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Discussion

Dr. William D. Holden (Cleveland): Doctors Nick and Dodd have entered an unusually difficult but very likely rewarding field of endeavor. The cellular biology of lethal shock is an almost totally untrammeled area and yet it is only here within the cell that the ultimate answers to the pathophysiology and distorted metabolism of lethal shock will be found. The observations made by the authors suggest that in shock nuclear DNA or its component nucleotides antigenically induce the formation of specific antibodies that are carried predominately in the 19S fraction of globulin and to a lesser extent in the 7S fraction. The ultimate course of the patients with antibodies related to guanine and cytosine was favorable whereas those with thymine specificities had less satisfactory courses. It is difficult to explain these observations and it is obvious that very complex biological phenomena are taking place. The technic of inhibition of agglutination is excellent and was used for the nucleotide bases. I could find, however, in the manuscript no mention of DNA itself being used in the patient's serum to attempt to qualify the extent of antibody formation.

There is so much of importance in the concept of a state of autoimmunity induced by DNA in shock that it would be highly desirable to test the hypothesis with more than one technic. The use of radioactive nucleotides and equilibrium dialysis with globulin would demonstrate the presence or absence of actual binding. The fractionation of the 7S globulin into F_{ab} and F_c fractions would permit identification of antigenic binding if true autoimmunity exists. In experimental animals, passive transfer studies could throw some light upon these phenomena. Since endotoxin has become such an important consideration not only in septic shock but possibly in hypovolemic shock, the use of E. coli DNA in place of calf thymus DNA to establish the DNA-benzidine-erythrocyte antigen might be a profitable pursuit.

It would appear important before the concept of DNA autoimmunity is prematurely seized upon and especially before nucleotide therapy is proposed for patients in shock that every technic be employed to establish unequivocally the specific nature of this process and that we are not observing some other non-specific phenomenon that is influenced by the presence of DNA, its nucleotides, or endotoxin.

The work is exciting to say the least, and we should all be pleased to see one of the most complex biological problems surgeons must deal with being attacked in a sophisticated investigative fashion by a young surgeon. Thank you. (Applause)

Dr. Fraser N. Gurd (Montreal): Mr. President, I was grateful for the opportunity to see the manuscript in advance, and would certainly like to reiterate Dr. Holden's compliments to the authors.

The approach which Dr. Nick has taken represents a most interesting attempt to explain the wide dissemination of organ damage which we are learning to recognize as a syndrome which may follow severe shock.

Our own approach has led us to favor the view that the fundamental metabolic handicap in the intestinal mucosa, to which we have assigned a certain primacy, is in the area of energy metabolism. The production of ATP and oxidative phosphorylation represent the initial areas of depression so far as we have been able to show.

Nevertheless, the creation of a deficiency of essential specific factors by immunological interference could indeed halt a necessary step in biosynthesis. Dr. Nick's concept is particularly exciting, because deficiencies can be treated when the time and place for the specific replacement therapy can be recognized.

What detrimental emanations could flow forth from tissues in the process of necrobiotic disin-

tegration? Certainly the flooding of the body by antigenic materials is a very real possibility. Drs. Sutherland and Bounous have some evidence of an enterolymphatic release of lysosomal enzymes from the intestinal epithelium during the early stages of necrobiosis in shocked animals.

May I ask Dr. Nick in conclusion if he could say a word as to what evidence he or others might have concerning the possibilities for the therapeutic replacement of nucleotides affected in an antigen-antibody reaction. Particularly, are the dosages which would be needed in a practical range? I enjoyed this paper very much indeed.

DR. W. V. NICK (Closing): I wish to thank the discussants for their comments.

I would like to say in closing that we have initially characterized this antibody in a multiplicity of ways. We are currently investigating means to detect its origin and mode of production to determine whether this results from an antigenic stimulus, a release of preformed antibody, or a biochemical alteration in circulating gamma globulins.

The DNA which we used in these experiments differs slightly from that of the living cell, in so far as its percentage composition of cytosine, guanine, adenine, and thymine.

Our rationale for the investigation of nucleotides in the treatment of shock is based upon the possible effects of nucleic acid antibodies, studies by Sharma and Eiseman indicating that adenosine triphosphate has a protective effect in hemorrhagic shock, and our observations that the use of nucleotides in hemorrhagic and septic shock in primates seems to give us recoveries when we would expect 100 per cent mortality. (Applause)

Book Reviews

Peripheral Arterial Disease. Volume IV in the Series Major Problems in Clinical Surgery. WILEY F. BARKER, M.D., J. ENGLEBERT DUNPHY, M.D., Consulting Editor, Philadelphia, W. B. Saunders Co., 1966. 229 pp. $8.50.

A SHORT 229-page book on the surgical treatment of peripheral arterial occlusive disease written by an expert in the field. The text is largely an account of personal experiences with various operative methods of treatment, examples of occlusive lesions cited by brief case histories, and analyses of results achieved by the author and results published in reports. Index, bibliographic references, and illustrations are good. The book is excellent reading for surgeons and an authoritative reference for all physicians.

Viruses Inducing Cancer Implications for Therapy. Edited by WALTER J. BURDETTE, A.B., A.M., PH.D., M.D., University of Utah Press, 1966. Salt Lake City, Utah. 498 pp.

THIS attractively printed and bound volume is based on a conference of some eighty scientists interested in viral etiology of cancer. About thirty short papers on many aspects of the subject and a well-edited transcription of question and answer discussion are presented. Extensive bibliographic references and an author and subject index make the book valuable for those interested in this important field.