Observations:

The Cellular Aspect of SHOCK

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The concept of shock is a complex one. It encompasses a broad spectrum of manifestations and etiologies while demanding the attention of many medical and surgical disciplines. Its definition is equally complex. In the most general terms, however, shock can be defined as *that state of damage to a cell or group of cells caused by a condition of stagnant hypoxia and its biochemical results.* This definition says nothing about the clinical etiology or severity of shock but does, however, stress the important principle of shock: that being the damage to cells by a lack of oxygen.

It should be noted first that while this discussion deals with the cellular aspects of shock, the data cited have been gathered from experiments performed on animals, or groups of cells. It should also be emphasized that effects of shock on an organism equal the sum total of those effects happening to the individual cells. It is obvious that at any one time, not all the cells are in equal states of distress. The number of cells involved and the duration of time that the individual cell is subjected to stress both contribute to the total effect shock has on the organism. It is from this point, then, that the observations will begin.

The energy for cellular function comes from adenosine triphosphate (ATP) produced by the breakdown of glucose to compounds of lesser energy content via the glycolytic pathway (Embden-Meyerhoff pathway) and the Tricarboxylic acid cycle (Krebs cycle). It is well known that the majority of ATP is produced in the Krebs or Aerobic (with oxygen) phase of the complete pathway. The anaerobic (without oxygen) portion, the breakdown of glucose to pyruvic acid, is barely self-sustaining in comparison. Thus, it is easy to see that if oxygen is withdrawn from the cell, as in an hypoxic state, the aerobic portion of metabolism will be severely compromised, with ATP production begin cut drastically.

That is not the only manifestation of cellular hypoxia, however. Since the Krebs cycle is no longer utilized to its previous extent, the raw materials which feed into it from the glycclytic pathway will be in excess supply. This means that the pyruvic acid, which usually is converted to acetyl coenzyme A (CoA) and subsequently fed into the Krebs cycle, will begin to accumulate behind the metabolic barrier.

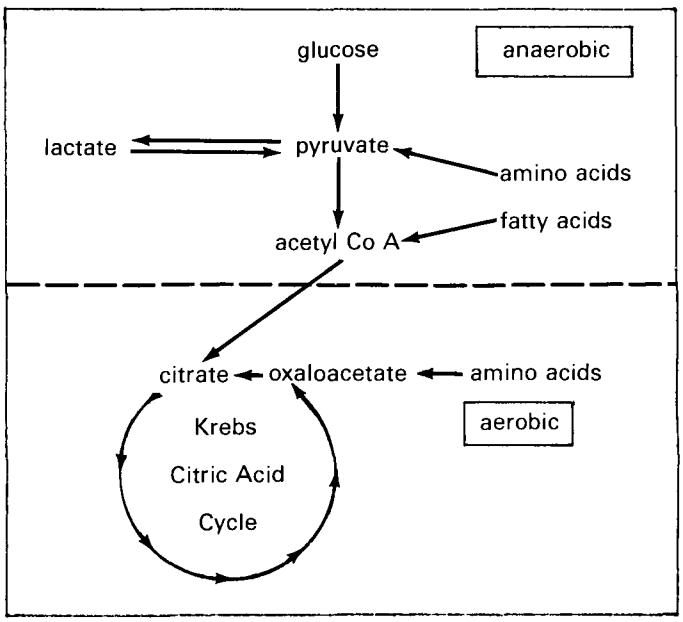
There is little doubt that the block caused by oxygen deprivation is between pyruvate and acetyl CoA, thereby accounting for the predicted increased amounts of pyruvate. (13) In actual fact, during hypoxia, there is not an increase in pyruvate levels but in lactic acid. *This is so because, under anaerobic conditions, pyruvate is converted to lactate instead of to acetyl CoA.* This quantity of lactic acid is released into the blood stream, causing a decrease in pH and an acidemia.

In addition, there are other substances which add to the total acidemia. Normally, in a stressful situation, cortisol is released from the adrenal gland. This steroid is a gluconeogenic agent; that is, *it promotes the conversion of amino acids to carbohydrates.* This action is mediated by enzymes, the transaminases, which transfer the amino group of the amino acid to a receptor molecule, leaving a carbohydrate.

The amino group itself brings about the incorporation of glycine into purines, the nucleotides found in DNA and RNA, thus stimulating production of more enzyme. (2) Specifically, two of these enzymes are the transaminases, glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT). In one case, GPT catalyzes the conversion of alanine to pyruvate and, in the second, GOT mediates the transamination of aspartic acid, with oxaloacetic acid resulting. It should be noted that pyruvate is on the *anaerobic* side of the hypoxic block and oxaloacetate is on the *aerobic* side.

Thus, in a stressful situation such as shock, there should be increase gluconeogenesis, with conversion of amino acids to carbohydrates. This *does* happen to some degree but, soon, as cellular hypoxia increases, this conversion is diminished.

The reasons for this are two-fold. First, hypoxia inhibits the effects of the transaminases. (15) Thus, there will be an increased pool of amino acids. Second, since there is already an increased amount of pyruvate from the hypoxic block, the conversion of alanine to pyruvate will be facing an unfavorable equilibrium. In a like manner, aspartic acid will not be converted to oxaloacetic acid. This, too, adds to the hyperaminoacidemia (excess amino acid).

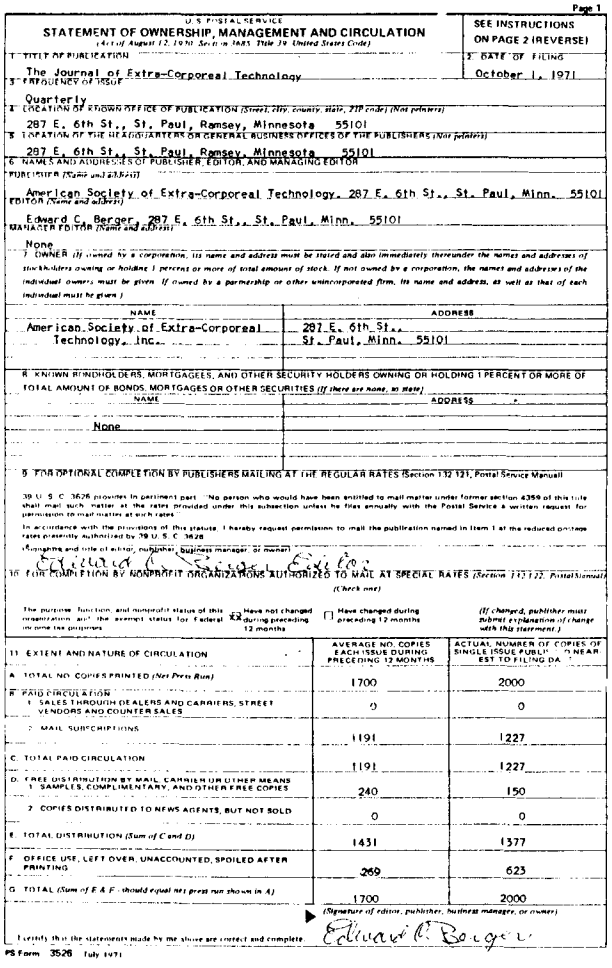


During a situation where ATP is needed and the normal breakdown of carbohydrate cannot supply it, fatty acids are utilized; they are converted to acetyl CoA and incorporated into the Krebs cycle. In hypoxemia (low oxygen), this conversion is attempted but, since there is a stalling of the Krebs Machinery, there is a build up of fatty acids in the same way that there is an accumulation of amino acids and lactic acid. These substances enter the blood stream and *cause a lowering of the pH.* Also, ketone bodies, the results of an incomplete breakdown of fatty acids, contribute to this acidemia. (3)

The decrease of pH causes a *disruption of enzyme activity in the cell.* With this decrease, any process which would enable the organism to react to the shock situation will be depressed. For example, the enzymatic processes utilized to clear lactic acid from the cell would be interfered with, resulting in the *increase* of lactic acid and a further *decrease* of pH.

Thus, metabolic alterations bring about a lowering of plasma pH which, in turn, results in a continued depression of metabolic function. It can be hypothesized that, with the decrease in pH, almost anything can happen to cellular function. For example, it is know that there is a decreased contractility of the myocardium. (3) Certainly, decreased myocardial contractility would not aid in the recovery from a hypoxia-induced acidemia caused by diminished blood flow!

Decreased ATP production is another major deficiency caused by cellular hypoxia and blockage of the Krebs cycle. Since this substance is responsible for the vast majority of energy processes that occur in the cell, its lack is serious.



Page 1

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"Treatment for this condition is, obviously, return of the oxygen supply."

ATP is responsible for the maintenance of the selectivity of the cellular membrane. (16) Without the energy supplied by this compound, the Na/K pump (sodium-potassium ion transfer) ceases to function properly and there is an alteration in the normal concentration of these ions within the cell. (21) This, in itself, would cause *metabolic* alterations. Proteins would become altered (denatured) with the resultant loss of structure. Enzyme systems would be disrupted and mechanical barriers formed by structural proteins would be affected.

Also, the entry of sodium into the cell helps initiate the disruption of the lysosomes, the "suicide packets" of the cell. The lysosomes contain proteases, nucleases, lipases, and amylases, among others, which, when released, bring about the destruction of the structures in the cell. (6)

Another alteration brought about by the lack of high-energy compounds is in the actual synthesis of proteins. Normally, an amino acid is transferred to soluble RNA (sRNA), the molecule transporting it to the ribosome, through the action of a high-energy substance. Once sRNA has brought the building block to the protein "assembly line", it transfers the amino acid to the incipient protein. The position in which the amino acid is placed is determined by messenger RNA, which itself is formed by nuclear DNA. Thus, the order of the amino acid sequence in any protein is determined by nuclear DNA.

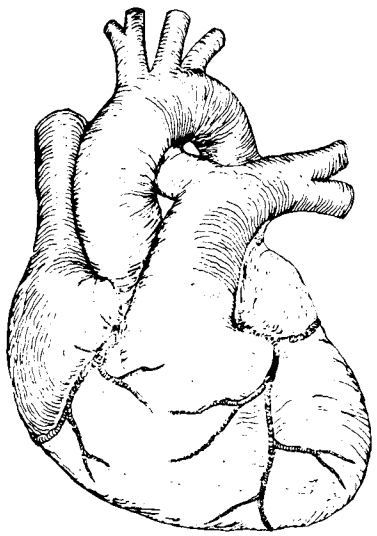
If, because of a lack of high-energy compounds, the amino acids cannot be incorporated into proteins, there will be an increase in free amino acids in the blood which further contribute to the acidemia. Also, without protein synthesis the enzymes necessary for proper cellular function are lacking and there will be a slowing down of the energy-producing machinery. Again, as in the case of acidemia, the cycle will perpetuate itself. A lack of high-energy compounds will inhibit enzyme synthesis, which, in turn, decreases the amount of high-energy compounds available. (18) Obviously, adequate enzyme activity is essential for survival.

Another factor working against the proper functioning of enzymes is the presence of antibodies against nucleotides. Nick (8) and his associates have found that, in shock, there is a rise in the titer (number) of antibodies directed against the components of DNA and RNA. The presence of these antibodies disrupts the normal transfer of genetic information, confusing the instructions for protein formation.

Another interesting finding in his work is that the amount of antibody present is related to the severity of the shocked state. In his patients with "moderate or severe" degrees of shock, all showed the presence of rising antibody titers. Those patients with transient (mild) shock stated showed none.

This evidence implies that there is a quantitative and/or time factor which determines whether or not antibodies are produced. It is logical to assume that, with cellular dissolution, antibodies are created against the cellular contents entering the plasma. When cellular destruction is present long enough or in great enough amounts, the antibody titers reach detectable levels.

It also seems logical to assume that once these levels reach a certain concentration, they interfere significantly with enzyme synthesis in unaffected cells, thus contributing to the general metabolic deterioration of the organism.



Proof that these antibodies can enter healthy cells can be found in examination of the pathogenesis of the autoimmune diseases where it is thought that antibodies to the material in cell nuclei are present. Conditions as Hashimotor's thyroiditis and lupus erythematosis are often explained on this basis.

This work by Nick also shows that those patients who had antibodies specific against thymine, a pyrimidine found in DNA, tended to die in shock while those patients that had antibodies specific against cytosine or guanine, substances found not only in DNA but also RNA, tended to survive. Since thymine is present only in DNA and not RNA, it would seem that when cellular damage is so great as to dispur the RNA-containing nucleus as well as the cytoplasm, there is more damage being effected.

If this is the case, then the decreased survival seen when the thymine antibodies are increased is logical. On the other hand, the presence of cytosine of guanine-specific antibodies implies that the nucleus has been relatively untouched.

The above seems to be logically consistent. If there were some cellular damage, with disruption of protein synthesis at the RNA level, the cytosine guanine-specific antibodies would rise. The cell could still recover, however, because the master builder, the DNA, is intact, capable of directing enzyme synthesis is at that time when the milieu of the cell is favorable to normal metabolic processes. If, conversely, the DNA is destroyed, the cell is incapable of ever functioning again. This perhaps explains the correlation of antibody titers and survival.

There is another method by which the delicate control of the cell could be injured by hypoxia. This hypothesis is much more theoretically than empirically (experimentally) based, however, and is included solely for interest's sake.

In 1960, Jacob and Monod published their classic paper dealing with the dynamic control of genetic expression. Although their results were based on observations of bacteria, it is still considered to be within the realm of science when one transfers this information to man while hypothesizing and fantasizing about him. Simply, Jacob and Monod states that a certain length of a DNA molecule, called an operon, is responsible for the amino acid sequence of one particular polypeptide. This operon is controlled from within by another length of DNA called an operator gene. This operator is, in turn, controlled by a regulator substance, a protein.

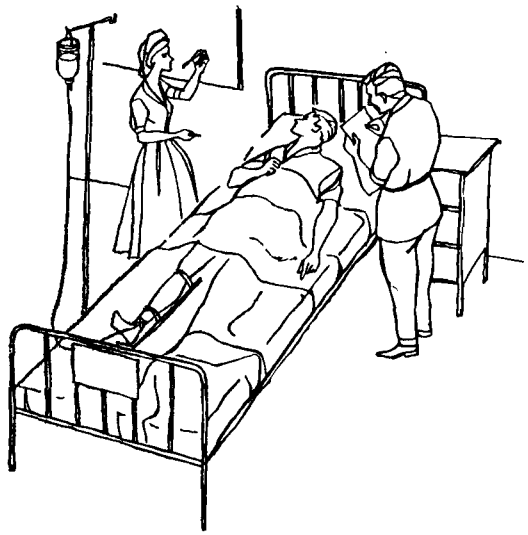
This protein, when present, will combine with the operator locus, causing it to stop the function of the rest of the operon and the subsequent production of polypeptides. If, however, another chemical interfers with or changes the configuration of the regulator, its influence ceases and the operon produces, albeit indirectly, its specific polypeptide chains. This process is called induction.

When this system is subjected to the internal changes found during a shocked state, all manner of abnormalities are foreseeable. For example, if depletion of ATP causes a deletion during formation in the repressor protein, thereby changing its configuration, this new protein might be incapable of repressing the operon and the resultant polypeptides would be produced unchecked, even at the cost of cellular death. Thus, it is seen that even minor changes can, hypothetically, bring about disasterous alterations in cellular function.

To this point in the discussion, various mechanisms for causing cellular disfunction have been set forth. These have either scientific validity or are based on tenable hypotheses. What remains to be seen is evidence that *these alterations actually do bring about significant changes.* If the metabolic changes due to hypoxemia actually do bring about a disruption of the cellular membrane, *there should be evidence in the plasma.* If there actually is a cessation of protein synthesis, *there should be a decreased concentration of certain proteins.* In actual fact, this evidence does exist and shall be examined.

The evidence that the cell membrane loses its integrity is found in the increased levels of intracellular enzymes measured in the plasma during a shocked state. During a period of hypoxia, increases in lactic acid dehydrogenase, (LAD) serum glutamic oxaloacetic transminase, (SGOT) serum glutamic pyruvate transaminase (SGPT) phosphohexose isomerase, creatine phosphokinase, and malic dehydrogenase have been reported along with an increase in serum proteases, the digestive enzymes of the lysomes. (11, 22)

The fact that nucleotide-specific antibodies are found in the serum implies that nucleotides becomes exposed to the antibody-producing mechanism. *This would not be possible* if the nucleotides remained protected by a functioning cell membrane. (9) This fact reinforces the belief that membrane integrity is lost.



The decrease in protein synthesis is in shock is a bit more difficult to explain with data. If there were a decrease in protein synthesis, there should be a decrease in enzyme levels found in the plasma during hypoxia. This assumes that during a shocked state, the integrity of the cell membrane is disrupted and enzymes are released into the plasma.

The evidence sited above seems to verify this. Since ATP depletion and acidosis are the first manifestations of hypoxemia and since the membrane integrity is dependent on proper pH and ATP supply the integrity (of the membrane) is compromised first. The evidence, however, seems to contradict this; during an episode of shock, there are *increased* levels of enzymes in the blood.

It is all a matter of degree, however. Obviously, if the organism is to survive shock, his cells will have to respond to the stress and overcome the tendency toward complete disfunction. There must be a compensation by the system to enable the destructive processes to be halted and normal metabolism to be reinstated. *It is in this compensation,* then, that there is an *increase* in enzyme production.

There are cases, however, in which shock is not overcome; in which the cellular destruction is so great that compensation cannot take place. When this occurs, *death ensues.* There is a point at which the cellular destruction is so great that, no matter what steps are taken, recovery cannot take place; the damage is irreparable.

Proof that irreversible enzyme inhibition is the actual mechanism of destruction has just begun to accumulate. LaBrosse and his co-workers (4) found that in patients not surviving a shocked state, there were significantly higher levels of seventeen of twenty-five amino acids measured in the serum. This implies a deficient apparatus for the incorporation of amino acids into proteins.

It is interesting to note that there is an *increase* in alanine levels in those patients that die and a *decrease* in those that survive. Since alanine is the amino acid transaminated to pyruvic acid, it can be assumed that its increased levels are due to a failure of GPT to convert to the carbohydrate.

This could be for three reasons: one, there is a large quantity of unused pyruvate because of the decreased use of the Krebs cycle with kinetics, therefore, favoring the alanine form; two, the lack of oxygen has inactivated the transaminase; and three, there is not enough transaminase present because of decreased enzyme synthesis.

Other evidence for the theory that there is decreased enzyme synthesis is seen in the work of Nick. (8) He found that the titers of nucleotide-specific antibody were higher in the survivors of shock than in those succumbing. Since antibodies are proteins and are subject to the same mode of synthesis as enzymes, their diminished amounts in non-survivors adds weight to the evidence.

Swynghedauw *et al* (19) found that malic dehydrogenase (MDH) content of the rabbit myocardium was less after prolonged anoxia than after a period of short duration. They also found that the oxygen level of the system did not have any effect on the release of MDH from the cell. This strongly implies that MDH is produced in diminished amounts during cellular hypoxia.

It has been shown, then, that during a shocked state, because of a pooling of the blood, there is a stagnant hypoxia resulting in the disruption of normal cellular function. If the disruption reaches a certain severity, possibly the point at which the DNA itself is destroyed, the mechanism for enzyme synthesis breaks down, or the lysosomes rupture, there is no hope for survival of the cell.

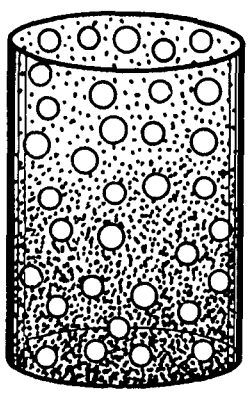
The logical question to ask at this point, then, is if there is any treatment which can be initiated during an episode of shock which will forestall the onset of the irreversible state. It would appear that there is such a treatment.

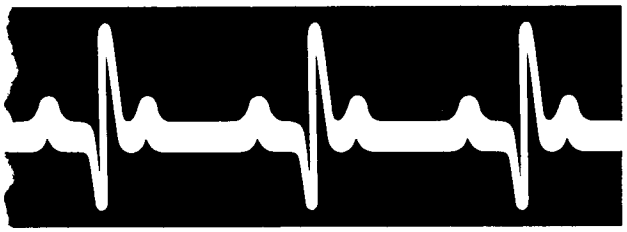
For the past several years, there has been an argument as to whether the hypoxemia caused by vascular pooling is best relieved by vasoconstrictors or by alpha-blockers, agents which open the constricted vascular network. The arguments involved are out of the scope of this essay and will not be reviewed. The point must be made, however, that if recovery is to be secured in shock, there must be a return of oxygen to the cells. In the meantime, certain steps—stop-gap measures—can be taken to protect the cells during the period of hypoxemia.

One suggestion is to inject nucleotides intravenously into the patient in shock. (8) The rationale for this is to overcome the damage wrought by the anti-nucleotide antibodies. This regime is obviously theoretical and has no empiric proof as to its efficacy.

Another suggestion has been to administer ascorbic acid. (3) This substance is thought to preserve the integrity of the cellular membrane and, thus, would forestall the destructive powers of the acidosis and lack of high-energy compounds. (21)

Other compounds suggested are mannitol, low molecular weight dextran, sodium bicarbonate, and buffering agents such as THAM. (5) Mannitol is suggested as a volume expander and as an osmotic diuretic to prevent the kidney from lapsing into oliguria. Low molecular weight dextran is used as a volume expander, in order to improve circulation. Recent work (1) suggests, however, that this compound may do more harm than good in treatment because it stimulates





the tissues to release stored quantities of material which are acid and increase the acidemia. The buffers and bases are used in order to negate the destructive effects of the acidosis.

The compounds which seem to afford the greatest cellular protection in shock, however, are the corticosteroids. Pharmocological doses of these compounds appear to work in a multiple of ways to preserve metabolic function and the integrity of the cell.

Oji and Shreeve (10) showed that cortisone facilitated the conversion of lactate to glucose by inhibiting the oxidation of NADH+ and by changing the catalytic function of some dehyrogenases. This action would tend to relieve the congestion at the pyruvate-lactate level of carbohydrate metabolism and decrease the level of lactate, thereby relieving the acidemia.

Weber *et al* (20) found that increased levels of ACTH (and, therefore, most certainly increased coritsol levels) increased the activities of various enzymes, among them being MDH and lactic dehydrogenase. This effect could be blocked by actinomycin, an inhibitor of protein synthesis, and was thought to indicate that the effect of ACTH addition was as an inducer of *de novo* enzyme synthesis.

Schumer has published a great deal of evidence indicating the beneficial effects of corticosteroids in shock, (13, 14, 15, 16). He found that cortisone increased the activity of the tricarboxylic acid cycle and that it brings about the conversion of lactate to energy pathway intermediates. In addition, corticoids have a vasodilatory effect which helps to initiate movement in the stagnant blood pooled in the intestinal vasculature.

Corticoids also have the effect of initiating the conversion of amino acids and fatty acids into the intermediates of the Krebs cycle i.e. gluconeogenesis, with an increased production of ATP being the result. The effect would be useful if the severity of shock had not reached levels where the machinery for metabolizing this increased quantity of substrate had broken down. If that were the case, the increased amino and fatty acids would just serve as a hinderance to improvement rather than as beneficial agents.

Schumer also states that cortisone protects the lysosomes, preventing their dissolution and the resultant digestion of the internal components of the cell. This action would be of great benefit in advancing shock, allowing for more time to initiate treatment before the onset of irreversibility.

In conclusion, then, shock might be thought of as a spectrum of cellular changes ranging from slowing of carbohydrate metabolism to complete destruction of the cellular integrity. It would appear that the forces causing damage to the cell are found in (1) increased hydrogen ion concentration, (2) decreased availability of high-energy compounds, and (3) interference of regulatory functions by nucleotide-specific antibodies. These three forces modify the enzyme-producing apparatus of the cell and if they damage this mechanism to a certain degree, render the cell incapable of ever recovering from the hypoxic conditions. *Treatment for this condition is, obviously, return of the oxygen supply.* In the meantime, permanent damage may be prevented by the administration of certain substances which negate the effects of the destructive phenomena. In this way, cellular survival is improved with the result that there is prolonged survival of the organism.

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