Hemorrhage in Normal Man: II. Effects of Mannitol on Plasma Volume and Body Water Dynamics Following Acute Blood Loss

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Introduction

FOR ABOUT 15 YEARS it has been evident that mannitol has a number of remarkable physiologic and pharmacologic properties of peculiar importance to the recently injured, volume-reduced, or operated patient.

Mannitol is an inert 6-carbon polyhydric alcohol, closely related to the monosaccharide mannose, but without the aldehyde grouping which makes it a sugar. It does not appear to enter into the carboxylic acid cycle and enters body cells only slowly, if at all. When infused intravenously in concentrations of 10–25 per cent, these large weights of mannitol contribute importantly to the total solute content of body fluids, with a resultant increase in total osmolality which drastically alters the distribution of body water. Through dilution, both of red cells and protein, changes in blood viscosity are produced.

The increase in total solute concentration withdraws fluid initially across the capillary into the plasma volume, and then, as low-molecular-weight crystalloid equilibrates into interstitial fluid and lymph, it increases the volume of the whole extracellular phase by withdrawing water from body cells. This produces an increase in the volume of plasma and extracellular fluid and, under conditions of reduced circulating volume, produces a demonstrable increase in glomerular filtration rate and renal blood flow.

Mannitol is readily filtered into the tubular lumen and is reabsorbed only to a limited extent, if at all. Water is held in the renal tubular lumen by this strongly hygroscopic solute, and as large weights of mannitol are loaded into the glomerular filtrate a brisk osmotic diuresis is produced. Although initial withdrawal of water from body cells produces an acute hyponatremia (exactly as with infusion of hypertonic glucose, sucrose or urea) the urine formed has a high water:sodium ratio, significantly higher than in plasma. For this reason the chronic infusion of mannitol over the period of several days will produce a gradual increase in plasma sodium concentration, finally leading to notable hypernatremia if a normal renal response is elicited. Its acute and chronic effects on plasma osmolality †

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† Clear distinction between total osmolality (approximately 295 mOsm./L. in plasma) and colloid osmotic pressure (approximately 12–30 mm. Hg in plasma) must be maintained in considering any such studies as these. The total solute concentration of body fluids (measured by freezing point depression) is a physico-chemical property traceable to the number of molecules in solution. It is affected strongly by the concentration of ionic species such as sodium, chloride or bicarbonate, and by low-molecular-weight crystalloids such as urea, sugar, amino acids, dipeptides, mannitol. By contrast, colloid osmotic pressure or oncotic pressure is a biologic property of fluids exhibited when fac-

are, therefore, in distinct contrast—an early acute hyponatremia, a chronic and long-lasting hypernatremia if repeated injections are employed.

In the original report on its prophylactic effects by Owen, Desautels, and Walter,[15] it was shown that in the dog subjected to experimental acute tubular necrosis, the lesion could be prevented by the use of mannitol, infused either prior to the insult or immediately following it. Many studies since that time have demonstrated the effectiveness of mannitol in aborting experimental acute tubular necrosis. Clinical evidence is more difficult to gather, but several reports suggest that in the face of acute volume reduction and renal ischemia, particularly in the presence of porphyrin breakdown products, the early use of mannitol has aborted the appearance of post-traumatic renal insufficiency.[9, 18]

With these factors in the background, the current study was undertaken to document certain of the metabolic effects of mannitol in the normal human subject after acute blood loss. In previous studies carried out in normal man,[7, 11, 13] basal rates and volumes of plasma volume refill, following a bleed, have been documented. The effect of two vasopressors (l-norepinephrine and angiotensin II) has been observed in the posthemorrhagic state, and both have the property of driving plasma out of the circulation during the refill phase. Effects of recent hemorrhage on the dispersal and disposal of balanced salt infusion, and their role in promoting movement of protein into the plasma volume, have likewise been reported. From these studies has emerged the conviction that the behavior of drugs and solutions used after reduction of blood volume cannot be predicted solely on the basis of their pharmacology and metabolism in normal resting individuals.

ing a membrane impermeable to the proteins or other colloids in the solution. A fluid containing albumin, for example, exhibits the property of colloid osmotic pressure when facing a membrane slowly or poorly permeable to albumin and having on its other side a fluid with less albumin in it.

Materials and Methods

The design of these studies followed closely those previously reported.[7, 11, 13] Seven volunteer subjects, all normal healthy young males, admitted to the hospital for about a week; preliminary medical screening and body compositional studies were carried out. The volume of phlebotomy ranged from 10–12 per cent of the blood volume, withdrawn in a period of 20–30 minutes.

A solution of 20 per cent mannitol in 1 per cent dextrose in water was prepared by adding 400 ml. of 25 per cent mannitol to 100 ml. of 5 per cent dextrose in water. This mannitol solution (total 500 ml. in 4 hr., or 125 ml./hr., or approximately 2 ml./min.) was administered intravenously commencing 4 hours after the hemorrhage. In control subjects the infusion was given without the preliminary hemorrhage.

Urine collections were done by voiding; no indwelling catheters were placed. This imposed some limitation on frequency and possibly on the accuracy of urine data. All the subjects, however, were trained to void on command, and bladder emptying appeared to be complete.

Prior to the bleed, during mannitol infusion and again at intervals up to 48 hours, plasma volume was recorded both by calculation from the change in large vessel hematocrit and, on occasion, by direct determination using Evans Blue dye. Previous studies have shown a close and highly significant correlation between sequential changes in plasma volume as measured by the concentration of red cells in the peripheral blood and that determined by separate repeated injections of Evans Blue dye, provided the basis for the former calculation is the radiochromate erythrocyte volume determined at the outset. As reported in the previous paper,[13] these data

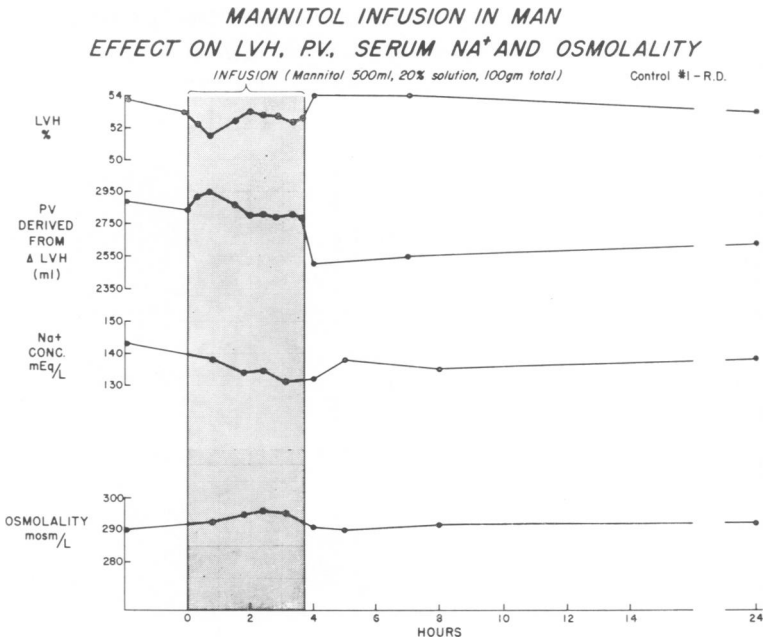

FIG. 1. Mannitol infusion in a normal control. Early fall in hematocrit with a rise in plasma volume is evident. Subsequently there is a fall in serum sodium concentration and a slight rise in serum osmolality.

on erythrocyte volumes show remarkable constancy; no consistent change in *WBH/LVH* ratio * occurs in such experiments; sequential plasma volume changes are thus linear with alterations in the peripheral concentration of erythrocytes. Judgments concerning the size of the plasma volume, as based on abnormalities on the disappearance curve of either Blue dye or radioactive albumin, are unreliable unless the only change being recorded is addition or subtraction of new water to or from the circulation.

All subjects were kept fasting during determination of the blood volume, and from midnight until 8–10 hours following the hemorrhage.

Laboratory methods for analyses of blood and urine, formulae used for the calculation of plasma volume changes and transcapillary refilling, have previously been reported.[7, 11, 13]

* The *WBH/LVH* ratio is the ratio of the whole body hematocrit to the large vessel hematocrit; the whole body hematocrit is given by $\frac{RV}{RV + PV}$.

Results

Figures 1 and 2 show typical protocols for these experiments—in Figure 1 the results in the normal resting subject, and in Figure 2 an individual after hemorrhage.

Initial fall in peripheral concentration of erythrocytes, indicated by the change in large vessel hematocrit (*LVH*), indicates the osmotic withdrawal of new water into the circulation as the load is initially presented in the plasma by intravenous injection of the mannitol. During the first half hour, there is only a minor fall of sodium concentration. Then, over the next 1½ hours, plasma volume and erythrocyte concentrations return to normal, but sodium concentration gradually falls, and serum osmolality slowly increases with additional loading of mannitol. These indicate the departure of mannitol, and its associated water, from the circulation outward into the extracellular fluid and an associated increase in extracellular fluid volume by the withdrawal of sodium-free water from body cells and erythrocytes. The gradual rise in osmolality indicates the disequilibrium produced by an infusion of solute faster than

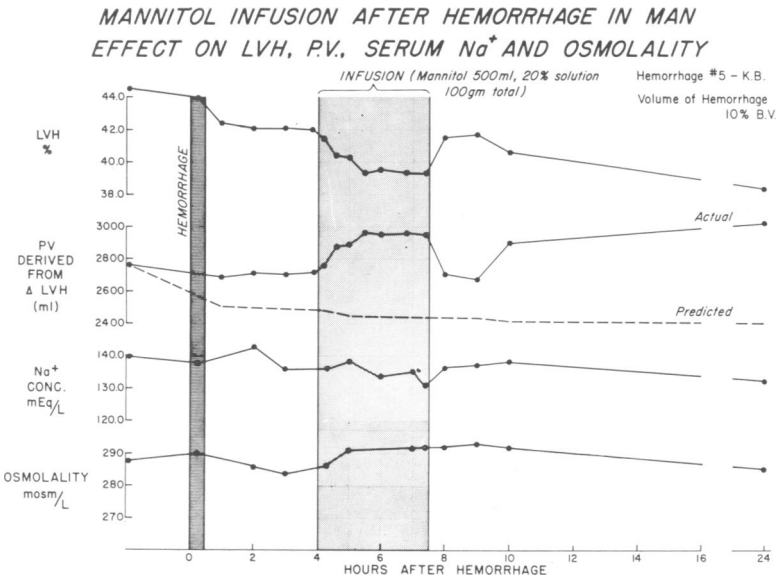

FIG. 2. Mannitol infusion following hemorrhage. Rise in plasma volume is maintained longer than in normal control. Sodium concentration-decrement is delayed and increase in serum osmolality more prolonged than in the normal.

the body can compensate by fluid ingress into the circulation.**

With cessation of the infusion there is a sharp rebound during which plasma components continue to leave the circulation rapidly, even though the infusion is stopped. Hematocrit rises even more abruptly than before and sodium concentration rises as the outward dispersal of mannitol and its water of hydration, initiated during infusion, continues briskly after the infusion stops. This rebound phenomenon is analogous to that noted following the cessation of balanced salt infusion.[13]

Figure 2 shows analogous events in an individual after hemorrhage who is receiving an infusion of mannitol as indicated. The most noteworthy feature is the more prolonged increase in plasma volume, noticeable now by a maintained fall in hematocrit up to the termination of the infusion, with some postponement of sodium fall until the last half-hour of infusions. After hemorrhage the mannitol-attracted water has maintained an intravascular position for a longer time. The rebound following cessation of infusion is marked, but after another period of approximately 2 hours, the fall in hematocrit is resumed, as the normal transcapillary refill returns to its normal course.

Table 1 shows data on volume of bleeds and infusions. All these bleeds were small—similar to an ordinary Blood Bank donation.† Mannitol infusions were all identical in total volume. Fluid and solute loading rates were clustered closely around a mean of 2.5 ml./min. and 3.0 mOsm./min. The total solute load was 605 mOsm. in all subjects. The total solute concentration of the infused material was 1,210 mOsm./L.

Table 2 shows changes observed prior to infusions of mannitol in those 5 subjects who were bled. These represent the net changes at 4 hours. The refill rate is 19–44 ml./hr. or approximately 0.5 ml./min. This slow initial rate of refill is to be related to the modest size of these hemorrhages. All these subjects had rather high *WBH/LVH* ratios (R), as indicated in Column 6.

** The withdrawal of water from erythrocytes should produce a minor reduction in hematocrit at these concentrations; the slow rise in hematocrit which is observed during the last hour of mannitol infusion is thus given added significance as evidence of movement of the new solute and its associated water out of the plasma volume and into the interstitial fluid.

† In Table 1, *RVL* indicates the red cell volume lost by bleeding. The symbol $H + S$ indicates the total loss by hemorrhage plus sampling.

TABLE 1. *Bleeds and Infusions*

Subj..	Bleed				Mannitol Infusion			
	Vol. (ml.)	% Cells	*RVL* (ml.)	*RVL* (H + S)	Vol. (ml.)	Time (min.)	Rate (ml./ min.)	Rate (mOsm./ min.)
1	2	3	4	5	6	7	8	9
				A. *Controls*				
D. M.	—	—	—	—	500	220	2.27	2.75
R. D.	—	—	—	—	500	195	2.56	3.10
Mean					500	208	2.42	2.92
				B. *Bled Subjects*				
D. M.	440	50.1	215	300	500	200	2.50	3.03
R. D.	520	50.1	260	345	500	205	2.44	2.94
J. B.	480	44.1	210	280	500	200	2.50	3.03
R. R.	450	44.2	200	275	500	195	2.56	3.10
T. V.	450	49.5	225	300	500	216	2.31	2.79
Mean	468	47.6	222	300	500	203	2.46	2.98

Table 3 shows changes as observed during the mannitol infusion in all seven subjects. Columns 2 and 3 show the starting and lowest hematocrits (LVH_S and LVH_L). Column 4 shows the maximum plasma volume increment, and Column 5, the time when it was observed. It will be noted that in the two control subjects who received the mannitol without hemorrhage, increases in plasma volume were maximal at 35 minutes, indicating an increase of 140 ml. of plasma volume. In the subjects who were bled, much larger increases of plasma volume were recorded (220–370 ml.) and these were maximal at a later time (50–205 min.).

Columns 6–9, Table 3, show analogous data on plasma sodium concentration. It will be noted from Column 7 that there is a fall in sodium concentration in all subjects. From this, assuming standard values for extracellular water volume based on body weight and plasma volume, it is possible to approximate the net increase in extracellular fluid volume required to produce this extent of sodium dilution, and indicating the influx of new water into the extracellular phase.* This is shown in Col-

* This calculation of maximum dilutional sodium influx neglects the loss of sodium in the urine. As shown later in the paper, this "new sodium" appearing in the urine during the 4 hours of infusion is very small, about 20 mE. Were this small urinary loss to be taken into consideration, the changes in extracellular fluid shown in Column 8 would be slightly smaller.

TABLE 2. *Changes following Hemorrhage Alone (3–4 Hours)*

Subj.	Starting					4 Hours		Refill Rate (ml/hr.)
	PV (ml.)	*RV* (ml.)	*BV* (ml.)	*LVH*	*R*	*LVH*	Δ*PV* (ml.)	
1	2	3	4	5	6	7	8	9
D. M.	2,295	2,130	4,425	51.0	0.94	50.0	+80	24
R. D.	2,690	2,880	5,570	52.4	0.99	50.6	+170	44
J. B.	2,790	2,010	4,800	43.6	0.96	42.1	+140	35
R. R.	2,510	1,830	4,340	44.1	0.96	43.2	+70	19
T. V.	2,670	1,800	4,470	45.5	0.88	44.6	+150	38
Mean	2,591	2,130	4,721	47.3	0.95	46.1	+122	32

TABLE 3. *Changes during Mannitol Infusion*

	Change in Plasma Volume				Change in Sodium				Solute			
Subj.	*LVH*$_S$	*LVH*$_L$	Δ *PV* (+ml.)	Time (min.)	Na_S	Na_L	Δ ECF (+ml.)	Time (min.)	Δ mOsm./L.	Δ Na mEq./L.	Net (mOsm./L.)	Total (mOsm.)
1	2	3	4	5	6	7	8	9	10	11	12	13
						A. *Controls*						
D. M.	51.0	49.7	140	35	140	134	530	55	+9	−6	21	300
R. D.	53.0	51.9	140	30	143	131	1400	177	+8	−12	32	536
Mean	52.0	50.8	140	32	142	132	965	116	+8	−9	26	418
						B. *Bled Subjects*						
D. M.	50.0	47.1	220	50	136	130	625	200	+8	−6	20	234
R. D.	50.6	47.2	360	205	136	131	570	205	+8	−5	18	245
J. B.	42.1	39.4	300	120	136	132	420	195	+8	−4	16	226
R. R.	43.2	39.4	370	110	136	130	600	165	+8	−6	20	258
T. V.	44.6	41.0	270	190	140	132	850	190	+9	−8	25	348
Mean	46.1	42.8	304	135	137	131	613	191	+8	−6	20	262

umn 8, and the time of the maximal extracellular fluid expansion in Column 9.

Extracellular volume-increments ranged from 420–1,400 ml.; the 500 ml. given in the infusion must be subtracted from this figure to indicate the net increment due to the mannitol itself. There appears to be no systematic difference in the volume of extracellular expansion in the two control subjects as contrasted with the five bled subjects, with the sole exception of Subject R. D. who showed the most drastic hyponatremia and hence the largest extracellular fluid expansion. With one exception the increases in extracellular volume were observed somewhat later in those subjects that were bled as contrasted with the controls. In any case, these extracellular fluid expansions were maximal somewhat later than the peak increases in plasma volume.

Columns 10, 11 and 12 show analogous data for total solute. Column 10 shows the increases in total solute measured as mOsm./L. Column 11 shows the decrease in sodium concentration as measured in mEq./L. This sodium decrement multiplied by two represents a first approximation of the total decrease in electrolyte solute as mOsm./L. The sum of this factor (twice the sodium fall) plus the rise in total solute concentration indicates the net increase in solute due to new crystalloid appearing in the circulation, largely mannitol. As noted in Column 12, this ranges from 16–32 mOsm./L. This increase in nonelectrolyte solute, when multiplied by the extracellular water volume, represents the total "new crystalloid" appearing in the extracellular fluid. This first approximation is indicated in Column 13 and ranges from 226–536 mOsm./L., with a close spread around the mean of 262 mOsm./L. These peak values for new crystalloid osmolality were observed at, or close to, the time of maximum extracellular fluid expansion, as shown in Column 9.

Table 4 shows further calculations on the distribution of water and solute at the end of the infusion. These data take into consideration the urinary excretions (see below). Here, the basal urine excretion rates during the first 4 hours (after hemorrhage in the five bled subjects) were contrasted with the urinary excretion rates of the subsequent 4 hours (during mannitol infusion). These data were then combined with the changes in the plasma and extracellular fluid to gain a view of the total distributional change achieved by the close of the infusion.

Column 2, Table 4, shows the extracellular fluid expansions calculated from the extent of the dilutional hyponatremia. These data are identical with those shown in

TABLE 4. *Distribution of Water and Solute at End of Infusion*

Subj.	Water			Crystalloid			Potassium				Sodium
	Δ ECF (ml.)	Δ Urine (ml.)	Total (ml.)	Δ ECF (mOsm.)	Δ Urine (mOsm.)	Total (mOsm.)	Δ Max. Conc. (mEq./L.)	Δ ECF (mEq.)	Δ Urine (mEq.)	Total (mEq.)	Urine (mEq.)
1	2	3	4	5	6	7	8	9	10	11	12
					A. *Controls*						
D. M.	530	960	1,490	300	501	801	+0.6	8.1	20	28.1	52
R. D.	1,400	912	2,312	536	559	1,095	+0.9	13.8	25	38.8	55
Mean	965	936	1,901	418	530	948	+0.8	10.5	22	32.3	54
					B. *Bled Subjects*						
D. M.	625	648	1,273	234	347	581	+0.4	4.4	17	21.4	27
R. D.	570	648	1,218	245	430	675	+0.4	5.2	12	17.2	13
J. B.	420	696	1,116	226	449	675	+0.3	5.3	18	23.3	29
R. R.	600	336	936	258	109	367	+1.2	14.5	−2	12.5	3
T. V.	850	720	1,570	348	324	672	+0.1	1.3	9	10.3	35
Mean	613	610	1,223	262	332	594	+0.5	6.1	11	16.1	21

Table 3, Column 8. Column 3 shows data for "excess water" in urine during mannitol infusion; the sum of these two, shown in Column 4, is, therefore, the "total new water" appearing in the extracellular fluid or in the urine as a result of mannitol infusion. These figures range from 936–2,312 ml., and from these totals must be subtracted in each instance the 500 ml. infused, giving a net "new water" of 436–1,812 ml. as a result of mannitol infusion, with a mean of 1,400 ml. in the control subjects and 723 ml. in the bled subjects.

Columns 5, 6 and 7, of Table 4, show analogous data for new crystalloid, again derived from measurements of the change in extracellular fluid osmolality (Table 3, Column 13); the change in ECF (Column 5) and the "extra solute" appearing in the urine during infusion (Column 6) is added in Column 7, this representing the total new crystalloid solute appearing in the extracellular fluid plus the urine, during the infusion. These range from 367–1,095 mOsm. The mean for the unbled subjects is 948 mOsm. and for the bled subjects, 594 mOsm. These figures should be compared with the total solute infusion of 605 mOsm. of mannitol; if the mannitol attracts no further crystalloid for excretion, then the total new crystalloid appearing should be equal to the mannitol infused. It is evident that in the bled subjects, the recovery is almost quantitative, with a mean new crystalloid appearing in the extracellular fluid and urine of 594 mOsm.; in the unbled controls, somewhat more crystalloid is excreted (948 mOsm.). As will be noted later, this is correlated with the fact that there is evidently more non-mannitol crystalloid attracted into the circulation in the unbled versus the bled subjects (see Table 5).

Columns 8–11 show analogous data for potassium as an indicator of cell water mobilization. It will be noted from Column 8 (maximum observed plasma potassium concentration increment) that during the infusion of mannitol, while sodium concentration is falling, potassium concentration is rising, though only to a modest extent. This is multiplied by the extracellular fluid volume (Column 9) and indicates the total amount of "new potassium" evident in the extracellular fluid. The new potassium occurring in the urine (Column 10) is the "extra" potassium excreted during mannitol infusions as contrasted with that in the 4 hours immediately preceding. The total of these two is shown in Column 11 and ranges from 28–39 mEq. in the control subjects and from 10.3–23.3 mEq. in the bled subjects. It is thus evident that the water withdrawn from body cells in response to this hypertonic infusion (700–1,400 ml.)

TABLE 5. *Rebound and Final Equilibrium*

Subj.	Hematocrit				Sodium				Solute				Final Change Solute (mOsm./L.)
	LVH_L	LVH_R	Time (min.)	LVH_F	Na_H (mEq./L.)	Na_R (mEq./L.)	Time (min.)	Na_F (mEq./L.)	mO_H (mOsm./L.)	mO_R (mOsm./L.)	Time (min.)	mO_F (mOsm./L.)	
1	2	3	4	5	6	7	8	9	10	11	12	13	14
						A. *Controls*							
D. M.	49.7	52.8	105	50.8	134	140	105	139	300	304	200	304	+15
R. D.	51.9	55.5	75	53.9	131	138	75	138	298	290	75	292	+12
Mean	50.8	54.2	90	52.4	132	139	90	138	299	297	138	298	+14
						B. *Bled Subjects*							
D. M.	47.1	50.7	180	46.4	130	141	180	138	298	289	180	298	+4
R. D.	47.2	47.2	180	50.9	131	132	90	141	294	292	90	288	−8
J. B.	39.4	41.8	150	40.6	132	137	180	138	292	293	180	285	−3
R. R.	39.4	41.6	130	41.4	130	136	120	136	295	290	120	288	+1
T. V.	41.0	43.1	160	42.0	132	138	60	140	291	290	60	290	+8
Mean	42.8	44.9	160	44.3	131	137	126	139	294	291	126	290	0

has appeared essentially without potassium. More potassium has appeared in the control than in the bled subjects.

Column 12 of Table 4 shows data for the "extra sodium" appearing in the urine.* It will be noted that in the control subjects these are 52 and 55 mEq., respectively, during the 4 hours of infusion, and in the bled subjects somewhat lower values of 3–35 mEq., with a mean of 21 mEq. This new sodium appearing in the urine during mannitol infusion changes only to a minor degree the calculation for the extent of extracellular increment indicated by the dilutional hyponatremia.

Table 5 shows the data for the rebound and final equilibrium conditions. Columns 2, 3 and 5 show the lowest hematocrit observed, the highest during rebound, and the final hematocrit (LVH_L, LVH_R and LVH_F). Column 4 shows the time following the close of the mannitol infusion when the maximum hematocrit was observed. Analogous data for sodium are shown in Columns 6–9. Columns 10–13 show analogous data for solute where the highest solute concentration of plasma (*during* infusion) is indicated by mO_H, the rebound by mO_R and the final mO_F. Column 14 shows the net final change in solute concentration in the plasma.

With one exception the rebound hematocrit was higher than the final hematocrit. This indicates that the transcapillary refill continued and finally stabilized the hematocrit at the end of the experiment. Rebound was maximal from 65–180 minutes after the end of the infusion. Continuous sampling of the peripheral concentration of erythrocytes and some sort of an automatic device would be required to establish the precise moment of peak rebound. This is a substantial limitation in calculating the rate of continued outward dispersal of mannitol-attracted water. The rebound sodium con-

* The "extra sodium" in urine is the incremental sodium excretion during infusion.

TABLE 6. *Protein Changes* (Gm./100 ml.)

	Controls		Bled				
	D. M.	R. D.	D. M.	R. D.	J. B.	R. R.	T. V.
Starting							
Total protein	7.4	6.7	7.2	6.7	6.9	6.8	7.1
Albumin	4.1	4.1	4.1	4.0	3.3	4.2	4.4
Globulin	3.3	2.6	3.1	2.7	3.6	2.6	2.7
Hemorrhage (min.)	—	—	240	200	240	150	240
Total protein	—	—	7.3	6.4	6.7	6.8	6.7
Albumin	—	—	3.6	3.5	4.0	4.4	4.1
Globulin	—	—	3.7	2.9	2.7	2.4	2.6
Mannitol (min.)	120	120	60	60	30	135	30
Total protein	7.1	6.4	6.7	6.2	6.4	6.5	6.4
Albumin	4.2	3.8	3.8	3.6	3.7	4.3	3.9
Globulin	2.9	2.6	2.9	2.6	2.7	2.2	2.5
End mannitol (min.)	220	195	200	205	200	195	215
Total protein	7.3	6.5	6.8	6.1	6.5	6.7	6.5
Albumin	4.1	3.5	3.8	3.4	3.7	4.1	4.1
Globulin	3.3	3.0	3.0	2.7	2.8	2.6	2.4
Later (min.)	240	—	—	240	60	120	150
Total protein	7.6	—	—	6.5	7.1	7.6	7.0
Albumin	4.0	—	—	3.6	3.9	5.0	4.5
Globulin	3.6	—	—	2.9	3.2	2.6	2.5
Final							
Total protein	7.0	6.6	7.7	6.4	6.7	6.8	6.7
Albumin	4.2	3.5	4.5	3.8	4.2	4.6	4.0
Globulin	2.8	3.1	3.2	2.6	2.5	2.2	2.7

centration also was higher than, or equal to, the final sodium concentration in most instances, as the new mannitol-attracted water was either excreted in the urine or redistributed itself back into the body cell mass.

An inverse rebound situation is noted for solute concentration, with final settling out of solute concentration at a value significantly higher than the starting figure; the data in Column 14 are calculated as they are in Table 3 and are based on the "spread" between the total solute change, and the sodium change multiplied by two. In the control subjects there was 12–15 mOsm./L. of new crystalloid at the close of the experiment, approximately 24 hours after commencing the infusion. In the bled subjects the mean for this figure is zero, with a spread from −8 to +8. Although the bled subjects were slower to lose plasma volume and slower to lose sodium and solute, by the close of the experiment (as likewise at the close of infusion) they had more new crystalloid in the circulation than did the control subjects.

The total refill (not shown in the tables) averaged 86.3 per cent in these experiments; the range was from 65–112.2 per cent. It will be recalled that the figure of 100 per cent refill indicates that the amount of new plasma attracted into the circulation exactly equals the sum of plasma and erythrocytes withdrawn in the bleed. Thus, in these particular experiments, the total refill was slightly short of complete.

Table 6 shows the changes in serum protein concentration. Of principal interest is that infusion of mannitol lowered the concentration of total protein in all subjects,

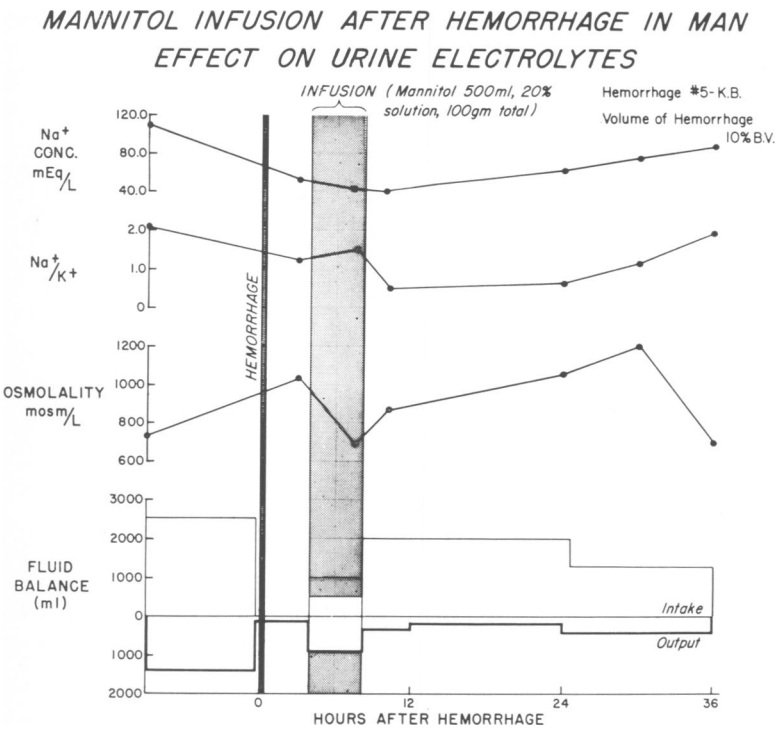

FIG. 3. Urinary changes with mannitol infusion after hemorrhage. Lowest sodium:potassium ratio is observed following the infusion rather than during infusion. During infusion, urine osmolality falls to about 700 mOsm./L., and there is a transient period of negative water balance.

and that this was often due principally to dilution of globulins rather than albumin. This strikes a familiar note in comparison with the balanced salt experiments. Again it appears that hemorrhage stimulates a continued ingress of albumin into the circulation, here coincident with the ingress of virtually solute-free water in response to the hypertonic crystalloid. None of these changes in protein concentration is large, but the trend is consistent. It is also of note that in four of five subjects in whom the measurement was made, there was a distinct period of hyperproteinemia 4–24 hours after the injection of the mannitol.* Total protein concentrations of 7.0–7.6 Gm.% were noted in Subjects D. M., J. B., R. R. and T. V. late in the evening of the day the mannitol was given (approximately 2–4 hr. after the close of the mannitol infusion). In Subject D. M., this period of hyperproteinemia (7.7 Gm.%) was noted as late as the following morning (approximately 24 hr. after the bleed). This mild dehydration (with hemoconcentration of proteins) produced by the mannitol probably accounts for the fact that all of the hematocrits are slightly higher at this period, and plasma volume refilling slightly lower than would otherwise be expected for hemorrhages of this magnitude. It is also noteworthy that the delayed reduction of sodium excretion (see below) noted late after mannitol infusion may be correlated with this mild dehydrating effect during the infusion itself.

Figures 3–6 show data for the urinary change, displayed in charts rather than tables, in the interest of brevity.

Figure 3 shows a typical protocol, indicating the transient negative fluid balance

* In Table 6 the time interval following hemorrhage refers to the number of minutes following the beginning of the bleed. The time interval after mannitol refers to the number of minutes following the commencement of the mannitol infusion. The same refers to the time at "end mannitol." The time of the "later" samples refers to the number of minutes following the cessation of the mannitol infusion that the sample was drawn. The "final" samples are all drawn at the same time, approximately 24 hours after the bleed.

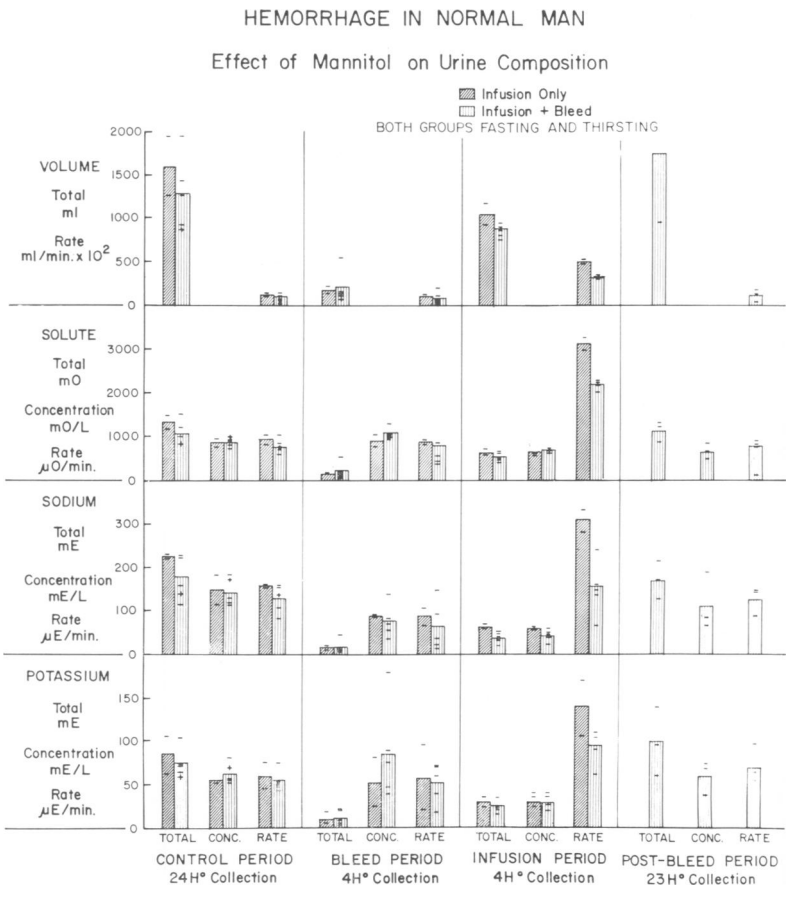

FIG. 4. Effects of mannitol on urine composition. Mannitol infusion produces a large increase in urine volume and in rate of excretion of total solute, sodium and potassium; effect is always less noticeable when hemorrhage has preceded infusion of mannitol. Effects on solute concentration are negligible compared with those observed on rate.

produced by mannitol infusion and later restored to normal by intake. The tendency for the urine sodium to be at a low fixed concentration and an osmolality around 700 mOsm./L. is noteworthy; also the fact that for the next 24 hours the urinary sodium: potassium ratio is low, as if the mannitol had depleted some circulatory component concerned with aldosterone regulation.

Figure 4 shows bar diagrams for the effects of mannitol on total urine volume, solute, sodium and potassium, as well as rate and concentration. Restrictive effects of the bleed are evident; the marked diuretic effect of mannitol is evident, together with the fact that in all instances the bled subjects had significantly lower rates of water and solute excretion in response to mannitol than did the unbled controls. Note that this effect of restriction due to the previous bleed is visible in *rate* but not in *concentration*. Figure 5 shows data for excretory rates produced by mannitol infusion, as compared with those seen with balanced salt solution as described in a previous paper.[13] It is noteworthy that both urinary volume and solute rate are notably increased by mannitol over analogous changes with balanced salt solution, whereas the subsequent excretion of sodium is clearly restricted, as is urinary volume; again, an explanation would be the mild dehydrating effect of the mannitol itself.

Figure 6 indicates the effects on urinary concentrations of these two types of infusions after hemorrhage. The differences between the two are not as notable when concentration rather than rate is expressed; but the decreased concentration of sodium in the urine, both during and after man-

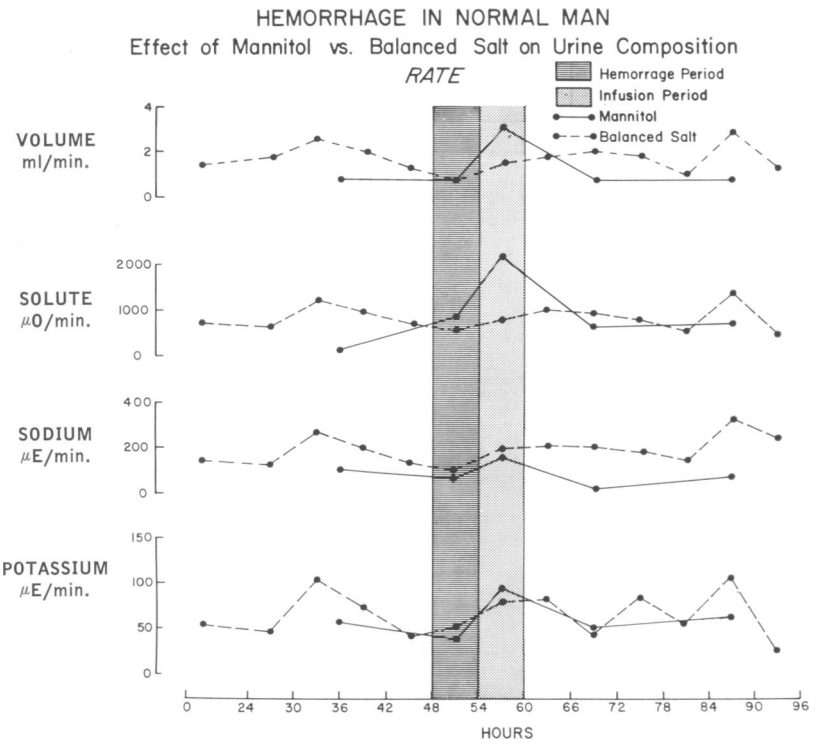

FIG. 5. Contrast of mannitol with balanced salt infusion (5), as regards urine excretory rates following hemorrhage. Volume and total solute excretion are much higher with mannitol than with balanced salt infusion. Subsequent to infusion there is a prolonged decrease in urine volume and in sodium excretion in the mannitol experiments as contrasted with those receiving balanced salt infusions.

nitol infusion, is evident, as well as the increase in potassium excretion following mannitol infusion. Tendency to a high urine volume with a low, fixed sodium concentration and a subsequent restriction in sodium excretion in the urine are responsible in part for the hypernatremia noted with chronic mannitol infusion.[14]

One of the most striking effects of mannitol on renal function is its tendency to produce a urine with a fixed osmolality, all urines being very closely grouped at 600–700 mOsm./L. In the period after the bleed the subjects had urine osmolalities ranging from 900–1,100 mOsm./L.; with the diuresis produced by mannitol all the urine osmolalities came to this fixed figure (600–700 mOsm./L.). Sodium and potassium concentrations fall abruptly to about 40 mEq./L. for each ion; the sum of these multiplied by two equals 160 mOsm./L. for electrolyte solute in the urine, as a first approximation, the remainder, approximately 500 mOsm./L., being due to mannitol plus urea. In previous experiments carried out in dogs, it was evident that mannitol increases the urinary excretion of urea, and this may account for the appearance of considerably more new crystalloid than was infused.[20, 21]

The mannitol-induced diuresis produces increase of urine flow up to the range of 3–5 ml./min., or 180–300 ml./hr. Subjects receiving infusion only, with no previous bleed, increased their sodium excretion rates to close to 300 μEq./min., while those who had the bleeds prior to the infusion showed increases only to 50 per cent of this value, or approximately 150 μEq./min.

The effect of mannitol infusion on glomerular filtration was inconstant in these experiments. In only four subjects were satisfactory data derived in the absence of urethral catheterization. In these four, the mannitol infusion left the glomerular filtration rate unchanged in one, increased in two, and lowered slightly in one. In no case were any abnormal values observed.

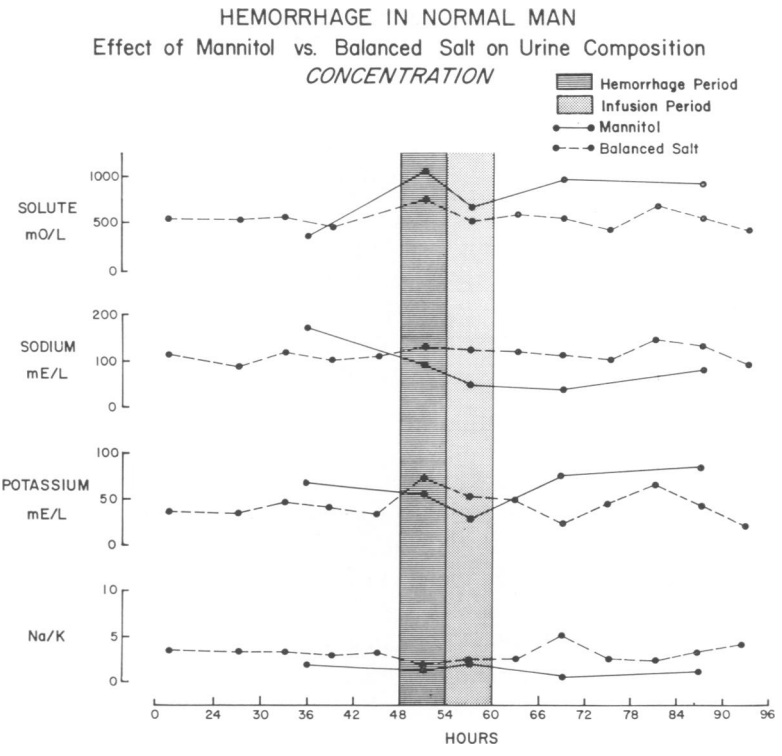

FIG. 6. Effects of mannitol vs. balanced salt infusion on urine concentration. There is an increase in total solute concentration with mannitol infusion; sodium concentration is markedly decreased with mannitol, as contrasted with balanced salt infusion, and decreased sodium concentration is prolonged, being accompanied by a lowered sodium:potassium ratio in the mannitol experiments. The latter is interpreted as due to a mild dehydrating and volume-reducing effect of mannitol over the long term—in those subjects who were bled, transcapillary refill was incomplete when mannitol was given.

Discussion

These experiments demonstrate the changes in distribution of body water as produced by the infusion of a hypertonic non-metabolizable low-molecular-weight crystalloid at a concentration about four times isotonic to serum (1,210 mOsm./L.).

At first, the material is circulated through the bloodstream. With a slower half-time of transit across the capillary than of water ingress, it produces a brief plasma volume expansion. As a plasma volume expander mannitol is obviously very transient in its effect.

With continuing infusion, and as the mannitol begins to cross the capillary, a much slower and much more marked expansion of extracellular fluid volume is produced. The data of Lillien *et al.*[12] leave little question that the erythrocyte participates in this donation of water to the extracellular fluid; but at the mannitol concentrations used here the erythrocyte effect is very small; during the time that hyponatremia is becoming most marked, the hematocrit itself is actually rising. Most of this water must come from body cells generally, and it is impossible to state which cells contribute the most.* The amount of new potassium appearing in the extracellular fluid and in the urine is small, representing at most 150 ml. of cell water. Since the amount of new water appearing (corrected for volume of infusion) is much closer to 750–1,400 ml., it is evident that the hypertonic crystalloid is withdrawing water from cells disproportionately to the withdrawal of intracellular electrolyte. This is not surprising in view of the fact that the mannitol itself penetrates cells to only a minor extent, and the water shift is osmotic in origin.

By the close of the infusion, most of these events have been completed, but the man-

* Direct evidence for participation of the brain in the water loss pursuant to mannitol infusion, comes from its use by neurosurgeons to shrink the brain prior to or during neurosurgical operations.[28]

nitol has not yet been accounted for in the urine entirely; another few hours would be necessary to document this.

With the cessation of the infusion, outward passage of mannitol continues, together with the recently attracted water. Mannitol plus its water of solution are both excreted in the urine. This diuresis continues at very high rates of urine flow (almost 10 times normal). The net result is a drastic alteration in blood concentration of erythrocytes, protein, sodium and total solute, identified as the "rebound" phenomenon.

Noteworthy among these events in plasma and interstitial water is the fact that previous hemorrhage biasses the retention of the mannitol-attracted water, so as to hold it in the circulation longer than in the control subjects. This finding is analogous to that previously reported [13] for infusions of balanced salt solution. Likewise, the previous hemorrhage restricts the excretion of water and sodium in such a way as to delay both, despite the strong diuretic activity of the mannitol.

It was unexpected to find that at the close of 24–30 hours, there was still some new crystalloid in the extracellular fluid; it was particularly unexpected to find that this was larger in the control than in the bled subjects. Whether these small changes are significant remains to be determined. In the dog,[20, 21] mannitol attracts an increased excretion of urea in the urine; it is conceivable that it also attracts other intracellular crystalloids into the extracellular phase. Precisely why these should remain in the plasma longer in the control than in the bled subjects is not clear.

A total solute load of 605 mOsm. of mannitol in 500 ml. should be expected to move approximately 1,500 ml. of body water if isotonicity were maintained in plasma water, interstitial water and urine water. Somewhat less water is moved as a result of the hypertonic infusion (about 750–1,400 ml.). This is due to the fact that the urine osmolality is approximately twice the isotonic level, accounting for mannitol excretion in urine osmolalities well above those observed in plasma. The fact that the renal tubule can concentrate mannitol and other solutes to a total osmolality of about twice that of serum, despite the massive diuresis in progress, accounts for the excretion of the total solute load without the appearance (either in urine or extracellular fluid) of the total predicted water volume. Were the mannitol, following injection, to be observed in urine and body fluids only at isotonic concentrations, then the full volume of 1,500 ml. should be accountable at some site; if not, one would have to postulate the movement of some mannitol into body cells.

That the latter may not be beyond possibility is supported by the fact that in two subjects at the end of the experiment (D. M. and R. R.) the entire mannitol infusion had not yet been recovered when calculated as new nonelectrolyte osmolality in plasma plus urine. This method of calculating the mannitol increment is an approximation only; it yields a value that is probably higher than the true mannitol recovery. Further experiments on the total body distribution of infused mannitol should help to answer whether or not, under conditions of chronic infusion, some mannitol can enter body cells. Here, with an *average* recovery of 594 of a possible 605 mOsm. in bled subjects, and of even more (948 mOsm.) in the controls, it is not necessary to postulate the entry of mannitol into body cells in the group as a whole.

In patients given mannitol who have continuing oliguria so that the mannitol cannot be excreted, its final distribution depends upon this question of cellular penetration or metabolism. It is conceivable that the rate constants for movement of mannitol into the cell are such that in a normal person with rapid brief infusion, little cellular penetration is evident prior to mannitol excretion. With renal failure or more infusions

of mannitol, cellular penetration might be evident.

Changes in protein levels were particularly interesting when compared with those documented for balanced salt infusion. It was to be expected that mannitol would produce a dilution of serum protein; but it was not predicted that globulins would be diluted more than albumin. Here, as in the balanced salt experiments, the available globulin appears to be less labile and thus more readily prey to plasma dilution; whereas a dynamic entry of albumin into the circulation after hemorrhage continues despite infusion of either mannitol or balanced salt, and albumin is thus diluted to a lesser extent. It should be emphasized that none of the protein changes observed was large, and that further work is needed to document the significance of these small changes.

There is little information in the literature on the precise questions of this work: the volume of fluid moved by mannitol infusion, its source and fate. The *in vitro* study of Rand and Lacombe[22] indicated the types of changes one might expect from an *in vitro* mixture of blood with a variety of isotonic, hypertonic or hypotonic diluents. Included was mannitol at a variety of concentrations and producing a net plasma osmolality varying from 275 to 450 mOsm./L. These diluents showed the effect on hematocrit due to hypertonicity of the plasma. This cell-shrinkage factor produced a fall in hematocrit of about 12 per cent (from 40–35) with an increase of plasma osmolality from 295 to about 350 mOsm./L.

This increased osmolality will produce cell shrinkage and decrease in hematocrit only if it is due to the presence of a material that does not move into the cell, such as mannitol or sodium salts. Similar increases due to urea produce no change in cell size, and the addition of glucose produces a much lesser decrement in hematocrit. The achieved plasma osmolalities with mannitol infusion never approach these excessive ranges. The small changes noted here, from 5–15 mOsm./L., would be expected to produce scarcely discernible changes in red cell size.

The same considerations apply to other measurements such as blood and plasma viscosity. Very high concentrations of mannitol produce readily discernible increases in blood viscosity, evidently due to red cell crenation. At the concentrations achieved here, when mannitol is injected into the entire circulation, no discernible change would be expected from the mannitol molecule *per se*. In sharp contrast, the volume of water brought into the circulation by mannitol would be expected to produce a noticeable decrease in both plasma and whole blood viscosity as red cells, protein and sodium salts are diluted. More studies of the type reported by Rand and Lacombe, using carefully controlled *in vitro* systems, would aid in interpreting many effects reported for blood viscosity-lowering substances.

Our work reported herein casts no light on the efficiency of mannitol in preventing acute tubular necrosis. Affirmative evidence, first from experimental studies of Owen, Desautels and Walter[15] has been extensively corroborated by others. Dudley *et al.*[9] reported the prevention of acute tubular necrosis in patients in whom it presumably would have occurred due to burns. The works of Barry are particularly significant in this regard, and one of his reports[1] yields possibly the most significant information on the prevention of acute tubular necrosis in a controlled series involving resection of abdominal aneurysms. In other studies, Powers[19] and Barry[14, 17] documented many of the renal and pathologic effects of mannitol infusion. Powers *et al.* also documented the prevention of acute tubular necrosis.

Barry and Berman[2] documented the effect of mannitol on whole blood and plasma volumes. They demonstrated a transient effect on blood volume using infusion con-

centrations and volumes similar to those employed here. Their studies document the negative fluid balance produced by mannitol in individuals with normal visceral function, and the fact that with renal or hepatic disease large positive fluid balances are produced because of the inability to excrete the material with, as one would predict, a much larger and more prolonged increase in blood volume. The authors were particularly interested in the fact that mannitol can be given to severely compromised cardiac patients without danger of circulatory embarrassment. Barry and his group [3] employed mannitol to assist in the excretion of ingested toxins, an effect traceable to the "washout" of other crystalloids during mannitol-induced diuresis. Our current studies cast no light on this problem. In a previous study in the dog [20, 21] it was demonstrated that even in the normal subject mannitol washes out some other low-molecular-weight crystalloids such as urea. Cirksena *et al.*[5] have made use of this in the treatment of certain types of intoxication such as barbital poisoning.

Barry and his group [4] contrasted various forms of water and solute loading as regards their effect on renal function during and immediately after surgical operations. They pointed out that the mannitol-induced diuresis was more effective in maintaining hydration and excretion of solute than the other substances they tested. This was in part, at least, due to the ability of an osmotic diuresis to break through sustained antidiuresis, producing the excretion of large volumes of water and solute despite the maintenance of maximum negative free water clearance.[8] *

In this latter regard Barry *et al.* postulate a "central circulatory volume" that is critical in determining volume-maintaining activity and that is, in turn, restrictive with respect to renal circulation. They emphasize the importance of starting such solute-loading prior to administration of the anesthetic, if the material is to be used in conjunction with an operation.

Parry and coworkers [16] noted the effect of mannitol in protecting against experimental acute renal failure. Coleman and Buckell [6] documented the increase in blood volume in a number of clinical patients given rapid infusions of urea or mannitol. Results were documented as percentage increases in blood volume, and the rates of mannitol infusion were very great—for example, 500 ml. of 20 per cent mannitol in 10–20 minutes. Transient increases in blood volume recorded ranged from 7–53 per cent. Most of them were between 20–30 per cent. Greater and more sustained volume-increases were produced when mannitol was given in a saline carrier. Increases in blood volume produced by urea were, of course, somewhat less. These patients (in the study of Coleman and Buckell) had raised intracranial pressure and were undergoing craniotomy. The mannitol infusions were given to decrease brain volume, and they concluded that cardiac embarrassment could result from this type of rapid infusion if the patient had imperfect cardiac function.

The slow rate of refill observed in these patients is due in part to the small magnitude of the bleeds, as compared with other recent studies from these laboratories. The final percentage of refill in these patients was lower than in some other series we have reported,[11, 13] probably due to the fact that with mannitol infusions some of these patients were in net negative water balance

* Under continued influence of antidiuretic hormone, large amounts of water and solute can be excreted if a nonreabsorbed solute, or one poorly reabsorbed, is presented to the kidney during antidiuresis. Examples are glucose, sucrose, mannitol and, to a lesser extent, urea. This excretion of large urine volumes during antidiuresis should not, however, be interpreted as indicating an abolition of the antidiuretic effect; quite the contrary, the highest rates of negative free water clearance observed during vasopressin-induced antidiuresis are at times when the kidney is excreting a large solute load.

for the period of study. Barry and coworkers [2] postulate that during the period of maximum plasma volume expansion (early after the onset of infusion) there is some competition between movement of water into the plasma and into the glomerular filtrate, and at least a transient period of suppression of urine flow may be observable. Our experiments were not designed to cast any light on this problem. With very rapid injections of very high concentrations of mannitol, urinary suppression might be observed, if for no other reason than increased viscosity; then, within a few minutes, as the hypertonicity of the mannitol infusion was slaked by the withdrawal of tissue water, profuse diuresis would result. Other mechanisms for the suppression of urine flow by mannitol depend on its very chronic administration over the period of many days, and the possibility that a renal tubular lesion is produced thereby.

Like any effective drug or hormone, mannitol can produce serious side effects. It is evident from the work reported in this paper that transient plasma volume increases can readily be produced. Such might be dangerous in patients with diminished cardiac reserve. Acute hyponatremia may also be produced by mannitol; in the fully digitalized cardiac patient, such an hyponatremia would be expected to produce electrocardiographic changes and even cardiac arrhythmias. These would resemble closely the changes of hyperkalemia. Thirdly, the prolonged chronic administration of mannitol will produce hypernatremia by the withdrawal of large volumes of urine having a water:sodium ratio higher than plasma. This is evident from the work reported herein. Careless use of mannitol over a long period of time might even produce a fatal hypernatremia.[10] The mechanism is analogous to any other dehydrating effect of a solute load, *e.g.*, the hypertonicity of diabetic coma and of tube-feeding solute diuresis. There is some evidence from unreported work in our laboratories that the prolonged administration of mannitol produces a renal tubular lesion characterized by cloudy swelling of the tubular cells. This resembles the renal tubular lesion of potassium deficiency. It appears to be a nonspecific change, but its significance deserves further study. And finally, in those patients with sustained oliguria, who have been given repeated injections of mannitol with the object of initiating urine output, one might expect an abnormal distribution of mannitol, possibly with cellular penetration, and possibly with diffuse effects on neuromuscular irritability. Thus mannitol must be used with care and with the full knowledge of its many biochemical and body compositional effects.

Summary

Infusion of 20 per cent mannitol produces a sudden dislocation of body fluid characterized by a transient increase in plasma volume with fall in the hematocrit, fall in the peripheral concentration of erythrocytes, followed by a slower and more marked increase in the extracellular fluid volume. There is an early fall in sodium concentration. These events, in turn, are followed by a solute diuresis characterized by urine of a fixed osmolality (about 600–700 mOsm./L.), and at rates of 4–5 ml./min. This urine has a water:sodium ratio higher than plasma, and its continued output under the stimulus of repeated mannitol infusions will produce severe hypernatremia.

The distribution of water, electrolyte, and solute at the close of the mannitol infusion indicates that the mannitol-attracted water has largely been excreted; the total new crystalloid solute presented by infusion has largely been excreted; there has been a net loss in body water. The total new water appearing in extracellular fluid plus urine is less than that predicted from the dilution of the injected solute because the kidneys are capable of excreting the solute at

a concentration higher than that observed in plasma.

Following cessation of the infusion there is a continued dispersal of mannitol and water out of the plasma volume, and a continued excretion of water, salt and crystalloid at a brisk rate. The over-all dehydration produced by these events may be noticeable as late as the following day, when continued hyperproteinemia is observed and sodium concentration is beginning to rise. Following hemorrhage the transcapillary refill tends to be incomplete when mannitol is used, probably due to this dehydrating effect. A prolonged restriction of sodium excretion is likewise noted.

Like any other useful drug or hormone, mannitol must be employed with full knowledge of its drastic effects; its toxic side effects (hyponatremia, later hypernatremia, plasma volume increment and renal tubular changes in chronic administration) need not be encountered if the material is used briefly and intelligently in the volume-restricted patient.

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