THE PLASMA VOLUME EXPANDERS • †

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INTRODUCTION

The United States stands at the same crossroads faced by Germany in 1939. German scientists and military advisers were aware that sufficient stocks of blood and plasma were not available for a prolonged military campaign. These scientists searched for a blood substitute and developed polyvinylpyrrolidone (periston or "PVP"), a derivative of acetylene. More than 100,000 bottles of periston were given to German soldiers, with excellent clinical results (1). Thousands of other soldiers and civilians succumbed in the large-scale barrages of the German cities because of the lack of adequate quantities of plasma volume expanders, or of a sufficient number of technicians trained in the administration of intravenous solutions, or both.

Dextran, gelatin and periston are not substitutes for blood in a physiologic sense. They are effective in the treatment of shock because they increase the oncotic properties of the plasma and expand the plasma volume.

HISTORY OF THE SEARCH FOR BLOOD SUBSTITUTES

The search for blood substitutes has been under way for many years. Denis (2), in 1667, reported successful transfusions in several patients with the blood of the lamb and cow. The French and English governments prohibited such transfusions after deaths were reported by other investigators (2). Latta (2), in 1831, was the first to advocate the use of normal saline solution in the treatment of patients in shock. Many patients returned to the shock state, however, as the normal saline solution diffused into the tissues or was excreted. During World War I, when the transfusion of whole blood was still a major procedure, Hogan (3) advocated the use of gelatin to expand the plasma volume. Gelatin was successful in elevating blood pressure temporarily but large quantities were required to maintain effects because of rapid excretion. A solution of acacia was tried (4). This substance, although highly effective in relieving hypotension, caused reactions and deaths. In addition, autopsy reports revealed long-term storage in the reticuloendothelial system.

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† Accepted for publication May 4, 1954.
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The imminence of World War II initiated another wave of experimentation in Europe and the United States. German investigators developed "PVP" (5). Swedish scientists reported that the dextrans, known for a century as contaminants of the sugar refining industry, would expand plasma volume and maintain blood pressures (6). Thorsen employed it clinically, with excellent results (7).

Other products investigated but found wanting included: isinglass, a fish gelatin; pectin, a common substance used in cooking; milk casein; globin; ascitic fluid; cadaver blood; methyl cellulose, and animal blood products.

The onset of World War II found our government with small stockpiles of blood and plasma. Immediate and extensive researches were initiated to discover techniques for the manufacture of dried plasma. It was decided that this was the most logical product from a viewpoint of transportation to, and use in, varied climates and battle conditions. Not until after World War II was there accurate correlation between the administration of plasma and the occurrence of serum hepatitis (8, 9). This disease, noted in many previous wars, had been thought to be caused by the unsanitary conditions in battle areas. When enough cases of serum hepatitis clearly implicated the plasma, the Air Force published the following directive (Excerpt from Directive Hq., USAF, subject "Clinical Use of Dextran," dated 4 June 1953):

"There is sufficient clinical evidence to indicate that dextran, a polymer of glucose, is a satisfactory plasma volume expander, and that, as a therapeutic agent in the preliminary or emergency phase of the treatment of shock, the results are essentially the same as may be expected from plasma. . . . Among the advantages of dextran over plasma are the simplicity of administration, lower cost, and the fact that it does not cause serum hepatitis. . . . Commanders of medical facilities are enjoined to requisition supplies of dextran and to use it as a substitute for plasma."

**Plasma Volume Expanders Under Active Investigation by the National Research Council**

The three main plasma volume expanders which meet the standards of the National Research Council and are being actively investigated are: gelatin, PVP and dextran. Criteria for an ideal plasma volume expander are listed as follows (10-11): (1) osmotically, it must be the equal of normal plasma; (2) its viscosity and retention in the blood stream must be approximately that of normal plasma; (3) it must be stable on storage; (4) it must be nonantigenic; (5) it must be nontoxic, and (6) it should be utilized in the body economy without unfavorable effects on cell structure and function.

**Gelatin**

The gelatin employed by Hogan (3) in 1915 was a 2.5 per cent solution in normal saline. It was effective, but was discarded because
of the need of continuing the infusion of large volumes of solution to prevent a return of the shock state. The gelatin was excreted almost as rapidly as it was infused. Rous and Wilson (12), in 1918, however, stated, "Six per cent gelatin in our experience is always effective."

Interest in the use of gelatin waned after World War I until Tolofson and Teller (13), in 1929, again reported excellent results with a 6 per cent solution.

Taylor and Waters (14), in 1941, in order to avoid dangers of anthrax and tetanus from the beef products, developed a solution of fish gelatin made from the swimming bladders of various species. This was of interest, but was not practical. Ravdin (15) reported on the administration of gelatin solutions in the Burma-India theatre in World War II. He stated that the only difficulties with ossein gelatin were the necessity of heating it before use and its slow degradation in hot climates.

During World War II, Campbell and Associates (16), at the California Institute of Technology, developed a solution called "oxypolygelatin." This is a form of gelatin manufactured by condensation with glyoxal and hydrogen peroxide. They reported it to be non-allergenic to animals and nontoxic to human beings. It is retained in the circulation for six hours and has osmotic properties similar to those of serum albumin.

Dripps (17) reported on the use of a modified fluid gelatin to the National Research Council on March 23, 1953. His group, after experimenting with it in Philadelphia, had administered it to wounded soldiers in Korea. He reported successful resuscitations but stated that it had the limitations of all the plasma volume expanders, that is, the measures were only temporary until blood could be obtained. Gropper et al. (18) reported that gelatin has a "specific diuretic action" and this may account for one of its drawbacks—rapid excretion.

**Polyvinylpyrrolidone (PVP)**

A 3 per cent solution of polyvinylpyrrolidone has approximately the same osmotic pressure as plasma. The product used for expansion of plasma volume is a 3.5 per cent solution in normal saline.

No severe reactions were reported by German investigators from its administration to German soldiers and civilians during World War II.

However, investigators in this country and abroad have not yet been able to determine the ultimate fate of PVP. Approximately 50 per cent is excreted through the kidneys within three days. Another 25 per cent is excreted in this manner up to ten days after infusion (19). Thus, 25 per cent cannot be accounted for with present methods of determination.

Histologic examinations of animals have revealed deposition in the
spleen, liver, bone marrow and lymph nodes (20). Similar findings have been noted in infants who were treated for severe toxemia of the alimentary tract, but who died from the disease (21). These infants have not been reported in the German soldiers or civilians who died of extraneous causes after receiving PVP infusions. The German investigators reported that the physiologic function of these organs has not been interfered with (21).

Experiments with radioactive PVP are now in progress to determine this vital information.

PVP would be an excellent product for stockpiling. It is easy to manufacture and to standardize because of its simple chemical structure.

**Dextran**

The German sugar chemist, Schleiber, discovered dextrans in the nineteenth century (6). During the process of sugar refining he noted a material that appeared to be hyaline masses joined in chains. On bacterial examination, the organism which had contaminated the sugar vats and had caused this "slime" was found to be Leuconostoc mesenteroides.

The material with which Ingleman first experimented was a pure, unhydrolyzed dextran which was toxic to all of the animals. A product hydrolyzed to 6 per cent and diluted in normal saline solution had a low reaction rate in animals.

In 1947 the dextran product, macrodex®, was released for general use by Pharmacia, Ltd., Uppsala, Sweden, and two years later Thorsen remarked (22):

"Five years after the first administration in a case of traumatic shock, more than 30,000 transfusion units have been distributed. Dextran is in use everywhere, from the Philippines in the west to Finland in the east, from Gallivare in the north (of Sweden) to Liberia in the south."

Agencies in the United States government awaited verifying clinical trials at many centers before purchasing large quantities of the Swedish macrodex. The results did not support Thorsen's statements.

Thorsen (7) had reported a reaction rate of 0.4 per cent as compared with 8.2 per cent with whole fresh blood or 2.3 per cent with conserved blood.

Trials in this country using a dextran product manufactured in the United States under Swedish license and using Swedish manufacturing techniques, were conducted by Turner and Associates (23). They revealed a reaction rate of 33.3 per cent (10 of 30 subjects). The reactions were not only frequent, but severe.

Trials at Brooke Army Hospital, using Swedish macrodex sent to this institution from Sweden, caused an over-all reaction rate of 33.9 per cent, of which the majority occurred in unpremedicated, un-
anesthetized volunteers [33 of 37 reactions with Swedish macrodex (24)].

A dextran product, however, manufactured by Commercial Solvents Corporation of America, in a comparable series gave an over-all reaction rate of only 8.2 per cent. Of the reactions, only 2 could unequivocally be attributed to the dextran. Both reactions occurred in the same person.

This discrepancy was partly cleared up when Aberg (25) stated at a meeting of the National Research Council, where he was a guest, that in Sweden, rashes were not considered as indicating a positive reaction and that their definition of a reaction was a condition in which treatment was required.

Because the majority of investigators here and abroad were not reporting reactions from the infusion of Swedish dextran and the reaction rates were so high in the Presbyterian and Brooke Army Hospital series, the National Research Council outlined a plan to determine the role of the routine "service immunizations" in these reactions.

The personnel at Lackland Air Force Base was chosen because they were ideal subjects for this type of test. An appeal was made to basic airmen, processing through the Air Force Indoctrination Center, who had not yet been immunized. When the explanation was made as to the importance of this work to the fighting men in Korea, entire flights volunteered. Another group, already immunized, was likewise obtained.

Before infusion, 200 cc. of whole blood was withdrawn from an arm vein. (It must be emphasized that, despite the withdrawal of this quantity of blood, these were considered to be normal volemic subjects.) In addition, nine intradermal wheals were made on each patient with various native and clinical dextrans. Skin tests were read during the entire experiment to determine the prognostic significance of skin reactions to systemic reactions.

Another 200 cc. of whole blood was withdrawn thirty days after the infusion. This blood was tested by the National Research Council for any rise in titers to Leuconostoc mesenteroides.

In a report to the National Research Council, the following statement was made (26):

"The data clearly show that there is no significant difference in the incidence of allergic reactions to infusion of dextran in individuals who have recently received the routine army immunizations as compared with a similar age group of individuals who have not been thus immunized. It is also evident from the data that the more recent lots of Swedish clinical dextran show no significant difference in incidence of adverse systemic reactions over that obtained with the older product. For further clinical studies of allergic reactions to dextran, it should no longer be necessary to consider the immunization status in the selection of subjects. It appeared, however, that the immunized group in some instances showed somewhat more extensive signs and symptoms than did the nonimmunized group, although the incidence of reactions did not differ sig-
nificantly. It is evident that skin tests with clinical dextran offer little prog-
nostic assistance for detecting individuals who will show systemic allergic
reactions."

The over-all reaction rates in this experiment in the 101 immunized
and nonimmunized volunteers was 51 per cent. This was similar to
the reaction rate for nonanesthetized volunteers at Brooke Army Hos-
pital. The over-all reaction rate of 33.9 per cent at Brooke Army
Hospital included anesthetized volunteers in the totals. These volun-
teers reacted very little.

At a later date, further experiments at Lackland Air Force Base
were carried out in the following manner:

1. 107 volunteers from three flights of basic airmen were tested with
several lots of the Commercial Solvent's product called expandex®.
This dextran was similar to the Swedish product, being a 6 per cent
solution of dextran in normal saline. The manufacturer, however,
had employed a different strain of Leuconostoc mesenteroides (No.
512). The mean molecular weight of this product was approximately
53,000 as compared with 70,000 for the Swedish product. (This was
at the lower limits of specifications by the National Research Council
which allowed a lower limit of 50,000.) One of the lots also tested was
a nonclinical lot with a mean molecular weight closer to 70,000; por-
tions of the product varied in weight to as high as 250,000.

2. By special arrangement with the Departments of the Army and
Air Force, 33 men who had previously received infusions of dextran
in the Brooke Army Hospital tests were returned to Lackland Air
Force Base from all over the United States for reinfusion tests.

The procedure for these tests was similar to that in the previous
tests. After withdrawing 200 cc. of whole blood, the patients were
skin tested with nine of the known dextrans, reactions to the skin tests
noted, and then an infusion with the Commercial Solvent's dextran
was given. The results were summarized as follows (27):

"Of 70 healthy volunteers tested with clinical Commercial Solvents Corporation
dextran, 10 exhibited mild reactions, several of which were limited to the
appearance of a single hive. Thirty-five reinusions were given to 33 individ-
uals. No reactions were encountered in 27 reinusions of Commercial Solvents
Corporation's dextran even though 2 of the individuals tested had reacted to
Swedish dextran and one had shown a moderately severe reaction to Commercial
Solvents Corporation's dextran on the first injection. Reinfjection of Swedish
dextran in 3 individuals who had experienced mild, moderate, and severe re-
actions to an initial infusion of Swedish dextran resulted in reactions of the same
severity as those experienced with the first injection. In no case was there any
evidence of enhancement of dextran sensitivity on a second injection."

In a report to the National Research Council, the following con-
clusions were reached (27):

"1. That dextran is antigenic in man, and can produce precipitins and skin
sensitivity.
2. That the degree of sensitivity as measured by skin test seems to bear no relation to systemic reactions.

3. That reinfusion after an interval of twenty-one days shows no enhancement of sensitivity from a first infusion of either Commercial Solvents Corporation or Swedish dextran.

4. That the results are reassuring with regard to the use of dextran of the Commercial Solvents Corporation type. Apparently, this material under the usual conditions of manufacture and administration does not produce a marked sensitivity. However, it would be important to have those administering dextran well informed as to the possibilities of reaction.

5. That the sera of a variable, but by no means negligible, fraction of the population will agglutinate one or more strains of Leuconostoc mesenteroides. This bears no correlation to previous immunizations. The presence or absence of agglutinins to Leuconostoc mesenteroides does not provide a basis for predicting systemic reactions to dextran. Finally, the intravenous administration of dextran results in the appearance of agglutinins to Leuconostoc mesenteroides and a rise in titer in about 50 per cent of individuals."

Since the basic research, clinical testing has continued. Amspacher, reporting from Korea, stated that dextran was effective in the resuscitation of wounded patients (28).

In a report to Headquarters, United States Air Force, dated July 10, 1953, from Lackland Air Force Base, the following report was made by the Anesthesiology Section, Lackland Air Force Base:

"Reaction rates in 113 anesthetized patients given 132 bottles of dextran in the previous six months caused a reaction rate of only 2.65 per cent."

**Summary**

The history of the search for plasma substitutes is outlined. The problem of hepatitis after the administration of plasma is summarized.

The attributes of an ideal plasma volume expander are listed. The uses and drawbacks of gelatin in its various forms are discussed.

P.V.P. and the problem of its storage in the body are discussed. Details of experimental and clinical studies with dextran are outlined.

Stress is placed on reaction rates, not to disparage dextran, but to emphasize the need for caution in its administration.

**REFERENCES**