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PREVENTION OF HEMOGLOBINURIC NEPHROSIS.(U)
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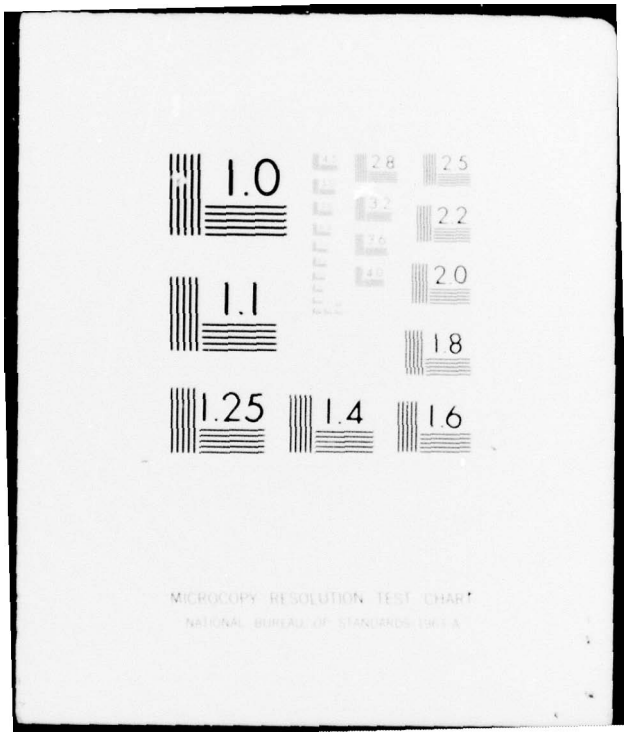
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(6) PREVENTION OF HEMOGLOBINURIC NEPHROSIS.

(9) Final Scientific Report.
1 February 1973-31 May 1975

(10) Peter V. Sacks, M.D.
Scripps Clinic and Research Foundation
La Jolla, California

(11) April 1977

(12) 6p.

(15) DADA17-73-C-3041
Supported by

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

-17-
Contract No. DADA-73-C-3041

1473

410 373

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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)

PREVENTION OF HEMOGLOBINURIC NEPHROSIS

5. TYPE OF REPORT & PERIOD COVERED
Final Scientific Report
2/1/73 to 5/31/75

6. PERFORMING ORG. REPORT NUMBER

7. AUTHOR(s)

Peter V. Sacks, M.D.

8. CONTRACT OR GRANT NUMBER(s)
DADA-17-73-C-3041 new

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Division of Hematology-Oncology New
Scipps Clinic and Research Foundation
10666 N. Torrey Pines Road
La Jolla, CA 92037

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS

11. CONTROLLING OFFICE NAME AND ADDRESS
Scripps Clinic and Research Foundation
10666 N. Torrey Pines Road
La Jolla, CA 92037

12. REPORT DATE
April 1977

13. NUMBER OF PAGES
3

14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)

15. SECURITY CLASS. (of this report)

15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

4 copies HQDA
12 copies Defense Documentation Center
1 copy Superintendent, Academy of Health Sciences, US Army
1 copy Dean, School of Medicine, Uniformed Services University of the Health Sciences

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

Same as above

18. SUPPLEMENTARY NOTES

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

Hemoglobinuria
Hemoglobinuric nephrosis
Plasma hemoglobin
Paroxysmal nocturnal hemoglobinuria

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

Intravenous injection into rabbits, baboons and humans of large volumes of hemoglobin (in frozen-thawed blood) caused hemoglobinuria without any evidence of renal disturbance, nor was there evidence of clinically significant disseminated intravascular coagulopathy (DIC). The rate of urinary hemoglobin excretion was determined. In the baboon, the simultaneous injection of dextran solution did not modify the rate of (cont on #1473B)

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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

20. (Abstract continued: P 1473A)

hemoglobin excretion. In one patient with nocturnal hemoglobinuria, infusion of dextran solution was associated with decreased hemoglobin excretion.

1473B

Contract Number: DADA-73-C-3041

PREVENTION OF HEMOGLOBINURIC NEPHROSIS - Peter V. Sacks, M.D.

FINAL SCIENTIFIC REPORT

1973-1974

Human studies on the efficacy of dextran infusions for the prevention of experimentally induced hemoglobinura were deferred upon instruction from the Army Investigational Drug Review Board pending the outcome of preliminary experiments on two animal species.

Rabbit experiments were performed first, to standardize procedures and methods. We found no evidence of DIC (disseminated intravascular coagulation). The dextran had no effect on tests for DIC, or on the clearance of plasma hemoglobin. The urinary sediment showed no abnormality.

In baboons, coagulation studies showed a moderate, although significant, fall in platelet count with prolongation of the partial thromboplastin time following the infusion of autologous hemolyzed whole blood, and shortening of the thrombin time after dextran infusion. Fibrin split products developed in 4 of 5 experiments after hemolysate injection, with the suggestion of a facilitated response when dextran was infused prior to the hemolysate. We concluded from these studies that the induction of acute experimental hemoglobinemia in baboons using autologous hemolyzed whole blood resulted in the development of mild DIC, and that a preliminary infusion of 70,000 $M\bar{w}$ dextran may facilitate the development, or impede the clearance, of fibrin split products. None of these changes approached levels of clinical significance so that the response, when it occurred, could be classified as mild, subclinical, DIC.

Prior to the granting of the contract we undertook standardization of the experimental model in human subjects. Autologous, stroma-containing, hemoglobin solutions were prepared by freezing and thawing whole blood and the resulting lysates were infused into ourselves and other human volunteers. In other experiments hemoglobinuria was induced by the rapid injection of small volumes of distilled water. None of these procedures induced untoward symptoms. Replicate testing after induction of hemoglobinemia-hemoglobinuria in human subjects demonstrated no evidence of DIC. Urinary sediments remained normal throughout. We concluded from this, and from the work of others who have done similar experiments in humans, that the induction of hemoglobinuria with autologous hemolyzed red cells produces no DIC, renal damage or unpleasant side-effects.

We performed in vitro experiments with dextran and hemoglobin using column chromatography, cellulose-acetate electrophoresis and membrane ultrafiltration, but were undable to demonstrate complex formation between the two molecules.

1974-1975

On instruction from the Army Investigational Drug Review Board, experiments designed to examine the effects of 6% Dextran-70 on induced hemoglobinemia and hemoglobinuria in normal human subjects were again deferred. The Board was concerned by the proposal to use autologous stroma-containing hemoglobin solutions (whole blood lysates) in these studies. A subjsequent opinion of the Board (reported to us verbally by Maj. B. Brient on 30 May 74 indicated that the use of autologous stroma-free hemoglobin solutions to induce hemoglobinuria would be permitted. The study protocol was redesigned to use autologous, stroma-free hemoglobin solutions to induce hemoglobinuria. Because the production of such stroma-free hemoglobin solutions requires considerable processing, it was questioned whether such solutions should be classified as a "drug" therapy requiring permission from the AIDRB for use as an 'Investigational New Drug'--even though these autologous solutions were to be used to gather experimental data and not for therapeutic evaluation. We await a ruling by the AIDRB on this point and have been obliged to defer these studies.

A single patient with paroxysmal nocturnal hemoglobinuria (PNH) was given 6% Dextran-70 in saline on two separate occasions during phases of active hemoglobinuria. Simultaneous measurements of plasma hemoglobin levels and urine hemoglobin output (mg/min) were made before, during and after the infusion of dextran. Dextran was rapidly effective in halting hemoglobinuria on both occasions. It is not clear whether this effect is mediated at the level of reducing intravascular hemolysis of PNH cells or through an effect on the renal clearance of plasma hemoglobin. Further patients with active PNH need to be studied to establish dextran's mode of action. Such patients are difficult to come by.

Pending clarification of the status of our studies on induced hemoglobinuria in normal human subjects, we initiated further experiments in rabbits in an attempt to develop a satisfactory animal model for chronic intravascular hemolysis. We showed that adaptation of ultrasound and wire wool-containing prostheses to extracorporeal arterio-venous shunts in rabbits did not provide satisfactory models for this purpose.

Publications

1. Spector, J.I., Wilson, C.B., and Crosby, W.H.: Coagulation studies and correlative histology during experimental hemoglobinemia in rabbits. Am. J. Path. 74:567, 1974.
2. Spector, J.I. and Crosby, W.H.: Coagulation studies during experimental hemoglobinemia in humans. J. Appl. Physiol. 38:195, 1975.
3. Spector, J.I., Lang, J.E. and Crosby, W.H.: Coagulation changes in baboons during acute experimental hemoglobinemia and dextran infusion. Am. J. Path. 78:469, 1975.

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