

# Meetings

## Hemorrhagic Shock: Metabolic Effects

The injurious effects of hemorrhage and oligemia are believed to result from subliminal perfusion of tissues with blood. Cellular metabolism loses its support from the circulation. Essential elements do not reach the cells at an adequate rate; metabolic products are not removed. Progress has been made in identifying some of the metabolic consequences of poor tissue perfusion, especially in the experimental animal. In order to discuss the present status of the problem, a workshop on the metabolic effects of hemorrhagic shock was held at Rockefeller Institute, New York City (19 June 1962).

F. A. Lipmann stated that one function of the circulation is to provide cells with oxygen and food for energy production and that investigations of energy metabolism in shock should properly be carried out at the cellular level. Irreversibility might be associated with a reduction in the production and supply of energy and with a breakdown of the cellular membrane. Tissues vary in their requirements for oxygen. The kidney is a particularly "aerobic" organ, hence its great susceptibility to poor circulation and anoxia.

The question of adequacy of oxygen supply to tissues is a difficult one, according to W. E. Huckabee. If the supply of oxygen to a tissue is gradually decreased, a steadily progressing biochemical abnormality in the cellular activity can be detected, but the change is not abrupt. However, one may state that, if the rate at which NAD (nicotinamide adenine dinucleotide, formerly called DPN) is reduced in a tissue exceeds the rate at which it is restored, the cells are being inadequately supplied with oxygen.

While techniques for precise and

direct studies of cellular energy production can be used in excised tissues, indirect methods are necessary for obtaining information in intact animals and in man. One possible method is the calculation of excess lactate production. Such excess occurs when lactate accumulates over and above the amount expected from the accumulation of pyruvate.

Lactacidemia may result from a variety of causes which fall into two groups: (i) non-lethal, in which the accumulation is not in excess of that which would be expected from the increased pyruvate, as in artificial hyperventilation; and (ii) deleterious, often lethal conditions, in which the lactacidemia is in excess, as encountered in severe and progressive hemorrhagic shock.

Another way in which anaerobic metabolism in a physiologic sense can be estimated in intact animals is by measurement of oxygen-debt. When this was done under a variety of circumstances, as in muscular exercise, hypoxemia, alkalosis, and so forth, excess lactate production and removal were closely correlated quantitatively with changes in oxygen-debt; lactate accumulation did not show such correlation with oxygen-debt.

Interpretation of findings in the blood must be made with the understanding that they do not necessarily reflect the condition in every part of the tissue. Organs or parts of them that may be excluded temporarily and completely from the circulation have extreme anaerobiosis but may provide no indication of it in the blood.

The crux of the matter is whether excess lactate is, in fact, quantitatively related to anaerobic metabolism. Liver, skeletal muscle, and possibly other organs can remove lactate from the blood, and when the functions of these organs are depressed, lactate may accumulate in the blood. According to

Lipmann, a breakdown of the Pasteur effect, the inhibition of glycolysis, and lactic acid production in the presence of oxygen could also result in a relative increase in lactate.

J. G. Strawitz described the function of isolated mitochondria from the liver and heart of dogs which were subjected to severe hemorrhagic shock. Shock was produced by the removal of 40 to 45 percent of the circulating blood volume. The blood pressure was maintained at 40 mm of mercury for 3 to 5 hours. Mitochondria were examined with the phase contrast and electron microscopes. After hypotension, the mitochondria prepared from myocardium and examined by phase contrast microscopy appeared enlarged and misshapen in the experimental animals when compared with those of the controls. There was no significant enlargement when examined by the electron microscope, but honeycombing of the internal structure was seen in the shock preparations. When the myocardial mitochondria were studied in the Warburg apparatus, with alpha-ketoglutarate as the substrate, only small reductions in oxidative activity could be demonstrated. ATP (adenosine triphosphate) was not being produced at normal rates and this was reflected in lowered ratios of phosphate to oxygen. In shock, the total and soluble phosphate was significantly increased.

Liver mitochondria showed greater morphologic changes than did those of the myocardium in response to a period of hypotension and oligemia. They become irregular, enlarged, and formed clumps which were visible under the phase contrast microscope. When examined with the electron microscope, the liver mitochondria showed marked enlargement and disruption of the internal structure. In the Warburg apparatus, mitochondria from the livers of dogs showed a greater uptake of oxygen than did normal controls. On this basis, the tentative conclusion had been reached that prolonged severe oligemia and hypotension did not appear to injure hepatic mitochondria functionally despite the marked morphologic changes.

Lipmann pointed out that the increased utilization of oxygen by the mitochondria does not necessarily signify that they are functioning normally. Indeed, it simply may mean an "uncoupling" of the electron flow in the production of high energy phos-



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phate bonds so that these are not produced. The cessation of flow of electrons in the high-energy phosphate system removes the normal feedback mechanism which controls the rate at which mitochondria utilize oxygen.

R. A. Cowley cited a publication which suggested that the ability of animals to survive shock was improved by the intravenous administration of mitochondria. This theory was received with interest and great skepticism.

Observations were made by G. G. Nahas on two groups of dogs which were bled to mean pressures of 50 mm of mercury and reinfused after  $2\frac{1}{2}$  hours. All animals breathed 100 percent oxygen by nasal catheter. The first group of 36 animals received an intravenous infusion of a buffer; the second group received an equal volume of isotonic salt solution. All animals secreted catecholamines, mainly epinephrine, during the period of hypotension and oligemia. The levels of catecholamines were nearly at control values 30 minutes after normovolemia had been reestablished. The animals that received salt solution instead of buffer secreted about twice the amount of catecholamines as those that did receive buffer. Only 37 percent of the control animals survived, while 70 percent of those receiving buffer survived. Administration of oxygen alone or of buffer alone did not improve the survival rate. These observations led to a discussion of the interrelationships among acidosis, the catecholamines, and oxidative metabolism.

The decrease in work performed by the heart while oxygen utilization is maintained near control levels results in lowered efficiency (D. B. Hackel). During oligemia and hypotension, about 20 percent of the cardiac output goes to the heart, as compared with the 4 or 5 percent under normal conditions. The normal myocardial pyruvate extraction is decreased during shock, and in severe shock the myocardium may actually contribute pyruvate to the blood flowing through it. "Excess lactate," as described by Huckabee for other organs, is not produced by the myocardium in shock.

There is some evidence that enzyme systems in the myocardium may become irreversibly changed or depleted after prolonged shock. Thus, if oligemia is corrected by transfusion within an hour after bleeding, extraction of myocardial pyruvate, lactate, and oxygen return to normal. But if the oligemia and hypotension are not

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corrected until after 3 hours, the oxygen extraction is depressed to levels significantly below normal and the abnormalities in pyruvate and lactate extractions are no longer reversed by transfusion.

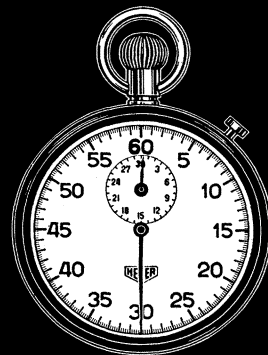
In hemorrhagic shock, tissues appear unable to phosphorylate thiamine and are low in cocarboxylase content. Myocardial metabolism of dogs deficient in thiamine resembles that of dogs in hemorrhagic shock. The administration of thiamine and cocarboxylase to dogs in hemorrhagic shock had no effect. According to F. A. Lipmann, although there may be a cocarboxylase deficiency in shock since ATP is needed to form thiamine pyrophosphate (cocarboxylase), cocarboxylase would not be expected to enter the cells.

Injury results in a rapid drop in the plasma level of ascorbic acid, its urinary excretion, and its "tissue saturation." Studies of wound healing in the experimental animal reveal that this biochemical scurvy indicates physiologic scurvy (S. M. Levenson).

As part of a series of experiments designed to determine the mechanisms of these changes, tests were performed to determine whether the microflora normally present in healthy animals influences ascorbic acid metabolism. For this, the response of germ-free and of normal guinea pigs to a scorbutogenic diet was followed. The germ-free guinea pig does develop scurvy, but at a much lower rate than in guinea pigs harboring the normal microflora. It is postulated that this is the result of utilization of ascorbic acid by the intestinal flora, a process which cannot occur in the germ-free guinea pig. Supporting evidence for this is provided by finding a more rapid decline of tissue ascorbic acid levels in the normal guinea pigs on a scorbutogenic diet than in their germ-free counterparts. The increased "requirement" for ascorbic acid brought about by serious clinical infections may be due in part to destruction of the vitamin by bacteria in the infected area. However, the increased "requirement" is more likely due to increased "utilization" (details not known) of ascorbic acid by the host as part of the overall metabolic response to serious infection, which is similar to that which follows severe injury.

The observations that the administration of vitamin C can influence the lethality of hemorrhagic shock were viewed with skepticism.

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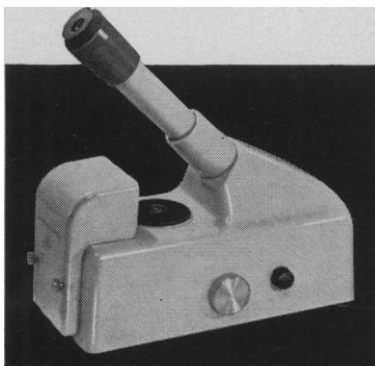
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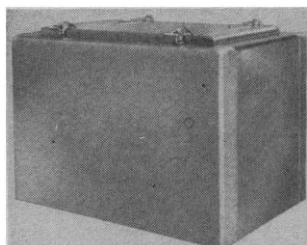
Levenson also noted that severe prolonged shock in animals is accompanied by an increase in the concentration of "total amino acids" in the plasma. This was not found in examinations of the blood of casualties during the Korean conflict when the individual amino acids were measured. This relative constancy of the concentration of total plasma amino acids was not the result of unvarying concentrations of the individual amino acids; some of these rose, while others fell or remained unchanged. The fluctuations in concentration of any of the amino acids were minimal in comparison with the changes of the other nonprotein nitrogen substances; the physiologic basis or consequence of the amino acid changes are not known.

A striking finding in patients who have been injured is an increase in what Levenson, Howard, and Rosen called "amino conjugates." This was found especially among those casualties with renal failure. The conjugate fraction increases remarkably in the plasma of such patients, and while normally it is composed of threonine, glutamic acid, and glycine, it contains a greater variety of amino acids after trauma. The exact nature, function, and significance of these compounds are not known; investigations of these problems should be fruitful.

On the assumption that "irreversible" shock produces decreased tissue perfusion and decreased utilization of oxygen, the employment of hypothermia is reasonable in so far as it would be expected to decrease the requirement for oxygen. R. A. Cowley reported encouraging results in man from the use of hypothermia in "septic" shock provided the body temperature was not brought below 32° C. In experimental septic shock in the dog, hypothermia did not improve survival, but prolonged the survival time from 3 to 4 hours to 10 or 18 hours.

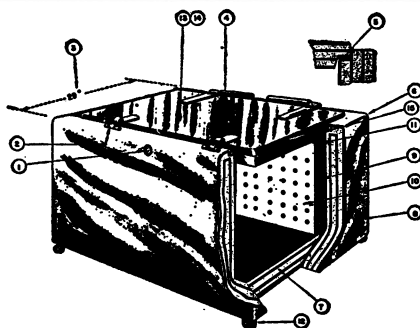
W. R. Drucker noted that hemorrhagic shock causes a marked elevation in the blood concentrations of glucose, pyruvic and lactic acids, and serum inorganic phosphorus. These alterations are characteristic of anoxia and persist with increasing severity until the animal dies. If, however, the withdrawn blood is reinfused there is a rapid and progressive decline in the concentrations of these compounds, more than can be explained by dilution from the transfused blood. In those

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animals that have a transient recovery of their mean arterial blood pressure and subsequently die in so-called normovolemic "irreversible" shock, there is no secondary rise in the concentrations of glucose, pyruvic and lactic acids, and inorganic phosphorus, concurrent with the terminal fall of blood pressure. Also the ratio of lactic to pyruvate, which is markedly elevated during hypovolemic hypotension and which declines following transfusion, does not rise again as the animal dies despite a prolonged period of hypotension prior to death. But if a hemorrhage is produced during the terminal phase of "normovolemic hypotension," all of the metabolic alterations characteristic of the initial period of hemorrhagic hypotension will reoccur.

These observations suggested that it is the decreased blood volume rather than the hypotension which reduces tissue perfusion with consequent anoxia and metabolic acidosis. Accordingly, it was postulated that any reduction in oxygen requirement during hypovolemia should lessen the severity of metabolic alteration and possibly promote an improved tolerance for hypovolemia.

To test this hypothesis, a series of animals were subjected to hypothermia at 30°C prior to hemorrhage. Preliminary studies had indicated that hypothermia of this order, produced in normovolemic dogs, caused a significant reduction in oxygen consumption with no metabolic acidosis. Thus, the reduction in oxygen consumption reflected a decrease in tissue need for oxygen rather than faulty oxygen transport. Hypothermia did promote the survival of animals subjected to hemorrhagic hypotension. The relation between this effect of hypothermia and the role of adrenal steroids, catecholamines, endotoxin, and other factors requires clarification.

This workshop was the 48th meeting of the Committee on Shock, Division of Medical Sciences, National Research Council. It was supported by the Department of Defense. Participants included F. A. Simeone (chairman), R. A. Cowley, W. R. Drucker, F. L. Engel, D. B. Hackel, W. E. Huckabee, J. M. Kinney, S. M. Levenson, F. A. Lipmann, G. G. Nahas, J. G. Strawitz, and M. G. Weidner.

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