Metabolic and Hemodynamic Changes Induced by the Prolonged Administration of Dextran

By John R. Jaenike, M.D., and Christine Waterhouse, M.D.

Large amounts of dextran were administered to human subjects under standardized metabolic conditions, with the following results: Dextran is a potent osmotic substance which produces marked salt and water retention and rapid plasma volume expansion. About 50 per cent of the amount given is excreted in the urine during the injection period. Nitrogen and phosphorus sparing and an antiketogenic effect are produced during the period of administration. A fraction of the dextran remains circulating for a prolonged period of time and is associated with a sustained depression of venous hematocrit. Metabolism of this fraction cannot be demonstrated, and its ultimate fate in the body is unknown.

The present study was set up for the purpose of determining the nature and duration of the hemodynamic and metabolic changes induced by dextran. In addition an attempt has been made to define quantitatively the ultimate fate of dextran, and to correlate this information with the observed hemodynamic and metabolic effects. Human subjects, showing no evidence of cardiovascular or metabolic disease, were selected for this purpose. Dextran* was administered in large amounts and relatively long-term observations were carried out.

Procedures and Patients

The clinical background of the patients concerned in this study was as follows:

S. M., a Negro male, age 47, was admitted because of increasing dementia. A diagnosis of syphilis of the central nervous system with paresis was established. The process was considered inactive, and his clinical disease remained unchanged during the course of study.

W. W., a Negro male, age 38, and J. J., a Negro male, age 43, had syphilis of the central nervous system with predominant meningoovascular involve-

* The dextran used in this study was generously supplied by Commercial Solvents Corporation. Although several lots were administered, the molecular weights of various lots were relatively uniform. Molecular weight ranged from 25,000 to 185,000 with an average of 70,000.
ment. Both were treated with penicillin and showed clearing of the acute process at the time of this study.

T.L., a white female, age 58, had a chronic stasis dermatitis with epidermophytosis and generalized id reaction. No other organic disease was in evidence.

G.D., a white male, age 23, was a patient with idiopathic epilepsy. He was otherwise clinically well. Two separate studies were performed on G.D., and will hereafter be designated as G.D. No. 1 and G.D. No. 2.

M.L., a white female, age 19, had a chronic neurodermatitis involving chiefly the head, ears, and perineal region. It was felt that psychogenic factors were of prime importance in her disease. The dermatitis was well controlled at the time this study was initiated.

R.T., a white male, age 21, was considered to have a psychopathic personality disorder. Despite a history of rheumatic fever, no definite evidence of residual cardiac damage was present, and there was otherwise no evidence of organic disease.

All subjects were admitted to a special metabolic division where well-controlled balance studies could be conducted. Diets were weighed and cooked under the supervision of the dietitian, and sample diets, duplicating in all respects the food served to the patients, were analyzed frequently throughout the course of the experiments.

Nitrogen, phosphorus, calcium, sodium, chloride, and potassium balances were carried out on all patients. Urine was collected in 24-hour periods, analyzed daily, and the results checked on pooled aliquots at the end of the metabolic periods. Stools were pooled into corresponding periods, separation being accomplished with carmine markers.

Each subject received a low caloric, low carbohydrate diet which induced ketosis in all, and negative nitrogen balance in all subjects but two (T.L. and M.L.).

A constant daily diet was given to five subjects, and two- and three-day rotating diets to S.M. and R.T., respectively. In the latter instance, the daily intake varied but slightly in composition.

Repeated dietary analyses revealed the following average daily intakes:

<table>
<thead>
<tr>
<th>Sub.</th>
<th>N Gm.</th>
<th>P Gm.</th>
<th>Ca Gm.</th>
<th>Na mEq.</th>
<th>Cl mEq.</th>
<th>K mEq.</th>
<th>Calories</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.M.</td>
<td>10.55</td>
<td>.88</td>
<td>.328</td>
<td>172</td>
<td>171</td>
<td>52</td>
<td>1173</td>
</tr>
<tr>
<td>W.W.</td>
<td>8.06</td>
<td>.90</td>
<td>.307</td>
<td>114</td>
<td>114</td>
<td>54</td>
<td>1064</td>
</tr>
<tr>
<td>J.J.</td>
<td>8.06</td>
<td>.90</td>
<td>.620</td>
<td>158</td>
<td>152</td>
<td>34</td>
<td>1028</td>
</tr>
<tr>
<td>G.D. #1</td>
<td>10.32</td>
<td>.87</td>
<td>.53</td>
<td>78</td>
<td>76</td>
<td>56</td>
<td>1293</td>
</tr>
<tr>
<td>G.D. #2</td>
<td>10.23</td>
<td>.88</td>
<td>.49</td>
<td>80</td>
<td>81</td>
<td>53</td>
<td>1312</td>
</tr>
<tr>
<td>M.L.</td>
<td>10.47</td>
<td>.86</td>
<td>.543</td>
<td>65</td>
<td>65</td>
<td>61</td>
<td>1203</td>
</tr>
<tr>
<td>T.L.</td>
<td>9.03</td>
<td>.83</td>
<td>.446</td>
<td>23</td>
<td>21</td>
<td>56</td>
<td>976</td>
</tr>
<tr>
<td>R.T.</td>
<td>10.19</td>
<td>.87</td>
<td>.48</td>
<td>73</td>
<td>74</td>
<td>52</td>
<td>1210</td>
</tr>
</tbody>
</table>

Five Gm. of sodium chloride were added daily to the diets of S.M., W.W., and J.J., and are included in the above dietary analyses. During the period of dextran administration the dietary salt supplement was withdrawn, and an equivalent amount was given in the infusions. G.D. No. 2, M.L., and T.L. received supplemental intravenous saline daily during the control period immediately preceding dextran administration, corresponding to the quantity given in the dextran infusions. The two remaining subjects, G.D. No. 1 and R.T., received no supplemental salt, and consequently their sodium chloride intake was considerably higher during the dextran period.

Dextran was administered intravenously to all subjects; 6 per cent dextran in 0.9 per cent sodium chloride solution was given in five experiments, in the following dosage:

<table>
<thead>
<tr>
<th>Sub.</th>
<th>Daily infusion cc.</th>
<th>Gm dextran daily</th>
<th>Days given</th>
<th>Total dextran dose, Gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.D. #1</td>
<td>2000</td>
<td>120</td>
<td>6</td>
<td>720</td>
</tr>
<tr>
<td>G.D. #2</td>
<td>2000</td>
<td>120</td>
<td>6</td>
<td>720</td>
</tr>
<tr>
<td>M.L.</td>
<td>2000</td>
<td>120</td>
<td>4</td>
<td>480</td>
</tr>
<tr>
<td>T.L.</td>
<td>2000</td>
<td>120</td>
<td>2</td>
<td>240</td>
</tr>
<tr>
<td>R.T.</td>
<td>1000</td>
<td>60</td>
<td>10</td>
<td>570</td>
</tr>
</tbody>
</table>

Subject R.T. received only 30 Gm. of dextran on the eighth day of administration, thus accounting for a total dose of only 570 Gm.

Twelve per cent dextran in 0.5 per cent sodium chloride was administered to three subjects: S.M., W.W., and J.J. Each received 1000 cc. daily (120 Gm. dextran) for six days, a total dose of 720 Gm.

For brevity's sake, the period of dextran administration will hereafter be referred to simply as the "dextran period."

Suitable control observations were made prior to the dextran period to allow each subject to equilibrate metabolically with the diet. This usually required 10 to 18 days. Balance studies were continued following dextran until metabolic data returned to control levels.

Serum electrolyte and protein concentrations and venous hematocrit were determined at the beginning of each metabolic period, and more frequently when indicated. Urine dextran levels were determined daily until excretion became negligible, and serum concentrations were measured at frequent intervals.

The degree of ketosis was estimated from blood ketone determinations in three subjects, and urinary acetone tests in the remainder.

Renal function was evaluated by inulin and para-aminohippurate (PAH) clearance determinations and determinations of maximum tubular excretory capacity for para-aminohippurate (TrPAH) in two subjects, and urea clearance tests in the remainder.

**Methods**

The analytic procedures were carried out as follows: nitrogen in the urine, diet, and stool was
determined by macro-Kjeldahl; phosphorus in the diet, urine, and stool by a modification of the method of Fiske and Subbarow; calcium in the diet, urine, and stool by the method of Kochakian and Fox; sodium and potassium by internal standard flame photometry; chloride by the Volhard titration, following digestion by the open Carius method. Serum proteins were determined electrophoretically in a Tiselius apparatus and turbidometrically using cationic detergents. Serum and urine dextran was determined by the anthrone method. Inulin and para-aminobiphrurate were determined as outlined by Goldring and Chasis.

Blood ketone concentrations were estimated by a modification of the Scott-Wilson method. The insoluble ketomercureic compound formed was quantified turbidometrically in a Lumetron colorimeter against acetone-reagent standards. This method, while not precise, proved an adequate gage as to the degree or ketonemia present. Urinary acetone was estimated by Rothera's nitroprusside method. Venous hematocrit was determined as described by Wintrobe. Serum osmotic pressures were determined by the vapor pressure method of Baldes and Hill.

Plasma volume was estimated from changes in hematocrit, according to the following formula:

\[ PV_2 = PV_1 \times \frac{H_1(100-H_2)}{H_2(100-H_1)} \]

where \( PV_2 \) = unknown plasma volume; \( PV_1 \) = control plasma volume; \( H_1 \) = control hematocrit and \( H_2 \) = hematocrit at time of \( PV_2 \).

A control plasma volume of 50 cc. per kilogram of body weight was assumed in all subjects. The validity of this equation is dependent upon the assumption that total blood volume varies inversely with the venous hematocrit. The latter premise may be considered valid if: (1) total red cell mass remains unchanged during the period of study, and (2) changes in venous hematocrit are reflective of hematocrit changes in the entire vascular compartment.

Results

Clinical Effects of Dextran

All subjects tolerated the dextran infusions well. There were no vasomotor or pyrogenic reactions. In all instances weight was gained during the dextran period, from 3 to 5 Kg., in those subjects receiving large amounts, 720 Gm. over a six-day period. Headache, presumably due to expanded plasma volume, was occasionally experienced several hours after an infusion.

In two subjects it was necessary to discontinue the injections because of complications. T.L. developed evidence of pulmonary congestion after two days (240 Gm.) of dextran. This patient had no previous evidence of cardiac disease, but was mildly hypertensive and was in an older age group. It was apparent that the rapid plasma volume expansion routinely resulting from dextran administration precipitated cardiac failure in a subject with a reduced cardiac reserve.

Subject M.L. experienced an exacerbation of her chronic dermatitis, manifest on the third day of dextran administration. The skin lesions became exudative and hemorrhagic. The severity of the exacerbation necessitated discontinuance of dextran administration, and the large protein and electrolyte losses from the skin invalidated subsequent metabolic data.

A bleeding tendency was noted in M.L., and in all subjects receiving 12 per cent dextran. J.J., W.W., and S.M. showed microscopic hematuria and bleeding from venipuncture sites and the gums. In addition W.W. had epistaxis, a subconjunctival hemorrhage, and prolonged bleeding from shaving cuts. M.L. experienced a brief episode of metrorrhagia, in addition to the bleeding into the skin lesions.

In all instances bleeding appeared after two to four days of dextran administration, and subsided two days after discontinuing the infusions. Bleeding time was prolonged in these subjects, and clotting time normal. Prothrombin concentration and consumption in J.J. and W.W. were not significantly depressed. No hematologic studies were performed in the remaining subjects in this study.

Hematocrit and Calculated Plasma Volume

As shown in table 1, in all subjects the venous hematocrit fell during dextran administration. This was most striking in those subjects receiving 12 per cent dextran, in whom an average decrease of 23 per cent below control values was observed. Two subjects (W.W. and J.J.) showed a continuing fall in hematocrit after the discontinuance of dextran, reaching a low point in 16 and 13 days respectively. (See figures 2 and 4.) A similar, but less marked, tendency was noted in T.L.
The maximum hematocrit depression occurring in G.D. no. 2 after only two infusions may be related to prior plasma volume expansion by the administration of intravenous saline in the predextran control period. In all subjects the hematocrit remained depressed throughout the period of observation, which exceeded 40 days in four subjects.

Plasma volume expansion, calculated from the venous hematocrit, exceeded 90 per cent of control levels in two subjects (table 1).

**Serum Proteins**

Serum protein concentration fell in all subjects during the dextran period, the decrease ranging from 22 to 53 per cent below control levels (table 2). In all instances, the globulin concentration fell relatively more than the albumin. Total circulating protein appeared to decrease in all but one subject after the course of dextran, accounted for largely by a fall in the globulin fraction.

In four subjects there was an apparent rise of total circulating protein above control levels occurring from 13 to 23 days after the dextran period (table 3). The rise was greater than 30 per cent in all, and appeared to be significant. Failure to observe this phenomenon in the other subjects in this study may be attributable to the relatively short period of observation following dextran, as there was only one subject in this group in whom serum...
proteins were followed for more than 12 days after the dextran period. All patients receiving 12 per cent dextran manifested a rise in circulating proteins, most marked in the albumin fraction. In M.L., circulating albumin and globulin increased approximately in equivalent amounts. Figures 2 through 4 depict this post dextran rise in circulating proteins in the subjects receiving 12 per cent dextran. As noted there, this rise appears to occur as serum dextran concentration and total circulating dextran levels are falling. This change was accompanied by a concomitant rise in plasma volume in all three subjects, despite the fact that dextran was being the circulation. In contrast, figure 1 reveals the changes seen in G.D. no. 2, in whom a significant rise in circulating protein and further expansion of plasma volume were not observed. This was the usual course seen in the remaining patients in this study, although observations were of shorter duration in this group.

Fate of Administered Dextran

Calculations of the fractions of dextran excreted, circulating and unaccounted for were made on each subject and are presented in table 4. Urinary excretion was maximal during the dextran period, when it accounted for over 50 per cent of that injected, in all but one subject. Excretion rapidly diminished thereafter and was negligible several days after the dextran period.

The maximal serum dextran concentrations shown in table 4 were present at the end of the dextran period. Levels of 3170 mg. per 100 cc. were attained in subjects receiving 12 per
dextran re-entered the circulation at this point. Serum dextran concentration and total circulating dextran diminished very slowly in W.W. (fig. 2), relative to other subjects in this study, and he showed a continuing plasma volume expansion during this period. Significant serum dextran concentrations, greater than 200 mg. per 100 cc., were observed in three subjects (S.M., J.J., G.D. no. 1) 46, 58, and 110 days following the dextran period. No other long-term observations were made.

Circulating dextran was calculated from the serum concentration and estimated plasma volume. As shown in table 4, 11.2 to 32.5 per cent of administered dextran was intravascular at the end of the dextran period. The remainder of the dextran injected was unaccounted for, and is presumed to have been metabolized or present in extravascular fluid or body cells.

**Metabolic Effects**

**Nitrogen and Phosphorus.** As shown in table 5, nitrogen and phosphorus were observed in all subjects during the dextran period, and, occasionally, to a lesser extent in the immediate postdextran control period. This effect was manifested on the second or third day of injections, and rapidly diminished following the dextran periods. Only three subjects (S.M., W.W., and J.J.) were on identical regimens, and in these a comparable metabolic effect might be expected. Complications necessitating the cessation of dextran
administration in M.L. and T.L., and failure to allow for equilibration with an increased salt intake in G.D. preclude a comparative quantitation of metabolic effects in these subjects. The metabolic data on R.T. are incomplete and thus are excluded from this presentation.

An effort has been made to correlate the degree of nitrogen and phosphorus sparing with the amount of dextran unaccounted for in the three subjects receiving 12 per cent dextran. For this purpose, it must be assumed that a constant fraction of this dextran moity is metabolized from one subject to the next. As shown in Table 6, there appears to be a relationship between the metabolic effect and the amount of dextran "metabolized." J.J., in whom the most pronounced nitrogen and phosphorus sparing was observed, showed the largest fraction of dextran unaccounted for. Glucose was administered to subject S.M. in an attempt to correlate its metabolic effect with that of dextran; 12 and 24 Gm. daily for six day periods elicited no metabolic

<table>
<thead>
<tr>
<th>Subject</th>
<th>Period</th>
<th>Days</th>
<th>Body Wt. Kg.</th>
<th>Nitrogen (Average per day)</th>
<th>Phosphorus (Avg. per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In</td>
<td>Urine</td>
</tr>
<tr>
<td>S. M.</td>
<td>I</td>
<td>6</td>
<td>78.22</td>
<td>10.55</td>
<td>11.02</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>6</td>
<td>76.38</td>
<td>10.55</td>
<td>9.80</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>6</td>
<td>79.24</td>
<td>10.55</td>
<td>11.03</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>6</td>
<td>79.22</td>
<td>10.55</td>
<td>11.12</td>
</tr>
<tr>
<td>W. W.</td>
<td>I</td>
<td>5</td>
<td>66.42</td>
<td>9.08</td>
<td>9.99</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>6</td>
<td>66.08</td>
<td>9.08</td>
<td>8.78</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>7</td>
<td>69.42</td>
<td>9.08</td>
<td>10.00</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>5</td>
<td>66.51</td>
<td>9.08</td>
<td>10.25</td>
</tr>
<tr>
<td>J. J.</td>
<td>I</td>
<td>5</td>
<td>67.22</td>
<td>8.06</td>
<td>11.52</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>6</td>
<td>65.51</td>
<td>8.06</td>
<td>9.36</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>6</td>
<td>69.03</td>
<td>8.06</td>
<td>9.85</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>3</td>
<td>68.01</td>
<td>8.06</td>
<td>10.43</td>
</tr>
<tr>
<td>G. D. #1</td>
<td>I</td>
<td>4</td>
<td>55.72</td>
<td>10.32</td>
<td>12.48</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>5</td>
<td>55.13</td>
<td>10.32</td>
<td>9.43</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>5</td>
<td>60.00</td>
<td>10.32</td>
<td>10.38</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>6</td>
<td>55.93</td>
<td>10.32</td>
<td>13.13</td>
</tr>
<tr>
<td>G. D. #2</td>
<td>I</td>
<td>8</td>
<td>57.18</td>
<td>10.23</td>
<td>11.14</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>6</td>
<td>56.28</td>
<td>10.23</td>
<td>10.41</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>9</td>
<td>59.48</td>
<td>10.23</td>
<td>12.09</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>7</td>
<td>54.08</td>
<td>10.23</td>
<td>13.97</td>
</tr>
<tr>
<td>T. L.</td>
<td>I</td>
<td>8</td>
<td>88.77</td>
<td>9.93</td>
<td>8.04</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>2</td>
<td>86.87</td>
<td>9.93</td>
<td>6.80</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>6</td>
<td>88.66</td>
<td>9.93</td>
<td>6.80</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>6</td>
<td>87.54</td>
<td>9.93</td>
<td>7.83</td>
</tr>
<tr>
<td>M. L.</td>
<td>I</td>
<td>4</td>
<td>73.80</td>
<td>10.47</td>
<td>7.98</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>4</td>
<td>72.75</td>
<td>10.47</td>
<td>6.00</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>8</td>
<td>74.03</td>
<td>10.47</td>
<td>5.25</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>5</td>
<td>71.63</td>
<td>10.47</td>
<td>5.96</td>
</tr>
</tbody>
</table>

Table 5.—Nitrogen and Phosphorus Metabolism in Subjects Receiving Dextran

I—Pre-dextran control period; II—Dextran period; III—First postdextran control period; IV—Following control period.

Body weight recorded is that at the onset of each metabolic period.

Table 6.—Relation between Nitrogen and Phosphorus Sparing and Calculated Dextran Metabolized, during the Dextran Period

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dextran Metab. Gm.</th>
<th>N spared Gm.</th>
<th>Ratio mg. N spared/Gm. Dextran Metabolized</th>
<th>p spared Gm.</th>
<th>Ratio mg. P spared/Gm. Dextran Metabolized</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.M.</td>
<td>117</td>
<td>7.32</td>
<td>62.6</td>
<td>.97</td>
<td>8.3</td>
</tr>
<tr>
<td>W.W.</td>
<td>115</td>
<td>7.26</td>
<td>62.7</td>
<td>1.44</td>
<td>12.5</td>
</tr>
<tr>
<td>J.J.</td>
<td>163</td>
<td>13.08</td>
<td>80.1</td>
<td>1.62</td>
<td>9.9</td>
</tr>
</tbody>
</table>
effect. On 50 Gm. glucose daily, there was sparing of 0.85 Gm. nitrogen and 0.03 Gm. phosphorus daily. This subject was in a malnourished state at the time of this study. Similar studies have been performed on a normal, well-nourished subject previously. In this instance, amounts of glucose up to 20 Gm. daily had no significant metabolic effect. Thirty Gm. of glucose daily resulted in sparing of 0.47 Gm. nitrogen daily, but had a negligible effect on phosphorus balance. Comparing these two studies, the number of milligrams of nitrogen spared per gram of glucose was 17 in S.M., and 16 in the second subject, an apparently close correlation. The metabolic effect of glucose may thus be contrasted with that calculated for dextran, shown in table 6.

**Electrolytes**

Sodium and chloride were retained during the dextran period, and were lost during the post-dextran diuresis. S.M. and J.J. continued in positive salt balance for as long as six days following dextran, and presumably continued to accumulate extracellular fluid during this period. Moderate potassium retention was noted in all subjects during the dextran period, and balance subsequently rapidly returned to control levels. No significant effects on calcium balance were noted.

**Antiketogenic Effects**

Semiquantitative urinary acetone determinations were done in all subjects. All developed significant acetonuria during the control observations, which became diminished or absent during the dextran period. Total blood ketones were estimated daily in the three subjects receiving 12 per cent dextran. All showed elevated levels prior to dextran, and only in J.J. was there an apparent effect from dextran administration. In this subject blood ketone fell two days after the dextran period and continued to drop towards normal during the ensuing seven days that observations were made. This apparent antiketogenic effect appeared later than the nitrogen-sparing effect, which was maximal during the dextran period, but which did persist during the post-dextran control period.

Blood ketones were also determined during the glucose feeding experiments on S.M. No effect was noted from 12 and 24 Gm. daily, but on 50 Gm. daily blood ketone concentration fell to one third of control levels, indicating a definite antiketogenic effect.

**Renal Function**

Blood urea nitrogen levels, determined in all subjects, and urea clearance tests, done in four, showed no significant change after dextran administration. Results of determinations of maximum tubular excretory capacity for para-aminohippurate, and inulin and para-aminohippurate clearances in two subjects are shown in table 7. Although a fall in tubular excretory capacity for para-aminohippurate in J.J. was observed, the post-dextran levels were not significantly depressed below the normal. The initial reduction of renal function in S.M. was unexpected and unexplained clinically.

The urine was examined microscopically at frequent intervals in four subjects. In three, those receiving 12 per cent dextran, transient hematuria and red cell cylinduria were noted during and immediately following the dextran period. No albuminuria was noted. The sediment reverted to normal several days after the dextran period. The fourth subject so examined, M.L., showed no abnormalities of the urine sediment.

**Serum Osmotic Pressure**

Total serum osmotic pressures were determined in five experiments at varying periods following dextran administration. No significant deviation from control values was noted in any of the subjects studied.

---

**Table 7.**—Effect of Dextran on Renal Function

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>Following Dextran</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GFR cc/min.</td>
<td>BPF cc/min.</td>
</tr>
<tr>
<td>S.M.</td>
<td>64</td>
<td>396</td>
</tr>
<tr>
<td>J.J.</td>
<td>99</td>
<td>424</td>
</tr>
</tbody>
</table>

All values corrected to surface area of 1.73M².
DISCUSSION

The distribution of a foreign macromolecular substance in the human body is initially dependent on molecular size and configuration and ultimately dependent upon the mode of destruction or elimination. The commercial dextran used in these studies is not a homogeneous substance; the range of molecular weights is relatively wide. This variation must be considered with respect to its effects on both the fluid shifts and metabolic changes induced by dextran administration, and on the manner in which this substance is handled by the body.

This study is in agreement with others in demonstrating a metabolic effect from dextran. Subjects in this study were placed on a grossly deficient diet in order to maximize this effect, and, if possible, to quantitate it in terms of the amount of dextran metabolized. The nitrogen sparing, with concomitant phosphorus retention, is presented as evidence that catabolism of tissue protein was retarded during the dextran period. Similarly, an apparent antiketogenic effect was manifested by the reduction in acetonuria in all subjects. On the other hand, the blood ketone concentration was not significantly affected in two subjects, S.M. and W.W., but it should be noted that nitrogen sparing was also minimal in these subjects. J.J., who apparently metabolized more dextran, showed a fall in blood ketones which occurred several days after the dextran period, when nitrogen sparing had virtually ceased. This apparent dissociation of the two metabolic actions is unexplained.

The attempt to correlate metabolic effect with dextran “metabolized” is admittedly inaccurate in the absence of accurate plasma volume measurements from which to calculate total circulating dextran. In addition, until more is known of the fate of dextran in the body, it cannot be assumed that all the dextran unaccounted for, or a constant fraction thereof, has been metabolized. Despite these obvious sources of error, a rough correlation between this calculated dextran fraction and the amount of nitrogen and phosphorus sparing has been observed, as shown in table 6. The chemical structure of dextran suggests that it would be ultimately metabolized as glucose. This concept is supported in this study by the observation of phosphorus sparing in excess of nitrogen sparing during the period of dextran administration, suggesting the active deposition of glycogen. For this reason an attempt has been made to correlate the metabolic effects of dextran and glucose. As noted, less than one-third as much nitrogen was spared per gram of glucose than per gram of dextran unaccounted for. Assuming that the dextran fraction unaccounted for was not entirely metabolized, this discrepancy becomes even greater. On the other hand, the studies on S.M. revealed a marked antiketogenic effect, as manifested by a fall in blood ketones, during administration of 50 Gm. of glucose daily, an effect which was not seen during the administration of dextran to this subject. This lack of correlation between the metabolic effects of glucose and dextran precludes an accurate quantitation of the amount of dextran metabolized in our subjects, but is in itself worthy of comment. It is suggested that the rate of metabolism may be a factor, in that dextran is presumably slowly and constantly being utilized, whereas glucose administered with meals to a calorically deficient subject would presumably be rapidly burned for energy purposes. The observed discrepancy in the antiketogenic effect of these two substances further suggests a fundamental difference in the mode of metabolism or utilization. Present knowledge concerning the metabolism of dextran in animal tissues is scanty, and precludes any definitive explanation of the metabolic effects observed in this study.

Of particular interest is the observation that nitrogen sparing ceased immediately, or within a few days, after the dextran period, despite the fact that serum levels indicated the retention of significant amounts of dextran in the body. This suggests that the circulating dextran was either not available for metabolism or was not susceptible to enzymatic action. The latter possibility appears unlikely, since there is no basis on which to postulate a basic alteration of the chemical structure of this moiety. More attractive is the thesis that this dextran fraction, because of physical properties (namely, molecular weight), remains confined to the
vascular space and does not diffuse into those tissues where enzymatic degradation takes place.

As reflected by changes in hematocrit and electrolyte and water balance, there was significant fluid retention and plasma volume expansion during the dextran period. Thereafter the retained salt and water was rapidly excreted and the body weight fell to control levels. This suggests a rapid disappearance of dextran from the interstitial fluid space, since it is assumed that expansion of this compartment was due to diffusion of dextran into it from the intravascular space. In contrast, the depression of the venous hematocrit persisted and in some cases was intensified after discontinuing dextran.

Although a reduction in red cell mass resulting from dextran administration cannot be positively excluded, acute studies have shown no such change; other marrow elements are apparently not affected by dextran, and, chemically, dextran has no resemblance to substances known to depress hematopoiesis. It therefore seems more likely that the reduction in hematocrit reflects a prolonged and, in most instances in this study, a marked expansion of plasma volume. Of interest is the retention of dextran in the serum for a protracted period after administration has ceased. This may be contrasted with the rapid excretion, during the dextran period, of about 50 per cent of that administered. Other studies have established that dextran of low molecular weight, below 50 and 60 thousand, is rapidly excreted in the urine. In this study there is evidence that a considerable fraction of the administered dextran, presumably of low molecular weight, is rapidly excreted in the urine, and that urinary excretion becomes negligible soon after discontinuing the infusions. A second fraction is metabolized, also rapidly, and the metabolic effect, like the urinary excretion, disappears while dextran remains in the serum in large concentrations. A third fraction, that remaining in the circulation, behaves in a different manner. It persists in the serum for a long period of time and exerts a potent osmotic effect. Further excretion or metabolism of this fraction cannot be demonstrated, although very slow metabolism of this moiety cannot be excluded by our present methods. It seems likely that this represents dextran of high molecular weight which tends to remain in the intravascular space. It does disappear slowly from the blood, but its fate is unknown. Dextran has been demonstrated histochemically and serologically in the reticuloendothelial system of experimental animals after it had disappeared from the blood. Some of this fraction may be engulfed by the reticuloendothelial system and eventually metabolized. However, it will require further study to establish definitively the fate of that portion of administered dextran which is not excreted or rapidly metabolized.

It is generally agreed that the concentration of serum proteins falls with plasma volume expansion by dextran. The acute effect of dextran administration on total circulating protein levels remains controversial. Hammarsten and co-workers, found no change in total circulating protein in normal humans followed for 24 hours after receiving 1000 cc. of 6 per cent dextran. Conversely, other studies have revealed a fall in total circulating protein, particularly albumin, in animal and human subjects infused with dextran. In these experiments, this effect was observed within a few hours after the infusion, and was accompanied by a comparable fall in circulating dextran and a reduction of plasma volume to a level only slightly above its control value. In the subsequent 8 to 12 hours, plasma volume again increased, although gradually, and albumin and dextran re-entered the circulation. These workers believe that acute overloading of the vascular space leads to a loss of fluid into the interstitial space, although no explanation is apparent for the subsequent return of this fluid and consequent re-establishment of an expanded blood volume. The discrepancies between these various studies may be related to the dextran blood levels attained, since, in the studies on dogs, the fall in circulating protein was produced only with large doses of dextran (40 ml per kilogram). In this regard, Thorsen has noted a relatively greater fall in albumin concentration than in globulin concentration, in acute experiments also, suggesting that al-
bumin may leave the circulation. No information is available on the long-term effects of large doses of dextran on the serum proteins. In this study, no attempt was made to document the acute changes induced by a dextran infusion. During the period of dextran administration there was an apparent fall in total circulating protein in most subjects. This fall was most pronounced in the globulins. Fractionation revealed no change in the relative concentrations of the various globulin components. Following the dextran period, two patterns were seen in those subjects showing an initial fall in total circulating proteins. In two subjects, G.D. no. 2 and T.L., total circulating protein subsequently rose gradually to control levels; at the same time, there was a fall in serum dextran concentration and a rise in venous hematocrit. On the other hand, four subjects (S.M., W.W., J.J., M.L.) showed a significant rise in circulating protein above control values in the postdextran period. In two (W.W. and J.J.) this was associated with a further depression in hematocrit below the level observed immediately after the dextran period. Thus, in two patients there was evidence of further plasma volume expansion while serum dextran concentration was falling. In the other two subjects in this group (S.M. and M.L.) this continued fall in hematocrit was not seen, but both showed a prolonged depression of hematocrit near the level determined at the end of dextran administration. The association of the increase in total circulating protein with the prolonged, or continuing, expansion of plasma volume seems more than coincidental. It is possible to speculate that accommodation to the expanded plasma volume may occur, tending to maintain it at its artificially raised level. It would appear superficially that as dextran leaves the vascular space, plasma proteins enter and, by their osmotic effect, prevent a consequent fall in plasma volume.

The untoward reactions resulting from dextran administration were delayed in onset. The pulmonary congestion induced in T.L. after only 240 Gm. of dextran in two days is especially notable in the absence of any prior evidence of reduced cardiac reserve. It further attests to the potent osmotic effect of this substance. Thereafter, subjects in the older age group were not included in this study. The exacerbation of the chronic dermatitis in M.L. is best explained by the escape of dextran through previously damaged capillaries, serving to increase local edema in the diseased areas of the skin. In this connection, others have found significant concentrations of dextran in burn blisters from patients receiving dextran therapy. A clinical bleeding tendency was noted in four patients, including all three given 12 per cent dextran. Similar observations have recently been reported by Carbone and associates. These workers noted a prolongation of bleeding time in all subjects to whom sufficient dextran was given. Although prothrombin concentration was moderately reduced, this reduction was insufficient to explain the prolonged bleeding time, and was probably commensurate with the expected reduction in concentration of all serum proteins. Clotting time and platelet counts remained within normal range. That bleeding occurred in all subjects receiving 12 per cent dextran might be expected, in view of the significantly higher blood levels of dextran attained in this group. Further study is necessary to define the mechanism involved and to determine whether this is a specific effect of dextran, or one which can be produced with all foreign macromolecular substances.

Previous work in humans on the effect of dextran on renal function is somewhat contradictory. Fleming and co-workers found no impairment of para-aminohippurate or creatinine clearance, or maximum tubular excretory capacity for para-aminohippurate in normal subjects given 500 to 1500 cc. of 6 per cent dextran. Michie and Ragni gave 1000 cc. of 6 per cent dextran daily for six days to five normal subjects and four with pre-existing renal disease, and redetermined renal function four days after the last infusion. They found a reduction of maximum tubular excretory capacity for para-aminohippurate in two normals and three of those subjects with renal disease. Since dextran has been demonstrated in the renal tubule cells of rabbits up to 48 hours after acute administration, at least temporary
impairment of proximal tubular function might be expected. In this study, the decrease in tubular excretory capacity for para-aminohippurate in subject J.J. cannot be considered evidence of functional impairment, since the postdextran level does not deviate significantly from the normal. Subjects receiving large amounts of dextran demonstrated no impairment of glomerular filtration, or renal blood flow which is in agreement with previous studies. Studies on the effect of dextran on maximum tubular excretory capacity in a large group of subjects will be necessary to clarify this still unresolved question. Although the presence of transient microscopic hematuria in three patients might be interpreted as evidence of glomerular damage, albuminuria was not present, and these same subjects showed a generalized bleeding tendency which readily accounts for this finding.

While it might be argued that the amount of dextran administered to subjects in this study is far in excess of the usual clinical dosage, it was deemed necessary to induce changes of sufficient magnitude to render them measurable by our methods. A number of problems which remain unsolved have been raised by this study. While metabolism of dextran has been demonstrated, the site and mechanisms involved remain to be demonstrated. Similarly, a relationship between molecular size and rate of metabolism is suggested, and requires more detailed investigation. Shifts of serum protein out of and into the vascular space are phenomena which at present defy our understanding. The apparent maintenance of a supernormal plasma volume by protein shifts is to us a previously unknown occurrence and raises interesting questions concerning the role of plasma proteins in the regulation of blood volume.

**Summary and Conclusions**

The administration of large amounts of dextran to human subjects on a metabolic ward has led to further observations concerning the effect of dextran in man.

1. As has been previously established, dextran is a potent osmotic substance which produces marked salt and water retention and rapid plasma volume expansion in normal man. In addition it has been demonstrated that a prolonged depression of venous hematocrit, presumably indicative of increased plasma volume, is induced when large amounts of dextran are given.

2. Rapid urinary excretion occurs during the period of dextran administration, and thereafter quickly diminishes. This is dependent upon molecular weight and in the case of the material studied amounted to over 50 per cent of the total dose in all but one subject.

3. Nitrogen and phosphorus sparing and an antiketogenic effect are produced by dextran administration. These effects are transient, and subside soon after discontinuance of injections. The metabolic effects of glucose and dextran were not comparable in the subjects studied.

4. A fraction of the administered dextran, presumably of high molecular weight, remains circulating over a protracted period of time and produces no discernible metabolic effect. Its ultimate fate in the body is unknown.

5. Serum protein appears to leave the circulation during the period of rapid plasma volume expansion. In some subjects, total circulating protein later reaches supernormal levels. In these subjects there is evidence that plasma volume remains expanded or continues to expand at a time when serum dextran concentration is falling.

6. The administration of sufficient amounts of dextran will produce a prolongation of bleeding time, which may be manifested by a clinical bleeding tendency.

7. No evidence of renal functional impairment secondary to dextran administration was found in this study.

**Summario in Interlingua**

Grande quantitates de dextrano esseva administrate per via intravenose a humanos con le objectivo de esclareci un definitio plusr exacte del efectos metabolic e hemodynamic de iste agente. Omne le studios esseva executate in un section de casos metabolic. Il esseva constatate
que dextrano es un substantia de alte potentia
osmotic; in homines normal illo produce un
marcate retention de sal e aqua e un prolongate
expansion del volumine plasmatic. Rapide ex-
cretion urinari occurre durante le periodo de
administration; postea iste excretion se diminue
rapidemente. Le quantitates assi excernite
depende del peso molecular. Un influente
metabolic de dextrano eseva manifeste in le
preservation de nitrogeno e phosphoro e etiam
in un effecto anticetogene. Isto eseva de natura
transitori e dispareva tosto post le discontinue-
lation del injectiones. Un fraction del dextrano
administrate—apparentemente de alte peso
molecular—persiste in le circulation durante un
prolongate periodo e produce nulle observabile
effecto metabolic. Su destino final remane
incognoscite. Proteina del sero pare quitar le
circulation durante le periodo del rapide expansion
del volumine plasmatic. In alicun subjectos le
total del proteina circulante attinge plus tarde
valores supernormal. Il pare que in tal subjectos
un constante o accrescente expansion del volu-
mine plasmatic es accompaniate de un reducete
concentration de dextrano in le sero. Le admin-
istration de sufficiente does de dextrano produce un
prolongation del tempore de san-
guination lo que pote manifestar se in un
tendentia clinic a hemorrhagia. In iste studio
nulle constatation eseva facite que poterea
indicar un dysfuncionamento del renes in
consequentia del administration de dextrano.

REFERENCES

1 Maycock, W. d'A.: Analysis of reports on the
infusion of dextran solution. Lancet 1: 1081,
1952.

2 Thorsen, G.: Dextran as a plasma substitute.

3 Bloom, W. L.: Present status of plasma volume
expanders in the treatment of shock; clinical

4 Hammarsten, J. F., Heller, B. I., and Ebert,
R. V.: The effects of dextran in normovolemic
and oligemic subjects. J. Clin. Investigation 32:
340, 1953.

5 Fiske, C. H., and Subbarow, Y.: Colorimetric
determination of phosphorus. J. Biol. Chem. 66:
375, 1925.

6 Kochakian, C. D., and Fox, R. P.: Micro
determination of calcium by titration of the oxalate
with ammonium hexanitratocerate. Industrial

7 Peters, J. P., and Van Slyke, D. D.: Quanti-
tative Clinical Chemistry Methods, Vol. 11.
Baltimore, Williams & Wilkins, 1932.

8 Zeldis, L. J., and Alling, E. L.: Plasma protein
metabolism—electrophoretic studies. J. Exper.

9 Jacox, R. L.: Quantitative fractionation of compo-
ponent proteins of human serum with cationic

10 Bloom, W. L., and Willcock, M. L.: Determina-

11 Goldring, W., and Chasis, H.: Hypertension and
Hypertensive Disease. New York, Common-
wealth Fund, 1944.

12 Scott-Wilson, H.: A method for estimating
acetone in animal liquids. J. Physiol. 42: 444,
1911.

13 Baltes, E. J.: A micromethod of measuring os-

14 Hill, A. V.: A thermal method of measuring the
vapor pressure of an aqueous solution. Proc.

15 Metabolism of plasma expanders dextran and
polyvinyl pyrrolidone. Nutrition Reviews 11:
281, 1953.

16 Carbone, J. V., Furth, F. W., Scott, R., Jr.,
and Crosley, W. H.: An hemostatic defect as-

17 Wasserman, K., and Mayerson, H. S.: Relative
importance of dextran molecular size in plasma
volume expansion. Am. J. Physiol. 176: 104,
1954.

18 Grotte, G., Knutson, R. C., and Bollman,
J. L.: The diffusion of dextrans of different
molecular size to lymph and urine. J. Lab. &

19 Persson, B. H.: Distribution of dextran in the

20 Bull, J. P., Ricketts, C., Squire, J. R., May-
cock, W. d’A., Spooner, S. J. L., Mollison,
P. L., and Patterson, J. C. S.: Dextran as a

21 Dextran and its applications. Nature 173: 235,
1954.

22 Rosenqvist, H., and Thorsen, H. G. R.: Macro-
dex in the treatment of extensive burns. Arch.

23 Fleming, J. W., Cargill, W. H., and Bloom,
W. L.: Effects of intravenous administration of

24 Michie, A. J., and Elgini, M. C.: Effect of re-
peated infusions of dextran on renal function.
J. Appl. Physiol. 5: 625, 1953.
Metabolic and Hemodynamic Changes Induced by the Prolonged Administration of Dextran

JOHN R. JAENIKE and CHRISTINE WATERHOUSE