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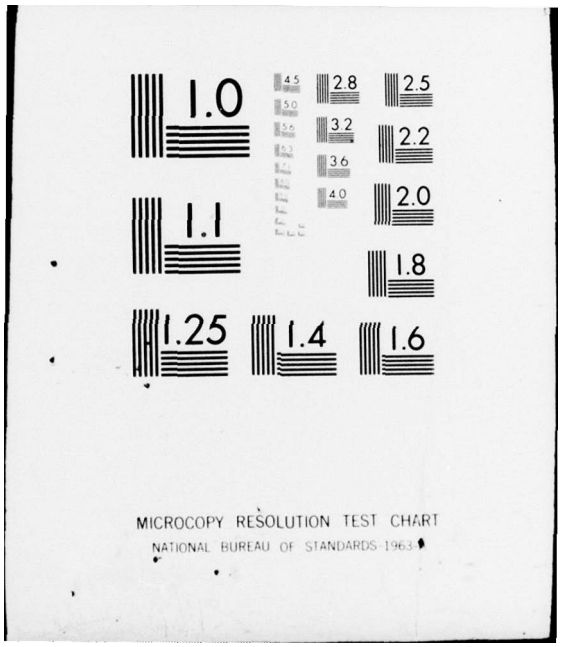
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Investigation of Immunoregulatory Alphaglobulin (IRA)

Annual Report

October 1975

By

John A. Mannick, M. D.

Supported by

U. S. Army Medical Research and Development Command
Washington, D.C. 20314

Contract No. DA 49-193-MD-2621

Boston University Medical Center
University Hospital
Boston, Massachusetts 02118

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER

2. GOVT ACCESSION NO.

3. RECIPIENT'S CATALOG NUMBER

4. TITLE *(and Subtitle)*
(6) Investigation of Immunoregulatory Alphaglobulin (IRA).

5. TYPE OF REPORT & PERIOD COVERED
(9) Annual Report. 1974-1975

6. PERFORMING ORG. REPORT NUMBER

7. AUTHOR(s)
(10) John A. Mannick, M. D.

8. CONTRACT OR GRANT NUMBER(s)
(15) DA-49-193-Md-2621

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Boston University Medical Center
University Hospital
Boston, Massachusetts 02118
(12) 44

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
62110A
(16) 3A162110A821 00.041

11. CONTROLLING OFFICE NAME AND ADDRESS
US Army Medical Research and Development Command
Washington, D. C. 20314

12. REPORT DATE
(11) October 1975

13. NUMBER OF PAGES
6

14. MONITORING AGENCY NAME & ADDRESS *(if different from Controlling Office)*
(12) 4p.

15. SECURITY CLASS. *(of this report)*
Unclassified

15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT *(of this Report)*
Approved for public release; distribution unlimited

17. DISTRIBUTION STATEMENT *(of the abstract entered in Block 20, if different from Report)*

18. SUPPLEMENTARY NOTES

19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

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SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)* AB

During the past year with the support of this grant, we have fractionated the immunosuppressive peptide (resembling the IRA-peptide) obtained from the serum of traumatized patients. G25 Sephadex gel filtration is use as the initial step in this fractionation. The active material is usually recovered in the third peak from the G25 column. This material has been further purified by preparative high voltage electrophoresis. It is apparent that most, if not all, of the immunosuppressive activity in this peptide fraction is contained in a single polypeptide moiety resolved by high voltage electrophoresis at the basic end of the electrophoresis pattern. This area we have called spot 10 is exactly the same area in which immunosuppressive activity has been purified from normal serum and from the serum of cancer patients by preparative high voltage electrophoresis in our laboratory. A tentative amino acid composition has been determined for this pure peptide from normal serum and from cancer serum. We have not yet obtained amino acid composition of the peptide prepared from trauma serum. However, its identical electrophoretic behavior suggests that it is very similar to, if not identical with, the peptide obtained from normal serum. The peptide from normal and cancer serum has a single N-terminal, lysine.

During the past year we have also studied more patients who have undergone various degrees of trauma and have found that the levels of immunosuppressive peptide and the persistence of the peptide in the serum of these patients correlates with the clinical course of these individuals. Patients suffering major trauma with complications, particularly septic complications, have persistently

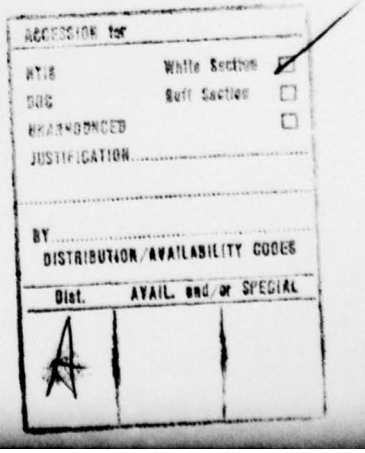
high levels of this activity for days or weeks. Those suffering uncomplicated trauma have high levels of suppressive peptide activity for 24 to 72 hours only. The degree of serum suppressive activity is also correlated with the degree of trauma as indicated by the fact that about 60% of the patients undergoing moderate trauma have suppressive serum whereas 90% of those subjected to severe trauma have suppressive serum and the degree of lymphocyte suppression by these sera is in general higher. It should be emphasized that serum suppression, as defined in these experiments, has always occurrred without any evidence of lymphocyte cytotoxicity as indicated by Trypan blue exclusion.

During the past year, we have also studied the responsiveness of lymphocytes from patients who have suffered major truama to PHA stimulation in vitro. As anticipated, the lymphocytes from such patients are ordinarily hyporesponsive to PHA as compared with control lymphocytes from normal individuals even when incubated in the same normal reference serum. However, we recently have found that when lymphocytes from traumatized patients are washed six times as opposed to one or two times prior to culture with PHA the responses return toward or to normal. Thus, it appears that one reason for the hyporesponsiveness of peripheral blood lymphocytes reported by a number of workers following traumatic injury is likely to be due to lymphocyte surface coating with a substance that can be removed by multiple washings with tissue culture medium.

During the past year, we have also performed initial studies in CD-1 mice to determine the effect of suppressive peptide from

trauma serum on the resistance of these animals to infection with Listeria organisms. Initial experiments have shown that the administration of trauma peptide 3.0 mg. intraperitoneally to mice at the time of innoculation with a borderline lethal dose of Listeria will produce an 80% mortality in the treated mice as opposed to 20% mortality in the untreated mice and those injected with normal human serum protein. This is the first direct confirmation that this peptide material interferes with the ability of mammals to ward off infection with bacterial organisms. Since it is well known that T lymphocyte function is necessary for resistance to virus and fungal invaders, these studies suggest that a wide spectrum of infectious complications might be increased in the presence of high circulating levels of this IRA-like peptide.

Finally during the past year we have, partially with the support of the contract, studied the serum of a number of individuals with advanced cancer and have discovered that in these individuals as well one can detect high levels of a circulating IRA-like peptide and that at the presence of high levels of this peptide is associated with clinical anergy as determined by failure to react to standard skin test antigens and the ability to be sensitized to DNCB.



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