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Research Article

EFFECTS OF INFUSION OF HYPERONCOTIC DEXTRAN IN CHILDREN WITH THE NEPHROTIC SYNDROME [1]

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Dextran is a bacterial polysaccharide which is being increasingly used as a plasma substitute (1–4). Dextran molecules frequently have a molecular weight of several million, and consist of long branched chains of glucose units. For clinical use these large molecules are broken down artificially to an average molecular weight of 70,000. In the body, the larger molecular aggregates are further broken down and excreted as smaller fractions having (approximate) molecular weights less than 20,000, or are slowly metabolized.

Dextran has been reported to induce diuresis regularly in patients with the nephrotic syndrome (5, 6). In addition to determining the clinical value of dextran, the intravenous infusion of hyperoncotic (12 per cent) dextran in water was used as an approach to the study of the following questions:

1) Effect of increased plasma volume on glomerular filtration rate;

2) The relation of plasma volume, serum albumin concentration, and glomerular filtration rate to the glomerular permeability to albumin;

3) The effect of increased post-glomerular colloid osmotic pressure on tubular reabsorption of water and solutes;

4) The nature of the dextran-induced diuresis.

METHOD

Nephrotic children who showed no clinical evidence of renal failure were selected (*i.e.*, no concomitant acidosis, azotemia and anemia). The children were recumbent during the study period. Infusions were administered in the morning after an overnight fast; during the fasting period water was given when requested by the children, but no deliberate attempt was made to pre-hydrate them. A 12 per cent solution of dextran in distilled water [4] was used, 300 to 400 ml. per M^2 (1.2 to 1.8 gm. dextran per Kg. body weight) given by infusion daily or on alternate days at a rate of 2 to 4 ml. per minute. The blood pressure was checked at 20 minute intervals and if the systolic pressure reached 140 mm. Hg, infusion was stopped.

Plasma volume was measured by modification of the method of Chinard and Eder (7) from dilution of T-1824 measured at 10, 20, and 30 minutes after injection. Where satisfactory extrapolation curves were not obtained in serial measurements, calculated values are presented, assuming an initial average plasma volume of 1.2 L. per M^2 (8). The change in plasma volume with dextran infusion was estimated. Since hemoglobin was not measured, the formula $PV_2 = PV_1\left(\frac{1 - Hct_2}{1 - Hct_1}\right)^2$ was used. This empirical formula is roughly comparable to the usual $\frac{PV_2}{PV_1} = \frac{Hb_1}{Hb_2} \times \frac{1 - Hct_2}{1 - Hct_1}$. Hematocrits were determined by the usual Wintrobe method (9) and were not corrected for trapped plasma. In calculating the infusion volume required and in the data presented in the tables, estimates of surface area were based on height and presumed (age-height) or observed non-edematous weight. Total solute concentrations in serum and urine were measured by freezing-point depression using a Thermistor 1B resistance probe and a wheatstone bridge osmometer.[5] Serum and urine dextran levels were measured by the methods of Bloom and Willcox (10) and Metcalf and Rousselot (11). Since endogenous creatinine clearance may be an unreliable measure of glomerular filtration rate (GFR) in the presence of renal disease (12) and dextran interferes with the standard Roe method of de-

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[2] Milton Fellow, 1951–53, Department of Pediatrics, Harvard Medical School.

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[4] Batches No. 263 H7 and 278 P7, kindly prepared for us and supplied with the following comments by Commercial Solvents Inc., Terre Haute, Indiana. About 80 per cent of the polysaccharides in these batches had an average molecular weight of 70,000. About 10 per cent had a low molecular weight of 30,000; 10 per cent had a high molecular weight of 180,000.

[5] Made by Fiske Associates, Boston, Massachusetts.

termining inulin,[6] glomerular filtration rate was measured by continuous infusion (rather than a single injection [14]) of sodium thiosulfate in four patients although this substance is known to produce a solute diuresis. Effective renal plasma flow (RPF) was measured by p-aminohippurate in these four and an additional three patients. In these patients the urines were collected by catheter and the bladder emptied with distilled water and air rinses in the usual fashion. Albumin in serum and urine was determined immunochemically (15) in four patients. Sodium and potassium in serum and urine were determined by an internal standard flame photometer (16), and chlorides in urine were measured by the method of Wilson and Ball (17).

[6] Quantitative methods for the simultaneous determination of separate sugars in biological fluids are available (13), but to date have not given consistent results in our hands.

RESULTS

The clinical efficacy of hyperoncotic dextran as a diuretic agent in the nephrotic syndrome is indicated in Table I. Primary and derived physiologic data are presented in Tables II–IV, and Figure 1. A complete protocol of the course of diuresis in one patient is given in Table V, and estimates of glomerular permeability to albumin and water in Table VI. The effect of pitressin on dextran-induced diuresis is shown in Figure 2.

TABLE I

Clinical results of dextran infusions

Patient	Age yrs.	Number of infusions*	Wt. before therapy Kg.	Least wt. after therapy Kg.	Least wt. days after last infusion	Wt. loss Kg.	Estimated non-edema weight Kg.	Proportion of edematous wt. lost %
S. L. B.	11 6/12	4	60.0	46.0	1	14.0	46.0	100
S. L. B.	11 10/12	8	57.5	47.7	1	9.8	46.0	85
M. N.	3 1/12	5	18.5	14.5	2	4.0	14.0	88
W. D.	9 3/12	4	43.3	30.8	3	12.5	27.0	77
S. W.	6 7/12	4	27.0	21.4	2	4.3	21.0	93
J. R.	3 0/12	3	16.2	13.9	2	2.3	12.0	55
J. F.	3 6/12	3	18.1	17.1	6	1.0	14.5	27
N. McC.	4 1/12	5	25.7	22.7	1	3.0	20.0	54
C. B.	2 9/12	5	20.0	15.9	2	4.1	14.5	74
C. B.	2 11/12	4	21.6	15.1	2	6.5	14.5	92
B. L.	3 0/12	5	24.7	13.0†	8	11.7	13.0	100
B. L.	3 1/12	3	18.2	18.7	—	—	13.0	0
D. G.	4 11/12	4	19.5	16.5‡	1	3.0	15.0	67
C. F.	6 8/12	4	23.1	22.1	1	1.0	19.0	24
J. G.	4 8/12	3	19.4	18.9	1	0.5	14.0	10
P. M.	6 3/12	3	28.4	27.5	1	0.9	18.0	9

* Each infusion on separate, usually consecutive, days.

† Also receiving ephedrine sulfate for asthma during this period. Ephedrine sulfate, p.o., may produce diuresis in occasional patients with the nephrotic syndrome (18).

‡ Slight paracentesis drainage persisted on first two days of infusions.

TABLE II

Effect of dextran on plasma volume—all data adjusted to 1 Sq.M. S.A.

Patient	Intravenous dextran gm.	HCT % Initial	HCT % Final	Pl. vol.* ml. Initial	Pl. vol.* ml. Final	%Δ	ΔPV per gm. infused dextran‡ ml.
D. G.	43.5	26	14	1,240	1,675	+35	10.0
S. B. (1)	32.6	42	35	1,360	1,710	+26	10.7
(2)	33.4	45	36	1,910	2,580	+35	19.8
C. B.	49.1	35	25	1,200†	1,600	+33	8.1
M. N. (1)	30.0	40	28	1,320	1,900	+44	19.3
(2)	49.0	34	23	1,980	2,690	+36	20.9
J. L.	37.3	35	21	1,200†	1,770	+48	15.3

* Initial plasma volume determined by T-1824 dilution. Final plasma volume calculated from change in hematocrit.

† Not measured but estimated as normal volume.

‡ Plasma volume increments would be higher if quantity retained was used, rather than quantity infused. These data were available only in S. B. (2), C. B., and M. N. (1).

TABLE III

Effect of plasma volume expansion on total circulating albumin

Patient	Δ plasma volume %	Total circulating albumin		Excreted albumin gm.	Albumin from "Extravascular Pool" gm.
		Initial gm.	Final gm.		
D. G.	+35	1.4	1.3	0.5	0.4
S. B. (1)	+26	10.3	7.9	1.9	—
(2)	+35	27.5	27.4	0.7	0.6
M. N. (1)	+44	2.2	2.2	0.5	0.5

Clinical effects (Table I)

Courses consisting of three or more daily infusions have now been given to thirteen children and three children have received two or more such courses. A significant loss of edema occurred in nine children, and diuresis was virtually complete in six. Least body weight was usually attained within 24 to 48 hours after the last infusion. Of the remaining four children, two (J. G. and P. M.) were known to have reduced values of inulin and PAH clearances and have since died of renal failure. Figure 1 depicts some features of a successful course of treatment.

The majority of children developed mild hypertension (20 mm. + elevation of systolic and occasionaly diastolic pressure),[7] during the infusions, associated in some instances with headache, nausea and abdominal pain. These symptoms subsided within 24 hours in all instances. Infiltration of dextran into the subcutaneous tissues in

[7] If hypertension exceeded 140/100 mm. Hg, infusions were discontinued.

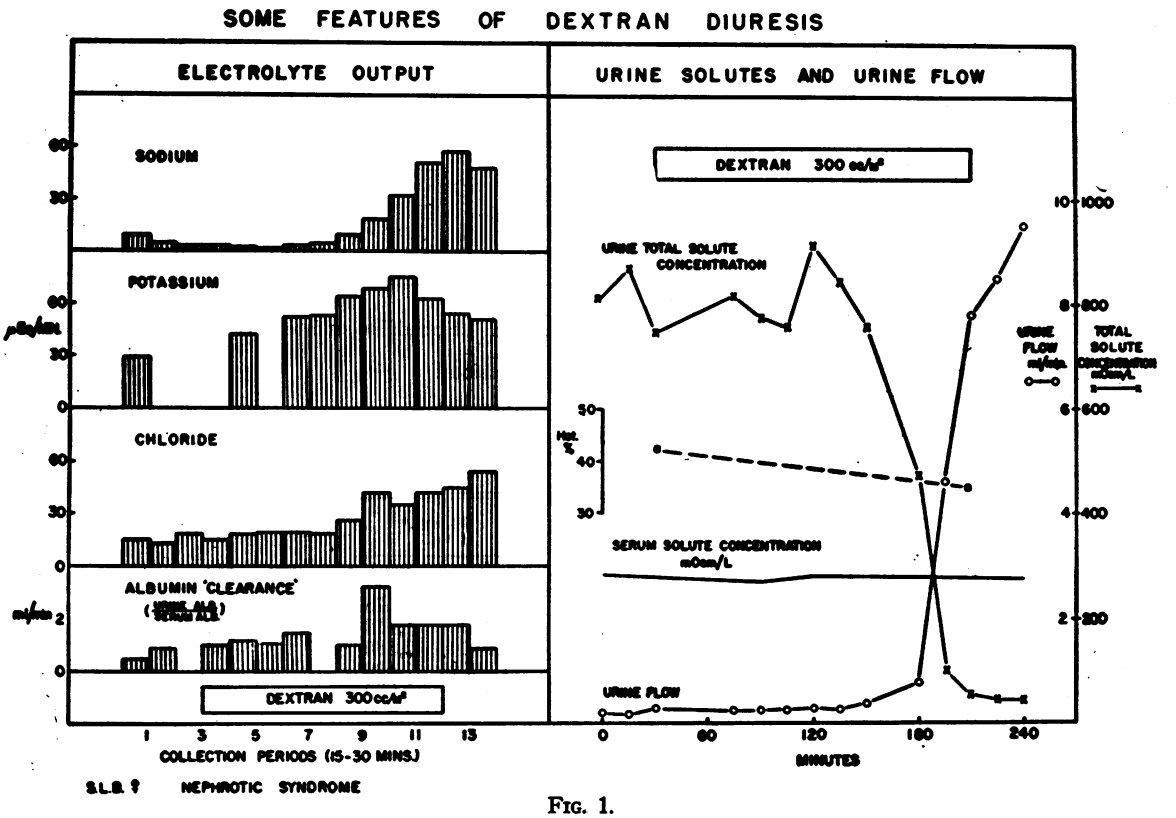

FIG. 1.

Patient S. B.(1) received 380 ml. of 12 per cent dextran in water. Renal functions were within normal limits immediately prior to infusion (Table IV). Water diuresis preceded the increased excretion of solute.

TABLE IV

Average values for three consecutive periods before dextran infusion and during maximal dextran diuresis

Patient	Sex	Age yrs.	S.A. M^2	Date	Infusion 12% dextran ml.	Period numbers (incl.)	minutes	Rates of excretion in urine/M^2/min.									Serum concentrations					Renal clearance			
								H_2O	Na	K	Cl	S_2O_3	Total solutes		Alb.	Dextran	Na	K	T.S.	Alb.	Dextran	GFR	RPF	FF	C Alb.
								$\mu Eq.$					$\mu Osm.$	$mOsm./L.$	mg.		$mEq./L.$		$mOsm./L.$	mg./ml.		ml./min./M^2			
D. G.	M	4 11/12	0.62	12/11/52	225	2–4	33–79	0.4	7	41	9	—	234	492	6.0	—	131	3.6	280	1.8	—	25*	266	0.10	3.8
						11–13	201–246	10.3	266	64	232	—	774	75	4.3	—	129	3.1	279	1.2	—	—	356	—	4.2
S. B. (1)	F	11 6/12	1.40	12/30/52	380	2–4	30–75	0.2	16	25	22	—	165	806	3.5	—	153	4.2	293	5.4	—	57*	331	0.17	0.6
						18–20	315–360	6.2	37	40	34	—	292	47	6.7	—	144	3.7	275	3.3	—	—	464	—	1.1
(2)		11 10/12		4/17/53	390	2–4	30–75	1.1	241	107	5	241	681	618	1.5	—	—	—	275	10.6	—	91	208	0.44	0.1
						9–11	180–225	6.6	261	85	18	109	672	103	4.4	98	—	—	258	7.6	18.7	122	404	0.30	0.6
C. B.	F	2 7/12	0.55	3/13/53	225	2–4	30–75	0.4	4	49	2	—	276	783	—	—	140	4.9	273	—	—	27*	317	0.09	—
						9–11	167–212	3.5	30	67	37	—	403	118	—	47	126	3.8	271	—	19.2	—	450	—	—
M. N. (1)	F	3 1/12	0.60	5/1/53	150	2–4	30–75	1.0	87	403	—	208	598	619	3.1	—	156	2.2	290	2.8	—	49	185	0.25	1.1
						8–10	175–220	10.5	392	163	—	216	889	84	9.0	56	145	1.0	274	1.9	14.4	72	402	0.18	4.8
(2)				5/29/53	245	2–4	30–75	1.2	102	115	15	193	461	390	—	—	141	4.6	287	—	—	68	318	0.21	—
						7–9	135–180	7.1	200	136	116	218	640	92	—	—	139	3.0	268	—	—	67	524	0.13	—
J. L.	M	1 7/12	0.45	6/9/53	140	2–4	30–75	1.2	81	207	21	191	538	455	—	—	140	1.6	268	—	—	61	408	0.15	—
						6–8	105–160	7.3	182	239	108	162	746	138	—	—	140	0.5	257	—	—	69	615	0.11	—

* Inulin. Other GFR's determined with $Na_2S_2O_3$.

TABLE V

Protocol: M. N. (1) 3 1/12 yrs. SA = 0.60 W = 18.9 Kg. H = 97 cm.; 5/1/53
Simultaneous thiosulfate and p-Aminohippurate clearances, 150 ml. dextran from 75 to 235 min.

Time min.	Urine excretion/min./M²									Serum						Renal clearance				Plasma volume	
	H_2O ml.	Na µEq.	K µEq.	Cl µEq.	Thio µEq.	Total µOsm.	Solutes mOsm./L.	Alb. mg.	Dextran mg.	Na	K	Thio	T.S. mOsm./L.	Dextran	Alb.	Alb.	GFR	RPF	FF	HCT %	PV_{TBM} ml.
										mEq./L.				mg./ml.		ml./min./M²					
−68–0	0.2	1	60	71		182	910			156	2.2		290		2.9					40	794
0–30	1.2*	112	430	62	228	724	604							0.02							
45	1.0	100	422	7	232	624	624	3.2				5.7			2.9	1.1	40	133			
60	1.0	88	424	7	207	624	628	3.5				3.8				1.2	55	200			
75	0.9	72	363	3	191	544	604	2.7	0.3			3.6			2.7	1.0	53	222			
75–115	0.9	87	395	5	207	342	380	2.2	17.7			3.6				0.9	57	334	0.17		
145	1.0	83	387	4	195	562	562	3.6	33.4			3.6		14.9	2.2	1.6	53	388	0.14		
175	3.3	118	526	27	243	740	224	3.9	69.2			3.1	268		2.1	1.9	77	516	0.15		
190	8.3	225	205	28	226	697	84	6.7	91.8			3.0				3.4	77	378	0.20	28	
205	14.3	489	148	—	236	930	65	10.9	88.0			3.0	274			6.0	80	462	0.17		
220	10.0	463	135	282	190	1,030	103	9.4	68.0			3.2				5.5	60	367	0.16		
235	4.8	447	132	259	211	1,186	247		59.2	145	1.1	3.4		13.9	1.6		63	400	0.16	28	1,145
265	3.7	374	107	87		926	250		42.2												
295	1.5	168	95	50		485	323		30												
325	1.2	142	97	43		492	410		32												
355	0.9	112	90	30		423	470		48												

* The increased excretions of water and solutes, particularly sodium and potassium, during the pre-dextran periods resulted from sodium thiosulfate infusion.

TABLE VI

Hypothetical estimates of relative "filtration" of albumin compared with that of water during dextran diuresis (M. N. 5/1/53)

Time *min.*	Serum albumin *mg./ml.*	Filtered/min. H_2O *ml.*	Filtered/min. Albumin* A *mg.*	B *mg./100 ml.*	C *mg./100 ml.*	C/B	Excreted/min. H_2O *ml.*	Excreted/min. Albumin *mg.*	"C Alb" *ml./min.*
C	2.9						0.12	—	—
0–30							0.70	—	—
30–45	(2.9)†	24	70	1.9	7.9	4	0.60	1.89	0.65
45–60	2.9	33	96	1.9	6.3	3	0.60	2.08	0.72
60–75	2.7	32	87	1.8	4.9	3	0.56	1.58	0.58
75–115	(2.5)	34	85	1.7	3.9	2	0.54	1.34	0.54
115–145	2.2	32	70	1.5	6.8	5	0.62	2.18	0.95
145–175	2.1	46	97	1.4	5.1	3	2.0	2.33	1.1
175–190	(2.0)	46	92	1.3	8.7	7	5.0	4.0	1.97
190–205	(1.9)	48	91	1.3	13.6	10	8.6	6.52	3.5
205–220	(1.8)	36	65	1.2	15.7	11	6.0	5.66	3.2
220–235	1.6	38	61	1.1	—		2.9	—	—

* Albumin

A = GFR_{H_2O} × serum albumin (mg./ml.) = "maximal" filtered albumin (mg./min.).

B = $100 \times \left(\frac{0.020}{3.0} \times \text{serum albumin (mg./ml.)} \right)$ = "proportional" filtered albumin/100 ml. glomerular filtrate.

C = $\frac{\text{urine albumin (mg./min.)}}{GFR_{H_2O}} \times 100$ = "minimal" filtered albumin/100 ml. glomerular filtrate.

$\frac{C}{B}$ = ratio of "minimal" to "proportional" filtered albumin; *i.e.*, estimate of glomerular permeability to a constant fraction of serum albumin.

Note that neither A nor B have physiologic validity (see Discussion).

† Figures in ( ) interpolated from semilog plot. Periods 0–75 minutes before dextran; 75–235 minutes, during dextran.

three instances led to a swollen painful arm for several days. Several children had post-infusion epistaxis.[8] Possible adverse effects of repeated infusions are undetermined.

Edema recurred rapidly in all patients, the longest period of remission following therapy was one month.

Physiological effects

Plasma volume: The hyperoncotic dextran infusions regularly induced increases of 25 to 50 per cent in plasma volume. The oncotic effect of dextran in acutely expanding plasma volume varied, but averaged about 15 ml. per gm. dextran infused per square meter surface area (Table II) by the end of the infusion. Satisfactory measurements of urinary dextran excretion were made in two patients (S. $B._2$ and M. $N._1$). These indicated that 29 and 43 per cent (respectively) of the infused dextran was excreted during the period of infusion; and if the oncotic effect was calculated from the amount retained at the end of infusion rather than the total quantity infused, higher values were obtained (28 and 34 ml. per gm. rather than 20 and 19 ml.). This calculation can only be an approximation since the final estimated value for total circulating plus excreted dextran in M. N. was slightly greater than the amount actually infused, also the estimates of final plasma volume increments from fall in hematocrit may be inaccurate.

The increment of plasma volume was associated with a decreased concentration of serum albumin; however, the total circulating albumin decreased in only one of four instances in which it was measured (Table III). If the amount of albumin excreted in the urine during dextran infusion was considered, then the maintenance of total circulating albumin during acute episodes of depletion seems to have been at the expense of the "extravascular pool." Calculations of this type based on crude estimates of plasmas volume must be interpreted cautiously.

[8] Since this report was prepared, two children have developed hematuria during the 2nd or 3rd dextran infusion. This cleared spontaneously in 4 to 7 days.

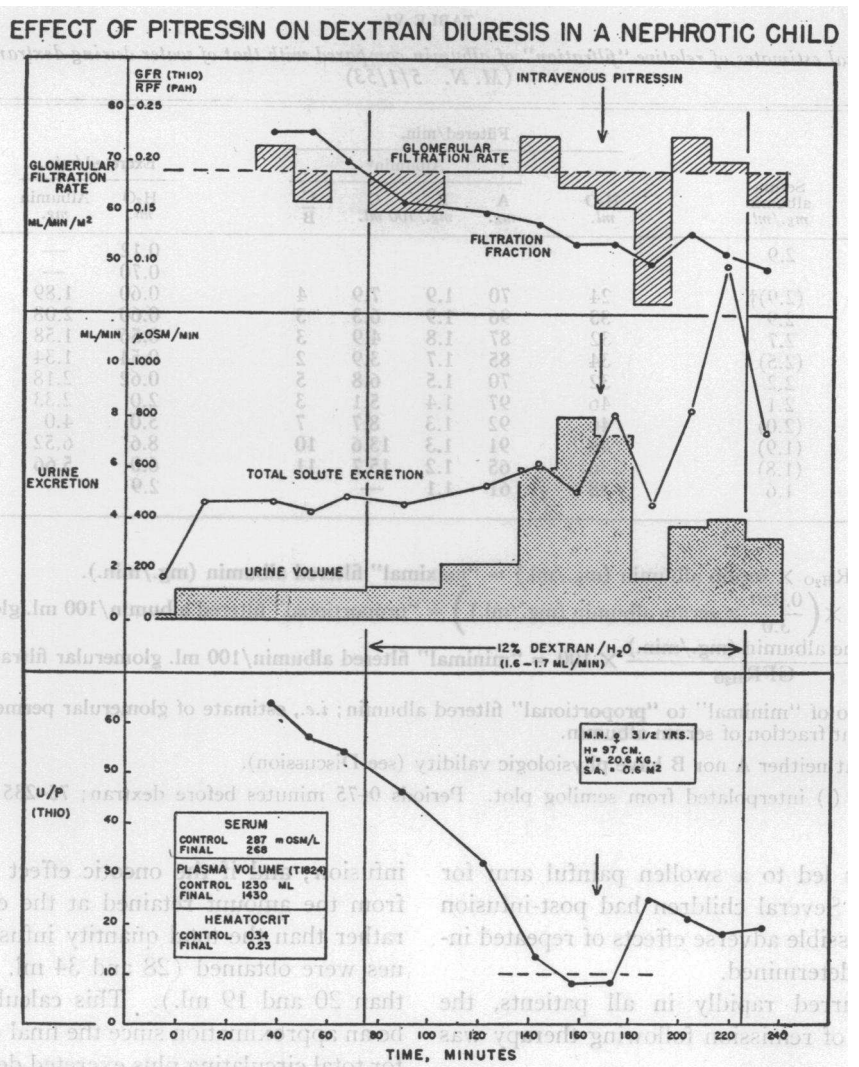

FIG. 2.

Patient M. N.(9). Note reduction in filtration fraction, and water diuresis preceding solute diuresis prior to pitressin injection. The pitressin response indicates that the renal tubules were responsive to increased antidiuretic hormone in the presence of high levels of circulating dextran.

Serum solutes: Serum total osmolarity and electrolyte concentrations decreased during dextran infusion, typified by examples cited in Table IV.

Diuresis: Averaged data for three consecutive control periods and three consecutive periods during maximal diuresis obtained during seven studies on five patients are noted in Table IV.

Urine flow during the control periods was usually low. No change was noted until the infusion had been running for about 1½ to 2 hours, when a sharp increase in urine flow occurred, output often increasing 10-fold within 30 minutes (Figure 1). The urinary total solute output increased in all but one instance, although total solute concentration fell to a level much below that in the plasma, indicating a water diuresis.

The protocol of M. N. (Table V) indicates that the peak excretion of dextran more or less coincides with that of water, and both precede the periods of maximum total solute excretion. The

terminal rise in dextran excretion may be insignificant.

Sodium and chloride excretion increased during the later phases of diuresis in all cases, often to a striking degree. Usually, maximal water diuresis preceded maximal sodium output. There were insignificant fluctuations in potassium excretion.

In one child with persistent edema (C. B.),[9] dextran infusion failed to produce significant diuresis in spite of adequate infusion volume and a marked fall in hematocrit. Profuse diuresis had been induced two days, and two months previously. Sodium excretion during the control period was relatively high, and increased slightly during the infusion. There was no significant change in urine solute concentration.

In most cases urine flow and electrolyte output returned to control levels during the several hours following infusions. In a few patients, however, increased urine flow persisted accompanied by continued excretion of sodium and chloride.

Glomerular filtration rate (C Thio) was measured satisfactorily during dextran infusion in four cases, and increased significantly in two. It did not change significantly in the other instances despite significant increases of plasma volume. Renal plasma flow (C PAH) was increased markedly in all seven cases in which it was determined. Owing to the proportionately greater increase in p-amino-hippurate clearance, filtration fraction fell in all instances where estimated.

Effect of pitressin on diuresis

In two children, (J. L. and M. N.), pitressin (2 units per M^2) was given intravenously after diuresis had become established. Injection was associated with nausea, retching and pallor. After a latent period of about ten minutes, urine flow decreased to levels similar to those seen in the control periods (Figure 2). Electrolyte excretion fell simultaneously but to a lesser extent so that urinary total solute concentration rose. Glomerular filtration rate and renal plasma flow were also transiently reduced. The filtration fraction was not definitely altered. With the exception of urine flow, which increased only slightly, after about 30 minutes all measurements returned toward their previous diuretic levels.

Albumin excretion

Serum dextran levels rose to about 2.0 gm. per 100 ml. during the infusions. (Maximal urinary dextran excretion rates occurred prior to the onset of diuresis, due probably to the early excretion of smaller molecules.) Measurements of serum and urine albumin concentrations were made in four patients.[10] Although total circulating albumin was not usually changed (Table III), serum albumin concentration consistently fell during dextran infusion (Table IV). Urine albumin excretion increased in three of the four patients in which it was measured and fell in one. Albumin "clearance" (C Alb) increased in three of the four patients. In two of these, the filtration of water was measured and also appeared to be increased.

DISCUSSION

The present findings confirm previous reports (5, 6) that dextran infusions induce a temporary diuresis in the nephrotic syndrome. Dextran therapy may prove to be of value when it is desirable to reduce edema prior to other therapeutic procedures, and measures, ordinarily used to reduce edema, are either impracticable or contraindicated. Contraindications to dextran therapy are pre-existing hypertension, which may be aggravated, and massive anasarca, when a rapid increase in plasma volume may further embarrass the cardiovascular system. Some data are available suggesting that dextran may have a hemolytic effect (19). In general better diureses were obtained when a greater number of infusions were given. From present experience it appears that at least three to five consecutive infusions should be given to obtain maximum benefit.

A marked increase in plasma volume was produced, and in the patients studied this was associated with rise in renal plasma flow. Glomerular-filtration rate, however, rose in only two of four patients in whom observations were made. The general effects appear to resemble those produced by infusion of hyperoncotic salt-poor human serum albumin (20, 21), except that in the patients stud-

[9] This study, and two others, were not included in Table IV since renal clearance data were not obtained.

[10] We are indebted to Dr. Dominick Conway for these measurements.

ied by Orloff, Welt, and Stowe the solute concentration (sodium) in the extracellular fluid increased during infusion.

In previous studies to determine the effect of dextran on renal function, a 6 per cent solution of dextran was used, producing an average drop of 12 per cent in hematocrit and slight increases, thought to be insignificant, in renal function in normal subjects (22). Increases in both glomerular filtration rate and renal plasma flow have been noted in animals (23). In the present study, a 12 per cent solution was used, and the average fall in hematocrit was 30 per cent indicating that a larger increase in plasma volume was achieved, due perhaps to the hyperoncotic solution used and the existing hypoproteinemic state (21). This larger increase in plasma volume may account for the increases in renal plasma flow observed in the present study. The increased plasma volume may be the stimulus to diuresis by increasing glomerular filtration rate as previously suggested (20, 21, 24); however, the data indicate that increased plasma volume and systemic hypertension both favoring increased filtration pressure do not necessarily increase the glomerular filtration rate. It is possible that the combined counteracting colloid osmotic effects of dextran plus albumin were approximately equal to the rise in filtration pressure or that the basement membranes were sufficiently altered by disease to make acute changes in filtration unlikely. Therefore, in the patients in whom glomerular filtration rate did not increase, dextran diuresis was clearly a renal tubular phenomenon. When glomerular filtration rate was increased, it would seem that either rise in filtration pressure exceeded the counteracting colloid osmotic effect and/or an increased number of glomeruli were being perfused. One might speculate, for instance, if severe interstitial renal edema caused partial extrinsic occlusion of some afferent glomerular arterioles, the rise in mean blood pressure might be sufficient both to improve individual glomerular perfusion and to increase the total number of glomeruli perfused. Increased colloid osmotic pressure in the post-glomerular blood flow might reduce intrarenal peritubular edema.

The apparent relationship between filtration of water and albumin is largely dependent upon how the amount of albumin filtered is estimated. This is indicated by several different methods of handling the same data obtained in M. $N._1$ (Table VI). Three possible series of values for filtered albumin are shown in the columns headed A, B, and C. "A" defines a glomerular clearance situation in which all serum albumin is filtered. This is obviously a maximal limiting value and is physiologically unlikely. "B" defines the situation in which some constant proportion of serum albumin is filtered, the actual amount being dependent upon the level of serum protein and the glomerular filtration rate. The constant 0.020/3.0 was chosen since it has been assumed on the basis of studies in rats and guinea pigs (25) that with normal levels of serum albumin (3.0 gm. per 100 ml.), 0.020 gm. are filtered per 100 ml. of filtrate formed (26). Estimated in this way, the concentration of albumin per 100 ml. of glomerular filtrate appears to *decrease* with dextran diuresis. Actually, this result need not imply any change in permeability to albumin but depends upon the fact that the decrease in concentration (dilution) of serum albumin was proportionately greater than the increase in filtered water. This is particularly evident upon comparison of the periods from 45 to 115 minutes with those of 205 to 235 minutes. However, the arbitrary ratio 0.020/3.0 × serum albumin (mg. per ml.) × GFR yields values for albumin filtered per minute which are less than amounts appearing in the urine per minute in the respective periods. If the average observed ratio of albumin recovered in the urine to the "maximal" filtered albumin 1.85/84 is used, it would appear that reabsorption of filtered albumin occurs in the control periods, but during dextran diuresis again more albumin is recovered in the urine than can be accounted for by this hypothetical filtration calculation.

In contrast to columns A and B, column C indicates the result obtained if one assumes that the albumin recovered in the urine represents at least the minimal amount filtered (27) (assuming no tubular secretion of albumin). In this case, the quantity of albumin filtered per 100 ml. of filtered water appears to *increase* during dextran diuresis. This result again does not necessarily imply change in glomerular permeability, since it is based on the relatively greater increase in excreted albumin over filtered water. It does not take account of either change in serum albumin concentration or tubular reabsorption of albumin.

The formula C/B relates albumin excreted per unit of water filtered to a fraction of the serum albumin concentration which is assumed to be filtrable normally. The use of such a ratio only serves to emphasize that any calculation of glomerular permeability must at least take account of these simultaneous variables. If C/B is an expression of glomerular permeability to albumin, it is apparent from the values derived that the relative permeability to albumin may be increased 3 to 5 times during dextran diuresis independently of that for water.

Other phenomena relating to plasma proteins also may be explored. For example, the existence of a pool of mobile plasma protein in tissue about as large as that in the plasma was suggested some time ago (28). An extravascular "pool" of plasma proteins in nuclei and cytoplasm of many organs and in the interstices of connective tissue has recently been demonstrated (29). These extravascular sources presumably were drawn upon to replace the albumin lost in the urine during dextran induced diuresis, and thereby limited the reduction of circulating albumin. However, with the continuous proteinuria observed during the nephrotic syndrome, both concentration and total circulating albumin are reduced. Apparently this homeostatic mechanism is more responsive to acute changes in plasma protein content. Since the extravascular sources of plasma protein appear to be available in children who have had the nephrotic syndrome for some time, reduction in concentration or quantity of circulating albumin does not signify exhaustion of these stores.

The increased excretion of water with dextran infusions appears to initiate increased excretion of solutes, essentially sodium and chloride. This is not always observed, as demonstrated by Greenman and associates (30). Their patients, however, were maintained on severe dietary sodium restriction (2 mEq. per day); our patients were ingesting 30 to 50 mEq. of sodium per day. Since osmolarity of the already expanded extracellular water was either unchanged or decreased, and hypertonic solutes were not infused, the hypothesis of cellular dehydration (31) seems an unlikely explanation for the increased excretion of sodium and chloride. Since the quantity of sodium filtered per minute appeared to be either decreased or unchanged, increased sodium excretion obviously resulted from decreased tubular reabsorption of this ion. A similar phenomenon was observed by Strauss, Davis, Rosenbaum, and Rossmeisl during hypotonic expansion of extracellular fluid volume in recumbent subjects (32). They postulated that the locus of action of the expanded volume is in the cephalad portion of the body.

The actual mechanism by which the renal tubular reabsorption of salt is modified, however, remains unexplained.

The precise mechanism of the observed water diuresis also remains undetermined. Unresponsiveness of renal tubules to antidiuretic hormone during dextran diuresis seems excluded since intravenous injection of pitressin produced antidiuresis. The total solute concentration of the extracellular fluid was usually reduced during dextran infusion and diuresis. In two instances, this was not observed although profound diureses occurred. In five other patients, the acute reduction of total solute concentration in the extracellular water approximated 4 to 6 per cent. Verney (33) and Baldes and Smirk (34) showed that a rapid diminution in osmolarity of the extracellular water of 1.5 to 2 per cent initiates diuresis, presumably through inhibited elaboration of antidiuretic substances (A.D.S.) mediated *via* osmoreceptors. Other hypothetical possibilities also could account for the observed dextran-induced water diuresis.

SUMMARY

1. The intravenous infusion of hyperoncotic (12 per cent) dextran into children with the nephrotic syndrome often initiates a water diuresis followed by increased urinary excretion of sodium and chloride with removal of most of the edema fluid. Transient hypertension is the most common complication of dextran infusion. The safety of repeated infusions is not yet ascertained.

2. Diuresis was associated with a marked increase of plasma volume and with increased effective renal plasma flow in seven patients in whom it was measured; however, glomerular filtration rate was increased in only two of the four instances in which it was simultaneously measured.

3. At its maximum, the water diuresis was characterized by a urinary total solute concentration of less than 100 mOsm. per L., and a thiosulfate U/P ratio approximating 10. This

maximal diuresis could be transiently inhibited by intravenous injection of pitressin. The exact cause of the water diuresis initiated by dextran infusion has not been determined.

4. Observations during dextran infusion in four children suggested that the calculated permeability of the glomerular membranes to albumin (a) is relatively increased in the nephrotic syndrome as previously demonstrated by others, (b) may increase further during dextran infusion, and (c) appears to be independent of that for water. These interpretations depend upon the method of calculation applied to the observed excretion of albumin.

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