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Dextran and PVP and plasma expanders

John E. Hansen
University of Nebraska Medical Center

DEXTRAN AND PVP AS PLASMA EXPANDERS

John E. Hansen

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I. Introduction:

To begin this thesis, let us first define a plasma expander. The most suitable definition suggests that a plasma expander is an agent which will overcome the disparity of the circulatory system that exists in shock and thus tide the patient over a critical period until such materials as are specifically needed can be given, or the patient can himself manufacture and disseminate enough materials to restore his own blood volume.

Man, in his constant struggle to better himself, over the ages has been aware at least of the desirability of a suitable blood or plasma expander. It is recorded by an early histerian that Aam, leader of the Persian Armies in the reign of King Ben-Adad, when stricken with leprosy was treated by having blood withdrawn and then replaced by blood from a healthy male. Heirenymus Cardamus and Magnus Pegelius as early as 1505 suggested transfusion of blood from the blood vessels of one person to those of another. Andreas Libavius in 1615 outlined with some practicability the actual technique of blood transfusion (Gerdon 18). Blood transfusions and thereby intravenous infusions as everyday occurences were first born in the early anxious days of World War I.

Experience in the 1914-1918 war showed that restoration of the circulatory blood volume was the most effective single restorative measure in patients who had sustained severe injury. This was further borne out by experience in World War II. Boylis (1919) showed that a fluid which contained colloids having an osmotic pressure similar to that of plasma proteins could be used as a substitute for blood. He proposed the use of gum arabic solutions. This substance was eventually discarded because of untoward reactions due to antigenicity, storage phenomena in the liver. (Hendersen 24). Fish Gelatin or isinglass as proposed by Taylor and Waters was not thoroughly evaluated, and Pectin, use of which was proposed by Hartman and co-workers in 1941 was also not accorded full investigation. Human albumin has been widely used but it requires three times as much blood to produce one unit of this as it does to produce one unit of plasma.

In 1942, the Blood Substitute Committee of the National Research Council listed eleven requirements for a satisfactory plasma volume extender. They are: maintainence of a satisfactory colloid osmotic pressure; constant composition; suitable viscosity; stability with temperature change; stability in storage; ease of

sterilization; freedom from pyrogens; absence of immediate adverse effects; absence of immediate or delayed organic derrangement; absence of antigenicity; and reasonable price. (Hammarsten 20).

Interest in a substance or substances which can fulfill most of these requirements has been greatly heightened by the possibility of national emergency in the case of atomic attack. The available supplies of blood and plasma would certainly be inadequate and the problem of logistics virtually insoluble. Another drawback to plasma is the fact that no fully effective means has been found for controlling its contamination by the virus that causes homologous serum jaundice.

Although no one of the substances tested meets all of the specifications, some have been found which meet the more important requirements and are clinically acceptable. Two of these substances which have seemed to elicit the greatest interest are Dextran, a "natural" product, and Polyvinylpyrolidone, hereafter referred to as PVP, a synthetic polymes. Let us consider these substances in the light of present knowledge.

II. History:

Of the two substances which we are considering, Dextran was probably the first to be discovered. It was first discovered in Germany as a mucoid material

formed during the extraction of sugar from beets. It was first reported on by Schleiber, a German Sugar Chemist, who noticed it during the sugar refining operations (Artz 4). Except for its nuisance value, for it clogged the pipes in refining operations, little note or attention was accorded the substance. In 1943, Gronwall and Ingelman, two Swedish workers suggested the use of dextran as a substitute for plasma (Thorsen 53). Since that time a great deal of investigation has been carried out on dextran. The Swedes, of course, were the first to carry out extensive investigation and Gunnar Thorsen and Gronwall and Ingelman are prominent workers in this country. England was next to realize the possibilities of dextran and extensive investigations were soon underway in that country. J. P. Bull has been a leading investigator in that country. In our own land, J. S. Lundy, W. L. Bloom, F. W. Hartman and Edw. Gall are leading names in the field.

PVP was first prepared by the Germans from acetylene by a process devised by Reppe in 1938 (May 38). As "Periston" (PVP in Ringer's solution) it was announced as a new plasma substitute by Hecht & Weece in 1943 (Hecht & Weece 23). They called the new product "Kolliden".

It was used extensively by the Germans in World War II, some investigators estimating that as many as 500,000 injections of PVP were given. However, since the records were destroyed, there can be no confirmation of this or the results received.

III. Chemistry:

The physico-chemical use of dextran and PVP is feasible because of the similarity of molecular weights of these substances and the plasma proteins of the blood. The blood plasma proteins are the components which are largely responsible for the oncotic pressure of the blood. The blood plasma proteins are commonly separated into three major groups: fibrinogen, albumin, and globulin.

Fibrinogen is a large asymmetric molecule (see Figure I) which is highly elongated having an axial ratio of approximately 20:1. Molecular weight is between 350,000 and 400,000. It constitutes normally 4-6% of the proteins of the plasma.

The albumin fraction of the serum protein is not absolutely homogenous. There is one component, mercopt-albumin, which has been isolated and found to account for approximately 2/3 of the total (see Figure I).

The globulin fraction of the serum proteins is a complex mixture. Among its components may be found

beta- and gamma-globulins and also the lipeproteins. Molecular range is between 90,000 and 1,300,000 (see Figure I). Most of the plasma proteins are derived from the liver although certain of the globulin fraction are derived from other tissue sources.

Chemically, dextran is a polysaccharide formed by growth of a coccus, Leuconostoc mesenteroides, on a medium consisting of a sucrose solution with mineral salts, principally sodium ammonium phosphate. An added extract of fresh baker's yeast is also innoculated into the media. The normal habit of the organism is decaying vegetable matter (Ricketts 48). During its growth it produces an exocellular enzyme which polymerizes the glucose portion of the sucrose in the medium to form dextran. This is then subjected to controlled depolymerization (Ohlke 42). Growth in a medium containing 20% sucrose will result in conversion of the 1/3, the available glucose to dextran.

The dextran formed is thus a bacterial starch composed of glucose molecules linked in chains, but the chains are coiled since the linkage pattern is different than ordinary starch. The glucosides formed are joined through a 1:6 glucoside linkage. The main chain of glucose units thus formed has frequent branches which

are probably joined through 1:4 glucoside linkages. In native state, dextran chains comprise approximately 200,000 glucose units, making a molecular weight of approximately 40 million. Since a medium size is best for use as a plasma expander, the crude culture requires depolymerization.

Fractionation to remove the unwanted very large and very small molecules is performed by adding different strengths of acetone-water mixtures, which precipatate various sized molecules of dextran as judged by viscosity measurements (9).

Some consideration or comparison of molecular size might be pertinent at this point. Serum albumin molecules average 150 Å units long and 36 Å units diameter. It has been calculated that a dextran molecule with a molecular weight of 36,000 or more is 360 Å units long but only 14 Å units diameter. These small molecules of dextran tend to pass through the kidneys rather readily. The larger molecules, which tend to remain in the circulation longer, run from 84,000 to 141,000 in molecular weight, and measure 500 Å units long with diameters 17-19 Å units. (Lundy et al 34).

The clinical preparation most often used is a 6% solution of the polydispersoid glucose-polymer dextran

with isotonic saline solution added to it. Its viscosity lies between that of blood and that of plasma, and its specific gravity somewhat exceeds that of human plasma. Its thread-like molecules are electircally neutral and chemically indifferent (Thorsen 53). The clinical product has a fairly narrow range of molecular weight, 75,000 ± 15,000, somewhat approaching albumin.

Dextran has certain advantages over other non-protein colloids in that: (1) it is free from acidic radicals, and therefore not likely to form storage complexes; and (2) it can be hydrolyzed into glucose by acids and by certain living organisms, which suggests that the human body may be able to metabolize it slowly (Bull, et al 10).

PVP was first prepared in Germany by Hecht and Weece in the early 1930's. The compound is a whitish amorpheus powder which is water soluble. Through acetylene chemistry, the I. G. Farbenindustrie in Germany was able to polymerize a polyvinyl-pyrolidone to give a colloid with a molecular weight of about 25,000 which could be used as a volemic substance when placed in solution (Knutson 29). In the last stage of the process, polymerization of the monomer, N-vinyl pyrolidone, is carried out in aqueous solution with hydrogen peroxide as a

catalyst, the concentration of the latter controlling the degree of polymerization (May 38). (See Figure 2).

PVP was first used in 2.5% concentration in Ringer's solution but Weece recommended to Lundy that a 3.5% solution be used since a 3% solution has almost the same colloidal osmotic pressure as the plasma.

Commercial preparations now available are mixtures of polymer chains averaging 35,000 to 40,000 molecular weight. The PVP develop an osmotic pressure of 300-350 mm. of H_2O. Hydrophilic properties are ascribable to -N-C=O grouping. No groups are titrable by either acid or alkali and the solution exhibits no buffer capacity. Therefore, any electrolyte alterations following PVP administration must be ascribable to the diluting solution used (Singleton 50).

IV. Physiology:

Since use of plasma expanders per se is principally to maintain or replace plasma volume it is not surprising to find that practically all investigators report an increase in circulating plasma volume in the blood stream after infusion of dextran. Artz (4) reports that one liter of dextran infused to replace a 1000 cc. blood loss causes a corresponding increase of plasma volume of approximately one liter in one hour which is well

maintained at six, twelve, and twenty-four hours. One investigator reports that plasma expansion is optimal in bled animals infused with non-renal excretable fractions of dextran. (Wasserman, et al 55). This same investigater also reports that dextran infusions into bled animals does not significantly alter the total circulating plasma protein levels.

Thorsen (53) reports that in his investigations, after an intravenous injection of one to two liters of dextran, the plasma dextran level rises to 1-2.5 gms./ 100 ml. Next after an initial fall, due principally to elimination of low molecular fractions through the kidneys, the plasma dextran level falls at an even rate.

Bloom reporting in the Journal of Clinical Investigation (7) states that on five patients tested, there was an increase in cardiac output in every case. Up to 38% increase was noted if determinations were done within ten minutes after injection. There was a change in the stroke volume commensurate with this increase, but the average pulse rate showed no change. There was a gradual rise in pulmonary artery pressure during injection and the peak was noted immediately following injection. The peak was maintained only twelve to twenty minutes. An increase in heart work was noted amounting to 98% increase in right ventricle and 41%

increase in left ventricle. Harrison (21) reports similar findings.

Leusen, et al, (32) did some fairly extensive studies on changes in cellular elements of the blood produced by administration of dextran. He used a Swedish preparation in dosage of 1/2 ml/Kg body weight. He found extensive and prolonged adherence of leukocytes to the walls of the blood vessels after the first injection but little change after a second injection 24 hours later. A profound leukopenia was noted the first few minutes after injection corresponding to the period when leukocytes were clinging to the walls. Leukopenia diminished and leukocytosis finally occurred. Differential counts revealed a marked shift in the ratio of polymorphonuclear cells to mononuclear cells. There was an absolute decrease in numbers of both type cells, however. The erythrocyte sedimentation rate is increased after dextran administration (10, 17, 27, 45).

It is difficult to evaluate the role of the liver in subjects who have received dextran since there are so many conflicting reports. Engstrand (14) reports that there is little or no evidence of significant dextran uptake by, or clearance from, blood in the liver, or intestines and that any uptake was very small. He states that a small amount is taken up by the reticuloen-

dothelial system. In another series of investigations Rheinhold (47) reports that there is little if any change in liver function tests following dextran administration. Injections were given in one liter amounts to a total dosage of one to six liters at a rate of three to sixteen ml./minute. Liver tests selected were total serum bilirubin concentration, Bromsulphephthalein retention, plasma concentration of dextran, thymol and zinc turbidity, total serum protein, and urine urobilinogen. No doubt more can be told about the affect of dextran on the liver and liver functions will be possible after investigations over a number of years is carried out.

The main route of excretion of dextran from the body is via the kidney. Low molecular weight fractions are first excreted, (average 25,000). Jaenike (26) reports that approximately 50% of the amount of dextran given is excreted in the urine during the injection period. Others do not report such a high figure for excretion. It is the belief of Goldenberg (17) that the bulk of urinary excretion occurs during the first or second day instead of the first few hours. He does report some histological changes which can be demonstrated in the kidneys following dextran administration. There is swelling and granularity of the epithelial cells of the

kidney tubules associated with some granular debris in the lumens of the tubules. In some instances marked vocuolization of the epithelium and dilatation of the tubules were noted. The changes involved in order of frequency: (1) proximal convoluted tubule; (2) distal convoluted tubule; (3) loop of Henle. The glomerulus of some units showed the debris noted above. There was noted in some areas active glomerular and epithelial cell hyperplasia. Despite these findings the kidneys were not permanently damaged. Renal function is not impaired. Dextran not excreted is seemingly metabolized although this cannot be proven definitely. Squire (51) makes the statement that being metabollically inert, no mammalian tissue is known to break it down. BUN and urea clearance are apparently unchanged by dextran administration.

Thorsen (53) reports that in subjects given repeated infusions of dextran, so that the total amount of dried material corresponds to 1/3 of body weight, no dextran has been discovered in brain, lungs, heart muscle, kidneys or bone marrow. Engstrand (14) reports that 56 days after dextran infusion, the substance could be demonstrated serologically in the tissues. In his investigations, Olive (43) reports that the dextran not excreted in

the urine is metabolized in the tissues to CO_2 and H_2O and by tagging dextran with radio active carbon, this may be demonstrated in the tissues. In one group of subjects so tested, results were obtained as follows: 65-70% in urine; 4-6% in expired CO_2; 0.5% in extracellular tissues; 3-5% in viscera; 25% unaccounted for. There were traces in liver, lymph nodes, and spleen. Wasserman (55) reports that all fractions of dextran used have been found in thoracic duct lymph. Lundy (34) reporting on Maycock's work indicates that serologic determinations have demonstrated dextran in skin, bone marrow, and brain of rabbits up to 16 weeks after injection of 9.2 gm/Kg.

In the early reports on dextran there was note of fairly high rate of anaphylactoid reaction in patients infused with the substance. While Swedish literature reported little if any anaphylactic response, Lundy reported as high as 30-40% reaction to the Swedish preparation. He noted little reaction to the substance prepared in this country.

Tarrow (54) carried out a series of investigations on patient volunteers to determine relative antigenicity of the various preparations. Swedish, English, and American dextran preparations were used. Experiments

were carried out on both anesthetized and unanesthetized patients. Five Hundred cc. was the average amount given. Observed symptoms and signs were: headaches, chills, flushing, urticaria, nausea or vomiting or both, cramps, chest pain, vasomotor rhinitis, hypotension or syncope on standing, delayed pain in the joints, and swelling of the extremities. There was noted 44.4% incidence of reaction with the English preparation, 33.9% incidence with Swedish "macrodex" and only 8.24% incidence with the American product. In persistent reactions, symptoms were ameliorated by antihistaminic administration intravenously. Preinfusion medication did not seem to limit the severity of reactions. All indications seem to point to the strain of Leuconostoc mesenenteroides used in preparation as being responsible for antigenicity of the product. Kabat (31) reports that the dextrans, because of their chemical structure, are antigenic themselves. Lundy (34, 35) mentions that incidence of reaction is much less in anesthetized patients than in unanesthetized patients, even though spinal anesthesia was used.

Some of the aspects of PVP resemble results obtained by use of dextran but there are some which are entirely different. The mode of action is practically

identical. After PVP infusion, there is rapid kidney excretion of the smaller molecules, 1/3 being excreted in six hours, 1/2 during first twelve hours, and 2/3 during first 24 hours. A small amount is excreted in the feces (Loeffler 33). Korth (30) reports no overloading of the circulation and no other ill effects. Blood pressure and pulse pressure are maintained by stabilization of plasma colloid pressure. Some hemodilution is noted by practically all authors, but there is no mention of increase in ESR, rouleaux formation, or increased clotting time. May (38) reports in his studies that electrophoretic and ultracentrifuge analyses indicate that there is no reaction between PVP and plasma proteins. Ravin (46) suggests that absence of appreciable amounts of PVP in brain or fetus seems to indicate that transfer across a double barrier is far more restricted than transfer across simple capillaries.

Arthur A. Nelson (40) reporting on a series of tests on animals, particularly rabbits, after repeated injections of PVP states that this substance causes definite, though slight splenic enlargement. Foam cell storage phenomena are noted which may best be demonstrated in the spleen but are also seen in other organs. The foam

cells had reticular type nuclei, basophilic and markedly vacuolated cytoplasm and were from 15 to 100 u. diameter (usually 20 to 25). The foam cells contained PVP or some near derivative. Other organs showing foam cells were lymph nodes, bone marrow, adrenal medulla and to a lesser degree liver, lungs, and thymus. There was also noted slight testicular atrophy and slight epithelial swelling and rarefaction in the distal portion of the proximal convoluted renal tubules.

Moderate splenic enlargement and balloning of Kupfer cells in the liver and formation of similar vocuolated mocrophages in the perifollicular areas of the spleen and in reticulum of the lymph nodes was noted by Stern in 1952 (52).

Edward Gall (15) in an extensive investigation found changes in liver parenchyma which he thought were significant. He reports presence of smudgy, pale, basophilic globular aggregations resembling coalescent soap bubbles. Size range was from barely perciptible granules to 50 u. diameter. The larger amounts distended the phagocytic cells and more often lay free within the sinusoids. In a few specimens isolated spindle cells, identified as filroblasts appeared in some regions. Sometimes a scant inflammatory exudate was seen. Gall

suggests that some of the confusion as to presence or absence of liver lesions following PVP administration may result in varying times between infusion and histologic study. The substance seems to be chemically inert.

Loeffler (33) states that there is no constant deposit in any organ. He observes that inconstant findings of engorged Kupfer cells and large numbers of phogocytes in lungs, spleen, and lymph nodes are consistent with severe physiologic and pathologic processes, not only PVP storage. Results therefore are not conclusive and positive proof must await further study and evaluation of a larger series of cases.

By use of preparations containing radio active carbon, C^{14}, Fine has shown 35-40% storage of C^{14} in extravascular locations, 15-20% in the reticuloendothelial system and 60-75% in skin and muscle (Cameron 11).

There have been very few reports of allergic reactions to PVP as contrasted with dextran in which allergic reactions sometimes quite severe, are occasionally seen.

V. Clinical Applications:

The clinical use of the plasma expanders Dextran and PVP has thus far been almost entirely confined to

treatment of shock or shock-like states. One of the first large scale clinical trials of dextran was carried out by the military during the late Korean crisis. Both of these substances have been used in burn treatment where fluid loss and shock were factors. Criteria for diagnosis of shock include paller and claminess of the skin, decreased blood pressure - usually 90/60 or less, rapid feeble pulse, decreased respiration, restlessness, anxiety and occasionally unconsciousness.

Plasma expanders, for best results, are administered by intravenous infusion. Six per cent Dextran solution and 3.5% solutions of PVP have been found to be the most efficacious. Recommended dosage is generally set at 500 cc. given at 20-40 cc/minute with the total amount administered in 15-30 minutes. For hemorrhage the dosage should be limited to an amount sufficient to elevate systolic blood pressure not more than 80-85 mm. Hg. to avoid production of further bleeding and dangerous dilution of circulating blood (27).

Wm. Abbott (1) reports that Dextran and PVP may be administered intraperitoneally to combat shock but the results are inconclusive. He also reports work done experimentally on administration of dextran by hypodermoclysis. Experiments indicated that hyaluronidase

had little effect on the rate of absorption. His studies seemed to show that there may be an actual decrease in circulating plasma volume. There were noted also extracellular fluid volume deficits indicating that an intracellular fluid shift had occured.

Amspacher et al (2) reports on the use of dextran in control of shock resulting from war wounds. Dextran was given to sixty wounded men. On entrance to the hospital, each case was evaluated in terms of the extent of shock and the type, number, and location of wounds. In six cases infusion of dextrose was all that was required, but all six later required dextran during surgical debridement. Dextran alone was given to thirty-three patients; dextran plus dextrose was given to eleven dehydrated patients. In every instance in which dextran was used as initial resuscitation therapy, the blood pressure promptly approached a normal level and the pulse was of good quality. In order to determine the value of dextran, blood was withheld unless the hematocrit level decreased to 20% of normal or below. In the majority of people who were treated with dextran the wounds were caused by mines, grenades, shell or mortar fire. Study of the postoperative periods reveals stable normal blood pressures and low hematocrit levels

which indicate continued expansion of the fluid component of the blood volume after administration of dextran. There were no recorded alterations in renal function.

In treatment of burns Bull (8) has been able to show that the percentage of patients surviving when dextran solutions were used closely approximated to the results expected on the basis of a statistical study of patients similarly treated with plasma during the preceding years. Ideally, of course, replacement of whole blood is preferred. If blood is not available, dextran will maintain blood pressure and circulation. However, with considerable RBC losses, the hemo-dilution accompanying this treatment may be serious. One to one and one-half liters of dextran are required for each 10% of body area burned. Five to six liters is probably the limit of the dextran which should be used. Gelin (16) believes that there is no indication for blood transfusion in shock caused by severe burns unless severe anemia is present. He suggests O_2 administration coincident with dextran infusion to combat shock, capillary permeability changes, and local hypoxia. This author feels that by adequate treatment with dextran in shock, aggregation is prevented, and thereby the

secondary anemia often seen after extensive burns is ameliorated. He suggests 2 cc. of dextran per percent burned area and Kg body weight for burns up to 30% of body surface and 2½ cc. of dextran per percent burned area and Kg body weight for burns more severe than this.

Haynes and DeBakey (19) recommend for mild shock, up to 20% blood volume loss, treatment with saline plus dextran. Dextran alone is used in moderate shock, up to 35% blood volume loss, and dextran plus whole blood in blood losses over the latter figure.

In most of the articles reviewed, administration of dextran was followed by increase in the circulating blood volume by 10 to 50%. With return of blood pressure to near normal levels there is also a decrease in hematocrit and protein values of blood, because dextran increases the intravascular colloidal concentration and water from intracellular spaces enters the circulation causing dilution.

Scratchard reports the possibility of straining the heart through use of plasma expanders depending on the viscosity of the agents used (49).

Olive, Mills and Lundy (43) have used dextran in experimental treatment of nephrotic edema. Rationale for the treatment is based on the assumption that the

edema is caused chiefly by severe hypoproteinemia. It should be possible, therefore, to eliminate the edema by increasing simultaneously the colloidal osmotic pressure of the plasma as well as the plasma volume and glomerular filtration rate. Their series includes treatment of twelve children with nephrotic edema. The children were given an average daily dose of 1.43 grams per Kg of body weight of dextran.

Similar results have been recorded by use of PVP in 3.5% solutions (Lundy 37). Cordice (12) in reporting a series of cases using PVP in severe burn shock records that in all cases there was definite recovery from shock, decrease in hematocrit, improvement in toxicity, and increase in urinary output. There was no significant alteration in blood electrolytes following infusion of PVP. The cases reported involved areas of burns varying from 20 to 75% body surface, and the volumes of PVP administered ranged from 1000 to 3000 cc. infused in periods from one to eight and one-half hours.

In an experiment involving sixteen healthy females in labor, Posner (44) reports the effects of PVP in obstetrical cases. These women were given 500 cc. of PVP. At delivery, cord blood samples were examined for concentrations of PVP. Results seemed to indicate

that there is no definite correlation between cord blood concentration of PVP and time elapsing between administration of PVP and collection of cord blood specimens. The substance does not enter the fetal circulation.

O'Connell et al (41) report the use of PVP in management of a condition in which the clinical picture was that of cholera-profound shock, anuria, rice water stools, and peripheral vascular collapse. There was prompt relief of shock with administration of 1000 cc. of PVP on two different occasions. There was complete recovery after anuria of six days duration.

VI. Future:

The future of these plasma expanders seems bright. Simplification of intravenous infusions, new materials and sterilization techniques, combined with modern medical knowledge, have opened an era which demonstrates a tendency toward increasing methods of therapy by the intravenous route. Through use of the plasma expanders the horizons of surgery will be notably advanced because of the availability of an adequate plasma expander which causes few or no reactions and the supply of which may be, practically speaking, unlimited. The plasma expanders are important not only from the standpoint of

civilian surgery but also to the nation as a whole in the event of any future catastrophe. Under the conditions of modern warfare, it is highly possible that we shall not have the amount of blood adequately necessary to take care of the casualties which may occur. Because of the great difficulties in building up stockpiles of whole blood and blood derivatives for a national emergency, the use of plasma expanders presents itself as suitable treatment in large scale emergencies. These substances can be made available at prices considerably cheaper than whole blood or blood derivatives. These may be stored for long periods of time without deterioration. Estimations based on available data indicate a demand of upwards of 100,000 pints of blood, plasma, or substitute per atomic explosion (3). Plasma expanders will therefore make it possible to stockpile fluids for such an eventuality.

Because of their inherent physico-chemical properties, the plasma expanders will lend themselves to the study of certain fundamental physiological problems. These are: (1) measurement of membrane permeabilities, (2) further study of the reticuloendothelial system, (3) the nature of antigen-antibody reactions, (4) characteristics of cell surfaces and (5) the blood clotting mechanism.

VII. Summary:

1. A brief history of both Dextran and PVP, with discoverers and early workers is presented.

2. Chemistry of the two substances is discussed concerning preparation of the clinical products.

3. Physiological basis of action is described and the effects of both substances on the body is brought out.

4. Clinical Application of Dextran and PVP are presented. Various indications, methods, and results are reported on.

5. Some possible future uses of Dextran and PVP are presented.

VIII. Conclusions:

A. Dextran is a macromolecular polysaccharide produced by the action of a coccus, Leucenostoc mesenteriodes, on a sucrose solution. Its molecular weight approachs that of plasma albumin. It acts to maintain blood pressure in shock by replacing needed volume and also by its oncotic pressure due to the large molecules which prevents shift of fluid from extracellular to intracellular fluid compartments. The main route of excretion from the body is via the urinary route, where up to 50% of the infused product may be excreted in

24 hours. Some is metabolised in the body to CO_2 and H_2O and some leaves via the intestinal tract. Some changes in kidney tubule structure may be seen in the form of storage phenomenon. This does not affect vital function apparently.

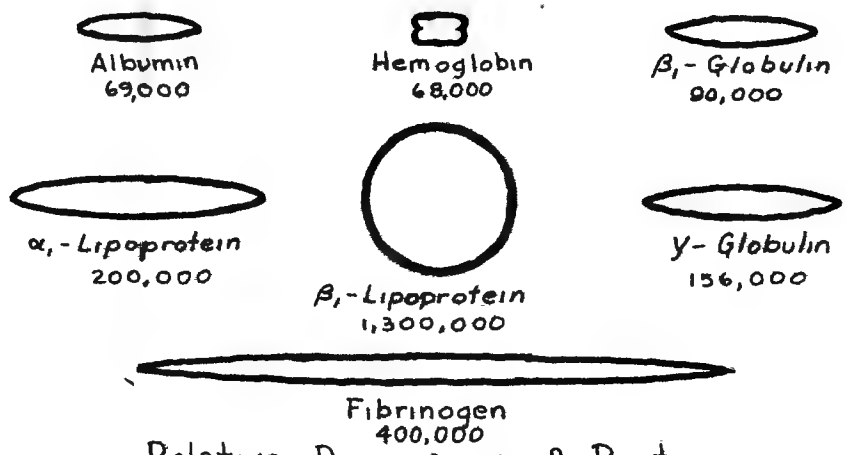
B. PVP is a macromoleucular product of acetylene chemistry which is used as a volemic substance. It is most effective when used in 3.5% concentration in Ringer's solution. Its mode of action is the same as that of dextran. Like Dextran it is excreted by the kidneys, but no fraction of PVP is metabolized by body tissues. Use of PVP may cause appearance of foam cells in the spleen and liver. Storage phenomena was prominent in the liver, but unfortunately cannot be fully evaluated at this time.

C. Use of these substances has been chiefly as volemic solutions to maintain blood pressure in shock cases, no matter what the cause. It is especially valuable in the management of traumatic shock since it can be administered early, perhaps before blood would be available.

D. These substances seem to be partially the answer in case of atomic attack since the supply is nearly inexhaustible, can be easily sterilized and

stored, is available at a lower price than blood or blood derivatives, and does not present a problem of spreading homologous serum jaundice, as does plasma.

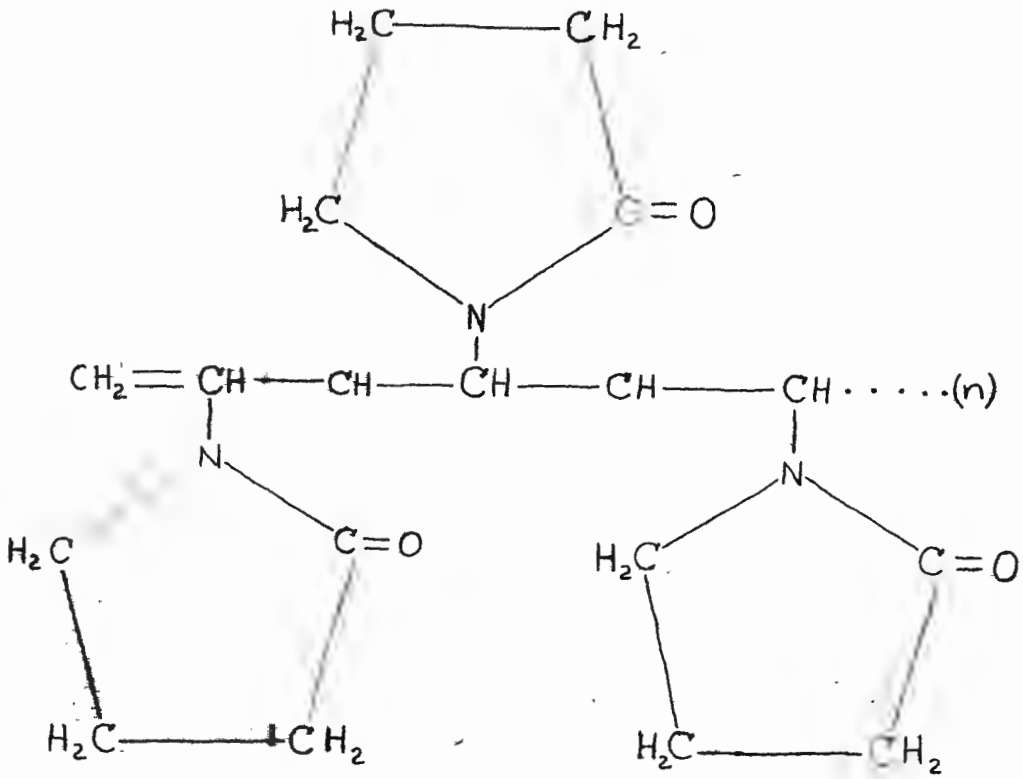
APPENDIX



Relative Dimensions of Protein Molecules in Blood

Figure 1

APPENDIX



Structure of PVP

Figure 2

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