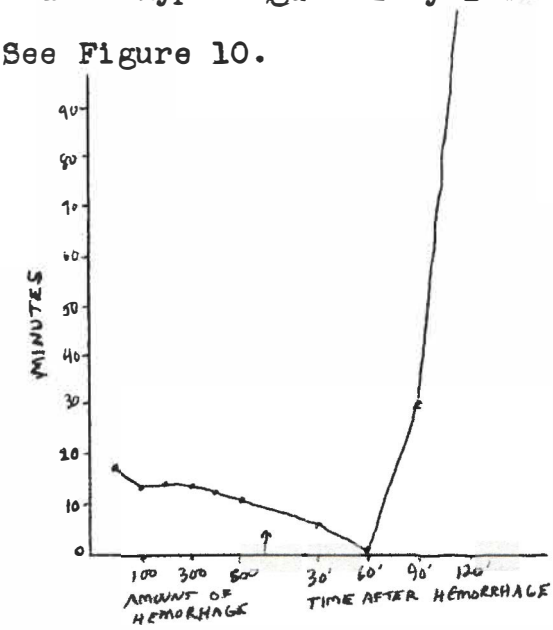

Figure 10. Hypercoaguability followed by hypocoaguability. (18)

Only scanty information is available concerning the mechanism forthe hypercoaguability in the early stages of shock. Capillary stasis, increased blood concentrations of thromboplastin, possibly as the result of a more rapid lysis of platelets; and release of calecholamines have been suggested as causes of hypercoaguability. (28) The later reversal to hypocoaguability is believed to occur (1) secondary to intravascular coagulation leading to depletion of fibrinogen, prothrombin, platelets, Factor V and Factor VII, (2) following secondary reactive increases in blood levels of heparin and fibrinolysin. (28)

Autopsy findings in dogs following endotoxin shock led Harding (18) to suspect that hypercoaguability exerted a primary role in initiating irreversible shock. Hemorrhagic necrosis of the gastro-intestinal mucosa, hemorrhagic lesions in the lungs, pancrea and kidneys were present. Microscopically there was necrosis of the superficial part of the gastro-intestinal mucosa associated with the occlusion of mucosal capillaries by eosinophilic staining plugs. Similar plugs were found in capillaries of the lungs, kidneys, and central vein of the liver. Focal necrosis in the kidneys and pancreas and central necrosis in the liver were present. He concluded that decompensating shock occurs when capillary thrombi are deposited and remain in place long enough to cause a local tissue necrosis. If necrosis is sufficiently severe the animal will due in a course complicated by hemorrhage. He found that heparin given prior to induction of endotoxin or hemorrhage shock was very effective in preventing decompensating shock; 50% survival among heparinized dogs as compared to almost 100 % mortality in control dogs. No capillary plugs or necrosis were found in the tissues of these animals. Fibrinolysin was highly effective in preventing decompensating shock even following hemorrhage. Fourteen of seventeen dogs given fibrinolysin after hemorrhage

survived apparently because of increased ability to wash away thrombotic plugs. (18) However, Lillehei et al, could not substantiate prophylactic results with heparin, and were not as convinced that disorders in lood coagulation play such a spectacular role in causing decompensating shock. (54)

Similar changes, capillary thrombi and hemorrhagic necrosis, are found in the kidneys of experimental dogs following death from hemorrhagic or endotoxin shock. However, these changes are much less severe than those which occur in the gastro-intestinal tract. (18) (24) In the normal human being 25% of the blood supply arrives at the kidney for nutritional and filtration purposes. In shock the kidney under catecholamine stimulation receives even less than 25% of a blood volume which is decreased or relatively ineffective. Urine output is greatly diminished. Acute tubular necrosis usually does not appear, but the kidney by its inability to function properly, contributes to acidosis and the build-up of metabolic waste products. Renin also is released by the ischemic kidney, resulting in increased blood levels of angiotensin, which could donceivably further impede flow in splanchnic and renal capillary beds by causing a further increase in peripheral resistance.

In conclusion, the pathogenesis of decompensating shock cannot be blamed on any one organ or pathophysiologic process. The heart, lungs, CNS, gastro-intestinal tract, Reticulo-Endothelial System, liver, kidneys, hematogenesis and endocrine systems are involved to varying degrees depending on the (1) age, (2) general health, including the presence of prior disease processes, (3) the type, severity and duration of initiating cause(s), and finally (4) the timing and adequacy of treatment. Thus, each case must be individualized.

Therapy: The principal basis for the treatment of the shock syndrome is that of maintaining optimal blood flow. The clinician may be forced to curtail the blood flow to one organ of the body in order to assist another organ more vital to survival at that time. Certainly, this seems to be the natural response that occurs when shock is initiated. The epinephrine and nor-epinephrine response preserves blood flow to the heart, brain and lungs while sacrificing splanchnic, skin and kidney blood flow. The epinephrine response in a crisis of short duration seems a good defense mechanism. However when shock is prolonged decompensation and positive feedback mechanisms develop within the splanchnic bed, as discussed above.

In the past clinicians frequently have used vasopressors such as nor-epinephrine and metarterinol to

maintain blood pressure. The action of these drugs increases blood pressure mainly by increasing peripheral resistance, with slight drop in overall cardiac output. Thus overall blood flow decreases slightly, although again more blood is shunted to brain, heart and lungs at great expense to splanchnic, skin and kidney blood flow. The recent realization of the role of the gastro-intestinal tract and liver in shock mortality have led clinicians to experiment clinically with therapeutic trials of drugs which encourage high cardiac outpout, low peripheral resistance, high blood flow systems, in place of low cardiac output, high peripheral resistance, low blood flow systems encouraged by use of drugs such as nor-epinephrine and metarterinol. Several of these recent clinical trials with such drugs will be discussed in detail during consideration of the specific aspects of therapy of the shock syndrome.

Before the treatment of the shock syndrome can begin the diagnosis must be made. In the "classical" shock syndrome the skin is pale, cold and clammy, capillary filling of the skin and nail beds is poor; blood pressure is lower than normal; the pulse israpid, regular and thready; respiration is rapid and shallow; the patient is restless; urine output is decreased. However it must be emphasized that diagnosis does not depend on any one finding, but rather on the total clinical picture.

For example, when an elderly diabetic, who is three weeks post-op and also catheterized, complains of a severe chill, the clinician is tipped off to the high probability that endotoxin shock is ensueing. The shock syndrome is a common final pathway toward death sued by an innumerable number of disease processes.

Not only is it of vital significance to pinpoint the initiating cause of the shock syndrome, but to continue to diagnose secondary problems predisposing the patient to decompensating shock, even while he is being treated for initiating cause(s). For example MacLean (31) found in endotoxin shock disorders of hypovolemia and poor cardiac action existed to varying degrees simultaneously.

Because any number of secondary problem(s) can and do develop during therapy, most clinicians in large medical centers advocate the use of shock teams and numerous moniters for evaluation of the various factors involved in the shock syndrome. Such a shock team (31) (9) is usually under the direct full-time supervision of a senior resident, including surgical and medical house officers, an anesthesiologist, and a full-time technologist skilled in blood gas analysis and blood lactate determinations. A speciallroom is set aside and equipped. The patient is monitored via (1) central venous pressure; (2) continuous blood pressure via percutaneous radial artery puncture; (3) cardiac

output by use of dye technique and calculation; (4) cardiac index by calculation; (5) peripheral resistance by calculation; (6) urine output; (7) frequent determinations of arterial $_{p}H$, CO_2 and O_2; (8) frequent determinations of lactic acid and base deficit; (9) blood volume calculations; (10) EKG. Rushmer (41) would emphasize the importance of monitorization of all factors illustrated in figure one as the only means to really gain a thorough knowledge of the pathophysiology involved in the shock syndrome.

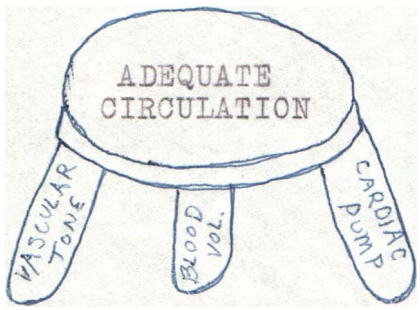

Figure 11. The three major determinants of adequate circulation

Wilson (56), (57), (58), MacLean and others have simplified the problem by recognizing that adequate circulation depends on the interaction of three variables: (1) the cardiac pump, (2) optimal blood volume and (3) vascular tone. Adequate circulation can then be represented as a three-legged stool (see figure 11); the loss of any leg leads to collapse of the stool. Lillehei (29), emphasizes how, using this simple principle, the patient's clinical progress can be followed without the use of complicated monitors, which are

unavailable to many physicians. Cold and clammy skin indicates an increased vascular tone (peripheral resistance). Central venous pressure, which is cheap and easily measured, indicates the circulating blood volume being presented to the heart in relation to cardiac ability to pump. In addition to the use of CVP some indication is gained of the cardiac output by the pulse pressure. Both the condition of the skin and the urine output can be used as indicators of visceral--especially splanchnic--blood flow. Certainly "if flatus is music to the surgeon's ears, urine is the wine of life." (29)

Cardiac and respiratory function must be maintained at all cost. This may necessitate resuscitation, including closed heart massage, breathing for the patient, and/or tracheostomy, even before the patient is monitored.

Circulating blood volume must be adequate. The best single determinant of optimal blood volume is the central venous pressure (4), (2), (17). CVP is determined by percutaneous injection of the external jugular vein, subclavian vein, cephalic vein or the anticubital fossa with an inter-cath. which is then easily threaded into the superior vena cava or right atrium. It is a determinant of right atrial pressure and normally

varies between 8-12 mm. H_2O. In the presence of congestive heart failure, cardiac temponade or overhydration, a value of greater than 15 mm. H_2O typically will be obtained. In hypovolemia, a value of less than 5 mm. H_2O typically will be obtained. Accordingly Wilson (57) advocates vigorous fluid replacement therapy when CVP is 0 - 5 mm. H_2O, trial of replacement therapy when CVP is 5 - 15 mm. H_2O and no replacements with suspicions of a cardiac problem when CVP is greater than 15 mm. H2O. However, it must be emphasized that it is not as much the actual value of CVP that is most important, as it is the trend of the CVP in the face of pathophysiologic processes and therapy going on at that moment. A rising CVP, even in the face of replacement therapy, indicates that fluid is being lost from effective circulatory volume even faster than it can be replaced. A falling CVP following use of a cardiac stimulant would indicate that the heart is pumping blood more effectively. A high and rising CVP accompanied by widespread lung rales would indicate pulmonary edema and the need for immediate appropriate treatment; and so on.

The advantages of CVP over older methods of evaluating blood volume are many (57). Hemoglobin and hematocrit determinations crudely indicate the volume relationships of red blood cells to plasma and may be helpful in estimating fluid loss in shock secondary to burns or

or during gradual hemorrhage. However the long labile period and gross inaccuracies which occur, when these determinants are used to estimate acute internal loss of fluid (peritonitis, hemorrhage) make them unreliable. Jacob Fine of the Howard group (9) advocates use of RISA dye dilution technique as a quick and accurate method to determine blood volume, and only mentions use of CVP in passing. However, Wilson (57) is quick to point out the weaknesses of blood volume determinations: (1) normal values vary 20 % in controls; (2) optimal blood volumes vary at different times in the same patient depending on cardiac ability to pump blood; (3) the measured blood volume quickly becomes obsolete in unstable cases; (4) the number of determinations is limited by practical, economic and safety considerations; (5) reliable blood volume determinations are not available to most physicians. MacLean (31) found that in their series of 20 patients, who were excellently monitored, optimal blood volume during shock was always greater than the calculated blood volume for the same individual in good health. This would add support for the virtues of a high volume, high output, low peripheral resistance and high flow system over a low volume, low output, high peripheral resistance and low flow system. Note that in the latter situation blood pressure might actually be higher

than in the former.

Once the criteria for replacement fluids are fulfilled, the clinician must decide what type of fluid replacement to use. The principle basic to replacement therapy is to use the fluids which will most physiologically replace the lost volume. Most clinicians advocate replacement of blood lost via hemorrhage with fresh whole blood. Shires (23) differs with this opinion on the basis of blood volume determinations in hemorrhaged dogs accomplished by utilizing a triple tag technique to measure extracellular fluid, plasma, and red blood cell volumes. His studies indicated that during severe hemorrhage RBC and plasmal volume decreased 30 % while extracellular fluid dropped almost as much, 29 %. On the basis of these findings he advises the rapid influx of 1,000 to 2,000 ml. of Ringer's Solution following severe hemorrhage. Ringer's Solution (1) would tend to alleviate ECF, as well as intravascular deficiency; (2) is free from harmful side effects; (3) would allow time to cross-match blood properly; (4) lower viscosity allows better flow, tending to prevent the aggregation and sludging of red blood cells. Wilson agrees that the patient can tolerate a low hematocrit as long as adequate blood volume and adequate respiratory support are maintained. He also recommends the use of 25 grams

of concentrated serum albumin in each 400 ml. of lactated Ringer's Solution, if rapid expansion of blood volume is needed. Wilson (57) further recommends that blood transfusions should be withheld until indicated by the need for blood volume expansion associated with a significant hematocrit reduction, except when blood loss is rapid and hematocrit becomes unreliable.

Fluid replacement can be continued until, hopefully, shock alleviates, or until CVP rises over 12 mm. H_2O, at which time the patient should be re-evaluated. Maintaining the CVP at less than 15 mm. H_2O is regarded as a very accurate means of preventing pulmonary edema by over replacement by all except one authority (11) who felt that frequent auscultation of the lungs was necessary.

Maintenance of cardiac function is a must. Heart failure may be the initiating cause of the shock syndrome or may intervene at any time during its course. The patient in congestive heart failure should be rapidly digitalized. Arrhthymias must be diagnosed and immediately treated, Calcium, potassium and acidotic imbalance have an adverse effect on the heart and should be corrected.

Cardiac stimulants may be needed. Several investigators (31), (57), feel that the limited success achieved

in the past using nor-epinephrine and metaraminol has been due to their cardiac stimulatory effect. Epinephrine has a greater stimulatory effect on the heart than these drugs but has not been used in the past because of its propensity toward causing arrhythmias (57). MacLean et al have had excellent success using the most potent of the beta-effectors, isoproterenol. This drug has a marked inotropic and chronotropic effect on the heart and decreases peripheral resistance of the arterioles, thereby lessening the load against which the heart mustpump. Cardiac output was increased in each of the nine cases where it was used; cardiac output increased about one liter/min. Tissue perfusion was increased as evidenced by the increased urine output and the drop in blood lactic acid noted in several patients after its use. On the basis of this limited clincial experience, MacLean recommends the use of isoproterenol in I.V. drips, 0.1 - 0.2 mg./hour, for the purposes of increasing cardiac output and tissue perfusion. MacLean further notes that his results were achieved with cardiac rates under 110. Rates of administration which cause heart rates over 130 may predispose to cardiac arrhythmias.

Vasopressors are indicated when shock is accompanied by vasodilitation, as frequently occurs in anaphylactic shock, the crush syndrome and peritonitis.

If the vasodilatory component is accompanied by some degree of heart failure, then drugs such as nor-epinephrine or metaraminol could be used. If no cardiac component is present, a drug which acts solely on the peripheral vasculature such as methoxamine, phenylephrine or angiotensin could be used effectively.

In shock syndromes characterized by hypovolemia vasopressors should not be used (57). In acute hemorrhage Frank feels that vasopressors would be life-saving when used to shunt more of the limited supply of blood into cerebral and coronary circulation (11). Frank states that the pressor amines should only be used when the blood pressure has decreased below seventy mm Hg., and patient is aged with arteriosclerotic disease. He advocates titrating blood pressure to 70-75 mm. Hg and not above. When used thus, the patient must be weaned off the pressor amines as soon as possible.

Several agents are presently receiving therapeutic trials because of their vasodilatory properties. Dibenzyline, an alph-receptor antagonist, has received the widest popularity thus far. Kalas (23) has emphasized its protective role against endotoxin in the dog. Robert Wilson (59), using dybenzyline and pushing fluids in a clinical trial on 18 patients in different types of severe shock, found an overall improvement in

the clinical picture. Blood pressure became more obtainable, but at a lower level, urine output increased substantially, skin usually became pink dry and warm. Cardiac output actually increased; nor-epinephrine following Dibenzyline resulted in tremenduous increase in cardiac output. Nickerson (40) holds Dibenzyline in high regard. He notes that Dibenzyline causes a drop in blood pressure proportional to fluid deficit and uses this proportion clinically as a means to indicate whether his patient is hypovolemic and to what degree.

Isuprel holds some of the same advantages as Dibenzyline, besides being a powerful myocardial stimulator.

Collins (4) used Chlorpromazine, an adrenergic inhibitor, in 36 patients who developed shock during anesthesia and surgery and compared them to 32 similar patients used as controls. Mortality with Chlorpromazine was only 22 % as compared to 53 % mortality when Chlorpromazine was withheld. Average twenty-four hour urine output compared 2260 cc to less than 400 cc in favor of chlorpromazine patients. However this study was not necessarily well controlled.

Epidural block of the adrenergic fibers to the splanchnic bed is also believed to exert a protective role against decompensating shock (59).

Weil, (56) in his study of 169 patients in endotoxin shock, indicates that the place of vasodilators in treatment of endotoxin shock is not yet established. The outlook, however, continues to be optimistic and the vasodilators, at the very least, have indicated importance of maintaining perfusion in the splanchnic capillary bed (23), (59), (40), (31), (4).

Infection with shock is likely to be the cause of shock according to Frank (11). Weil (56) found that prophylactic antibiotics did not appear to prevent the development of endotoxin shock, but was most important factor in treatment. Eighty-three percent of one hundred-fifty-three cases cultured were sensitive to Chloramphenicol, 65 % to streptomycin, 50 % to Oxytetracycline or Tetracycline. On this basis Weil recommended treatment with Chloramphenicol and streptomycin combination.

Cortisosteriods have been advocated by many (35), (56), (45) for treatment in shock, especially in endotoxin shock. In pharmocological doses they appear to protect the cells from injury by stabilization of lysosomes and by maintenance of the membrane integrity. Steroids appear to exert an inotropic action on the heart. Weil (59) found significant increases in survival rates (P lessthan .01) when doses greater than 300 mg/day were used, but not statistically significant difference in survival rates was present in doses of

less than 300 mg/day.

Lillehei (29), Collins (32) and others recommend the use of low molecular weight dextran as an aid to prevention of sludging. This agent is a deviscosity agent which increases microcirculation by coating red blood cells and protecting them from "sticky" proteins.

Acidosis frequently becomes a serious problem in the course of therapy. MacLean (31) feels it is most consistent sign of a poor prognosis. Frank (11) recommends peritoneal dialysis if (1) $_{p}H$ becomes less than 7.25, (2) serum CO_2 becomes less than 15 mEq/L, or (3) serum potassium rises to greater than 6 mEq/L. Everis (8) and MacLean recommend hyperbaric oxygen as the last opportunity for reversal of decompensating shock before death ensues. Everis' results in dogs have been excellent to date. However the procedure is cumbersome and only available in limited number of medical centers (8).

Summary: During the course of this thesis the different approaches which clinicians have utilized to define shock are enunciated and criticized. The basic control mechanisms of the Cardio-Vascular System are discussed. Some background information regarding the pressor amines is imparted, with emphasis on the adverse effects of such drugs on the splanchnic capillary bed. The importance of the microcirculation is

explored.

Almost all of man's major organ systems can be involved in, and perhaps initiate, decompensating shock. The roles of the heart, lungs, CNS, gastro-intestinal tract, Reticulo-Endothelialsystem, liver, and Endocrine System are discussed, as is the role of endotoxin in causing decompensating shock.

Two different approaches for monitoring the patient are compared. A simplified means of following the patient's progress utilizing (1) the cardiac pump, (2) vascular tone and (3) optimal blood volume, is recommended. The important role of central Venous Pressure in encouraging a more scientific approach to therapy is stressed. Recent clinical trials with Dibenzyline, Chlorpromazine, Adrenal Steroids and Hyperbaric Oxygen are discussed.

Conclusions: 1. Shock cannot be clearly defined, and the term probably would be best discarded. However, since this is unlikely, it would be well to use the term in relation to its initiating mechanism.

2. The use of Pressor Amines has been abused in the past.

3. The pathogenesis of decompensating shock is, presently, poorly understood; innumerable factors appear to be involved.

4. The use of Central Venous Pressure Monitoring during shock is strongly recommended..

5. Agents which increase cardiac output and/or decrease peripheral resistance are playing an increasingly important role in the therapy of the shock syndrome.

BIBLIOGRAPHY

1. Bacz, Silvia, Orkin, Lewis R., Microcirculatory Effects of Anesthesia in Shock. In Shock by Hershey, pp. 206-226. Boston, Little Brown and Company, 1964.

2. Braude, A.J., Bacterial Endotoxins. Scientific American, pp. 36-45, March, 1964.

3. Braunwald, E. et al., Hemodynamic Determinants of Coronary Flow, Effect of Changes in Aortic Pressure and Cardiac Output on the Relationship Between Myocardial Oxygen Consumption and Coronary Flow. American Journal of Physiology, Vol. 192, No. 1, pp. 157-163, Jan., 1958.

4. Brorck, G., Remarks on Shock. Pathogenesis and Therapy. An International Symposium, pp. 267-268. Gerlin, Gottinger, Heidelberg, Springer-Verlog, 1962.

5. Collins, Vincent J., Clinical Experiences in the Prophylaxis and Treatment of Shock. The New Physician, Vol. 13, No. 11, pp. 428-431, Nov, 1964.

6. Crowell, J.W., Guyton, A.C., Cardiac Deterioration in Shock, II. The Irreversible Stage. In Shock by Hershey, pp. 13-26. Boston, Little, Brown and Company, 1964.

7. Eckstein, John W., Abloard, Francis M., Circulatory Effects of Sympathominetic Amines. American Heart Journal, Vol. 63, No. 1, pp. 119-135, Jan. 1962.

8. Everis, William E. et al., The Use of Hyperboric Oxygen in the Treatment of Endotoxin Shock. Surgery, Vol. 56, No. 1, pp. 184-192, July, 1964.

9. Fine, Jacob, Traumatic Shock. Sur. Cl. of No. Am., June, 1963.

10. Folkow, Bjorn, Autoregulation in Muscle and Skin. Circulation Research, Vol. 15, No. 2, Supplement, p. 22, August, 1964.

11. Frank, Edward D., Septic Shock. In Shock by Hershey, pp. 129-138. Boston, Little Brown and Company, 1964.

12. Gilbert, R.P., Possible Role of Endotoxin in the Perpetuation of Shock. In Shock. Pathogenesis and Therapy. An International Symposium, pp. 40-44. Berlin, Gottinger, Heidelberg, Springer-Verlog, 1962.

13. Goldberg, Leon I., Dorney, Edward R., Treatment of Shock Following Myocardial Infarction. Post-graduate Medicine, Vol. 37, No. 1, pp. 52-57, Jan, 1965.

14. Goth, Andres, Medical Pharmacology, pp. 64-83. C.V. Mosby Company, St. Louis, 1961.

15. Greenfield, A.D.M., The Effects of Emotional Stress on the Circulation Through Voluntary Muscles. In Shock. Pathogenesis and Therapy. An International Symposium, pp. 177-179. Berlin, Gottinger, Heidelberg, Springer-Verlog, 1962.

16. Grissom, Robert, Lecture. University of Nebraska. Oct.,1963.

17. Guyton A.C., Crowell, J.W., Cardiac Deterioration in Shock, I. Its Progressive Nature. In Shock by Hershey, pp. 1-12. Boston, Little Brown and Company, 1964.

18. Hardaway, Robert M., Hohnson, Dale, A Unified Theory of Shock. The American Surgeon, Vol.29, No. 4, pp. 292-298, April, 1963.

19. Hershey, S.G., Dynamics of Peripheral Vascular Collapse in Shock. In Shock by Hershey, pp.27-42. Boston, Little Brown and Company, 1964.

20. Hodgson, Paul, Lecture. University of Nebraska. Oct., 1963.

21. Janoff, Aaron, Alterati in Lysosomes (Intracellular Enzymes) During Shock, Effects of Pre-conditioning (Tole ance) and Protective Drugs. In Shock by Hershey, pp. 93-112. Boston, Little Brown and Company, 1964.

22. Johnson, Paul C., Review of Previous Studies and Current Theories of Autoregulation. Circulation Research, Vol. 15, No. 2, Supplement, pp 4-7, Aug.,1964.

23. Kalas, John P., Jacobson, Eugene D., The Effect of Vasoactive Antaganists in Endotoxin Shock. The American Heart Journal, Vol. 64, No. 6, pp. 764-776, June, 1964.

24. Krantz Jr., John C., Carr, C. Jelleff, Pharmacologic Principles of Medical Practice, pp. 826-840. The Williams and Wilhems Company, Baltimore, 1961.

25. Kraus, Hans, Raab, Wilhelm, Hypokinetic Disease. Charles C. Thomas, Springfield, Illinois, 1961.

26. Lepper, Mark, The Treatment of Medical Shock. Ped. Cl. of No. Am. Vol.11, No. 2, May, 1964.

27. Levenson, Stanley M., Negler, Arnold L., Einheber, Albert, Some Metabolic Consequences of Shock. In Shock by Hershey, pp. 79-92. Boston, Little Brown and Company, 1964.

28. Levy, Mathew N., Blattberg, Benjamin, Blood Factors in Shock. In Shock by Hershey, pp. 65-78. Boston, Little, Brown and Company, 1964.

29. Lillehei, Richard c., Experimental Aspects of Shock Due to Hemorrhage, Infection, and Myocardial Failure. The New Physician, Vol. 13, No., 11, pp. 419-428, Nov., 1964.

30. _____, The Nature of Experimental Irreversible Shock with its Clinical Application. In Shock by Hershey, pp. 139-206, Boston, Little Brown and Company, 1964.

31. MacLeau, Lloyd D., Duff, John H., Scott, Hugh M., Peretz, Dwight J., Treatment of Shock in Man Based on Hemodynamic Diagnosis. Surgery Gynecology and Obstetrics, Vol. 120, No. 1, pp. 1-16, Jan., 1965

32. Marshall, Robert J., Darby, Thomas D., Newer Agents in the Treatment of Shock, The Medical Clinics of North America. Vol. 48, No. 2, March, 1964.

33. Matthes, K., Myocardial Shock. In Shock. Pathogenesis and Therapy, An International Symposium, pp. 253-266. Berlin, Gottenger, Heidelberg, Springer-Verlog, 1962.

34. Mattingly, Thomas W., Changing Concepts of Myocardial Diseases. J.A.M.A., Vol. 191, No. 1, pp. 36-37, Jan. 4, 1965.

35. Mazzia, Valentine D.B., Rapaport, Felix T., Manage-ment of Traumatic Shock. In Shock by Hershey, pp. 297-305, Boston, Little Brown and Company, 1964.

36. Melby, James C., Corticosteroids in Shock in Man and Animals. The New Physician, Vol. 13, No. 11, pp. 426-428, Nov., 1964.

37. Moore, Francis, Tris Buffer, Mannitol and Low Viscous Dextran, Sur. Cl. of No. Am., June, 1963.

38. Musselman, Merle, Lecture. University of Nebraska, Nov., 1963.

39. Neil, B. E., Reflex Mechanisms and the CNS. In Shock. Pathogenesis and Therapy. An International Symposium, pp. 172-176. Berlin, Gottinger, Heidelberg, Springer-Verlog, 1962.

40. Nickerson, Mark, Vasoconstriction and Vasodilatation in Shock. In Shock by Hershey, pp. 227-240, Boston, Little Brown and Company, 1964.

41. Ossipov, B. K., On the Pathogenic Therapy of Shock. In Shock, Pathogenesis and Therapy, An International Symposium, Berlin, Gottinger, Heidelberg, Springer-Verlog, 1962.

42. Reeve, E.V., Development of Knowledge of Traumatic Shock in Man, Fed. Proc. 20 (Supp. 9), 12, 1961. Quoted in Rushmer, Robert F. etal., Shock, A Semantic Enigma. Circulation, Vol., 26, pp. 445-459, Sept.,1962.

43. Rushmer, Robert, Cardiovascular Dynamics, pp. 103-125, W.B. Sanders Company, Philadelphia and London, 1961.

44. _____, Shock, A Semantic Enigma. Circulation, Vol., 26, pp. 445-459, Sept., 1962.

45. Sambhi, M.P. et al., Adrenocorticoid in the Management of Shock. In Shock by Hershey, pp. 273-276. Boston, Little Brown and Co., 1964.

46. Sarnoff, S.J. al., Hemodynamic Determinants of Oxygen Consumption of the Heart with Special Reference to the Tension-Time Index. American Journal of Physiology, Vol. 192, No. 1, pp. 148-156, Jan., 1958.

Selkert, Ewald E., Role of Liver and Toxic Factors in Shock. In Shock by Hershey, pp. 43-64. Boston, Little Brown and Company.

48. Shires, G., The Role of the Extracellular Fluid in Shock. In Shock by Hershey, pp. 277-296. Boston, Little Brown and Company, 1964.

49. Simeone, Frorindo, Shock, Trauma, and the Physician. The New Physician, Vol. 18, No. 11, pp. 415-419, Nov., 1964.

50. Stoner, H.B., Critical Analysis of Traumatic Shock Models. Fed. Proc. 20 (Supp. 9), 38, 1961. Quoted in Rushmer, Robert F., Shock: A Semantic Enigma. Circulation, Vol. 26, pp 445-459, Sept., 1962.

51. Stratbucker, Robert, Lecture. University of Nebraska, April, 1962.

52. Udhoji, Vasant N., Weil, Max H., Circulatory Effects of Angiotensin, Levarterevol and Mearaminol in the Treatment of Shock. New England Journal of Medicine, Vol. 270, No. 10. pp. 501-505, March 5, 1964.

53. **Udhoji, M., Sambhi, M.P. and Rosoff, Hemodynamic Studies on Clinical Shock Associated with Infection. Am. J. Med., 34: 434, 1963.**

54. _____, Pressor Amines and Angiotensin in the Treatment of Shock. In Shock by Hershey, pp. 241-262, Boston, Little Brown and Company, 1964.

55. Weil, Max Harry, et al., Shock caused by Gram-Negative Micro-organisms. Annals of Internal Medicine, Vol. 60, No.5, pp. 384-400, March, 1964.

56. **Wilson, John, et al., C.V.P. in Optimal Blood Volume Maintenance, Archives of Surgery, 1962.**

57. _____, The Management of Acute Circulatory Failure. Sur. Cl. of No. Am., Vol. 43, No. 2, 1963.

58. _____, Use and Abuse of Vasopressor Therapy. The American Surgeon, Vol. 27, No. 5, pp. 374-382, May, 1963.

59. Wilson, Robert F, The Useage of Dibenzyline in Clinical Shock. Surgery, Vol.56, No. 1, pp. 172-183, July, 1964.

60. Zweifoch, Benjamin W., Relation of the Reticulo-Endothelium System to Natural and Aquired Resistence in Shock. In Shock by Hershey, pp. 113-128, Boston, Little Brown and Company, 1964.