JCI The Journal of Clinical Investigation

THE TREATMENT OF SHOCK DUE TO SALT DEPLETION; COMPARISON OF THE HEMODYNAMIC EFFECTS OF ISOTONIC SALINE, OF HYPERTONIC SALINE, AND OF ISOTONIC GLUCOSE SOLUTIONS

T. S. Danowski, … , A. W. Winkler, J. R. Elkinton

J Clin Invest. 1946;25(1):130-138. https://doi.org/10.1172/JCI101682.

Research Article

THE TREATMENT OF SHOCK DUE TO SALT DEPLETION; COMPARISON OF THE HEMODYNAMIC EFFECTS OF ISOTONIC SALINE, OF HYPERTONIC SALINE, AND OF ISOTONIC GLUCOSE SOLUTIONS [1, 2]

By T. S. DANOWSKI, A. W. WINKLER, AND J. R. ELKINTON

(From the Department of Internal Medicine, Yale University School of Medicine)

(Received for publication September 15, 1945)

In the preceding paper, the peripheral vascular collapse induced in untraumatized dogs by the removal of sodium chloride has been described (1). In its effects on plasma volume, plasma protein, blood pressure, cardiac output, and circulation rate this type of peripheral vascular collapse is indistinguishable from that observed in traumatic shock. Depletion of water without salt, on the other hand, depresses the circulation much less severely. The reasons for this are not clear. Comparable contractions of extracellular volumes can be obtained in both, but their effects on the tonicity and distribution of body fluids are diametrically opposed. Salt depletion causes intracellular overhydration and generalized hypotonicity, while water depletion causes intracellular dehydration and generalized hypertonicity. Salt deprivation is associated with a considerable loss of protein from the circulating plasma while water depletion is not. Whether this is a cause or an effect of the severe vascular collapse could not be determined.

The present experiments seek further to characterize these differences in the effects of the two procedures by studying the response of salt depletion shock to therapy. Isotonic glucose infusions will reexpand the extracellular volume, increase the intracellular overhydration, and make both compartments still more hypotonic. Isotonic and hypertonic saline infusions, on the other hand, while reexpanding the extracellular volume also will relieve intracellular overhydration and correct the generalized hypotonicity. By a comparison of the effect of these two procedures on the circulation, the importance of contraction of extracellular volume in the pathogenesis of salt depletion shock can be compared with that of hypotonicity and intracellular overhydration. From the speed and completeness of recovery of the circulation following therapy, a further comparison of the character of salt depletion shock with that of traumatic shock is possible. Tentative conclusions can then be drawn concerning the effects of saline and glucose infusions in salt depletion shock, as well as in other forms of shock.

EXPERIMENTAL PROCEDURES

In 22 experiments using 9 dogs, sodium chloride without water was removed by the intraperitoneal route, by the method described in the preceding paper (1). Single large infusions were then administered intravenously, using the following solutions: 5 per cent saline (7 experiments), 0.9 per cent saline (3 experiments), and 5 per cent glucose (7 experiments). Five untreated animals served as controls.

Body fluid and hemodynamic measurements were made 3 to 4 hours after the start of salt depletion, *i.e.*, just before the commencement of therapy, and again 1.5 to 2 hours following therapy. Changes in intracellular and extracellular volume, in plasma volume, in blood pressure, in cardiac output, and in circulation rate were followed. The analytical procedures and the calculations have been described in detail previously (1).

RESULTS

The data are presented in Tables I, II, and III. The effects of each type of procedure are compared in Figure 1. In Table IV the mean values of the various changes are presented.

Extracellular fluid volume reexpanded above the initial value following isotonic saline and almost to the initial value following hypertonic saline. With glucose solution the volume also increased, but in 5 of 7 experiments by

[1] Aided by grants from the Fluid Research Fund of the Yale University School of Medicine.

[2] We are indebted to Dr. S. C. Harvey and to Dr. J. S. Lockwood for the use of the Laboratories of the Department of Surgery, and to Dr. J. F. Fulton and Dr. D. H. Barron for the use of the Laboratories of the Department of Physiology.

TABLE I

Treatment of acute salt depletion with infusion of saline solutions

Analytical data, hemodynamic measurements, and changes in body fluids

Experiment	Time from start of experiment	Weight*	Intake			Output				Serum		Blood		Circulation time	Mean arterial pressure	Oxygen		Cardiac index	Change in			
			Intravenous		Intraperitoneal	Peritoneal fluid‡		Urine		Cl	Total protein	Relative cell volume	Hemoglobin			Consumption	A-V difference		Total water	Extracellular fluid	Plasma volume	Circulating plasma protein
			H_2O	Cl	H_2O†	Volume	Cl	Volume	Cl													
	hours	*kgm.*	*ml.*	*m.eq.*	*ml.*	*ml.*	*m.eq.*	*ml.*	*m.eq.*	*m.eq. per liter*	*grams per cent*	*percentage of cells*	*grams per cent*	*seconds*	*mm Hg.*	*ml. per minute*	*volumes per cent*	*liters per minute per square meter*	*liters*	*liters*	*ml.*	*grams*
Isotonic (0.9 per cent) saline:																						
53D	0	7.16								105.0	6.53	29.1	7.9	8	138							
	4.5	7.19			1075	981	60	10	0	99.0	9.96	40.6	9.7	11	102	43	12.3	0.95	+0.03	−0.47	−125	+ 1.1
	7	7.73	1000	147		24	2	225	16.5	106.5	5.13	23.7	6.3	7	121	110	5.7	5.22	+0.54	+0.96	+264	+ 0.6
23R	0	10.06								105.8	6.18	33.4	6.3	7	131							
	4	9.77			1350	1437	107	60§	8.2§	84.5	9.23	51.7	8.7	11	88	81	12.9	1.37	−0.29	−0.64	−262	− 7.3
	7	10.45	1000	154		33	3	240	23.0	101.6	5.59	30.0	6.3	7	129	93	6.2	3.26	+0.68	+0.89	+291	+ 5.6
42H	0	14.48								106.3	5.95	30.6	8.7	8	132							
	4.5	13.92			2100	2394	180	16§	2.0§	86.2	8.72	51.9	12.7	13	74	131	12.4	1.77	−0.56	−1.11	−419	−14.4
	8	15.06	2300	329		19	2	1030	62.4	110.3	4.65	29.3	7.5	7	128	113	4.5	4.18	+1.14	+1.70	+565	+10.9
Hypertonic (5 per cent) saline:																						
61A	0	9.39								110.2	5.06	44.4	11.9	9	116							
	3.5	9.24			1410	1427	106	40§	4.1§	89.1	7.43	60.3	14.2	14	92	87	8.6	2.30	−0.15	−0.60	−207	− 3.1
	6	9.27	100	86		16	1	38	5.8	105.7	5.40	43.5	11.9	9	116	87	4.8	4.11	+0.03	+0.40	+216	+ 5.4
42D	0	13.60								111.3	5.91	44.6	11.6	8	134							
	3.5	13.10			2040	2322	151	24§	3.0§	88.6	8.78	61.2	14.9	15	110	110	9.1	2.12	−0.50	−0.75	−340	− 8.3
	7	12.99	175	149		18	2	230	27.0	113.3	6.03	46.5	13.2	8	130	96	7.2	2.34	−0.11	+0.42	+227	+ 2.4
23N	0	9.81								104.2	6.51	37.1	10.2	10	125							
	4.5	9.56			1460	1476	115	97§	11.5§	86.4	8.65	48.3	12.8	10	120	66	5.4	2.65	−0.25	−0.82	−141	− 0.7
	7	9.55	132	113		21	2	53	6.5	108.0	6.60	32.7	9.0	9	110	85	6.2	3.00	−0.01	+0.57	+339	+14.2
68A	0	7.10								99.4	6.05	32.2	8.8	8	130							
	5	6.93			1065	1151	82	0	0	81.5	8.02	43.6	9.9	12	60	58	8.1	1.95	−0.17	−0.53	−102	− 0.5
	8	6.97	150	113		27	2	125	18.7	111.7	5.20	29.1	8.2	6	95	73	4.7	4.19	+0.04	+0.43	+149	− 0.4
53B	0	7.70								110.3	5.86	26.9	7.3	8	137							
	4	7.54			1170	1206	83	15	1.0	89.0	8.36	37.8	9.3	17	70	85	11.2	1.95	−0.16	−0.42	−140	− 1.1
	6.5	7.58	160	120		28	3	55	8.9	119.7	5.29	22.6	6.7	10	122	55	5.8	2.44	+0.04	+0.47	+206	+ 2.2
71B	0	8.70								101.1	6.35	39.9	10.4	8	146							
	5	8.37			1350	1524	107	3	0	89.3	8.93	52.5	12.5	11	54	93	15.5	1.43	−0.33	−0.81	−164	− 2.2
	8	8.39	200	171		21	2	100	13.4	117.7	5.88	37.4	9.8	7	110	81	4.9	3.93	+0.02	+0.88	+216	+ 3.0
55B	0	10.29								109.6	5.99	44.8	12.2	8	120							
	5	10.04			1000	1035	86	55	2.6	93.9	8.12	55.3	14.2	9	94	66	7.8	1.81	−0.25	−0.45	−173	− 2.0
	8	10.03	100	86		18	2	0	0	112.4	6.14	45.0	12.0	8	114	102	6.7	3.23	−0.01	+0.34	+180	+ 3.3

* Weight at end of period corrected for solids lost as feces and red cells in blood taken for analysis.

† Given as 5 per cent glucose solution.

‡ Peritoneal fluid as tabulated in first period of each experiment includes the small amount of serum in blood taken for analysis; in second period serum alone is represented.

§ Includes vomitus.

In Tables I, II, and III time from start of experiment indicates end of period at which time serum analyses and hemodynamic measurements were made. Balance data are expressed per individual period rather than cumulatively. In designation of experiment, number refers to individual dog, letter refers to successive experiments.

TABLE II

Treatment of acute salt depletion with infusion of glucose solution

Analytical data, hemodynamic measurements, and changes in body fluids

Experiment	Time from start of experiment	Weight*	Intake		Output				Serum		Blood		Circulation time	Mean arterial pressure	Oxygen		Cardiac index	Change in			
			Intravenous	Intraperitoneal	Peritoneal fluid‡		Urine		Cl	Total protein	Relative cell volume	Hemoglobin			Consumption	A-V difference		Total water	Extracellular fluid	Plasma volume	Circulating plasma protein
			H_2O†	H_2O†	Volume	Cl	Volume	Cl													
	hours	*kgm.*	*ml.*	*ml.*	*ml.*	*m.eq.*	*ml.*	*m.eq.*	*m.eq. per liter*	*grams per cent*	*per-centage of cells*	*grams per cent*	*seconds*	*mm. Hg*	*ml. per minute*	*volumes per cent*	*liters per minute per square meter*	*liters*	*liters*	*ml.*	*grams*
61B	0	9.42							113.4	5.75	38.9	10.3	7	116							
	4	9.23		1410	1383	106	43§	6.5§	96.9	7.57	52.6	13.3	13	50	97	7.8	2.84	−0.19	−0.67	−207	− 6.2
	7	9.44	300		19	2	0	0	91.3	6.33	48.1	11.6	9	50	85	8.8	2.20	+0.21	+0.10	+129	+ 4.3
53A	0	7.73							102.8	5.76	35.0	10.6	10	140							
	3	7.54		1170	1189	77	14	0	90.9	7.27	48.7	12.0	20	106	72	8.4	2.21	−0.19	−0.52	−128	− 2.9
	6.5	7.96	1000		23	2	450§	16.9§	74.5	5.68	44.2	10.6	15	120	48	9.9	1.23	+0.42	+0.11	+ 69	− 0.8
55D	0	10.82							111.0	5.69	37.9	10.5	10	137							
	4	10.62		1620	1639	119	25§	2.8§	84.8	8.76	57.3	14.2	15	94	89	7.1	2.55	−0.20	−0.53	−292	− 7.4
	7.5**	11.16	1600		17	1	855§	27.9§	67.6	6.69	49.5	12.7	13	114	108	6.4	3.45	+0.54	+0.23	+ 97	+ 0.3
42E	0	13.24							105.2	5.83	42.5	11.9	8	134							
	4	12.92		2200	2017	158	5	0	88.4	9.00	62.3	15.4	15	132	133	11.5	2.07	−0.32	−1.03	−359	− 9.2
	7	14.37	1800		15	1	265	1.7	60.7	5.24	61.4	14.9	18	104	90	14.4	1.13	+1.45	+1.11	+ 38	−12.7
23O	0	10.19							101.6	6.71	46.4	12.3	8	152							
	3.5	10.12		1530	1526	99	45§	5.2§	79.2	10.42	61.0	15.0	9	112	68	10.5	1.38	−0.07	−0.53	−226	− 2.8
	6.5**	10.78	1325		16	1	540§	22.1§	63.9	7.37	53.0	12.3	12	118	100	10.2	2.08	+0.66	+0.25	+158	+ 1.4
71A	0	9.20							108.9	6.29	44.0	10.7	7	141							
	4.5	8.86		1380	1540	110	5	0	84.4	8.89	55.8	13.7	8	106	122	17.7	1.41	−0.34	−0.53	−193	− 4.0
	7.5**	9.63	1450		22	2	440§	16.5§	71.0	6.09	48.5	12.0	11	108	161	13.0	2.53	+0.77	+0.17	+ 54	− 5.4
75B	0	12.12							103.1	5.94	43.6	12.2	7	141							
	5	11.93		1800	1684††	104	13	0	82.4	10.00	64.8	16.0	16	66	89	16.5	1.02	−0.19	−0.47	−345	− 7.5
	8**	13.10	1400		14	1	175	4.4	59.6	4.62	47.0	12.7		76	95	10.0	1.79	+1.20	+1.08	+290	− 3.9

* † ‡ § See footnotes to Table I.

** Convulsions of water intoxication.

†† Peritoneal fluid withdrawn contained 1.8 grams of protein.

TABLE III

Control experiments of acute salt depletion: no treatment

Analytical data, hemodynamic measurements, and changes in body fluids

Experiment	Time from start of experiment	Weight*	Intake	Output				Serum		Blood		Circulation time	Mean arterial pressure	Oxygen		Cardiac index	Change in			
			Intraperitoneal	Peritoneal fluid‡		Urine		Cl	Total protein	Relative cell volume	Hemoglobin			Consumption	A-V difference		Total water	Extracellular fluid	Plasma volume	Circulating plasma protein
			H_2O†	Volume	Cl	Volume	Cl													
	hours	*kgm.*	*ml.*	*ml.*	*m.eq.*	*ml.*	*m.eq.*	*m.eq. per liter*	*grams per cent*	*per-centage of cells*	*grams per cent*	*seconds*	*mm. Hg*	*ml. per minute*	*volumes per cent*	*liters per minute per square meter*	*liters*	*liters*	*ml.*	*grams*
60A	0	6.80						113.0	5.21	52.7	14.0	10	130							
	4	6.66	700	679	56	20	2.4	93.7	7.20	63.3	16.3	21	60	65	11.3	1.66	−0.14	−0.24	−125	− 1.6
	9	6.66		11	1	2	0	93.2	5.74	53.3	14.0	10	84	62	5.2	3.43	±0	+0.02	+120	+ 3.3
55C	0	10.58						103.0	6.25	45.0	12.0	11	120							
	4	10.36	1587	1536	110	50§	4.7§	90.7	9.61	62.1	17.6	12	82	79	8.3	1.98	−0.22	−0.82	−308	−10.0
	7	10.26		15	1	0	0	86.0	8.16	57.2	17.5	15	92	75	9.3	1.69	−0.10	+0.11	+ 78	+ 2.3
23P	0	9.98						101.1	6.65	38.8	11.7	10	134							
	4.5	9.75	1500	1538	104	25§	2.9§	82.4	9.89	62.5	15.4	17	70	79	16.9	1.02	−0.23	−0.54	−293	−11.2
	7.5	9.65		13	1	0	0	79.2	8.56	58.6	14.7	13	76	81	11.7	1.50	−0.10	+0.08	+ 41	+ 0.1
42F	0	13.24						110.2	6.07	40.3	10.7	9	136							
	4	12.86	2100	2310	167	48§	5.8§	87.0	10.56	66.8	16.3	17	96	131	17.5	1.34	−0.38	−1.00	−459	−15.8
	7	12.70		13	1	38	0.7	86.9	8.51	57.4	14.6	15	82	100	13.9	1.29	−0.16	+0.03	+117	+ 4.5
53C	0	7.58						109.4	6.11	30.3	7.8	8	140							
	3.5	7.43	1150	1184	75	3	0	90.9	8.75	42.1	9.5	13	104	50	12.4	1.08	−0.15	−0.39	−133	− 0.7
	7	7.36		23	2	5	0	90.9	8.12	37.4	9.1	15	98	35	9.8	0.95	−0.07	−0.01	+ 37	+ 1.3

* † ‡ § See footnotes to Table I.

TABLE IV

Therapy of acute salt depletion

Effects of saline solutions, glucose solutions, and no solutions, on the body fluids and on the circulation, expressed as mean values with standard deviations

Therapy	Number of experiments	Δ Extracellular fluid volume		Δ Plasma volume		Δ Circulation time		Δ Mean arterial pressure		Δ Oxygen arteriovenous difference		Δ Cardiac index	
		percentage of initial value		*percentage of initial value*		*seconds*		*mm. Hg.*		*volumes per cent*		*liters per minute per square meter*	
		mean	σ	mean	σ	mean	σ	mean	σ	mean	σ	mean	σ
Saline	10	+32	±15	+51	±15	−5	±2	+37	±22	−5.7	±3.6	+2.11	±1.29
Glucose	7	+20	±15	+24	±13	−2	±4	− 3	±16	−2.8	±3.2	+0.36	±0.97
None	6	+ 2	± 3	+16	±10	−5	±5	+10	±16	−3.8	±2.7	+0.72	±0.96

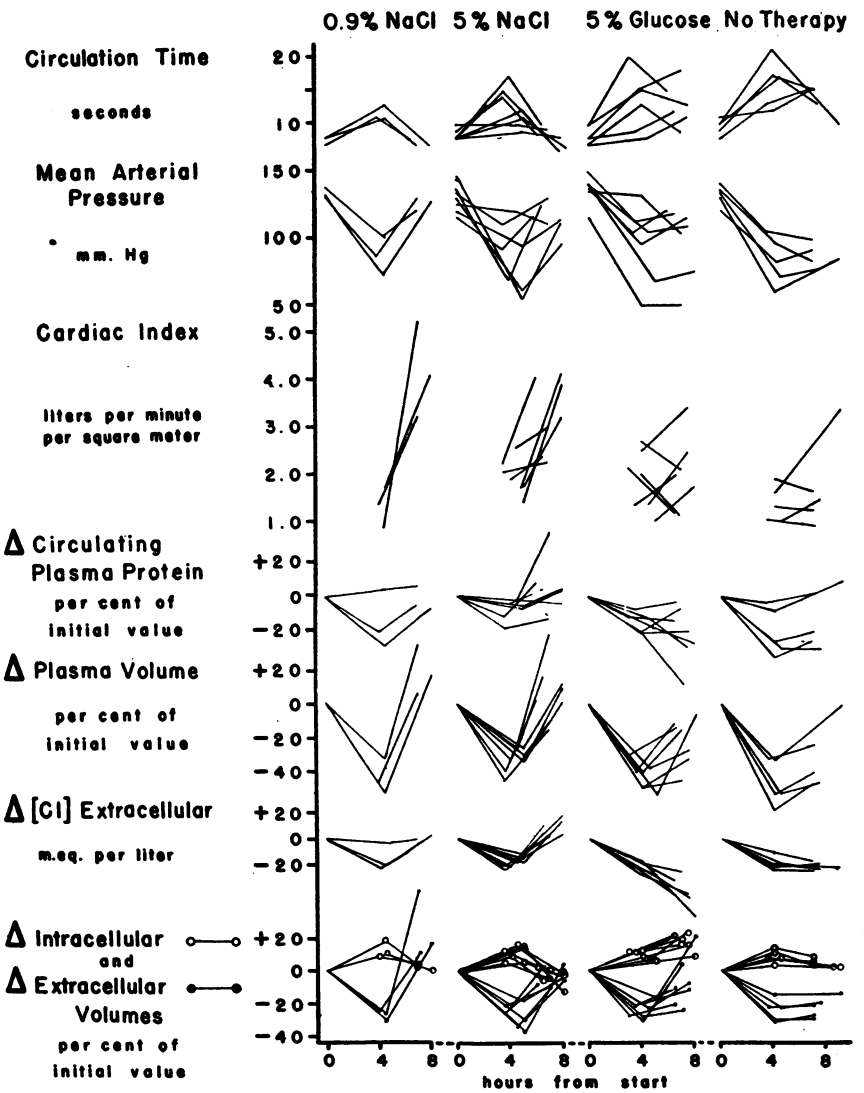

FIG. 1. EFFECTS OF THERAPY ON BODY FLUIDS AND ON HEMODYNAMICS

Salt depletion was induced between the first and second points (0 and 3 to 4 hours). Immediately after the second point, an infusion was administered of one of the solutions indicated at the top of the chart. Cardiac outputs were not determined preceding the salt depletion.

too small an amount to restore the initial volume. Without treatment, it was unchanged.

Intracellular fluid volume decreased from its overexpanded state to the initial value or below it following isotonic or hypertonic saline solution. Glucose solution caused a further overexpansion. With no treatment, it remained unaltered.

Tonicity of the body fluids, as indicated by concentration of chloride in serum, was restored from hypotonicity to isotonicity by isotonic saline and to hypertonicity by hypertonic saline. Glucose, on the other hand, made the body fluids still more hypotonic, while the untreated controls were unaltered.

Plasma volume rose above the initial value in all of the isotonic and in most of the hypertonic saline experiments. With glucose, there was only a partial restoration. Without treatment a slight spontaneous reexpansion occasionally was observed.

Total circulating protein was usually restored to its initial value by both isotonic and hypertonic saline, thus paralleling the change in plasma volume. With glucose solution, on the other hand, total circulating protein was but slightly restored or further depleted. Without treatment it was not significantly changed.

The hemodynamic responses were not always clearly differentiated in the various experimental procedures employed. Restoration of the *cardiac index* was most complete with the saline solutions. With glucose therapy, the cardiac index increased in 4 experiments and decreased in the other 3. With no therapy, the cardiac index remained unchanged or recovered slightly. Changes in *differences between arterial and venous oxygen content* reflected changes in cardiac output reciprocally. *Circulation time* returned to the initial value in all of the saline experiments. In no instance with glucose therapy did it return to its initial value. Without therapy, it behaved much as it did with glucose treatment. *Mean arterial pressure* returned nearly to initial levels with saline therapy but improved only slightly if at all without treatment or with glucose therapy.

Comparison of the effects of therapy by measuring the percentile change in each experiment from the onset of treatment (Figures 2 and 3 and Table IV) depends for its validity on a uniform degree of cardiovascular collapse. This assumption of uniform depth of shock is approximately true (Figure 1). Reexpansion both of extracellular fluid volume (ΔE) and of plasma volume (ΔPV) was greater with saline than with glucose therapy. In almost all experiments, however, ΔPV was proportionately greater than ΔE (Figure 2a), and this disproportion correlated well with the increase in circulating plasma protein (ΔCPP) (Figure 2b). These relationships are clearer in the saline than in the glucose experiments because of the relatively small changes in ΔE and ΔPV with the latter.

Hemodynamic improvement was definitely less marked

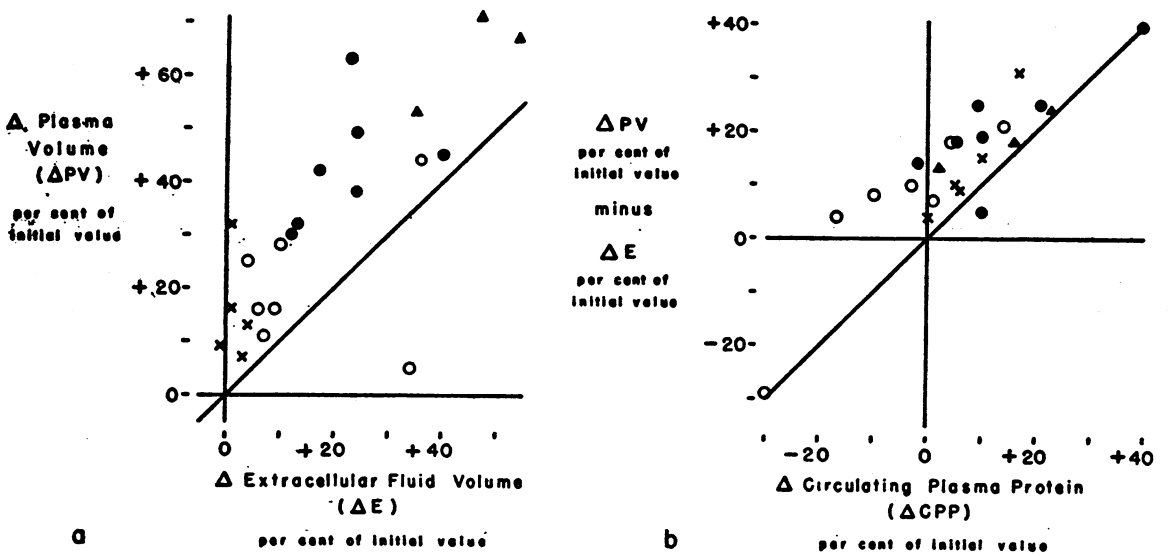

FIG. 2. COMPARISON OF (a) PERCENTILE CHANGES IN EXTRACELLULAR FLUID VOLUME WITH THOSE IN PLASMA VOLUME, AND (b) THE DIFFERENCE BETWEEN THESE 2 VALUES WITH THE PERCENTILE LOSS OF TOTAL CIRCULATING PLASMA PROTEIN

Closed figures represent the changes induced by saline infusions (triangles for isotonic, and round points for hypertonic solutions). Open circles represent the effect of isotonic glucose infusions, and crosses the effect of no therapy.

With the exception of 1 glucose experiment, the proportional reexpansion of the plasma volume was greater than that of extracellular fluid. The disproportions between the changes in these 2 fluid compartments correlated well with the changes in total circulating plasma protein.

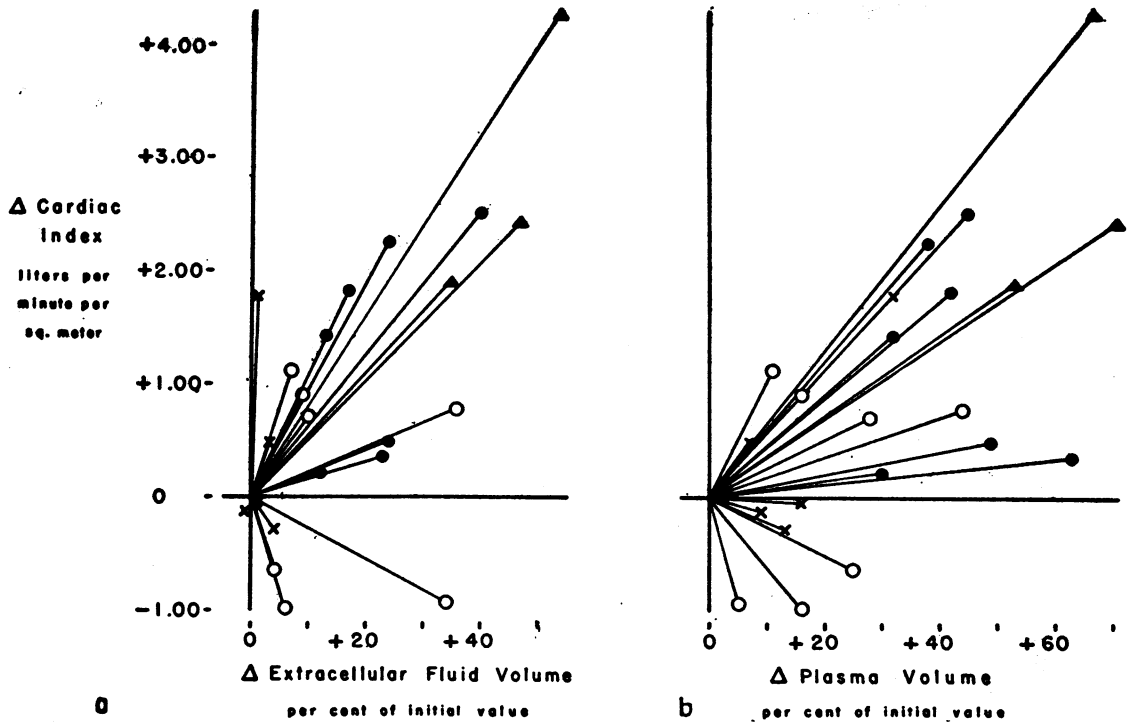

FIG. 3. COMPARISON OF CHANGES IN CARDIAC INDEX WITH THOSE IN (a) EXTRACELLULAR FLUID VOLUME, AND (b) PLASMA VOLUME

Symbols are interpreted in Figure 2.

Although the extracellular fluid volume and the plasma volume reexpanded in all of the saline and in all of the glucose experiments, the cardiac index decreased further in 3 of the glucose experiments.

with glucose than with saline. Indeed, the mean values in Table IV indicate that the effects of glucose were not distinctly different from those found after no treatment at all. While the extracellular fluid and plasma volume did reexpand to some degree in all the glucose experiments, the changes in cardiac output were not proportional nor even necessarily in the same direction since cardiac output actually decreased still further in 3 of the 7 glucose experiments (Figure 3). The improvement in cardiac output per unit volume of reexpansion of extracellular fluid was, therefore, much less in the glucose than in the saline treated animals (Figure 3a). The changes in cardiac output in all types of experiments were not directly proportional to changes in plasma volume and even differed in direction in some of the experiments (Figure 3b).

DISCUSSION

These experiments demonstrate the greater therapeutic efficacy of saline solutions at the 4- to 5-hour point in shock due to salt depletion, compared with that of isotonic glucose solutions. Cardiac output, blood pressure, and circulation time return almost to normal within 2 hours after treatment. Plasma volume expands to or above normal. Protein lost from plasma during the process of salt depletion is usually wholly replaced within this same period. These changes accompany a restoration of normal tonicity to body fluids, a reexpansion of extracellular fluid, and a contraction of the overexpanded intracellular fluid. These observations are consistent with the few clinical observations available on the administration of saline intravenously to patients depleted of salt (2, 3). It should be noted that studies of the effects of saline by various routes on the circulation in normal subjects are not directly pertinent (4 to 8).

At first sight, they may seem inconsistent with findings of other workers who have found that the intravenous administration of saline solutions to animals early in traumatic shock as the blood pressure is falling usually results in a further loss of circulating plasma protein, rather than its restoration (9, 10, 6). On the basis of these

studies, the administration of saline intravenously in large amounts in any form of shock has been held inadvisable. Our observations have been confined to a different type of shock. Moreover, at the time therapy was undertaken, the animals had been in circulatory inadequacy for 4 to 8 hours. With these two differences clearly in mind, it can be stated that when saline solutions are given to subjects with salt depletion shock, the protein is restored rather than lost. The other workers referred to above were dealing with shock due to *trauma,* in which salt depletion was only one of several factors. It is possible that the response to saline in our experiments would have been different had therapy been given earlier or withheld longer. Obviously, the response to saline depends on the phase of the shock, its reversibility, and on the importance of salt depletion in its etiology. In this connection, it is of interest that some investigators have found that in *hemorrhagic* shock saline solutions intravenously favor the restoration of plasma protein (10). It is not, of course, known whether the same protein which has been removed from the circulation during salt depletion is restored, or merely replaced by other newly formed plasma protein.

The unsatisfactory results of glucose therapy are obvious. In contrast to saline therapy, extracellular volume and plasma volume reexpanded to a lesser degree, protein was not restored to the circulating plasma, and the hemodynamic status of the animal was not distinctly improved. Even in the 2 glucose experiments in which considerable reexpansion of the extracellular fluid did take place, the circulation was not greatly benefited. In 1 of these experiments, the cardiac output actually decreased further in the presence of an increased plasma volume. These facts strongly suggest that contraction of extracellular volume alone is not the only factor in shock due to salt depletion.

On the other hand, the administration of glucose could hardly be said to be disastrous to the animals in most cases, since they not only survived the experiment but subsequently recovered completely with salt replacement. Indeed the one serious ill effect which could undoubtedly be directly attributed to the glucose infusion was the occasional development of the convulsions of water intoxication.[8] These experiments make it doubtful that hypotonicity and intracellular overhydration are the primary factors in the pathogenesis of salt depletion shock, since both of these abnormalities are made much more marked by glucose infusion.

No entirely adequate explanation of the peculiarly deleterious effects of extracellular salt depletion on the cardiovascular system can yet be offered. It is apparently not due primarily to contraction of extracellular volume, to hypotonicity, nor to intracellular overhydration. It is distinguished from other forms of dehydration by the loss of protein from the circulating plasma. It is possible that salt depletion acts by favoring this loss in some way, but the reverse may equally well be true, *i.e.,* the ill effects of salt depletion on the circulation may be responsible for the loss of protein rather than the result of it. At present it is only possible to reemphasize the fact that salt depletion or segregation, with or without loss of water, strongly favors the development of peripheral circulatory collapse.

The therapeutic rôle of saline is traumatic and other forms of shock is evident. Insofar as there is any element of salt depletion or segregation in the origin of the state of shock, administration of saline is urgently indicated. Insofar as other factors are operative, saline cannot be expected to be effective. The success of saline therapy in Rosenthal's experiments (12) with shock due to temporary constriction of the leg of a mouse was demonstrated under carefully controlled conditions. These were selected in such a way that pooling of body salt in the injured limb was prabably the main factor in producing the shock. With shorter or longer periods of occlusion, this situation was altered, and the therapeutic effectiveness of saline correspondingly reduced.

It is quite possible that administration of the saline by other routes than the intravenous would have been even more effective in our experiments, but no data bearing on this point are yet available. On the other hand, our experiments clearly prove

[8] These experiments furnish additional evidence that the manifestations of water intoxication are primarily due to intracellular overhydration. This interpretation, though perhaps implicit in the earlier work on the nature of water intoxication, has not always been clearly formulated (11).

that conclusions concerning the deleterious effect of intravenous saline derived from many experiments on traumatic shock cannot be applied to all other forms of shock (9, 10, 6). At the 4 or 5 hour point of a shock state produced by salt depletion, intravenous administration of saline is a therapeutically valid procedure. Whether saline containing protein (*i.e.*, serum or plasma) would be even more valuable therapeutically is now being investigated. Finally, whatever hypothetical dangers may result from administration of excessive amounts of saline (13, 14), the harmful effects on the circulation or failure to restore the saline lost are too evident to require discussion.

SUMMARY AND CONCLUSIONS

1. In shock due to acute salt depletion without trauma, the intravenous injection at 4 to 5 hours of either isotonic or hypertonic saline rapidly and almost completely restores the circulation to normal within 2 hours.

2. This improvement of the circulation with saline therapy is accompanied by a restoration of the plasma protein which had previously been lost during salt depletion.

3. In shock due to salt depletion, intravenous glucose is without distinct beneficial effect on the circulation, although extracellular and plasma volumes may reexpand somewhat. The protein lost from the circulating plasma is not restored.

4. It is not possible under the limited conditions of these experiments to assign any deleterious effects directly to such glucose infusions, provided that they do not provoke the convulsive manifestations of water intoxication. Additional salt may be lost in the urine.

5. Insofar as any form of shock has an element of salt depletion or segregation, salt administration is urgently indicated, and the intravenous route can be used.

BIBLIOGRAPHY

1. Elkinton, J. R., Danowski, T. S., and Winkler, A. W., Hemodynamic changes in salt depletion and in dehydration. J. Clin. Invest., 1946, 25, 120.
2. Nadal, J. R., Pedersen, S., and Maddock, W. G., A comparison between dehydration from salt loss and from water deprivation. J. Clin. Invest., 1941, 20, 691.
3. Stewart, J. D., and Rourke, G. M., The effects of large intravenous infusions on body fluid. J. Clin. Invest., 1942, 21, 197.
4. Holt, J. P., and Knoefel, P. K., Changes in plasma volume and cardiac output following the intravenous injection of gelatin, serum, and physiological salt solution. J. Clin. Invest., 1944, 23, 657.
5. Lyons, R. H., Jacobson, S. D., and Avery, N. L., Increases in the plasma volume following the administration of sodium salts. Am. J. Med. Sci., 1944, 208, 148.
6. Warren, J. V., Merrill, A. J., and Stead, E. A., Jr., The role of the extracellular fluid in the maintenance of a normal plasma volume. J. Clin. Invest., 1943, 22, 635.
7. Ashworth, C. T., Hutcheson, Z. W., Payne, W. T., and Jeater, A. W., The effect of crystalloidal and protein containing solutions on the body fluids and circulating plasma proteins. Am. J. Physiol., 1944, 140, 589.
8. Blalock, A., and Beard, J. W., The effects on the composition of the blood of the subcutaneous injection of normal salt solution into normal dogs and into dogs subjected to intestinal trauma, graded hemorrhages, and histamine injection. J. Clin. Invest., 1932, 11, 311.
9. Beard, J. W., and Blalock, A., Intravenous injections. A study of the composition of the blood during continuous trauma to the intestines when no fluid is injected and when fluid is injected continuously. J. Clin. Invest., 1932, 11, 249.
10. Beard, J. W., Wilson, H., Weinstein, B. M., and Blalock, A., A study of the effects of hemorrhage, trauma, histamine, and spinal anesthesia on the composition of the blood when no fluids are injected and when fluids are introduced intravenously. J. Clin. Invest., 1932, 11, 291.
11. Talbott, J. H., Heat cramps. Medicine, 1935, 14, 323.
12. Rosenthal, S. M., Experimental chemotherapy of burns and shock. IV. Production of traumatic shock in mice. V. Therapy with mouse serum and sodium salts. Public Health Reports, 1943, 58, 1429.
13. McCray, P. M., Barden, R. P., and Ravdin, I. S., Nutritional edema: its effect on gastric emptying time before and after gastric operation. Surgery, 1937, 1, 53.
14. Coller, F. A., Campbell, K. N., Vaughn, H. H., Iob, V., and Moyer, C. A., Postoperative salt intolerance. Ann. Surg., 1944, 119, 533.