

# Dextrans, Their Use in Surgery and Medicine

## With Emphasis on the Low Molecular Weight Fractions

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DEXTRANS have been known in the sugar industry since the latter part of the nineteenth century, as the carbohydrate slimes that clogged the pipes through which sucrose-containing solutions were carried. Pasteur, in 1861, showed that these slimes were formed by the action of bacteria, and in 1870 their carbohydrate nature was established (Scheibler, C.: *Zschr. Verdeutsch. Zucker. Ind.* 24: 309, 1874). It is ironical that a century later these ugly ducklings of the sugar industry are being introduced into medical practice as agents to improve blood flow in the vessels of the body.

### History

Historically, two lines of investigation led to the clinical use of dextran: (1) a search for a practical nontoxic plasma volume expander; (2) the study of microcirculation and the flow properties of the blood. The interest in a practical volume expander came about as an aftermath of both World Wars and received added impetus in the Korean War, when an acute shortage of blood was experienced and an alarming incidence of serum hepatitis following the use of pooled plasma was noted. The need for storage of unlimited amounts of a readily available plasma substitute in the advent of atomic warfare or mass disaster has become increasingly apparent.

Gum arabic was introduced by Bayliss (Bayliss, W. M.: *Proc. Roy. Soc. London* 89B: 380, 1917) in World War I and polyvinylpyrrolidone by the Germans in World War II. However, because of their retention in the liver and other organs without being metabolized

and because of certain other toxic factors, their clinical use was abandoned. Similarly, solutions of gelatin were found unsuitable because of gel formation at room temperature and because of their relatively small molecular size and rapid excretion in the urine. In addition, these and other colloid preparations gave rise to allergic reactions which made their use undesirable.<sup>1</sup>

In 1954, a group of Swedish scientists led by Crönwall and Ingelman<sup>2</sup> reported on the feasibility of using solutions of certain molecular weight fractions of dextran as plasma volume expanders. Since that time these solutions have been tested clinically in Sweden, in other European countries and in the United States. During the Korean War, dextran solutions were given an extensive trial in treatment of wounded soldiers with favorable results.<sup>3,4</sup> Thus a permanent place for the emergency use of dextran in hypovolemic shock was established.

In 1950, Thorsen and Hint<sup>5</sup> found that higher molecular weight fractions of dextrans resulted in red blood cell aggregation. The lower molecular fractions not only prevented aggregation but also counteracted some of these untoward reactions. Meanwhile, interest was rekindled in the suspension stability of the red blood cells, described by Fåhræus as early as 1921,<sup>6</sup> and in blood sludging, emphasized by Knisely<sup>7</sup> in 1945 and by Bigelow<sup>8</sup> in 1949.

In 1956, the classic report of Gelin<sup>9</sup> appeared, describing the circulatory disturbance, anemia, oliguria, and pathologic changes in various organs following injury and shock. These alterations were accompanied by aggregation and erythrocytosis and impaired flow in the small vessels. Later Gelin demonstrated that similar disturbances in blood flow can

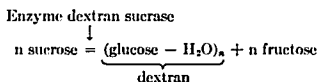
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be induced and reversed by infusion of dextrans of very high and low molecular weights, respectively. Thus, with increasing recognition of the importance of the rheologic properties of blood in health and disease, more interest has been expressed in the flow-enhancing qualities of certain fractions of dextran than in their ability to expand the blood volume. More recently another therapeutic possibility has been explored, the use of dextrans as antithrombogenic agents, and currently extensive experimental and clinical investigations are under way in this area.

### Chemistry

Dextrans are polymers of glucose produced by *Leuconostoc mesenteroides* and certain other bacteria through an enzymatic action upon sucrose:



In native dextran, the number of glucose units in the polymer is variable, resulting in a mixture of molecules of different chain lengths and molecular weights. In addition, depending upon the strain of bacteria, the detailed structure of the molecular glucose units, the type of bond linkage, and the degree of branching differ. These differences in molecular size, weight and structure have an important bearing on certain properties of dextrans, such as viscosity and ability to diffuse through semipermeable membranes. The dextran molecules suitable for clinical use have principally  $\alpha$  1-6 glycosidic linkages, with little branching. These facts also explain why dextrans prepared in different localities, because of different strains of dextran-producing organisms, may not be equivalent.<sup>1</sup>

From the ungraded dextrans, after purification, partial acid hydrolysis and fractionation, three types of dextran solutions have been prepared for clinical use:

(1) Low molecular weight dextran (Rheo-macrodex, a Swedish product) with an average molecular weight of 40,000, as 10 or 15 per cent solutions in glucose or saline.

(2) Medium molecular weight dextran (commercial dextran, United States and

Swedish products) with an average molecular weight of 75,000, in 6 per cent solution in saline.

(3) High molecular weight dextran (an English product) with an average molecular weight of 150,000. This dextran is not used clinically in this country. It must be differentiated from very high molecular weight dextran (several thousands—up to one million) which is used experimentally to produce intravascular aggregation and sludging.

It must be pointed out that these three types of dextran are not totally distinct in their chemical composition or properties. The upper end of the molecular spectrum of one type may overlap the lower end of the spectrum of another. For example, in low molecular weight dextran, 90 per cent of the preparation carries a molecular weight between 10,000 and 80,000. A small percentage possesses a higher weight falling within the range of the medium molecular weight dextran. Thus, to some extent, these two types of dextran share properties. Obviously, a narrower range of molecular weight distribution is more desirable for distinctive properties and avoidance of the side effects of the undesirable larger fractions.<sup>10</sup>

### Pharmacology

**Distribution and Fate of Dextran.** All dextran solutions, when infused, expand plasma volume. This is in contrast to normal saline which produces only a fleeting expansion of the plasma volume. The extent and duration of the expansion will depend upon the average molecular weight, the concentration and the rapidity of infusion of dextran.

Medium molecular weight dextran (dextran 75) expands plasma volume in accordance with the volume infused; this effect lasts up to four hours from the termination of infusion. A 10 per cent low molecular weight solution of dextran (dextran 40) correspondingly has a plasma volume expansion effect which lasts about 1½ hours. This does not imply, however, that all the infused dextran is eliminated from the plasma within these times. After infusion of 500 ml. of medium weight dextran a plasma concentration as high as 0.5 g./100 ml. may be present after 20 hours. Similarly,

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an appreciable quantity of low weight dextran may remain in the plasma hours after the plasma volume has returned to the pre-infusion value.<sup>11</sup> The plasma expanding effect of dextrans (in contrast to saline) is due to the colloid osmotic pressure. This depends upon the molecular weight, size and geometry of the dextrans and their relative inability to cross the semipermeable membranes of the body. The colloid osmotic (oncotic) effect should be differentiated from the total osmotic effect. The latter depends upon the number of particles regardless of the molecular weight. Actually, solutions of dextrans, because of the large and heavy particles, have much less total osmotic effect than solutions of saline of similar concentration. By the same token, a solution of low molecular weight dextran, because of lower average molecular weight, has more total osmotic effect and less oncotic pressure than a solution of medium molecular weight dextran of similar concentration. Thus, it takes a 10 per cent concentration of dextran 40 to achieve a colloid osmotic effect and a plasma expansion level equivalent to that of a 6 per cent concentration of dextran 75. Also, since lower molecular fractions of dextran 40 traverse the semipermeable membrane of the body, such fractions are found in the extracellular space and are filtered in the glomeruli. This explains the rapid excretion of dextran 40 and the associated osmotic diuresis, and why more than half of this dextran is excreted within three hours of termination of infusion.<sup>11</sup>

Dextran 75, because of the larger average molecular weight, is excreted more slowly (about 40 per cent in 12 hours) and exhibits very little diuretic effect, depending upon the amount of lower molecular fractions present. There is evidence that certain fractions of dextran diffuse into the cells and are stored for a time in the cytoplasm without producing toxic phenomena. The larger the molecular weight, the longer the storage time. However, permanent retention (unlike PVP and gum arabic) has not been reported.<sup>1</sup> Apparently the larger fractions are eventually metabolized.<sup>12</sup>

*Dextrans and Blood Viscosity.* Before the effect of dextrans upon blood viscosity is discussed, definition of a few terms is in order.

TABLE 1. Some Factors Which Increase Blood Viscosity

1. Increased aggregation of the red cells
2. Presence of macromolecules, increased level of fibrinogen, abnormal proteins and reversal of A/G ratio
3. Decreased internal fluidity of the RBC (affected by genetic factors, osmotic equilibria, nature of the red cell membrane)
4. Increased concentration of the blood cells and platelets (hemoconcentration, polycythemia, leukemia)
5. Low shear rate (decreased velocity gradient and slow flow rate)
6. Small and narrowed vessels
7. Vasoconstriction (autogenous or induced)
8. Axial concentration of the blood cells (plasma skimming effect)
9. Low pressure gradient
10. Decreased elasticity of the vessel wall
11. Rough endothelial surface of the vessels
12. Hypothermia
13. Low oxygen tension (as in sickle cell disease)
14. Acidosis

*Viscosity* (or resistance of flow) is defined as the ratio of shear stress to shear rate and is measured in poise or centipoise. *Shear stress* is the tangential force applied that causes sliding of one plane of fluid over an adjacent plane. This is expressed in dynes/cm.<sup>2</sup> *Shear rate* (or velocity of gradient) is the relative velocity between two moving parallel surfaces, expressed in units of inverse or reciprocal seconds (sec.<sup>-1</sup>). *Rheology* is the study of flow and deformation of matter.

Three basic types of flow systems have been described:

(1) *Newtonian*, in which viscosity is independent of time and rate of shear, as in water and chloroform.

(2) *Dilatant*, in which viscosity increases with increased shear rate, as in certain suspensions of polymers where there is a high concentration of dispersed particles in a minimum amount of liquid. With increased stress the particles become packed and form large aggregates.

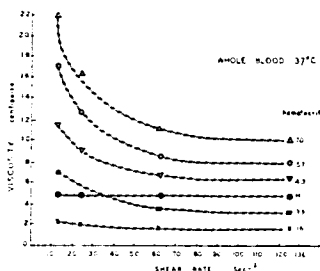


FIG. 1. Effect of hematocrit and shear rate upon blood viscosity. Note that with higher hematocrit values blood viscosity increases, and that this effect is further augmented at lower shear rates. (With permission from Wells, R. E., Jr., and Merrill, E. W.: J. Clin. Invest. 41: 1591, 1962).

(3) *Thixotropic*, describes a system in which viscosity decreases with increase in shear rate up to a critical value. Beyond the critical value the system behaves like Newtonian fluid and the viscosity remains constant and independent of further increase in shear rate.

According to Dintenfass,<sup>13</sup> in the thixotropic system there is a tendency toward flocculation or aggregation of particles exaggerated at lower shear rates. Such a system is reversible and time dependent. The recovery time may vary from a few microseconds to hours or days. Blood is considered to be a thixotropic system.

Blood viscosity depends upon a number of factors. Some of the factors that can increase blood viscosity are listed in table 1.

Poiseuille's law, though not entirely applicable to blood, indicates that flow is directly proportional to the diameter of a vessel and inversely proportional to viscosity. The study of viscosity of fluid, and that of blood in particular, is quite complex. The early observations with relatively high-shear viscometry had shown the influence of hematocrit values upon viscosity (fig. 1) at different shear rates. Determinations of blood viscosity with newer instruments that provide low shear rates (less than 0.1 sec.<sup>-1</sup>) reveal further differences in the thixotropy of the red blood cells and changes in plasma viscosity, hitherto obscure

(fig. 2).<sup>14, 15</sup> It must be realized that determination of viscosity of blood *in vitro* is not equivalent to that within the body. Observations of aggregation of erythrocytes in a glass tube connecting relatively large vessels do not reflect conditions within capillaries, venules and sinusoids.<sup>16</sup> Thus, it is not surprising that such data do not correlate with the pathologic states.

Infusion of very high molecular weight dextran or fibrinogen increases cellular aggregation and blood viscosity and produces erythrostasis, impaired microcirculation, decreased cardiac output and tissue anoxia. In the light of these observations, the finding of high levels of fibrinogen following injury or shock carries physiologic significance.

Low molecular weight dextran decreases both cellular aggregation and blood viscosity and minimizes reaction to infusion of higher molecular weight dextran. These effects are not all due to reduction of hematocrit. Litwin<sup>17</sup> has shown that despite hemodilution following infusion of high molecular weight dextran, the blood viscosity increases, especially at low shear rates. Gelin<sup>18</sup> has reported a decrease in hematocrit and blood viscosity in a severely burned patient one hour after infusion of low molecular weight dextran. However, 24 hours later the hematocrit had risen but the blood viscosity remained low.

The recent observations of Dintenfass<sup>13</sup> and Merrill and his associates<sup>19</sup> further confirm the fact that viscosity of blood varies not only with crowding of red blood cells (high hematocrit) but also with aggregation of the cells.

Low molecular weight dextran has been known to cause reversal of previously aggregated cells. This is achieved by adsorption of the dextran to the surface of the red blood cells. Aggregation of red blood cells does not require specific agglutinins. Agglutination occurs when adhesive forces (London, van der Waals electrostatic, etc.) between surfaces of individual cells is higher than the adhesive forces between the cells and the surrounding plasma. These adhesive forces are altered by the presence of various polar and nonpolar compounds showing surface-active properties.<sup>20</sup> Dextran 40 may also bring on changes in the internal fluidity of the cells and their ability

to change shape more readily in order to pass through capillaries.

### Blood Flow

It is generally agreed that the four cardinal factors which affect blood flow are (1) pressure produced by the cardiac pump, (2) blood volume, (3) vascular resistance and (4) blood viscosity. Normal blood pressure and blood volume do not necessarily guarantee adequate capillary flow. Shock is no longer considered a problem of blood pressure or hemoglobin concentration, but rather a problem of diminished flow at the capillary level and inadequate perfusion of the organs, hence the need for flow-improving agents in addition to volume replacement and restoration of effective pressure.

Inadequate capillary flow or poor tissue perfusion may be present because of excessive peripheral vascular resistance or increased viscosity. Proper interpretation of measurements of blood flow is also important. Gross blood flow to an organ can be determined either by direct collection of venous return or with a square wave electromagnetic flowmeter placed around the principal artery. Blood flow in the capillaries can be measured only indirectly. It has been observed that perfusion of an organ may be impaired despite normal blood flow measured in the major vessel (fig. 3).<sup>21</sup> This is explained on the basis of shunting between arterioles and venules with little distribution of blood to the capillaries.<sup>22</sup> Under such circumstances oxygen consumption will be low and arteriovenous oxygen difference small.

Another interesting phenomenon known as the "plasma skimming" effect should be mentioned. This means simply that when blood flows through capillaries with branches, the red blood cells occupy a position of axial flow. The plasma in the periphery tends to flow into the branches. Because of this "plasma skimming," there will be a gradual postcapillary accumulation of erythrocytes and selective hemoconcentration. This will result in higher blood viscosity and erythrocytosis.<sup>18</sup>

Another important aspect of blood flow to be emphasized is the priority system of the organs. For simple teleologic reasons, the brain and heart are paramount, the kidneys and

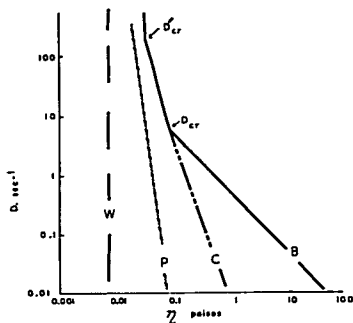


FIG. 2. Schematic representation of the flow curve of whole blood. Curve B indicates the flow curve of whole blood, while curves C, P, and W indicate viscosities of a deflocculated (disaggregated) blood, of plasma and of water, respectively. Contribution of the plasma polymers to the viscosity of blood is indicated by the area between lines W and P; it should be noted that the plasma itself is thixotropic, that is, viscosity decreases as the rate of shear ( $D$ ) increases. The second contribution to the viscosity of whole blood is the result of presence of the red cells; that is, the so-called crowding effect indicated by the area between lines P and C. These lines converge, and, therefore, the significance of a crowding effect decreases as the rate of shear increases. The area between lines C and B indicates structural viscosity, the result of reversible aggregation of red cells.  $D_{cr}$  indicates the critical rate of shear, above which the aggregates of red cells are no longer present.  $D'_{cr}$  indicates an assumed critical rate of shear corresponding to a complete gel-sol transition of the interior of the red cell. Numerical value of  $D'_{cr}$  is not yet known.  $D'_{cr}$  has been inserted into the figure for the sake of completeness of the rheologic picture. (Reproduced with permission from Dintenfass, L.: *Angiology* 15: 333, 1964.)

the musculoskeletal system at the bottom of the priority list in blood distribution. In states of circulatory inadequacy, blood is shunted away from the lower priority to the privileged organs. This selective distribution is of immediate importance to survival, but when unduly persistent or when the organism is not assisted in recovery, may result in damage to organs such as the kidney.

Infusion of both medium and low molecular weight dextran, as well as blood or plasma, improves gross blood flow and cardiac output when there is volume insufficiency. Low molecular weight dextran, in addition, provides

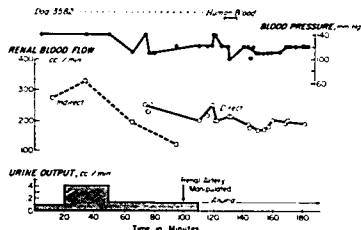


FIG. 3. Renal blood flow of a dog, determined simultaneously by an indirect method and directly by collection of blood from the renal veins. Note initial correlation between the two under stable conditions. However, following transfusion of incompatible human blood (20 ml./kg.), the animal becomes anuric and PAH clearance (which depends upon effective microcirculation) ceases, despite a relatively normal blood pressure, lack of apparent volume loss and fairly good renal blood flow measured directly. Note that at least 250 ml. of blood/minute passes through the kidneys of the dog without effective perfusion of the nephrons or significant renal function. This is a good example of impaired microcirculation in the face of fairly good blood flow in the large vessels.

better venous return than can be obtained with other agents (fig. 4).<sup>23</sup> This is presumably achieved by bringing into the circulation non-circulating pooled blood.<sup>24</sup> But the most unique property of low molecular weight dextran is improvement of flow in the capillaries even in the face of subnormal gross blood flow.<sup>21, 25</sup> This is achieved through prevention of red cell aggregation and in reduction of blood viscosity. It should be mentioned here that aggregation of blood cells occurs even in the healthy, and under normal conditions presents no problems.<sup>15</sup> In the presence of shock, injury, dehydration, vasoconstriction or certain diseases, however, blood flow is diminished and red cell aggregation is increased. This further curtails microcirculatory flow and results in poor tissue perfusion.

There is a growing body of evidence that blood coagulation is affected by blood viscosity and shear rate. Dintenfass<sup>26</sup> has found that the viscosity of abnormal blood (e.g., from patients with venous thrombosis) is 10 times greater than that of normal blood. It has been suggested that rapid aggregation of red cells may precede the initial stages of clotting. There is progressive increase in viscosity as

the blood flows from the relatively large vessels into the smaller vessels and capillaries. Concomitantly, there will be an increase in cellular aggregation with a corresponding decreasing velocity gradient. Thus, predisposition of certain sites of the vascular bed to thrombosis may be explained on the basis of hemodynamic consideration and changes in the rheologic properties of blood.

The importance of the effect of molecular and colloidal changes in plasma upon cellular aggregation and blood viscosity has already been referred to. It is conceivable that dextrans will also exert some influence upon these parameters.

### Clinical Use of Dextrans

The rationale for the clinical use of various dextrans should be apparent from the previous discussion. Dextrans are used principally for volume expansion, for improvement of microcirculation or for antithrombogenic effect (table 2).

(1) In hypovolemic shock, burns and peritonitis, dextran may be used as a blood volume

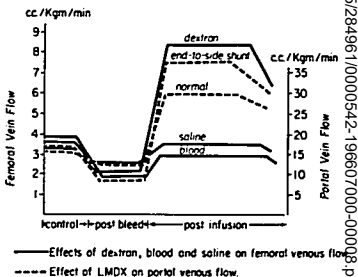


FIG. 4. Unique beneficial effect of low molecular weight dextran (LMDX) upon femoral (solid lines) and portal (broken lines) venous blood flow in dogs following bleeding (1.5 per cent of body weight). LMDX increased femoral venous blood flow to an average of 128 per cent above the control value and 254 per cent above the flow during the bleeding period. Autotransfusion of the shed blood and infusion with saline failed to result in a similar increase in femoral flow. Note the increase in the normal portal venous and in the porta caval shunt in another group of dogs which had received LMDX equal to the amount of blood removed. (By permission from Schwartz, S. I., and others: *Surgery* 55: 106, 1964).

TABLE 2. Characteristics of Various Dextrans

	Low Molecular Weight Dextran (Rheomacrodex)	Medium Molecular Weight Dextran (Macrodex, Commercial Dextran)	High Molecular Weight Dextran (British Dextran)
Average molecular weight	40,000	75,000	150,000
Range (90%) of molecules	10,000–80,000	25,000–200,000	25,000–1,000,000
Volume expansion	Fairly good, but transient	Good, lasts several hours	Good and prolonged
Relative increase in viscosity of RBC suspension in dextran with increasing hematocrit and decreasing shear rate	Least	Moderate	Marked
Effect on aggregation	Prevention—deaggregation	Slight variable	Very high fraction causes aggregation
Effect on microcirculation	Beneficial	Slight, if any	Detrimental
Antithrombogenic effect	Appreciable	Appreciable	Not studied

expander and plasma substitute. It must be pointed out that because of rapid excretion and a transient effect, low molecular weight dextran is not effective as a volume expander; its use for this purpose is therefore not recommended. Medium molecular weight dextran is preferred. Because of the hazard of increased bleeding tendency, the maximum amount to be given is limited (not exceeding 20 ml./kg./24 hours). The remaining volume deficiency should be corrected by blood, plasma, or balanced salt solutions. The apparent anemia observed following administration of dextrans is the result of hemodilution and is not a serious handicap. It is for the most part the acute hypovolemia, not the reduced red cell mass, that patients tolerate poorly. In the absence of hypovolemia, the patients survive with as little as 50 per cent of the red cell mass, at least temporarily. Anemia, to be sure, should be corrected later for the oxygen carrying capacity.

(2) When impaired microcirculation and poor tissue perfusion are present or anticipated, low molecular weight dextran is used for its beneficial qualities. The improvement is achieved not so much by volume expansion and hemodilution, but through prevention of cellular aggregation and reduction of blood viscosity.

The efficacy of medium weight dextran in this area is limited, useful only to the extent that it contains some of the lower fractions. Infusion of the high molecular weight dextran

actually may be deleterious because of increased blood aggregation and viscosity. Dextran 40 therefore may be indicated whenever impaired perfusion is present or anticipated, as in: shock of any etiology,<sup>26, 27, 28, 30</sup> local or generalized low flow states due to any cause,<sup>31</sup> prevention of acute renal failure,<sup>27, 28, 32, 34</sup> vascular insufficiency,<sup>27, 35–40</sup> extracorporeal circulation,<sup>41–47</sup> hypothermia and cold injury,<sup>48–52</sup> transfusion reactions,<sup>53</sup> anaphylactoid reaction,<sup>53</sup> drug toxicity,<sup>54, 55, 56</sup> fat embolism,<sup>57</sup> severe burns,<sup>58, 59, 60</sup> and organ preservation and transplantation.<sup>61–63</sup>

Space does not permit discussion of the experience of the numerous investigators with the use of dextran 40 in these conditions. The reader is referred to the bibliography for more detailed information. The theoretical reasons for the use of low molecular weight dextran under these circumstances seem to be sound. Sufficient experimental data are at hand in confirmation and initial clinical trials have been gratifying. However, well-controlled studies are necessary to prove the merit of dextran 40 beyond doubt.

Controversy over the efficacy of low molecular weight dextran has arisen because of failure to distinguish between the effect on the macro- and microcirculation. While several agents, including low molecular weight dextran, can improve blood flow in major vessels following shock, the superiority of dextran 40 cannot be appreciated unless the investigator determines the perfusion status of organs (fig.

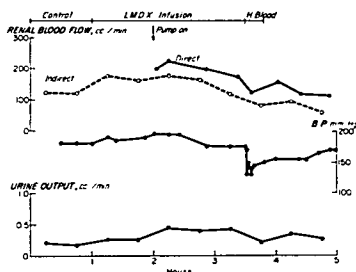


FIG. 5. Renal blood flow measured in a dog by a direct method and simultaneously estimated indirectly from PAH clearance. The indirect method reflects effective renal microcirculation. Note increase (25 per cent above the control value) in effective microcirculation after infusion of low molecular weight dextran, 10 ml./kg. Subsequent transfusion of incompatible human blood (20 ml./kg.) produced transient hypotension, but little change in the renal blood flow or in urinary output. (Compare with figure 3.) The close approximation of renal blood flow, by direct and indirect methods, remained parallel throughout the experiment, thus indicating that almost all of the amount of blood that flows in the major kidney vessels perfuses the nephrons. (From Atik, M.: *Amer. J. Surg.* 108: 384, 1964).

5). On the other hand, improvement in visceral function should not be expected upon infusion of dextran 40 in a normal individual with optimum perfusion. Another erroneous notion about low molecular weight dextran is to consider it as cure-all. A salutary effect should not be expected from the use of dextran 40 if cardiac function is not improved by correction of metabolic acidosis, electrolyte imbalance or by digitalization; if the volume loss is not replaced adequately with blood, or buffered saline; if respiratory acidosis or hypoxia is not corrected; if overwhelming infection is not controlled; if circulation to an organ is occluded for unduly long periods, or if damage to the tissue has already taken place. Dextran 40 should not replace the well-established therapies of surgery or medicine. It is considered a useful adjunct to improve blood flow where ultimately needed, at the tissue level.

When improvement of microcirculation is the objective, infusion of 10-15 ml./kg./24 hours of 10 per cent solution of dextran 40 in

saline is sufficient in addition to other appropriate fluid therapy. To establish a therapeutic level, 100 ml. of the agent is infused rapidly in about  $\frac{1}{2}$  hour, the rest infused slowly over several, preferably 24, hours to maintain the level. This infusion is continued for several days, until the dangers of impaired perfusion have been eliminated.

The best results from low molecular weight dextran are obtained if given early in the course of disease or upon anticipation of major circulatory disturbance; for example, soon after arrival at the hospital of a severely injured patient in shock; upon the start of anesthesia in an elderly man scheduled for resection of aortic aneurysm; and, when rapid transfusion is contemplated and release of a nephrotoxic substance is suspected.

The clinical use of dextrans as antithrombogenic agents is relatively new and quite intriguing. The medium molecular weight and the lower molecular weight dextrans both have been found to be beneficial in maintaining patency of vascular prostheses and sutured smaller vessels following anastomoses.<sup>67, 68</sup> Low molecular weight dextran offers the additional advantage of maintaining better perfusion of an organ or limb through the collateral circulation<sup>69</sup> during the temporary occlusion of major vessels.

Under the supervision of the author, 500 ml. of low molecular weight dextran have been infused during operation and daily for one to three days postoperatively in over 100 cases of elective vascular surgery. There has been no incidence of early thrombosis or progression of ischemia, except in two cases where the circulation could not be re-established at the time of operation. These operations consisted of aneurysmectomy with graft replacement, ileofemoral bypass grafting, thromboendectomy, renal and carotid angioplasty, venous thrombectomy and porta-caval shunt.<sup>70</sup>

The data from several medical centers regarding treatment of acute thrombophlebitis with dextrans are impressive. Our own experience has also been gratifying. Within the past year on the author's service, heparin and other anticoagulants have been replaced by dextran for treatment of all forms of thromboembolism. However, effectiveness and rapidity



of the response to treatment have been found to depend upon the duration of disease before institution of therapy.

While some authors have reported a better antithrombogenic effect with the medium molecular weight than with the low molecular weight dextran, we have not noticed a difference.<sup>27, 71-76</sup> This discrepancy may be due to the failure of some investigators to infuse low molecular weight dextran over a sufficiently long period. Low molecular weight dextran is excreted more rapidly than the medium weight dextran, hence requires a longer continuous infusion time.

The mechanism underlying the antithrombogenic effect of dextran is not known. Hemodilution, coating of the injured intima, adsorption on the surface of the red blood cells and platelets, production of repelling negative electrostatic charge and decreased aggregation and blood viscosity have been proposed as explanations.<sup>15, 77, 78, 79</sup>

Sickle cell crisis is a special type of impaired microcirculation where low molecular weight dextran may be profitably used. Here is an interesting example of how an alteration in a genetically controlled amino acid of the hemoglobin molecule brings about a marked increase in the internal structural viscosity of erythrocytes, responsible for changes in the shape of the red cell. This increased structural viscosity of the red blood cells, coupled with their bizarre shapes, leads to marked aggregation and erythrocytosis in the capillaries and venules where blood flow is reduced and the shear rate is quite low. Thus, a vicious cycle is produced. Flow is further reduced and erythrocytosis extended proximally into arterioles eventually resulting in thrombosis of these small vessels. It is interesting to note that such a chain of events often occurs in the anemic patient. Dintenfass postulates that the "plasma skimming" and increased hematocrit in the capillaries provide a plausible explanation for the localized blockage in the microcirculation.<sup>80</sup>

The reduction of pain in sickle cell crisis following infusion of low molecular weight dextran has not been uniform, possibly because pain is subjective and its evaluation difficult. The eventual reduction is sickling tend-

ency and associated pain depends upon the effectiveness of the correction of the precipitating cause (e.g., pneumonia, pyelonephritis, etc.). Promptness of therapy also has bearing.<sup>81</sup> However, when given prophylactically, low molecular weight dextran may prove useful in prevention of hemolysis and other serious manifestations of crisis. In the past four years we have observed 7 patients with known sickle cell disease who have undergone major operation. Three developed severe crises with jaundice, 2 following cholecystectomy and one after skin grafting. The other 4, who received dextran 40 prophylactically, showed no apparent evidence of sickling crisis following operations which consisted of cholecystectomy in two, drainage of subphrenic abscess in one, and skin grafting in a fourth. It is pertinent that two of these patients had developed crises following previous operations.

### Toxicity and Side Reactions

Major toxicity has not been observed with either of the two dextrans used clinically. Anaphylactoid reactions to the commercial medium weight dextran, however, have been reported sporadically. Dextrans, especially the higher molecular weight fractions, may act as heptenes and manifest antigenic properties but are not considered complete antigens. Another explanation for the occasional untoward reaction is the presence of impurities. With currently improved pharmaceutical preparations, these reactions are becoming less frequent.

The increased bleeding tendency reported in conjunction with infusion of dextrans may have been the result of one of several factors:

(1) The use of high molecular weight dextran, now abandoned for clinical use. Infusion of high molecular weight dextran prolongs the bleeding and coagulation time, induces thrombocytopenia and reduction of fibrinogen and other coagulation factors. According to Bergentz and his associates,<sup>82</sup> these changes are due to aggregations of platelets resulting in intravascular coagulation and consumption of coagulation factors. Infusion of therapeutic doses of low molecular weight dextran, in contrast, does not result in similar changes.<sup>83</sup> Gelin and his associates<sup>83</sup> have reported a

TABLE 3. Comparison of Dextrans Used Clinically

	Low Molecular Weight Dextran	Medium Molecular Weight Dextran	High Molecular Weight Dextran
Principal uses	<ol style="list-style-type: none"> <li>1. To improve microcirculation in shock and other low flow states</li> <li>2. For antithrombogenic effect</li> <li>3. In oliguria, to prevent acute renal failure</li> </ol>	<ol style="list-style-type: none"> <li>1. For emergency plasma volume expansion in hypovolemic shock, burns</li> <li>2. For antithrombogenic effect</li> </ol>	<ol style="list-style-type: none"> <li>1. For investigation; not recommended for clinical use</li> </ol>
Dosage	<ol style="list-style-type: none"> <li>1. 10-15 ml./kg./24 hours of 10% solution in saline,* daily for 3 to 5 days. To be given over 12-24 hours, preferred continuously</li> </ol>	<ol style="list-style-type: none"> <li>1. Up to 20 ml./kg. of 6% solution in saline in 6 hours for volume expansion</li> <li>2. 10-15 ml./kg./24 hours for 3 to 5 days for antithrombotic effect. To be given over 6-8 hours daily</li> </ol>	
Untoward effects			
1. Anaphylactic, allergic reactions	None reported	Occasionally seen	
2. Pulmonary edema	May be seen if given rapidly	More apt to occur if given rapidly	
3. Increased bleeding	Rarely seen at the recommended doses and speed of administration	Occasionally may be seen	
Excretion	Rapid by the kidney	Slow by the kidney	
Diuretic effect	Moderate, variable	Slight if any	
Interference with blood typing and cross-matching	Has not been reported; counteracts cold agglutinins	Has been reported	
Contraindications	<ol style="list-style-type: none"> <li>1. Marked thrombocytopenia</li> <li>2. Pulmonary edema</li> </ol>	<ol style="list-style-type: none"> <li>1. Coagulopathy of any cause</li> <li>2. Congestive heart failure and pulmonary edema</li> </ol>	

\* The preparation in dextrose solutions is used when saline is contraindicated.

slight and transient drop in platelet count, prolongation of bleeding time and other minor changes in hemostatic mechanism following infusion of 1,000 ml. of low molecular weight dextran to healthy subjects over a two-hour period. Thus, infusion of dextran in patients with thrombocytopenia and other bleeding diatheses is contraindicated.

(2) The use of large doses or too-rapid infusion of either medium or low molecular weight dextran. Longerbeam and Lillehei,<sup>84</sup> in their early experience with the use of low molecular weight dextran for treatment of shock, infused unduly large amounts (50 to 70 ml. of 10 per cent solution per kg. of body

weight). This dosage is four to five times higher than the recommended dosage and readily explains the bleeding which followed and the subsequent lack of enthusiasm for the use of low molecular weight dextran.

(3) Use of dextran in conjunction with heparinization in standard doses may give rise to excessive bleeding. Apparently dextran potentiates the heparin effect. To our knowledge this phenomenon has not been studied quantitatively, and further investigation in this area is needed. We have, however, empirically cut down the recommended dosage of heparin by one-half or one-third whenever dextran has been used concomitantly with heparin.

Development of pulmonary edema is another potential hazard associated with the use of dextrans. Here again, excessively rapid infusion or large doses may result in volume expansion beyond the capacity of the heart. If dextrans are given at the recommended dosage and if central venous pressure is monitored, this complication should be a rarity (table 3).

### Summary

Dextrans are polymers of the same basic chemical unit, glucose. They vary markedly in physiochemical properties and pharmacologic effects, depending upon internal arrangement and molecular weight.

Two types of dextran solutions are suitable for clinical use: (1) medium molecular weight dextran (average molecular weight of 75,000), used primarily for the colloidal osmotic effect to temporarily sustain plasma volume in hypovolemic shock; (2) low molecular weight dextran (average molecular weight of 40,000) used principally to reduce blood viscosity and cellular aggregation and to improve microcirculation at low flow states due to any cause. In this context, it has numerous potential applications. The plasma expanding properties of this type of dextran are transient; its use for this purpose is not recommended.

Both the medium and low molecular weight dextrans have been used as antithrombogenic agents with favorable results in the treatment of thrombophlebitis and in conjunction with vascular surgery.

The two dextrans when used with an understanding of their merits and limitations are safe and useful. They should be thought of as adjuncts to reduce the adverse effects of inadequate circulation. They should not supplant appropriate specific measures to correct disease, injury or deficiencies which initiate pathophysiologic disturbances in the circulation.

Before dextrans find wider application and their attributed merits find support, further investigation and well-controlled clinical studies are necessary. Nevertheless, the basic experience with dextrans, limited as it is, has focused attention on rheology, a science which promises an intriguing and widespread application in the medicine of tomorrow.

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**PLATELET TRANSFUSIONS** There is no truly scientific quantitative way to measure the effectiveness of platelet transfusion in human beings. One is always left with a value judgment based on clinical experience in which one cannot eliminate the possibility of the improvement being spontaneous. (Cronkite, E. P.: *Measurement of the Effectiveness of Platelet Transfusions*, *Transfusion* 6: 18 (Jan.) 1966.)

**PLATELET TRANSFUSIONS** With the present limited supply of fresh platelets and relatively limited serological tests for detecting immunization, it is not yet practical to crossmatch platelets routinely. However, with the progress of preserving platelets for transfusion and phenotype cells for significant antigens, it is quite likely that selection of appropriate donors will greatly extend the effectiveness of platelet transfusions. At present, empirical selection of donors based on survival of transfused platelets appears to be the best approach to platelet transfusion in sensitized individuals. (Shulman, N. R.: *Immunological Considerations Attending Platelet Transfusion*, *Transfusion* 6: 39 (Jan.) 1966.)

**SICKLE CELL TRANSFUSION** A random survey of 300 blood donors at Kings County Hospital was undertaken to determine what percentage of donors had abnormal hemoglobin traits. The incidence of sickle cell trait was found to be 4.7 per cent, e.g., a recipient at this hospital has almost a one in 20 chance of receiving sickle trait blood. In 13 patients receiving known sickle cell trait blood, no adverse effects were noted clinically. It is concluded from these studies and the almost total lack of any report in the literature of an ill-effect of sickle cell trait transfusion that transfusing sickle cell erythrocytes into patients is not hazardous. (Kaufman, M., and others: *Sickle Cell Trait in Blood Donors*, *Amer. J. Med. Sci.* 249: 56 (Jan.) 1965.)