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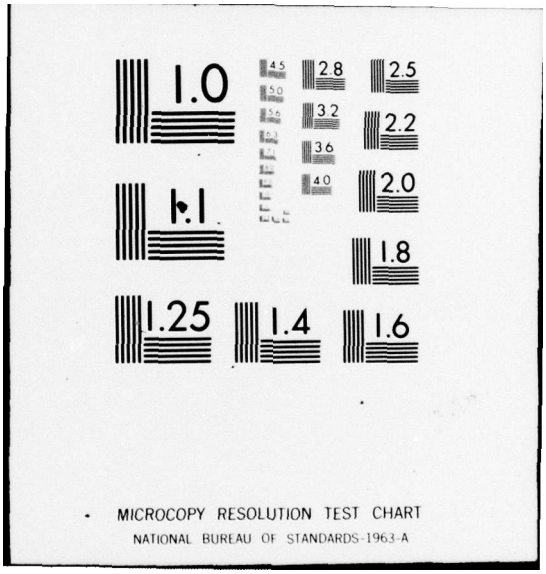
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ALTERATIONS IN TISSUE METABOLISM (THE LUNG) WITH INJURY AND SHOCK

Annual Summary Report

ARTHUR E. BAUE, M.D.

July 15, 1974

Supported by

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There has been exciting progress in the past year, particularly in the areas of membrane transport and energy metabolism and replenishment which have been supported by the present contract.

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Recent progress can best be summarized by citing the publications from our laboratory supported by the previous year's contract:

a. Baue, A. E. : The Energy Crisis in Surgical Patients. Arch. of Surg. In Press.

b. Malik, A. B., Baue, A. E., Geha, A. S. and Chaudry, I. H.: Regional Distribution of High Energy Phosphates in the Heart. Proc. Soc. Exp. Bio. Med. In Press.

c. Randall, G. R., Sayeed, M. M., Chaudry, I. H. and Baue, A. E.: Protein Synthesis by Rat Liver Slices in Hemorrhagic Shock. Fed. Proc. 33:318, 1974 (Abstract).

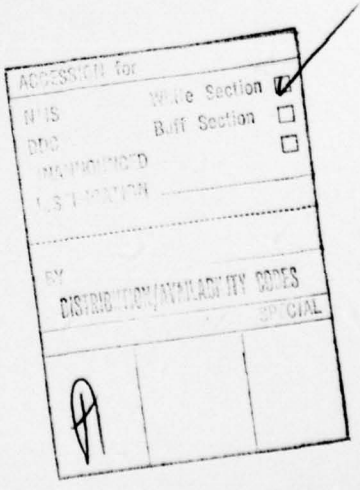
d. Chaudry, I. H., Adzick, N. S., Fishman, L. J., Planer, G. J., Sayeed, M. M. and Baue, A. E. : The effect of Insulin on Glucose Uptake in Soleus Muscle of Adrenalectomized Rats in Shock. Fed. Proc. 33: 261, 1974 (Abstract).

e. Chaudry, I. H. , Sayeed, M. M., and Baue, A. E. : Effect of Adenosine Triphosphate-Magnesium Chloride Administration in Shock. Surgery, 75: 220-227, 1974.

f. Baue, A. E., Sayeed, M. M., Chaudry, I. H., and Wurth, M. A. : Cellular Alterations with Shock and Ischemia. Angiology, 25: 31-42, 1974

g. Chaudry, I. H., Sayeed, M. M. and Baue, A. E. : Depletion and Restoration of Tissue ATP in Hemorrhagic Shock. Arch. Surg., 108: 208-213, 1974.

h. Wurth, M. A., Sayeed, M. M. and Baue, A. E.: Nicotinamide Adenine Dinucleotide (NAD) Content of Liver with Hemorrhagic Shock. Proc. Soc. Expl. Biol. Med., 144: 654-58, 1973`.



i. Chaudry, I. H., Planer, G. J., Sayeed, M. M., Baue, A. E.: ATP Depletion and Replenishment in Shock. Surgical Forum, XXIV: 77, 1973.

j. Baue, A. E., Wurth, M.A., Chaudry, I. H., and Sayeed, M. M.: Impairment of Cell Membrane Transport During Shock and After Treatment. Annals of Surgery, 178: 412-422, 1973.

k. Gaha, A., Abe, T., Chaudry, I., Malik, A., O'Kane, A., and Baue, A. E. : Metabolism of High-energy Phosphate Compounds in Stable Hypertrophied Myocardium. European Surgical Research, 5: 14, 1973, Supl. 2 (Abstract).

l. Sayeed, M. M., Hass, M., Chaudry, I. H., Wurth, M. A., and Baue, A. E. : Cation Transport by Rat Liver Slices in Hemorrhagic Shock. The Physiologist, 16: 441, 1973 (Abstract).

m. Chaudry, I. H., Sayeed, M. M. and Baue, A. E.: Beneficial Effects of ATP- $MgCl_2$ Infusion in Shock. Can.Fed. Biol. Soc., 16: 45, 1973 (Abstract).

n. Chaudry, I. H. and Baue, A. E.: The Effect of Low ATP on Glucose Uptake in Soleus Muscle During Hemorrhagic Shock. Proc. Soc. Expt. Biol. Med., 144: 321-325, 1973.

o. Sayeed, M. M. and Baue, A. E. : Na-K Transport in Rat Liver Slices in Hemorrhagic Shock. Amer. J. Physiol., 224: 1265, 1973.

p. Meyers, J., Meyer, J.,and Baue, A. E. : Does Hemorrhagic Shock Damage the Lung? J. Trauma, 13: 509-519, 1973.

The principal findings of the past year will now be summarized.

a. Continued studies of the lung with shock have been carried out. A method has been developed for measuring cation transport or cell membrane transport of sodium and potassium in the lung from animals in shock. It is found that even in late, prolonged shock, membrane transport in the lung for sodium and potassium remains at a reasonably normal level. This is in marked contrast to the liver where cell membrane transport for sodium and potassium is practically non-existent in late or severe shock, indicating a severe problem of cell membrane transport. This does not seem to occur in the lung. Reasons for this were sought and initial measurements were made of energy levels, particularly of the adenine nucleotides in the lung and liver. Energy level in the lung was found to be normal, whereas in the liver evergy levels had greatly decreased. Thus, there is a correlation between maintenance of membrane transport and normal energy levels, since the lung maintains these and the liver does not. Thus, again as with other previous studies from our laboratory, we find that lung tissue

metabolism or cellular metabolism is maintained quite satisfactorily in shock, whereas other organs such as the liver and kidney deteriorate rapidly. This adds further evidence to our concept that post-traumatic pulmonary insufficiency or pulmonary problems after injury are related to other factors rather than the primary insult of shock or injury on the lung. These other factors include fluid resuscitation, embolism, the possibility of toxic factors, aspiration and many other factors. By continuining to provide evidence that shock per se does not seriously damage the lung, although it may make it susceptible to further injury it makes it possible to develop concepts of prevention of post-traumatic pulmonary insufficiency by looking in detail at those clinical factors which seem to enter its production.

b. Studies of tissue energy levels and energy metabolism. We have made considerable progress in this area, going on from out intital finding of a great reduction in evergy levels of adenine nucleotides in liver, kidney and skeletal muscle during shock. Some of thsee results have been very exciting and predict very real possibilities for considerable progress in the future. First, we have documentaed that with treatment of shock by volume replacement with blood and Ringers lactate solution the energy levels of the various phosphate bonds are provided as ATP given with magnesium chloride, then the energy levels in the tissues are rapidly restored to normal. However, if high energy phosphate bonds are provided as ATP when infected intravenously from being complexed or chelated with calcium or magnesium within the vascular system. Whether or not the injected ATP actually provides energy, whether it has a surface effect on the cells, or whether is acts on the microcirculation is not well understood as yet. This is discussed in a little more detail in my review of the energy crisis in surgical patients which will soon be published in the Archives of Surgery and a copy of which is enclosed.

   We then went on with a study of survival following infusion of ATP-$MgCl_2$ in shocked rats and found that survival was increased from 0 to 70-80% when ATP-$MgCl_2$ was given after a prolonged period of shock. Again the exact effect of this administration has not yet been determined, but ongoing studies should provide information as to exactly how this agent is acting. A major thrust of the present contract proposal is to further study these effects and potential clinical application.

c. Further studies of alteration is cell membrane transport have been carried out. A correlation of alteration in membrane potential and alterations in transport has been completed and is being prepared for publication. Further studies of reversibility of this phenomonon with treatment programs have been carried out indicating that cell membrane transport returns more slowly toward normal and that this may be a limiting factor in the ability of the cell to compensate after treatment.

d. We have been the first to demonstrate that there is decreased responsiveness of peripheral tissues to insulin during shock. This helps to explain the hyperglycemia and diabetic tendency which occurs after severe injury.

Further work has been completed on alterations in insulin effect on the msucle and glucose transport during hemorrhagic shock. Hemorrhagic shock in adrenalectomized rats was produced by bleeding the animals to a mean arterial pressure of 40mm Hg which was maintained for one and one-half hours. Basal glucose uptake by isolated soleus muscle from normal adrenalectomized animals and adrenalectomized animals subjected to hemorrhagic shock increased with the increase in medium glucose concentration and uptake values were similar in both groups of muscles. This indicated again that shock per se did not produce any damage or alteration in the basal glucose carrier mechanism. Whereas, both anoxia and insulin (o.1 U/ml) increased glucose uptake in adrenalectomized control muscles, anoxia but not insulin increased glucose uptake in shock muscles was observed in an insulin concentration of 0.2 U/ml. These experiments indicate that insulin response in tissues is altered in shock. This could be due to conformational changes produced in the muscle membrane during shock, but does not seem to be due to an increase in catecholamines or adrenal steriods which are produced by shock.

e. We have completed an initial study of evaluating protein synthesis with circulatory failure and have found a 50-60% decrease in protein syntheses. These studies are being completed and could have potential significance for the regeneration and replenishment of various enzyme systems in the cell.

f. Studies have now been initated of the overall hemodynamic and toxic effects of ATP-$MgCl_2$ infusions in large animals, initiallyin the dog, preparatory to considering this possibility for therapy. It will probobly be necessary to have a prolonged series of hemodynamic and toxic studies in dogs first, followed then by primate studies before considering the possibility of applicability of these approaches of energy replenishment in man.

Thus, in summary, there has been exciting progress in the past year, particularly in the areas of membrane transport and energy metabolism and replenishment which have been supported by the present contract.

Reprints or copies of the manuscripts of these publications are enclosed for review. In addition, two abstracts have been submitted to the Surgical Forum for the present year and a number of papers are being prepared for submission for publication. Also, we have participated in a number of programs in which the work supported by this contract has been presented. This includes a Symposium on Cell Injury with Shock in Scottsdale, Arizona, the presentation of a course to the American College of Obstetrics and Gynecology on Shock, the program of the Southern Illinois Chapter of the American College of Surgeons with presentations on Shock, development of a program on Shock and Circulatory Failure for the Ohio Chapter of the American College of Surgeons, lectures on Shock to the Arkansas Chapter of the American College of Surgeons, and various other programs related to Shock.

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