

Plasma Substitutes Program
Progress Report

REPORT ON THE MACRODEX EXPERIMENT

I. BACKGROUND

Many thousand infusions of Swedish Dextran (Macrodex) have reportedly been administered to individuals of the Swedish population with a very low reaction rate. Lt. Colonel Edwin Pulaski of the Surgical Research Department of Brooke General Hospital has recently reported adverse reactions in convalescent Korean veterans given intravenous Macrodex. During a recent visit to Brooke General Hospital, Doctor Everett Idris Evans personally observed a number of adverse reactions to intravenous Macrodex during a clinical test sponsored by Lt. Colonel Pulaski.

Several of these reactions were considered by Doctor Evans to be so severe as to be truly alarming.

Although Lt. Colonel Pulaski's experience with Swedish Dextran (Macrodex) had been known for some months, it is fair to state that most investigators in this field have tended to underestimate its importance. (This was certainly true of our group at the Medical College of Virginia.) This was probably true because in the experience of Doctor Ravdin and Doctor Evans, working with civilians, the reaction rate to Swedish Dextran (Macrodex) has been very low.

With this simple background, (a high reaction rate in Pulaski's experience with Korean veterans, a low reaction rate in the Ravdin-Evans' experience with civilians), it appeared advantageous to point up this problem by giving Swedish Dextran (Macrodex) to a similar group of Korean veterans at Walter Reed Hospital. This report deals with that experiment.

II. MATERIAL USED AND PROCEDURE

Approximately thirty (30) ambulatory patients of the Forest Glen section of the Army Medical Center volunteered for the experiment after a preliminary explanation by their Executive Officer of the importance of the experiment. On Friday morning, 23 March 1951, Doctor Everett Evans personally explained to the volunteers the purpose of the experiment and something of the nature of the type of reactions that might develop. Thirteen men were picked at random from the group of volunteers with a special effort to select Korean veterans. The men were transported to the main section of Army Medical Center and ten of the thirteen put to bed, side by side, in the same room. Their lunch was omitted. Temperature, pulse, respiration and blood pressure were recorded prior to beginning the infusion.

Approximately 5.0 cc of blood was drawn from an antecubital vein through a twenty (20) gauge needle and an infusion of 500 cc of Macrodex, (Lot Y5740A) begun through the same needle at a rate of approximately twenty (20) to thirty (30) drops per minute. The actual work was performed by Captain Herman Nachman, M.C., Doctor Helge Heisto, and Doctor Everett Evans, assisted by 1st. Lt. Mulligan, ANC. In addition to those mentioned above the following persons were present: Doctors Sloan, Lawrason, and Turino of the National Research Council and Doctor Frank Gerbode of Stanford University. The following is an abstract of the clinical notes made during the visits to the volunteers between six (6) and seven (7) hours after the infusions were completed and again on the following morning, and during the experiment.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112

Accession #: 65A-3174

Box #: 59

File: Evans, Idris MD-99

Dr Evans MD-99
2/16

PATIENT NUMBER I

King, William B., Serial Number RA 45044971, Age 25

Temp. 98.2
Pulse 82
Resp. 18
Blood Pressure 120/85

500 cc Macrodex began 2:17 P.M., 23 March 1951. 500 cc Macrodex absorbed at 3:09 P.M. No reaction observed. 8:20 P.M. no complaints - patient has been somewhat thirsty. Urinary output not greater than usual in the patient's estimation. 24 March 1951 - 9:00 A.M. no complaints.

PATIENT NUMBER II

Landanno, Frank, Serial Number AF 6142608, Age 39

Temp. 98
Pulse 78
Resp. 16
Blood Pressure 130/90

500 cc Macrodex began 2:20 P.M., 23 March 1951. 500 cc Macrodex absorbed 3:07 P.M. 8:20 P.M. patient states that generally he feels flushed and hot and his mouth is dry. He has consumed a large amount of water. His hands feel somewhat swollen, particularly in the metacarpophalangeal joints. 24 March 1951 - 9:00 A.M. patient not located; gone to the main section of the Army Medical Center to appear before the Medical Board.

PATIENT NUMBER III

Ruckie, John, Serial Number RA 6890105, Age 33

Temp. 98.2
Pulse 68
Resp. 18
Blood Pressure 120/90

500 cc Macrodex began 2:25 P.M., 23 March 1951. Completed 3:20 P.M. At 8:20 P.M. patient complains of slight headache. 24 March 1951 - 9:00 A.M. no complaints.

PATIENT NUMBER IV

Lewis, Bruce, Serial Number RA 34939783, Age 37

Temp. 98.2
Pulse 84
Resp. 18
Blood Pressure 100/60

500 cc Macrodex began 2:28 P.M., 23 March 1951. At 2:34 P.M. minute urticarial spots on left upper arm. 2:44 P.M. another area of urticaria on right anterior rib margin. 2:55 P.M. temperature 98.8. Coughing - complains of dryness of throat. 2:55 P.M. wheezes throughout both lung fields--both inspiratory and expiratory. Infusion stopped after receiving 400 cc of Macrodex because of wheezes throughout chest.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112

Accession #: 65A-3174

Box #: 59

File: Evans, Idris MD-99

Patient breathes more easily while sitting up. Feels tightness in the chest. Blood Pressure 110/60. Given 2 cc of benadryl intramuscularly. 3:20 P.M. some itching - right forearm and left knee area. 3:50 P.M. patient walked to latrine in company of another patient. Returned complaining of weakness and nausea. Pulse 88 - good volume. Blood Pressure 110/70. Because of the clinical appearance of this patient it was deemed wise to retain him at the main section of Army Medical Center overnight. Patient refused his evening diet. 23 March 1951 at 9:00 P.M. Patient was sleeping - he was not awakened. 24 March 1951 - 9:15 A.M. Patient had awakened about 6:30 A.M., walked to breakfast and ate well. He was seen in the Dental Clinic at Army Medical Center. He had no complaints other than soreness in the wrist joint. There was no obvious swelling or increased heat in the wrist joint and there was no obvious limitation of the range of motion.

URINALYSIS: Specific Gravity: Quantity not sufficient.
 Albumin: Negative
 Sugar: Negative
 Acetone: Negative
 Micro: Few mucous threads.

BLOOD: WBC: 12,100
 Neut: 68
 Lymph: 30
 Mono: 2
 RBC: 4.85 million
 Hb: 17.4
 Bleeding Time: 1½ min.
 Coag. Time: 6 min.
 Sedimentation rate: 17
 Hmt: 53

PATIENT NUMBER V

Raines, Walter D., Serial Number RA 6385870, Age 37

Temp. 98.2
 Pulse 80
 Resp. 22
 Blood Pressure 120/70

500 cc Macrodex began 2:31 P.M., 23 March 1951. 2:48 P.M. erythema around the needle on the right arm and right upper arm. 3:00 P.M. temperature 98.4. Some urticarial blebs in the zone of the right lower quadrant incision. 3:15 P.M. patient complains of some dizziness, light headiness, tightness across the chest and in the throat. The urticaria around the right lower quadrant incision are more prominent. 3:20 P.M. infusion stopped after absorbing 400 cc. Patient complains of cold flashes. Some tightness across anterior chest. Itching on the right forearm. 3:40 P.M. patient complained of itching all over. Urticaria present on the right leg. 3:55 P.M. patient went to latrine. Returned complaining of nausea and weakness. Pulse 80, Blood Pressure 130/90. Complains of stinging and itching over all of lower extremities. 9:00 P.M. patient wanted very little to eat for supper. Vomited after supper. Urticaria had disappeared. 24 March 1951 - 8:30 A.M. patient only complains of slight headache, no itching or pulmonary symptoms.

URINALYSIS: Specific Gravity: Quantity not sufficient
 Albumin: Negative
 Sugar: Negative
 Acetone: Negative
 Micro: Occasional epithelial cells

Washington National Record Center
 Office of the Army Surgeon General
 Record Group 112

Accession #: 65A-3174

Box #: 59

File: Evans, Idris MD-99

EVANS, Everett I.

-4-

BLOOD: WBC: 11,700
Neut: 53
Lymph: 42
Mono: 5
RBC: 6.05 million
Hb: 17.4 grams
Bleeding Time: 2 min.
Coag. Time: 5 min.
Sedimentation rate: 13
Hmt: 51

PATIENT NUMBER VI

Ingles, Clifford, Serial Number RA 36075218, Age 31

Temp. 98.2
Pulse 60
Resp. 16
Blood Pressure 120/70

500 cc Macrodex began 2:33 P.M., 23 March 1951. 2:48 P.M. urticarial spots on left arm. 3:15 P.M. face slightly flushed with erythema over the abdomen. Coughing. Infusion completed at 3:20 P.M. 8:20 P.M. on 23 March 1951 no complaints. 9:00 A.M. - 24 March 1951 no complaints whatsoever.

PATIENT NUMBER VII

Thompson, Maurice, Serial Number AF 19126741, Age 30

Temp. 98.2
Pulse 80
Resp. 16
Blood Pressure 140/85

500 cc Macrodex began 2:34 P.M., 23 March 1951. 3:10 P.M. complaining of tightness of chest. 3:20 P.M. face quite flushed. 3:35 P.M. infusion completed - no further reaction. 9:00 A.M. - 24 March 1951 no complaints.

PATIENT NUMBER VIII

Culberson, Earthy, Serial Number RA 36788168, Age 32

Temp. 97.6
Pulse 64
Resp. 16
Blood Pressure 115/70

500 cc Macrodex began 2:37 P.M., 23 March 1951. 3:20 P.M. 500 cc absorbed. No reaction - 8:20 P.M. patient not located. 24 March 1951 - 9:00 A.M. no complaints.

PATIENT NUMBER IX

Sanders, Gerald, Serial Number, RA 34523971, Age 32

Temp. 98
Pulse 80
Resp. 18
Blood Pressure 125/80

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 65A-3174
Box #: 59
File: Evans, Idris MD-99

500 cc Macrodex began 2:40 P.M., 23 March 1951. 2:51 P.M. complaining of epigastric pain. 2:56 P.M. epigastric pain more severe. 3:00 P.M. Blood Pressure 120/70 pain somewhat diminished. 3:20 P.M. infusion completed. 3:30 P.M. generalized itching of all of both lower extremities. 9:00 P.M. some itching of the left upper arm. Patient vomited a small amount of undigested food particles at 6:00 P.M., shortly after taking a regular diet. 24 March 1951 - 8:20 A.M. no complaints. Patient allowed to return to Forest Glen.

URINALYSIS: Specific Gravity: Quantity not sufficient
Albumin: Negative
Sugar: Negative
Acetone: Negative
Micro: Mucous threads and amorphus urates

BLOOD: WBC: 4,600
Neut: 35
Lymph: 61
Mono: 4
RBC: 4.8 million
Hb: 14.3 grams
Bleeding Time: 2 1/2 min.
Coag. Time: 6 1/4 min.
Sedimentation rate: 6
Hmt: 47

PATIENT NUMBER X

Coye, James, Serial Number RA 34995139, Age 24

Temp. 98.8
Pulse 76
Resp. 18
Blood Pressure 115/65

500 cc Macrodex began 2:42 P.M., 23 March 1951. 2:55 P.M. slight erythema around the needle and on the right upper arm. 3:15 P.M. infusion completed. No complaints. 8:20 P.M. no complaints. 24 March 1951 - 9:00 A.M. no complaints.

SUMMARY OF PATIENTS:

(1) Of the ten subjects used; only three (3) absorbed 500 cc of Macrodex without observable reaction. These were Patients I, III, VIII.

(2) Four subjects had minor reactions. Patient X developed a slight erythema around the needle at the site of the vena puncture. Numbers VI and VII developed flushing of the face. Patient II developed a late symptom of tightness of the metacarpophalangeal joint approximately six (6) hours after infusion.

(3) Three subjects, Numbers IV, V, and IX, had moderately severe reaction necessitating their retention at the main section of Army Medical Center overnight. Number V developed generalized urticaria, itching, and symptoms of tightness of the chest during infusion and nausea and vomiting later. Number IV developed definite inspiratory and expiratory wheezes over both lung fields during infusion and joint symptoms some twenty (20) hours after infusion. The third moderately severe reaction occurred in Number IX and was characterized by epigastric pain, generalized itching of both lower extremities and nausea and vomiting.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 65A-3174
Box #: 59
File: Evans, Idris MD-99

COMMENTS:

While definite untoward reactions to infusions of Macrodex were observed in the experimental subjects at Army Medical Center we must be extremely careful not to draw too sweeping conclusions from this test. There were several circumstances which might have been better controlled.

(1) It was somewhat unfortunate that all of the patients were in the same room, side by side.

(2) There was too much activity, too much commotion, and too many observers were present.

(3) There was no control group of similar individuals, similarly instructed and handled receiving an infusion of an inert substance at the same time.

For the above reasons it would seem advisable that before concluding on desirability or undesirability of Swedish Dextran (Macrodex) the following suggestions be considered:

(1) Repeat on a larger scale under better controlled conditions, using both male and female subjects, (military and civilian) the experiment carried out at Army Medical Center on 23 March 1951.

(2) Under similarly controlled conditions test Commercial Solvents Corporation Dextran and British Dextran on a large scale for reaction rate. If no reactions occur with British or Commercial Solvents Dextran on military personnel, then Swedish Dextran is ruled out for use by the Armed Forces and the problem of the etiology of the reactions and the proof of acceptability of the Swedish product should rest in the hands of the manufacturers.

(3) If reactions occur with all makes of Dextran then we must consider whether the need for Dextran justifies the initiation of an extensive study to determine the etiology. Perhaps, it would be wiser to utilize our time and efforts to the clinical trial of some other plasma substitute, such as polyvinyl pyrrolidone. We must keep in mind that even if the etiology of the reactions is determined we might not be able to do anything about it.

(4) If it is deemed advisable to initiate a study to determine the etiology of the reaction to Dextran the following approaches to the problem are suggested:

- a. Careful examination of the service and medical records of all individuals who have had untoward reactions to Dextran to see if there is any common factor, (immunizations, antibiotic therapy, blood or plasma infusions, etc.) that sets them aside within their own group and apart from the general population as a whole.
- b. The problem as regards the Armed Forces is, can Dextran be given to a wounded casualty? The stress of the wound bringing into play the pituitary - adrenal mechanism may block the reactions observed in the convalescent, quiescent individual. If reactions continue to be observed under carefully controlled conditions the individuals who react may be given ACTH and a record infusion of Dextran. If reactions still occur then the continued use of Dextran might be unwise.
- c. The investigation of this problem will require careful thought and a lot of work by a team of investigators. The initiative should be undertaken with full Army participation (and/or initiation) because they and they alone have a reservoir of subjects in whom reactions have been observed.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112

Accession #: 65A-3174

Box #: 59

File: Evans, Idris MD-99