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Research Article

THE IMPORTANCE OF VOLUME AND OF TONICITY OF THE BODY FLUIDS IN SALT DEPLETION SHOCK[1]

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It is not known whether the deterioration in circulatory efficiency which follows sodium chloride loss is related primarily to the hypotonicity, to the changes in the volume of fluid in the various compartments, or to both. In experimental salt depletion produced by means of the intraperitoneal injection and subsequent removal of glucose solution, both of these factors invariably coexist. As sodium and chloride ions enter the intraperitoneal fluid, water moves into the cells in response to osmotic forces. Diminution of the volume of extracellular fluid and plasma, swelling of the cells, and generalized hypotonicity are the inevitable end results (1, 2, 3). Since these changes occur rapidly and almost simultaneously, it is difficult to ascribe the primary causative role in the circulatory collapse which ensues to any one factor. It is conceivable, on theoretical grounds at least, that all of these changes are important. It is quite possible, for instance, that the hypotonic and swollen cells of the cardiovascular system become inefficient, while the blood thickens and becomes more difficult to move through the vessels.

To clarify the relative significance of each of these changes in the production of salt depletion shock, further experiments have been conducted in which hypotonicity and the state of hydration of extracellular and cellular fluid have been altered in directions other than those seen in ordinary salt depletion.

MATERIALS AND METHODS

A. Dilution of the body fluids in nephrectomized animals. The effects of an infusion of 5 per cent glucose solution on the composition of the body fluids and the efficiency of the circulation were studied in 3 nephrectomized dogs on the day following removal of the second kidney. The kidneys were removed under nembutal anaesthesia via a retroperitoneal approach. Two to 7 days of convalescence were permitted following the first operation. The glucose solution was administered during a period of 1 hour in amounts sufficient to lower the concentration of serum electrolytes to approximately ¾ of the initial value. After 3 to 4 hours all 3 animals received additional infusions. Two were given 5 per cent saline in volumes sufficient to restore isotonicity of the body fluids. The third received 6 per cent gelatin solution containing sodium chloride in low concentrations (0.2 per cent).

B. Restoration of isotonicity by urea diuresis in salt-depleted animals. Two other dogs were first depleted of salt by the standard technique of injecting 5 per cent glucose solution intraperitoneally, 100 ml. per kgm., and withdrawing it after 3 to 4 hours (1). An overnight diuresis was then induced in these animals by means of an intravenous injection, 350 ml. of a 15 per cent solution and 300 ml. of a 10 per cent solution of urea in 5 per cent glucose, respectively. In one of these animals the effects of a subsequent infusion of hypotonic saline, 0.6 per cent, were investigated.

In all studies in Groups A and B, movements of water from the extracellular compartment were calculated from changes in the chloride space (4). Alterations in the plasma volume were estimated from changes in the relative blood cell volume and in the hemoglobin concentration of arterial blood (1). Changes in the volume of cell water were obtained by subtracting the increments or decrements of extracellular water from the changes in total body water. These later values were calculated from the changes in body weight; in the periods lasting 20 hours the weight change was corrected for water of oxidation according to the metabolic mixture (4). The possibility of transfers of sodium and potassium between extracellular and cellular compartments were also investigated from the changes in their concentration in extracellular fluid, corrected for the intake and output of these ions. The flame photometer was used in these cation analyses (5). The hemodynamic studies at intervals during the course of these experiments included measurement of: (*a*) the fore-paw to medulla circulation time by means of intravenous sodium cyanide, (*b*) the mean arterial blood pressure by direct arterial puncture, and (*c*) the cardiac output by the direct Fick principle based upon the rate of oxygen consumption and the difference in the oxygen content of arterial blood from the femoral artery and mixed venous blood from the right auricle (6).

RESULTS

A. Dilution of the body fluids of nephrectomized animals. The introduction of 5 per cent glucose

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[2] Dr. Winkler died June 26, 1947.

TABLE I

Exchanges of water, electrolytes, and nitrogen

Experiment	Procedure	Time after start of experiment	Weight*	Intake					Output										Balance†	
				Intravenous				i.p.	Peritoneal or G. I. fluid				Urine							
				H_2O	Cl	Na	N	H_2O	Vol.	Cl	Na	K	Vol.	Cl	Na	K	N	Cl	K
		hours	*kgm.*	*ml.*	*meq.*	*meq.*	*grams*	*ml.*	*ml.*	*meq.*	*meq.*	*meq.*	*ml.*	*meq.*	*meq.*	*meq.*	*grams*	*meq.*	*meq.*
A. Dilution of body fluids in nephrectomized animals with normal salt content																				
110B		0	8.82																	
	5 per cent glucose i.v.	2.5**	9.83	1250					100‡	10.2	5.3	—						− 12	± 0
		4.5	9.65															− 1	± 0
	5 per cent NaCl i.v.	7.3	9.83	250	213	213												+211	± 0
113		0	8.15																	
	5 per cent glucose i.v.	3.5	9.26	1100					30‡	3.2	1.8	—						− 6	± 0
	5 per cent NaCl i.v.	5.7	9.22	200	171	171			80§	7.3	9.1	—						+160	± 0
115		0	10.20																	
	5 per cent glucose i.v.	2.7**	11.28	1250					120‡	16.2	7.3	1.4						− 19	− 1
	6 per cent gelatin i.v.††	5.2	11.54	300	4.8	4.8	—											+ 3	± 0
B. Salt depletion and restoration of isotonicity by urea diuresis																				
114		0	9.10																	
	5 per cent glucose i.p.‡‡	4	9.08					1000	940‡‡	70.6	82.7	2.4	0					− 72	− 2
	15 per cent urea i.v.§§	25.5	8.25	350			25.2						710	2.4	2.1	12.8	13.4	− 6	−13
	6.7 per cent NaCl i.v.	28.5	8.60	800	92	92							360	7.1	11.1	10.5	6.1	+ 83	−11
116		0	7.85																	
	5 per cent glucose i.p.‡‡	4.3	7.74					800	830‡‡	59.3	75.7	1.9	0					− 61	− 2
	10 per cent urea i.v.§§	23	7.02	300			14.0						500	4.6	3.2	7.1	7.7	− 6	− 7

* Weight at end of period is corrected for solids lost as feces and red cells taken for analysis.
† See Table II for Na balance; balances are corrected for small amounts of Cl and Na lost in serum taken for analysis.
‡ Vomitus.
§ Diarrheal fluid.
** Convulsions of water intoxication.
†† Gelatin with low salt content obtained from the Knox Gelatine Co.
‡‡ Peritoneal fluid withdrawn at end of period.
§§ Urea given in 5 per cent glucose solution.
In both tables, balance data are expressed per individual period rather than cumulatively. Time from start of experiment indicates end of period at which time serum analyses and hemodynamic measurements were made.

TABLE II

Analytical data, hemodynamic measurements, and changes in body fluids

Experiment	Procedure	Time after start of experiment	Serum*			Blood				Circulation time	Mean arterial pressure	Oxygen		Cardiac index	Change in						
			Cl	Na	K	Total protein	Relative cell volume	Hemoglobin	NPN			Consumption	A-V difference		Plasma volume	Total water	Extracellular fluid	Intracellular fluid	Total body Na	Total ionic conc.†	Total osmotically active base
		hours	*meq. per liter*	*meq. per liter*	*meq. per liter*	*grams per cent*	*per cent*	*grams per cent*	*mgm. per cent*	*seconds*	*mm. Hg*	*ml. per minute*	*vol. per cent*	*liters per min. per sq. meter*	*ml.*	*liters*	*liters*	*liters*	*meq.*	*meq. per liter*	*meq.*
Dilution of body fluids in nephrectomized animals with normal salt content																					
110B		0	93.4	154.0	5.6	6.52	44.7	15.7	91	9	177										
	5 per cent glucose i.v.	2.5	68.5	113.8	5.0	4.69	43.5	16.2	—	9	177				− 5	+1.01	+0.70	+0.31	− 8	−43	−132
		4.5	76.3	123.8	4.2	5.03	45.8	15.9	—	10	162	89	7.3	2.84	− 12	−0.18	−0.32	+0.14	− 2	+10	+ 50
	5 per cent NaCl i.v.	7.3	122.8	155.1	4.4	3.13	28.3	10.7	86	9	170	97	3.0	7.52	+454	+0.18	+0.62	−0.44	+211	+29	+ 22
113		0	103.0	142.9	5.5	5.16	34.3	11.4	83	9	90	93	10.2	2.28							
	5 per cent glucose i.v.	3.5	78.0	113.6	4.4	3.71	26.4	9.0	—	10	87	84	5.9	3.53	+189	+1.11	+0.62	+0.49	− 6	−31	− 34
	5 per cent NaCl i.v.	5.7	101.2	146.6	4.4	3.05	20.0	7.2	83	11	74	91	4.2	5.40	+230	−0.04	+0.79	−0.83	+158	+32	+ 53
115		0	104.3	150.2	5.4	6.87	44.3	14.6	107	8	106	95	5.(	3.62							
	5 per cent glucose i.v.	2.7	68.3	114.5	3.2	5.57	37.5	12.8	119	8	106	91	2.9	6.68	+236	+1.08	+1.18	−0.10	− 11	−38	−124
	6 per cent gelatin i.v.††	5.2	70.5	122.4	3.1	‡	29.1	9.9	‡	6	132	71	3.(	5.05	+286	+0.26	−0.07	+0.33	+ 2	+ 8	+ 98
Salt depletion and restoration of isotonicity by urea diuresis																					
114		0	108.2	155.3	4.7	6.37	43.8	14.8	37	7	118										
	5 per cent glucose i.p.	4	90.7	133.0	4.2	8.72	55.0	17.3	—	11	92	83	8.2	2.35	−158	−0.02	−0.3(	+0.28	− 85	−20	− 45
	15 per cent urea i.v.§§	25.5	106.9	154.8	5.6	9.75	50.5	17.6	315	13	84	83	8.5	2.28	+ 28	−0.70	−0.3(	−0.33	− 7	+24	+ 52
	6.7 per cent NaCl i.v.	28.5	122.2	160.2	3.5	6.87	42.0	14.0	148	9	90	79	4.2	4.37	+175	+0.35	+0.44	−0.09	+ 78	+ 1	− 1
116		0	99.5	146.8	4.1	5.59	53.5	17.0	31	7	150										
	5 per cent glucose i.p.	4.3	84.6	130.5	4.3	7.50	62.8	20.0	39	12	120	83	10.4	2.05	−138	−0.11	−0.31	+0.20	− 78	−14	− 13
	10 per cent urea i.v.§§	23	94.3	137.2	7.0	7.76	58.7	19.3	240	12+	50	62	9.7	1.64	+ 45	−0.64	−0.24	−0.40	− 5	+ 7	− 48

* Water content of serum (W_s) calculated from the serum total protein concentration (P_s) by the formula (10): $W_s = 99.3 - 0.889\ P_s$.
† Total ionic concentration was assumed to equal the concentration of Na in extracellular water + 10 milliequivalents per liter (4).
‡ Serum total protein and NPN concentrations were not determined because of the presence of gelatin; water content of serum was assumed to be unchanged.
††, §§ See footnotes to Table I.

solution produced hypotonicity, an expansion of the extracellular fluid volume in all experiments, as well as an increase in the water of tissue cells in 2 of the 3 animals (Tables I and II). Despite this marked distortion in the concentration of the electrolytes and a swelling of tissue cells quite as great as that witnessed in salt depletion, circulatory efficiency was not adversely affected. The mean arterial pressure and the circulation time were unaltered. The cardiac output was moderately depressed prior to the dilution of body fluids in the 2 experiments in which initial observations are available. This was presumably related to the recent nephrectomy. It is highly significant, however, that it did not decline further following the intravenous glucose solution. As a matter of fact, in one of the dogs (Experiment 115), the cardiac output rose to a level that was well above normal.[8] These findings are in direct contrast to the profound deterioration of the circulation which accompanies salt depletion (1).

The subsequent restoration of a normal concentration of serum electrolytes in Experiments 110B and 113 by means of hypertonic saline resulted in a normal and a supranormal cardiac output, respectively, in contrast to the previous moderately depressed values. Expansion of the plasma volume without restoration of tonicity in Experiment 115 had no adverse effect on the already high normal level of cardiac output.

B. Restoration of isotonicity by urea diuresis in salt-depleted animals. It is evident from Tables I and II that even though the hypotonicity of the body fluids and the swelling of the cells were partially or fully corrected by this dehydrating procedure, circulatory dynamics either failed to improve or actually deteriorated. The volume of extracellular fluid declined further in both experiments. Replacement of the salt deficit and reexpansion of the extracellular fluid by means of saline partially restored the cardiovascular function which had not been improved by the correction of the hypotonicity (Experiment 114).

In none of the experiments in this group nor in the nephrectomized animals was any significant exchange of extracellular sodium for cell potassium detected. In the nephrectomized animals a large amount of intracellular base was apparently inactivated following the glucose infusion (Table II) (7). This was reflected in the disproportionately large volume of the administered fluid which remained in the extracellular phase. The alternative explanation is that a water gradient was present which decreased between 2.5 and 4.5 hours (Experiment 110B). It is hard to believe that such a long period was necessary for the distribution of water to equilibrium. The unequal phase of distribution could also be accounted for by the entry of chloride into cells; such a phenomenon, however, would in no way affect the calculation of exchanges of total water and total osmotically active base. Following the administration of hypertonic saline or of low salt colloid, this base once again became osmotically active.

DISCUSSION

For purposes of discussion published data on simple dehydration and on salt depletion studies are summarized in Figure 1 for comparison with the dilution experiments in the nephrectomized animals. Analysis of these 3 sets of experiments permits certain generalizations. It is immediately apparent that an expansion of the body water, as in the dilution studies with nephrectomized dogs, does not interfere with circulatory efficiency (Column A). A decrease in the total body water, on the other hand, such as that which occurs in simple dehydration does impair cardiovascular function to a limited degree (Column B). This is evident in the drop in the cardiac output, but the decrease is by no means marked or consistent. In the third group of experiments, those in which salt depletion was produced, profound deterioration of the circulatory efficiency was present (Column C). In these animals the total amount of body water remained essentially unchanged. It is apparent, therefore, that extensive alterations in the total amount of body water can be induced with only moderate, if any, effect on cardiovascular dynamics, and that marked circulatory inefficiency can develop even though the total volume of water in the body remains constant. These findings suggest that factors other than the total body water condition cardiovascular function.

Study of the changes which occur in the various subdivisions of the total body water in these 3

[8] Mean cardiac index in normal dogs was found by the authors to be 5.45 ± 1.43 liters per minute per square meter (1).

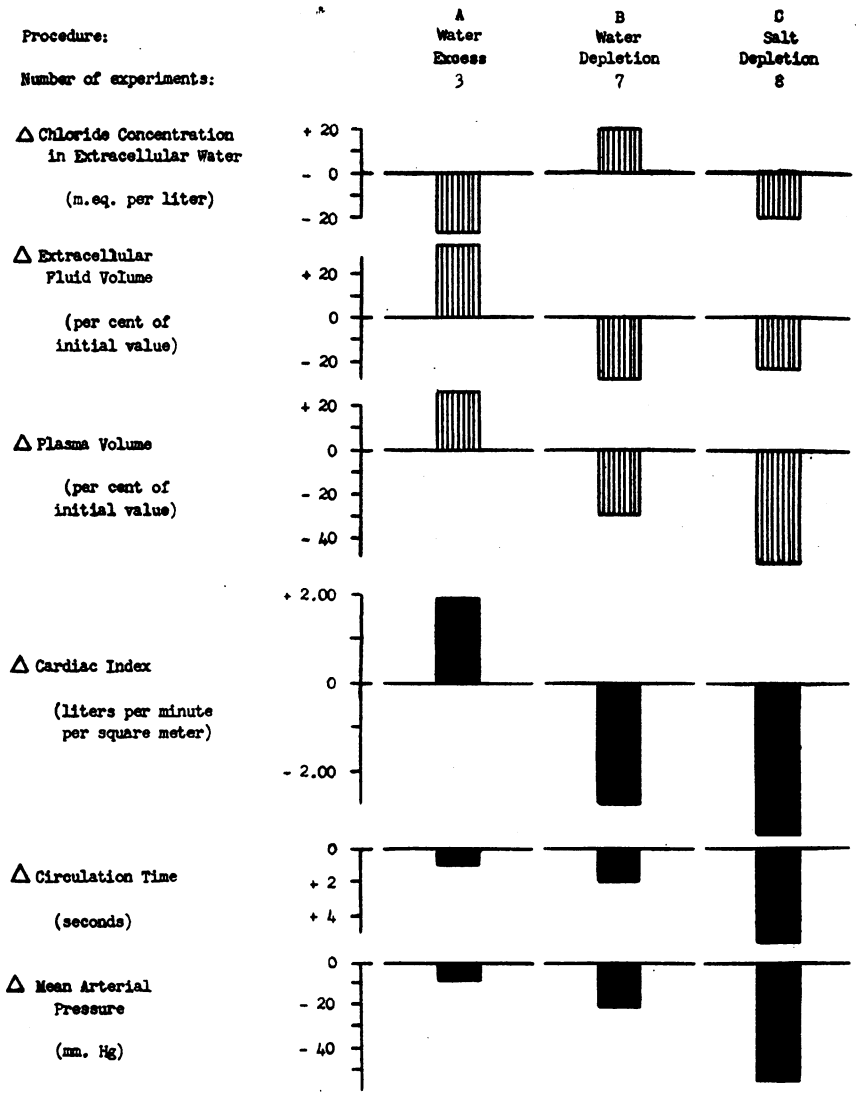

FIG. 1. CHANGES IN CIRCULATORY DYNAMICS FOLLOWING VARIOUS ALTERATIONS IN THE BODY FLUIDS

Each column represents the mean value for the number of experiments indicated. Columns B and C are taken from previously reported data (1). The changes shown were produced in animals with normal body fluids. It is evident that a decrease in both volume and concentration (salt depletion experiments in Column C) causes more profound circulatory deterioration than does a similar change in either volume alone (water depletion experiments in Column B) or in concentration alone (water excess experiments in Column A).

groups of experiments serves to identify some of these factors. In the dilution experiments with the nephrectomized preparations, cell water, extracellular water, and plasma water were all overexpanded without circulatory impairment. In the simple dehydration experiments all of these compartments were contracted in volume with some attendant deterioration of the circulation. In the third group of animals, those depleted of salt, only the extracellular water and the plasma water were decreased, and yet profound shock was present. The decrease in the plasma volume, however, was much greater in the salt-depleted dogs than in the simple dehydrated animals. It would appear, there-

fore, from these experiments, as it has from work on other types of shock, that the volume of plasma is an important factor in the development or manifestations of the salt depletion shock state. The increase in the volume of cell water which attends salt depletion is probably not a contributing factor, since similar degrees of cellular overhydration in the diluted nephrectomized dogs had no deleterious effect on the circulation.

Up to this point no account has been taken of the changes in tonicity which accompany these manipulations of the water in the various compartments of the body. The body fluids of the dehydrated animals were hypertonic, while the salt-

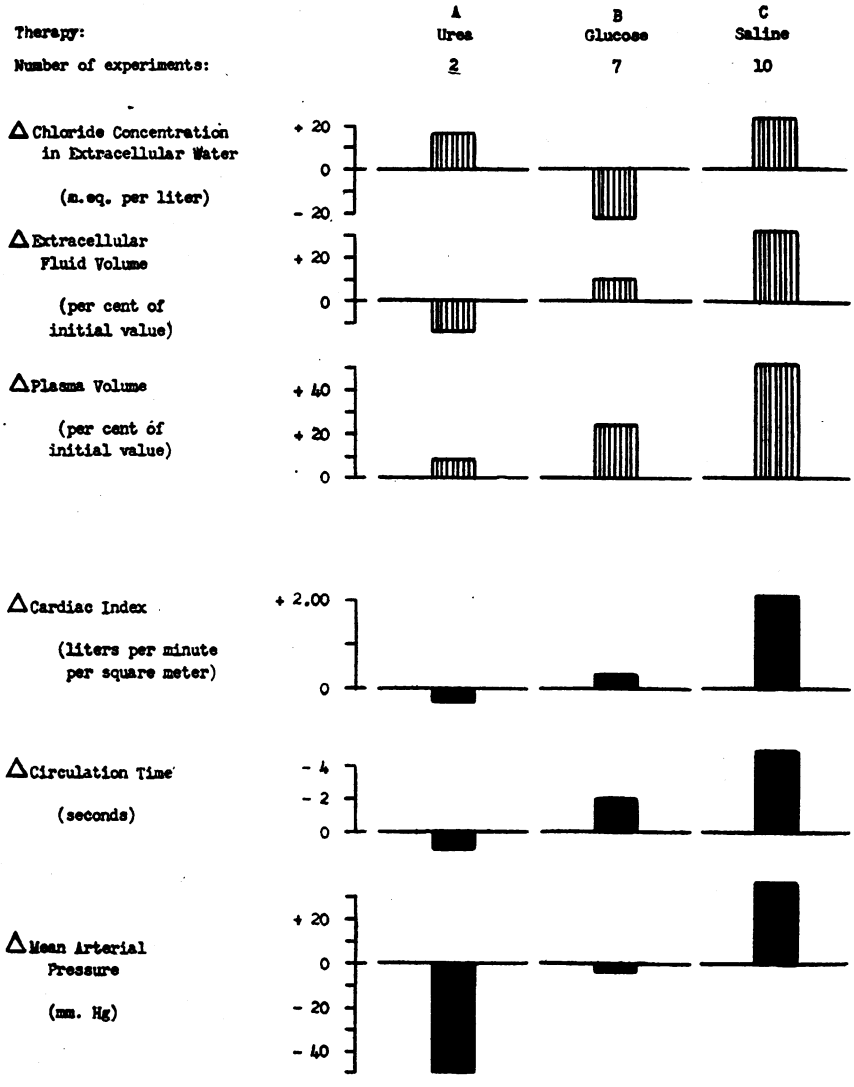

FIG. 2. CHANGES IN CIRCULATORY DYNAMICS FOLLOWING VARIOUS TYPES OF TREATMENT OF SALT DEPLETION SHOCK

Each column represents the mean value for the number of experiments indicated. Columns B and C are taken from previously reported data (2). The changes shown were produced in animals already in salt depletion shock. In such a state, restoration of concentration alone by urea diuresis (Column A), or of volume alone by glucose infusion (Column B), failed to improve the circulation. Restitution of both volume and concentration by infusion of saline (Column C) was followed by prompt recovery from the shock state.

depleted dogs became hypotonic. Since hypertonicity was accompanied by less striking changes in the circulation, hypotonicity, as seen in salt depletion, would appear to have a significantly greater adverse effect on cardiovascular function. Hypotonicity, however, cannot be the sole determinant, since a comparable lowering of the concentration of body electrolytes was produced in the dilution experiments with nephrectomized dogs without impairment of the circulation. In these animals, however, in contrast to those depleted of salt, the volume of body water was expanded rather than contracted.

These facts suggest, therefore, that not only the volume of fluid in the body and its various compartments, but also the concentration of electrolytes present are important determinants of whether or not salt depletion shock develops.

The statement that both the volume of extracellular fluid and plasma and the concentration of electrolytes in the body fluids operate in maintaining the integrity of the circulation can be further supported by analysis of the responses of salt depletion shock to various forms of treatment. From Figure 2 it is immediately evident that restoring concentration alone, as in the urea diuresis experiments (Column A), or restoring volume alone as in the animals given glucose solution (Column B), failed to relieve the circulatory collapse produced by salt depletion. Yet when both volume and concentration were restored by saline infusions (Column C), prompt recovery from shock was observed.

The finding that both the volume of body fluids, especially plasma, and the concentration of electrolytes in them are important factors in maintaining circulatory efficiency has many clinical implications. The most obvious of these lies in the well-known fact that extensive depletion of body water and electrolytes, as in patients who sweat or who have losses of gastrointestinal fluid, can coexist with isotonicity. These normal concentrations, however, can no longer be viewed with the assurance that they protect the organism against salt depletion shock, nor can they be interpreted as evidence against a need for salt and water. This is true even though isotonicity is encountered only in the less severe degrees of salt depletion. Nonetheless, in these patients as well as in those with greater salt deficits, when volume is restored tonicity should be maintained. If salt solutions alone do not restore cardiovascular efficiency, supportive treatment with colloid solutions is indicated.

It should be pointed out, however, that hypotonicity is not necessarily the result of a loss of salt in excess of water. It can also indicate simple dilution, as in anuric or oliguric patients treated with excessive amounts of non-electrolyte containing fluids. The problem becomes even more complicated when both depletion and dilution are present in the same subject, as in nephritics and patients on a limited intake of salt during periods of salt loss. Irrespective of whether the hypotonicity is the result of depletion or dilution, the patient should receive treatment which restores the concentration to normal. Withholding salt in such patients because of the fear of augmenting edema or congestive heart failure may prove to be a serious error, whereas the circumspect use of saline almost always turns out to be either beneficial or benign (8, 9).

SUMMARY AND CONCLUSIONS

1. Hypotonicity of body fluids produced by glucose infusions in nephrectomized dogs with intact body salt stores did not impair circulatory efficiency.

2. Elimination of hypotonicity and cellular overhydration following urea diuresis in dogs in salt depletion shock, without replacement of salt deficits and extracellular fluid reexpansion, failed to improve cardiovascular dynamics.

3. Both the volume of fluid in the body, particularly the volume of plasma, and the tonicity of this fluid are important factors in salt depletion shock.

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