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ALTERATIONS IN TISSUE METABOLISM (THE LUNG) WITH INJURY AND SHOCK

Termination Report

ARTHUR E. BAUE, M. D.

July 15, 1975

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Washington, D. C. 20314

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Report covering period 1969-1975

Washington University School of Medicine

and

The Jewish Hospital of St. Louis
St. Louis, Missouri 63110

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We have demonstrated that with circulatory failure in various organs, particularly the liver, kidney and muscle, that the initial change is an alteration in the membrane of the cell with the decreased cell membrane potential and with an alteration in cation transport and in responsiveness to various hormonal substances. Sodium then tends to enter the cell, water also enters, potassium tends tl leak out, $Na^+ + K^+$ -ATPase is activated, ATP is progressively used up, mitochondria are stimulated, cyclic AMP tends to decrease, further sodium gets into the cell and there is progressive cell swelling, there is mitochondrial swelling (cont.)

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and the endoplasmic reticulum swells. As this occurs, there seems to be alteration in the ability of insulin, glucagon and perhaps catecholamines and corticosteroids to exert their efforts upon the cell population. Metabolic capability further decreases, less ATP is produced, the glycolytic reactions may continue but oxidative metabolism is depressed, further deterioration occurs, and finally as an end stage result lysosomes leak and the cells are eventually destroyed. Toxic factors may then affect cell population in the same organ or elsewhere. We have demonstrated that these changes do not take place early on at least in the lung, supporting the concept that severe shock, per se, does not produce gross damage to the lung and is maintained for a considerable period of time. This, of course, then has focused efforts on post-traumatic pulmonary insufficiency toward other factors involved in this clinical syndrom. These, of course, are now being solved so this problem is less difficult than it once was, particularly during the recent Vietnam conflict. Details of the various findings and publications follow in the body of this report.

SUMMARY

The responsible investigator, Arthur E. Baue, M.D., is pleased to present this termination report representing a report of research carried out under Contract with the United States Army Medical Research and Development Command and the Jewish Hospital of St. Louis and Washington University School of Medicine. The termination of the contract is necessitated by the responsible investigator having accepted a position as Professor and Chairman of the Department of Surgery of the Yale University School of Medicine in New Haven, Connecticut, a position which he will assume in August of 1975. A new contract proposal for continuation of this work has been submitted from Yale University by the responsible investigator, Dr. Baue, to the U. S. Army Research and Development Command.

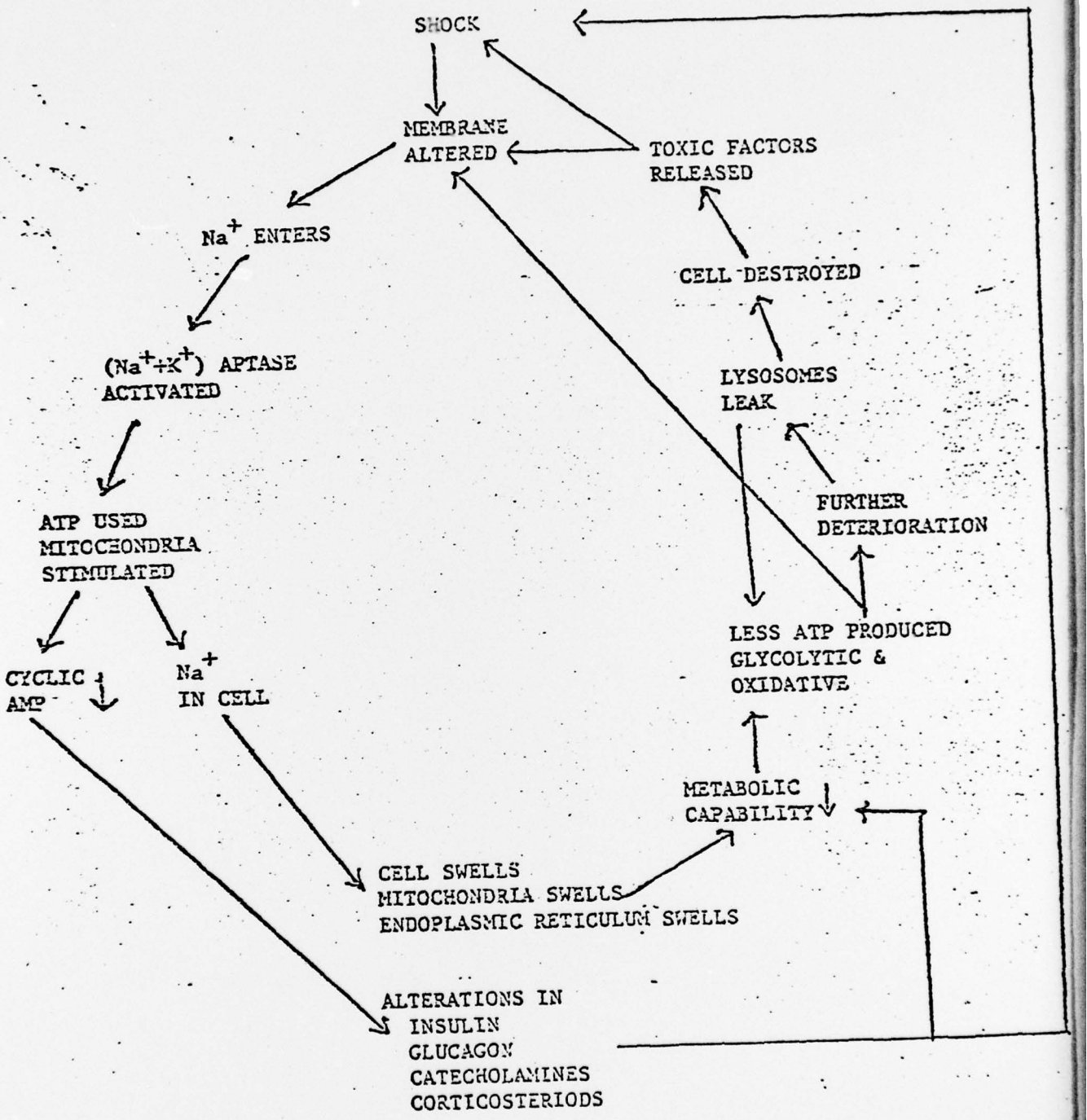
The thrust of research carried out under these contracts has been the study of the effects of injury and shock on individuals and biologic organisms and has been, therefore, directly relevant to injured individuals and particularly combat casualties. In such studies of tissue metabolism, particularly of the lung, but of other organs with injury and shock, we have developed a better understanding of the problems attendent to it and these are beginning to lead to better methods of management, resuscitation, treatment and survival. The significance of this work, therefore, has been that basic biologic information about injury has been developed which is now beginning to lead to a better understanding of the problems of circulatory failure and better approaches to treatment. We have, of course, approached the problem of the combat casualty in a very basic way by the study of cell function after injury or shock. This laboratory is one of the few in the country which is studying tissue injury on such a basic level, particularly as related to circulatory failure or shock. This has combined the efforts of basic scientists and biochemistry and physiology. Ultimately the function and survival of an injured individual is dependent upon satisfactory function of his various organ systems and these in turn are dependent upon the function of the various cells making up that organ. We have during the period of these contracts developed a concept of progressive cell injury with shock, have determined some of the early changes and are now further evaluating methods to combat these changes. It is difficult in such basic investigation of tissue injury and cell injury to predict how quickly useful information and basic models can be brought into clinical areas and out into the field. What often happens, however, as such basic information is developed is that it becomes crystallized in clinical thinking and provides for better input into clinical evaluation and care. In this summary, only the highlights of basic biologic research in trauma will be given. Following, however, in the body of the report as exserted from previous annual reports are details of the findings and publications resulting from this contract support over the years. Our initial hypotheses are now being upheld by the work of others and further details are being provided. The basic hypothesis which we have developed for progressive alteration in cell and, therefore, organ function with shock is shown. (See diagram next page)

Highlights of this work include:

1. Basic information about energy levels and cell membrane transport of the lung.

2. Energy levels of the liver and the kidney and various effects of administered ATP and ATP degradation and uptake of ATP by tissues.

HYPOTHESIS



3. Relationships of NAD and NADH and survival.

4. Studies of cell membrane potential and cation transport in the liver.

5. Hormonal effects on cell membrane prostheses, particularly the effects of insulin and insulin resistance.

6. The effect of glucocorticoids on sugar transport.

7. Decreased protein synthesis with circulatory failure.

8. The hemodynamic effects of ATP-MgCl infusion.

9. Demonstration that hemorrhagic shock in animal models does not produce serious pulmonary damage, drawing attention to the concept that there is probably no such thing as 'shock lung' per se.

10. Decreased energy levels and depression of all adenine nucleotides with hemorrhagic shock.

11. Alterations in active transport of Na and K in the liver and kidney with shock.

12. Depressed mitochondrial function with severe shock, particularly in the liver and kidney with other alterations in mitochondrial function, particularly some uncoupling and inability to utilize certain substrates.

13. Activation of the transport enzyme system $Na^{+}+K^{+}$-ATPase with shock.

14. The beneficial effects of ATP-MgCl infusion in hemorrhagic shock, suggesting utilization of high energy phosphate bonds to provide energy needs for cells.

Thus, in summary, we have demonstrated that with circulatory failure in various organs, particularly the liver, kidney and muscle, that the initial change is an alteration in the membrance of the cell with the decreased cell membrane potential and with an alteration in cation transport and in responsiveness to various hormonal substances. Sodium then tends to enter the cell, water also enters, potassium tends to leak out, $Na^{+}+K^{+}$-ATPase is activated, ATP is progressively used up, mitochondria are stimulated, cyclic AMP tends to decrease, further sodium gets into the cell and there is progressive cell swelling, there is mitochondrial swelling and the endoplasmic retriculum swells. As this occurs, there seems to be alteration in the ability of insulin, glucogon and perhaps catecholamines and carticosteroids to exert their effects upon the cell population. Metabolic capability further decreases, less ATP is produced, the glycolytic reactions may continue but oxidative metabolism is depressed, further deterioration occurs, and finally as an end stage result lysosomes leak and the cells are eventually destroyed. Toxic factors may then effect cell population in the same organ or elsewhere. We have demonstrated that these changes do not take place early on at least in the lung, supporting the concept that severe shock per se does not produce gross damage to the lung and is maintained for a considerable period of time. This, of course,

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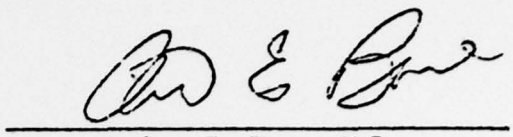

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