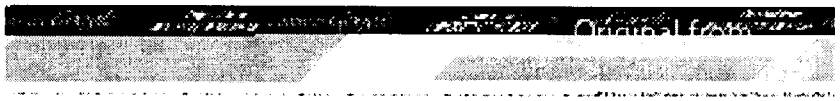
CHAPTER 9

SHOCK

In spite of the progress realized in the last decade, shock remains one of the most challenging problems in medicine. That lipids have a critical role in shock pathogenesis seems clear from a long-term study which began with an investigation of the activity of fatty acids in the induction of the abnormally dark color of blood seen in shock. The results of this study will be discussed here not only because of the intrinsic interest of the problem of shock itself but also because shock often represents the terminal phase of cancer as it does of many other diseases. In this presentation, we will try to remain as much as possible within the framework of our direct contribution to an understanding of shock. A portion of these researches was published in 1943. (40)

In studying the very complex phenomenon of shock, one has to consider a series of well-defined problems. Shock has been related not only to a large number of causes but also to a series of very varied clinical manifestations. An initial problem was to determine whether there is any common relationship between the different types—between the shock, for instance, which kills a subject within a few minutes after a severe sudden trauma, and the shock that kills in days through profound systemic metabolic impairments. What is common to, and what is different between them, from the point of view of pathogenesis? What constituents intervene and how, in shock? These and many other problems have been approached systematically.

Types of Shock—As a starting point, we attempted to classify the types of shock and found an interesting relationship according to the time of their appearance, that is, the interval between application of the noxious stimulus and onset of manifestations. Three types could be identified with this criterion.



There is an immediate type of shock which appears within a few minutes after the application of the noxious agent. It is induced experimentally in animals by intravenous injection of a noxious substance, by scalding the animal in hot water, or by strong mechanical trauma. It has predominant central nervous system manifestations, including exophthalmia and paralysis of the posterior limbs, followed by clonic convulsive movements, and usually is terminated by death. A similar *superacute* type of shock is occasionally seen in humans following transfusions of blood with an incompatible group. It also may be seen following very severe trauma. In the case of bullet wounds, for example, large calibre bullets may bring rapid death. Neither immediate hemorrhage nor any organ impairment is sufficient, in itself, to account for the speed of death in many of these cases. However, it can be explained by the rapid and intensive participation of the central nervous system in this superacute type of shock. Sometimes such shock is not lethal in animals or humans and is followed by a period of prostration and ultimate but slow recovery. We called this type of shock the "superacute."

In a second type of shock, more frequently encountered in humans, the manifestations appear after a certain period of time. Such shock often is seen after direct transfusions, when the rate of injection has been too rapid or when the syringe and tubes have not been well coated with oil or paraffin, or when there has been a subgroup incompatibility between donor and receiver. The patient usually experiences a severe chill within 30 minutes. The chill is succeeded by a rise in temperature which usually lasts 15 to 60 minutes or more. The patient next experiences diaphoresis, after which the episode usually is concluded. In some cases the symptomatology is different. At about the same time—30 minutes—after transfusion, for instance, hypotension with hypothermia, cold and clammy perspiration, and intensive dyspnea are noted. In these cases death can follow in a short time. The same reaction is sometimes seen to occur, usually also in about 30 minutes, after the release of a tourniquet. We have employed the term *"acute shock"* to describe this second type characterized by its appearance at approximately 30 minutes after the noxious intervention.

A third form, the *"state of shock,"* is considerably slower in onset and persists much longer. Characterized by hypotension, impairment of circulation, cold and clammy perspiration and marked enophthalmia, it may lead to death after several days during which the condition progressively increases in severity. It can, however, also end in recovery. This is the form

most often encountered in clinical medicine, in cancer and many terminal conditions.

The next problem was: could a common pathogenic mechanism be recognized despite the greatly varied manifestations of these three forms of shock?

Shock Mechanism

We saw one primary correlation between the three clinical types of shock in the fact that sometimes one type is followed by another. Superacute shock, if not lethal, may be followed by acute shock which, in turn, can change into a state of shock.

But it was the chemical analysis of blood, organs and entire bodies of animals killed by any of the three types of shock which indicated the possibility of a mechanism common to all three. A low antitryptic power of the blood, and the presence of substances resulting from protein hydrolysis were found to characterize all 3 types of shock. Additionally, an increase in the amount of free fatty acids, and the presence of abnormal members, occurred in all three types.

Fatty acids were studied from the point of view of the reciprocal position of their double bonds, through the oxidative fission method mentioned previously. The appearance of oxalic acid following oxidative fission indicates the presence of conjugated double bonds. The oxalic acid index obtained indicates the proportion of these conjugated double bonds. In normal rats, this oxalic acid index usually is zero in the total amount of fatty acids; in normal mice, values below 1 are seen. In all animals in shock, even in cases of superacute shock followed by sudden death, the oxalic acid index is invariably much higher. Furthermore, the death of an animal in acute shock or state of shock appears to be related to the presence of a critical oxalic acid index, indicating a concentration of abnormal fatty acids incompatible with life. Whether it appears in a relatively short time as in acute shock, or many days after the noxious intervention as in the state of shock, the oxalic acid index found in dying animals is between 14 and 17. Such high values are not found in superacute shock but the oxalic acid still is markedly increased. Thus, the presence of hydrolytic processes together with abnormal fatty acids appears to be a common pathogenic factor for the different forms of shock.

Pathological Changes

The three types of shock—because of the presence in all of hydrolytic processes and abnormal fatty acids—could be related to the first phase of

the immediate diphasic defense phenomenon or its prolonged form. The next problem was to determine what other factors might influence the development of differing manifestations so as to make shock appear in three forms.

The study of pathological changes characterizing each of these forms was undertaken. We found cellular vacuolation a characteristic lesion in animals in superacute shock. Vacuoles are present in the parenchymal cells of the liver, to a lesser extent in the alveolar cells of the lung, and to a still lesser extent in kidney cells. Of special interest was the fact that these vacuoles are often seen in the cytoplasm and even in the nuclei of brain cells. These findings explain the predominance of the neurological symptoms in this form. In a publication in 1943, we described this vacuolation as a characteristic of the superacute shock. The fact that the characteristic pathological change encountered in superacute shock is the presence of vacuoles in different cells suggests that this form of shock occurs principally at the cellular level.

In the acute type of shock, which usually appears half an hour after noxious intervention, there may be some evidence of cellular vacuolization, but the principal changes are at the tissular level. The changes are largely localized in the immediate areas damaged by the noxious agent and are manifested by vascular and interstitial pathology such as marked edema or capillary hemorrhage. Splanchnic vasodilatation and petechiae at the surface of pleura or peritoneum appear when the noxious agent acts indirectly in the blood or is applied directly to it through intravenous injection. The degree of generalized vascular damage corresponds to the degree of direct participation of the blood. We have discussed previously, in the chapter on defense, the changes occurring in the blood which characterize hemoshock. The characteristic leucolysis, which is followed by hydrolytic digestion, explains the high degree of breakdown of blood constituents and vessels observed in this kind of shock. While the participation of the cellular level—and especially of the central nervous system—characterizes superacute shock, participation of the tissular level leads to the acute form.

We consider pathologically characteristic of the state of shock—in addition to the changes seen in blood, such as hemoconcentration, dark color, tendency to form sludges, etc.—two other specific manifestations; milliar lesions in the gastric mucosa leading to hemorrhage and ulceration, and a manifest fluid accumulation in the first portion of the small intestine. Since the various changes in the state of shock affect the blood and two organs, the stomach and duodenum, they can be considered to involve the organic and systemic levels.

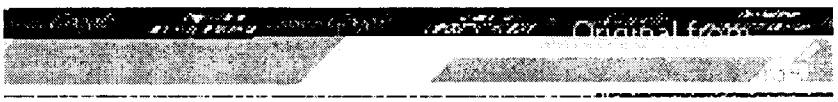
This analysis has permitted us to continue to develop the hypothesis that all three forms of shock stem from the same fundamental mechanism —the appearance of abnormal fatty acids as part of the first phase of the diphasic defense reaction. The differences in manifestations between the forms of shock are due to the level at which the mechanism operates, cellular for superacute shock, tissular for acute, and organic and systemic for the state of shock.

The study of a special condition, hemoglobinuria "a frigore," or paroxystic hemoglobinuria, has helped us to understand the time factor in shock. In this condition, immersion of the hand in ice water, for instance, induces hemoglobinuria and violent chill about half an hour later. We have been able to demonstrate that in the development of such a manifestation, two or often even three hemoshocks occur, each one characterized by a diphasic phenomenon. The first shock appears within ten minutes after immersion of the hand in icy water. Usually the first sensation and chill are very slight and while a reduced hemoglobinemia is present, hemoglobinuria is almost nil. It is the second hemoshock, appearing approximately 30 minutes later, which is usually very intensive with manifest hemoglobinuria. The third shock, which appears about two hours after immersion in ice water, is usually clinically inapparent and is revealed only by blood analysis.

The study of this condition has indicated that in the appearance of the three episodes of hemoglobinuria, besides the changes in the red cells under the influence of cold, which are characteristic for the condition as seen in the Donath-Landsteiner test, the important factor is the leucolysis occurring as part of the hemoshock. The subsequent hemolysis leads to free hemoglobin in the blood which, if in sufficient amount, passes into the urine. The changes induced in leucolysis will determine the degree of consequent hemolysis. The suppression of leucolysis by administration of morphine or other opium derivatives prevents any manifestation, while physical exercise undertaken following the immersion of the hand in icy water induces, in addition to a very intensive leucolysis, exceptionally intensive clinical manifestations. The time when the three hemoshocks appear also marks the time when the three forms of pathogenic shock—superacute, acute and state of shock—are seen. The intervention of three different noxious heterogenized constituents appears plausible. *(Note 1)*

Fatty Acids and Sodium Chloride in Shock

We noted that in all three types of shock, abnormal fatty acids can be found. A study of the role of these fatty acids permitted us to further un-



derstand the mechanism involved in these three types of shock. Since these same fatty acids have been seen to figure in abnormal metabolism of sodium chloride, the next logical step was to investigate the correlation between the latter and shock. Following this line, efforts were made to see if the differences between NaCl metabolism at different levels of organization would help explain the peculiarities of the different types of shock.

As we have noted, when abnormal fatty acids impair sodium chloride metabolism, two processes occur. First, there is abnormal fixation of chloride ions by abnormal fatty acids; then, sodium ions, freed following this chloride fixation, become bound to carbonate ions, resulting in alkaline substances. The pathological nature of chloride fixation results principally from the fact that the binding taking place at the conjugated double bonds is abnormally strong. Occurring in two steps, with a displacement of the double bond in the first, the bond between the conjugated fatty acids and chloride ions appear nonreversible. *(Note 8, Chapter 6)*

The great inequality in the ability of chlorides and sodium ions to pass through membranes can serve to separate, anatomically, the fixed chlorides from the free remaining cations. When this occurs, two distinct processes can be recognized, one involving the binding of chloride ions by abnormal fatty acids, the other involving the binding of carbonate ions by sodium ions and the resulting appearance of alkaline compounds. In the cells, the two processes take place separately, the sodium alkaline compound inducing the appearance of vacuoles. In tissues, the chloride fixation takes place predominantly in the cell, while the binding of carbonate occurs in the interstitial spaces. This leads to a localized intercellular alkalosis with consequent edema.

The same mechanism is involved in the changes associated with the state of shock, except that these processes occur at the systemic level. It is the part played by the sodium chloride of the blood in normal physiology, especially in the process of digestion, which explains the abnormal changes seen as characteristic of the pathological manifestations in the state of shock.

Normally, chloride ions are excreted into the stomach, where they are bound to hydrogen to form hydrochloric acid. An almost equal amount of sodium ions, bound to carbonate ions, is eliminated in a second step into the intestines via the pancreatic and intestinal secretions. The chloride and sodium ions are later liberated to form sodium chloride which is entirely reabsorbed in the distal portion of the intestinal tract, the colon. The sodium and chloride ions are not simultaneously secreted in the digestive tract. The interval between the excretion of chloride ions into the stomach

and of sodium ions into the intestines accounts for the physiological "alkaline tide" associated with digestion.

When chloride ions are pathologically fixed to abnormal fatty acids in the blood, they can no longer be dissociated and secreted by the stomach in the form of hydrochloric acid. Instead, they remain bound to the fatty acids and accumulate in this form within the gastric mucosa. The multiple milliar gastric mucosal ulcerations in the state of shock results from the intervention of these abnormal fatty acids brought into the mucous membrane by the chloride ions to which they are bound. The ulcerations are caused by the catabolic action of fatty acids. Thus, the first phase of abnormal sodium chloride metabolism leads to the characteristic multiple gastric ulcerations.

The second phase is related to the metabolism of sodium. The sodium ions are secreted as carbonates by the pancreas and intestinal mucosa in the first part of the small intestine. In the state of shock, because they do not encounter the chlorides normally coming from the stomach, they remain as carbonates. As sodium carbonate is accumulated in the first portion of the small intestine, a local alkalosis occurs, leading in turn to an important local retention of water. It should be noted that this is a very different situation from achlorhydria or hypochlorhydria in which, while the chloride ions are not secreted into the stomach, no excesses of sodium ions appear in the blood or in the intestines, and consequently no local alkalosis or fluid accumulation occurs.

The difference between the systemic and tissue processes in shock lies in the localization of the abnormal sodium chloride metabolism. In tissue anomaly, the separation of sodium chloride takes place between the cells and the pericellular structures. At the systemic level, it occurs between the stomach and intestines, with the blood serving as intermediary. This mechanism explains the larger amounts of water which distend the upper parts of the intestine, as observed in autopsies of animals which have died in this form of shock.

The close similarity between the abnormal processes that take place in sodium chloride metabolism at the tissue and systemic levels provides the basis for another working hypothesis concerning the mechanism in superacute shock. We have seen that the production of vacuoles in cells characterizes this latter form of shock. The unequal cellular permeability for chlorides and sodium in their dissociated form is known. Chloride ions can circulate much more easily between cells and the pericellular spaces than can sodium ions. An initial effect of the intervention of abnormal fatty acids in cellular pathology is the fixation of chlorides. At the same time, an

increased permeability in membranes occurs. This would permit more sodium ions to pass through cell membranes and to accumulate intracellularly, inducing a liberation of potassium, the cellular cation. As the chloride ions are bound to fatty acids in the cells, the sodium ions in the cells liberate potassium and join it to form alkaline compounds. Isolated in vacuoles, these compounds also accumulate water.

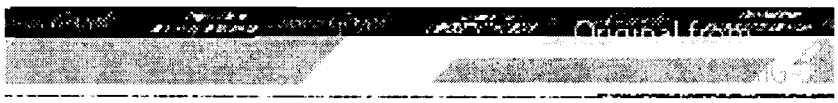
Thus, we have a concept of single pathogenesis for all three forms of shock based upon abnormal sodium chloride and water metabolism, with the abnormality taking place at different levels of the organization, cellular for superacute shock, tissular for the acute form, and systemic for the state of shock. The displacement of potassium by sodium in cellular physiology contributes to the increase in serum potassium found in all forms of shock.

Water Metabolism

The localized retention of water, prompted by the alkaline sodium compounds which result from abnormal sodium chloride metabolism, occurs in the cells, tissues or intestines in the different types of shock. Many of the differences in manifestations between the three forms of shock can be explained in terms of localization of this abnormal water metabolism. The sensitivity of the cells of the nervous system to intracellular changes explains the predominance and severity of the nervous system manifestations in superacute shock. Abnormal tissue water metabolism explains not only the predominantly local character of the manifestations seen in acute shock, but also the hemoconcentration values in these cases. As often seen in burns, important amounts of water are driven out of the blood into the damaged tissues.

The abnormal water metabolism however, appears to be the principal manifestation in the state of shock. Upper intestinal water accumulation, rather than a general unlocalized fluid loss, can be demonstrated in the pathogenesis of this form of shock. In opposition to the local lesion with a high retention of water, the general subcutaneous tissues sustain a loss of water rather than an accumulation during shock. This would not occur if there were a general increased permeability of all capillaries, allowing water to pass freely. The role of water accumulation in the first portions of the intestine due to the abnormal loss of systemic water was demonstrated in animal experiments. When the small intestinal tract had previously been removed, and a state of shock was later induced by trauma, no hemoconcentration occurred.

It is the participation of one or another of the three principal levels of the organization—cellular, tissular or systemic—which explains why the



same pathogenic process, abnormal sodium chloride and consequent abnormal water metabolism, produces such different manifestations in the various types of shock. It must not be forgotten however, that in the last analysis, the abnormalities in sodium chloride and water metabolism result from the intervention of abnormal fatty acids. Fatty acid intervention, together with the abnormal sodium chloride and water metabolism confirm the unitary pathogenesis of the three forms of shock.

Other Changes

Other changes associated with shock also can be related to the influence exercised by abnormal fatty acids. The appearance of rouleaux of red cells may be easily explained by fatty acid intervention. It is the replacement of the nonpolarity normally present at the surface of the red cells by a dipolarity which results in the formation of the rouleaux. This can be induced by fatty acids in vitro. Sludge formation would represent a still more advanced step in this same process and would appear to result from a polypolarity at the surface of the red cells. Sludge formations have been induced in vitro by fatty acids added in larger amounts to plasma. *(Note 2)* They contribute to the circulatory impairment considered to be an important factor in the tissular respiratory troubles seen in shock.

We have noted that the richness in free fatty acids interferes with the ability of the red cells to keep oxygen fixed, a fact which would impair its transport. This, together with hemoconcentration and circulatory impairment, has been found to account for the black color of the blood in shock. *(Note 3)* The clinical manifestations are characteristic of offbalance D.

Experimentally Induced Shock

The hypothesis that the three types of shock are caused by the intervention of the same factor—abnormal fatty acids—has been further confirmed experimentally. The cellular changes that characterize superacute shock can be induced by the rapid introduction into the blood stream of even minimal amounts of fatty acids in preparations in which they are bound to plasma constituents.

Pooled heparinized plasma of mice was treated by stirring it in a nitrogen atmosphere for one hour with a preparation of conjugated trienic fatty acids. The nonbound fatty acids were separated through short centrifugation. The plasma was injected intravenously in mice. For control, plasma treated under the same conditions with stearic acid was used. While control animals did not show any apparent discomfort, the mice injected with the plasma treated with conjugated fatty acids died immediately, in most

cases even during the injection itself. With such preparations, superacute shock was induced in what we consider a direct way, the sudden death contrasting with the cases of hemoshock where death occurs usually after an interval of a few minutes. This characteristic of direct immediate death is consistent with the pathogenic role of fatty acids in superacute shock.

The tissue changes that characterize the acute type of shock also may be induced by local administration of abnormal fatty acids with the condition that sufficient amounts are used. *(Note 4)* The systemic changes that typify the state of shock can also be produced by prolonged absorption of fatty acids, as when they are repeatedly introduced intraperitoneally. *(Note 5)*

The relationship between shock and lipids can be further seen in the antagonistic effect exercised upon shock induced with standardized trauma by two groups of lipids with positive and negative characters. We have utilized the Noble-Collipp drum on a large scale to induce shock in rats. In some groups of animals shock induction was constant; in other groups under the same conditions, shock could be induced only in some animals. Nevertheless, it was still possible to recognize opposite effects induced by the administration of the two groups of lipids. In some animals even apparently little influenced by the trauma, the injection of a mixture of conjugated fatty acids immediately after trauma brought death within a short time. In no other animals, traumatized under the same conditions, have we seen death occurring within the same short interval of time. This also applies to animals injected before trauma. In these cases, the animals died even during the trauma, that is, in the drum. *(Note 6)*

Conversely, the administration of sterols, especially preparations of the insaponifiable fraction of human placenta, before induction of trauma prevented lethal shock almost without exception, whereas under the same conditions the same trauma produced death in a high proportion of the controls. Even when injected immediately after trauma, this sterol preparation prevented the development of lethal shock in a high proportion of cases. *(Note 7)*

The different forms of shock, although resulting from the same fundamental abnormal process, appear to respond differently to therapeutic agents—again because of the localization of the abnormal processes at different levels. Adrenalin and related compounds, when administered in time, are able to control superacute shock, but they are almost entirely without influence upon the other forms. While acute shock can be influenced by the administration of a large amount of sterols and butanol, superacute shock is unaffected, possibly also because of the slow absorption of

the sterols. None of these agents is of significance in the treatment of the state of shock which is only mildly influenced by butanol and certain cortical hormones such as hydrocortisone, especially when introduced directly in the circulation.

In order to act upon the fatty acids and sodium which produce the abnormal water metabolism, we have utilized glycerophosphoric acid administered in large amounts parenterally. Diluted with saline, it was usually injected intravenously. The good results obtained are discussed later.

The use of heptanol and of polyunsaturated alcohols has also led to interesting results. It was however with preparations having several of these agents, working at different levels of the organization, that the best results were obtained.

The measurement of the chloride index and of the surface tension of the urine have represented valuable means to judge the changes occurring in shock, in their clinical evolution and especially in the action of the agents in relationship to the occurring recovery.

The study of shock has contributed to the knowledge of the therapeutic problems of cancer and other conditions. The cause of death, when a predominance of fatty acids occurs as a systemic manifestation, corresponds to the state of shock. The possibility of successfully influencing this form of shock would furnish a valuable tool for the treatment of all severe manifestations related to predominance of fatty acids.