INTERRELATIONS BETWEEN SERUM SODIUM CONCENTRATION, SERUM OSMOLARITY AND TOTAL EXCHANGEABLE SODIUM, TOTAL EXCHANGEABLE POTASSIUM AND TOTAL BODY WATER [1]

By I. S. EDELMAN,[2] J. LEIBMAN,[3] M. P. O'MEARA,[4] and L. W. BIRKENFELD [5]

(From the Department of Medicine, University of California School of Medicine, and the San Francisco Hospital, San Francisco, Calif.)

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Although much is known about the effects of changes in electrolyte and water balance on serum sodium concentration, the quantitative relationships between body composition and the concentration of sodium in serum have not been established. Also, no definitive study has been made of the correspondence between serum sodium concentration and total serum osmolarity. It is necessary that these relationships be defined to permit classification and interpretation of abnormalities of serum sodium concentration in clinical states, as well as to extend present understanding of the effects of electrolyte equilibria and acid-base disturbances on serum sodium concentration.

It has been definitively demonstrated that no overall correlation exists between body sodium content, or external balance of sodium, and serum sodium concentration (1–4). Serum sodium concentration, of course, is not independent of loss or gain of body sodium. Excessive loss of sodium leads to a fall in serum concentration; administration of hypertonic saline elevates serum levels (5–8). Retention of water in excess of sodium has been shown to occur, and accounts, at least in part, for the hyponatremia seen after major surgery and in patients with coexistent edema and hyponatremia (3, 4, 9). This phenomenon has been demonstrated experimentally by administration of vasopressin to patients with congestive heart failure (10). An integrated account of concomitant alterations in serum sodium concentration and body composition was first achieved by Deming and Gerbode (11), who observed that changes in serum sodium concentration paralleled net changes of sodium and potassium balance in relation to water balance in patients undergoing mitral valvulotomy. The influence of potassium balance on serum sodium concentration was confirmed by correlative studies in postoperative hyponatremia and by demonstration that administration of potassium can raise the serum sodium concentration in hyponatremic patients (4, 7, 12).

The dependence of serum sodium concentration on body sodium, potassium and water content has several important implications. The magnitude and character of this dependence will modify or extend current concepts of ionic redistributions between body fluids, of osmotic gradients across cell membranes, and of the participation of hydrogen ion in the regulation of serum sodium concentration (13–17).

Simultaneous measurements of total exchangeable sodium (Na_e), total exchangeable potassium (K_e), total body water (T.B.W.), and serum electrolyte concentrations, pH and osmolarity were made in a heterogeneous group of chronically ill patients. Statistical analyses were made of the correlations of serum sodium concentration (Na_s) with serum osmolarity (π_s), Na_e/body weight, K_e/body weight, T.B.W./body weight, Na_e/T.B.W., K_e/T.B.W. and $(Na_e + K_e)$/T.B.W. These data reveal striking correlations between Na_s, π_s and $(Na_e + K_e)$/T.B.W.

METHODS

Ninety-eight patients were studied. The age, sex, state of hydration of these subjects and the clinical diagnoses are listed in Table I. Maximum heterogeneity in

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[2] During tenure as an Established Investigator of the American Heart Association.

[3] Research Fellow of the San Francisco Heart Association.

[4, 5] Research Fellows of the National Heart Institute of the United States Public Health Service.

TABLE I

Summary of clinical data

Patient	Age	Sex	Body wt.	Transudate	Diagnosis
				Heart disease	
no.	*yrs.*		*Kg.*		
1	64	M	64.1	+2	Hypertensive and arteriosclerotic cardiovascular disease
5	64	M	53.9	+2	Hypertensive and arteriosclerotic cardiovascular disease
7	67	F	85.0	+3	Arteriosclerotic heart disease
10	66	M	119.5	+4	Arteriosclerotic heart disease
11	76	M	80.0	+2	Hypertensive and arteriosclerotic heart disease
12	68	M	59.8	+1	Arteriosclerotic heart disease; bronchiectasis
18	55	M	41.8	+1	Cor pulmonale; chronic pulmonary disease
21	60	M	59.8	0	Cor pulmonale; chronic bronchitis; pneumonia
23	51	F	55.2	+2	Cor pulmonale; chronic pulmonary disease
25	67	M	47.7	+1	Cor pulmonale; chronic empyema; auricular fibrillation
26	58	M	75.8	+4	Hypertensive heart disease
27	89	M	60.9	+2	Arteriosclerotic heart disease; chronic pyelonephritis
36	72	F	38.6	0	Arteriosclerotic heart disease; cerebrovascular disease
37	79	M	62.3	+1	Hypertensive heart disease
42	71	M	44.8	0	Cor pulmonale; asthma; bronchopneumonia
47	54	M	48.6	+3	Arteriosclerotic heart disease; duodenal ulcer
49b	86	F	51.8	+1	Arteriosclerotic heart disease
51	84	M	56.4	+2	Arteriosclerotic heart disease
53	54	M	49.8	+2	Arteriosclerotic heart disease
61	71	M	58.0	+2	Arteriosclerotic heart disease
75	66	M	53.6	+2	Arteriosclerotic heart disease
78	40	M	71.4	+2	Malignant hypertension
80	82	F	63.6	+1	Arteriosclerotic heart disease
80a	75	M	86.4	+4	Arteriosclerotic heart disease
82	53	F	103.9	+1	Arteriosclerotic heart disease
90	60	M	53.2	+4	Hypertensive heart disease
93	74	M	65.9	+4	Arteriosclerotic heart disease
94	77	M	55.7	+3	Rheumatic heart disease
56	54	F	70.0	0	Essential hypertension
57	46	M	86.6	0	Essential hypertension
58	40	F	56.1	0	Essential hypertension
67a	27	F	60.9	0	Essential hypertension
94a	33	F	55.0	0	Essential hypertension
				Liver disease	
2	50	M	67.3	+4	Cirrhosis
3	47	M	80.0	+2	Cirrhosis
6	51	M	41.8	+3	Cirrhosis
8	51	M	37.7	+2	Cirrhosis
13	66	M	88.4	0	Cirrhosis
16	74	M	101.3	+4	Cirrhosis
19	28	F	39.6	+1	Cirrhosis
20	45	M	50.9	+2	Cirrhosis
22	37	F	39.8	+1	Cirrhosis
24	59	M	67.0	+3	Cirrhosis
29	66	F	82.5	0	Cirrhosis
30	51	M	78.8	+3	Cirrhosis
35	43	F	51.8	+3	Cirrhosis
38	67	M	79.3	+4	Cirrhosis
43	56	M	112.5	0	Cirrhosis
44b	43	F	56.8	+3	Cirrhosis
48a	67	M		+4	Cirrhosis
50	39	F	65.7	+3	Cirrhosis
60	27	F	55.7	+1	Cirrhosis
66	48	M	55.5	+2	Cirrhosis
67	85	M		0	Cirrhosis
71	50	F		+3	Cirrhosis
73	48	F	57.7	+4	Cirrhosis
79	64	M	78.2	+4	Cirrhosis
81	64	M	81.4	+4	Cirrhosis
84	39	M	84.6	+4	Cirrhosis
86	51	M	66.4	+3	Cirrhosis
87	46	M	76.8	+2	Cirrhosis
88	50	M	60.0	+3	Cirrhosis
89	59	M	67.7	+4	Cirrhosis
91	42	M	64.0	+2	Cirrhosis
92	45	M	60.0	+4	Cirrhosis

TABLE I—*Continued*

Patient	Age	Sex	Body wt.	Transudate	Diagnosis
				Kidney disease	
no.	*yrs.*		*Kg.*		
17	47	M	70.7	+3	Nephrotic syndrome
28	58	M	47.7	0	Chronic glomerulonephritis; gastric ulcer
33	58	M	51.1	+3	Chronic glomerulonephritis
62	36	M	69.8	+4	Diabetic glomerulosclerosis
74	40	F	40.0	+2	Chronic pyelonephritis
				Lung disease	
31	69	M	48.0	0	Pulmonary emphysema
48b	48	M	52.3	0	Pulmonary tuberculosis; cirrhosis of liver
63	29	F	51.3	+1	Pulmonary tuberculosis
64	62	M	52.1	+3	Pulmonary tuberculosis; cirrhosis of liver; diabetes
59	64	M	60.2	+3	Carcinoma of lung, postoperative
				Gastrointestinal disease	
4	68	M	86.9	0	Gastric ulcer
9	45	M	69.2	0	Duodenal ulcer
44a	60	M	39.8	+2	Rectal carcinoma, postoperative
46	78	M	44.9	+1	Duodenal ulcer; chronic pyelonephritis
				Neurological disease	
40	78	F	41.4	0	Cerebrovascular disease
41	73	M	60.5	0	Cerebrovascular disease
65	45	M		+2	Transection of spinal cord
68	70	M		0	Subdural hematoma
72	77	F	43.2	0	Subdural hematoma, postoperative
77	55	F	39.1	0	Cerebrovascular disease
83	72	F	38.6	0	Cerebrovascular disease
34	90	M	43.6	0	Cerebral arteriosclerosis
				Miscellaneous	
14	67	F	59.5	0	Multiple abscesses
15	72	M	59.3	0	Cellulitis
32	39	M	168.2	+2	Obesity
39	28	F	36.4	0	Adrenal insufficiency
45	74	M	57.0	0	Senility; anemia
52	70	M	50.9	0	Chronic bromide intoxication
55	41	M	53.6	0	Primary aldosteronism
70	62	M	61.8	0	Panhypopituitarism
76	62	M	62.5	0	Panhypopituitarism
54	49	M	63.9	+4	Carcinomatosis, primary unknown
69	61	F	47.7	+4	Carcinoma of cervix with peritoneal metastases

clinical and metabolic status was sought to assure that any correlations between body composition and serum electrolyte concentrations would have general validity. The group consisted of 33 patients with a variety of heart diseases, 32 patients with cirrhosis of the liver, 5 patients with renal disease, 5 patients with pulmonary disease, 4 patients with gastrointestinal disease, 8 patients with neurological disease and 11 patients with other illnesses, including panhypopituitarism, adrenal insufficiency and primary aldosteronism. Sixty-six of these patients had one to four plus edema by clinical criteria.

All subjects were given an analyzed diet which contained 10 mEq. of sodium and 28 mEq. of potassium each day for one or two days prior to and for the three days of study. Food and fluid were withheld for the six hour period of D_2O equilibration.

The sequence and technique of isotope administration and collection of urine and blood for isotope assay have been described previously (18, 19). No subject received more than 360 microcuries of K^{42} and 150 microcuries of Na^{24}. The periods of isotope equilibration were 40 hours for K^{42}, 24 hours for Na^{24} and 6 hours for D_2O. These periods were previously shown to be adequate for isotope equilibration, even in very edematous subjects (19). Blood was drawn from the femoral artery just before injection of Na^{24}. Glycolysis in these samples was inhibited either by the addition of 0.5 ml. of saturated NaF or by icing.

The analytical methods for isotope assay have been described in earlier papers (18, 19). Serum osmolarity (π_s) was estimated by freezing point depression with a thermistor probe, using NaCl standards (20).[6] Sodium

[6] Freezing point depression actually is a measure of osmolality. Since osmolality is virtually equivalent to osmolarity at constant temperature, however, the latter term has been used in this communication to provide units comparable with the electrolyte concentration data.

TABLE II

Summary of laboratory data: Serum values

Patient	Na'_s	K'_s	Cl_s	$(HCO_3)_p$	Arterial pH	NPN*	Glucose	π_s	π'_s
				Heart disease					
no.	*mEq./L. of serum water*	*mEq./L. of serum water*	*mEq./L.*	*mEq./L.*		*mg. %*	*mg. %*	*mOsm./L.*	*mOsm./L.*
1	155.6	4.58	104.6	27.5	7.47	24	89	289.2	275.7
5	142.7	4.64	96.3	31.4	7.40	29	93	274.6	259.0
7	153.1	4.03	103.2	32.4	7.41	17	118	287.2	274.5
10	149.0	4.77	99.3	23.9	7.47	17	112	276.9	264.6
11	147.7	4.19	104.0	25.2	7.46	24	91	285.2	271.5
12	130.1	4.91	86.2	27.8	7.51	18	97	245.3	233.5
18	147.9	4.72	98.7	30.9	7.35	17	101	280.9	269.2
21	136.9	4.89	84.9	40.4	7.34	21	86	271.1	258.8
23	137.3	5.44	85.2	35.7	7.25	43	100	274.0	253.1
25	144.5	4.19	94.7	36.4	7.34	12	87	275.7	266.6
26	137.9	6.49	102.9	19.0	7.37	72	116	288.6	256.5
27	120.6	5.17	86.8	12.2	7.19	126	149	273.4	214.6
36	145.5	2.52	93.1	34.0	7.45	16	114	272.4	260.4
37	146.1	4.68	109.7	21.8	7.49	45	100	292.2	270.6
42	132.7	4.38	95.8	25.9	7.34	29	111	264.7	248.1
47	138.5	4.55		12.8	7.48	142	127	311.0	256.4
49b	141.6	2.85		25.3	7.54	21	198	272.0	253.5
51	120.3	4.77		21.5	7.58	11	80	232.0	224.0
53	117.6	4.39	72.6	26.8	7.49	98	95	248.0	208.0
61	123.4	4.99	77.2	29.2	7.48	10	100	228.0	218.8
75	126.1	5.92	88.5	22.8	7.52	22	144	254.5	238.5
78	140.8	3.36		25.9	7.39	76	83	290.0	258.2
80	123.0	4.91	83.5	22.4	7.49	23	120	243.4	228.5
80a	142.3	4.35				32	76	281.0	265.0
82	159.0	4.06				13	116	298.0	287.0
90	139.4	4.28		28.0	7.45	48	142	289.0	264.0
93	145.0	3.39		27.5	7.44	36	97	283.0	264.7
94	148.7	5.16		28.4	7.27	83	112	306.0	270.2
56	150.8	4.60				49	100	283.8	260.7
57	148.0	4.97				27	98	286.1	271.1
58	143.2	3.97				20	108	277.0	263.9
67a	152.6	4.58				15	108	283.0	271.6
94a	150.4	3.88				15	89	275.0	265.0
				Liver disease					
2	146.0	3.09	108.2	17.1	7.48	34	121	280.0	261.2
3	145.7	3.94	106.5	21.7	7.52	17	101	275.0	263.3
6	128.5	5.21	84.4	28.5	7.38	17	117	245.8	233.2
8	143.5		98.1	23.9	7.46	22	85	276.1	263.5
13	150.0	4.75	95.3	28.2	7.38	95	148	303.6	261.5
16	140.8	3.21	101.8	22.7	7.45	44	118	280.3	258.0
19	139.5	3.70	95.0	26.3	7.39	11	66	262.3	254.7
20	127.9	4.90	94.1	19.1	7.39	31	116	258.4	240.9
22	141.3	4.05	100.8	23.9	7.40	13	83	269.2	260.0
24	133.9	3.91	98.6	21.5	7.45	45	75	265.0	244.7
29	141.8	3.11	101.1	25.9	7.40	19	112	274.5	261.5
30	147.2	3.58	108.3	24.9	7.47	19	86	279.8	268.2
35	139.1	4.44	105.6	18.8	7.48	30	104	274.0	257.5
38	138.1	3.97	101.7	22.7	7.47	16	109	267.4	255.6
43	141.2	4.03				23	112	277.1	262.7
44b	131.6	3.93	94.3	26.5	7.49	12	70	252.1	243.9
48a	108.9	2.54				58	80	227.6	202.5
50	139.6	3.26		23.0	7.54	23	100	257.0	243.2
60	156.4	6.49	125.6	8.1	7.35	145	317	360.0	290.6
66	151.2	4.36	104.0	23.5	7.47	14	86	285.0	275.0
67	170.6					102	164	356.0	310.0
71	112.0	4.82	76.6	20.7	7.28	72	160	243.0	208.4
73	130.7	3.72	85.6	32.9	7.44	32	502	285.0	245.7
79	124.0	3.56				19	127	240.5	226.6
81	144.4	3.96				19	90	280.0	268.0
84	144.4	4.13				22	122	276.5	261.8
86	144.6	6.15				103	95	304.0	262.0
87	126.5	3.54		21.1	7.36	173	150	295.0	225.0
88	141.2	3.80		24.7	7.54	20	125	268.5	254.5
89	136.4	3.96		25.6	7.54	19	120	262.0	248.5
91	144.3	4.30				18	92	271.0	259.5
92	135.7	4.41				16	94	266.0	255.1

* Nonprotein nitrogen.

TABLE II—*Continued*

Patient	Na'_s	K'_s	Cl_s	$(HCO_3)_p$	Arterial pH	NPN*	Glucose	π_s	π'_s
				Kidney disease					
no.	*mEq./L. of serum water*	*mEq./L. of serum water*	*mEq./L.*	*mEq./L.*		*mg. %*	*mg. %*	*mOsm./L.*	*mOsm./L.*
17	146.4	7.00	103.6	15.3	7.28	100	87	304.8	264.3
28	144.0	3.90	103.3	19.3	7.31	139	109	317.3	261.6
33	111.2	4.76		22.4	7.40	127	136	260.0	207.0
62	134.3	5.13	76.3	28.1	7.49	165	157	309.0	241.4
74	137.3	4.54		17.7	7.30	212	139	310.0	226.6
				Lung disease					
31	146.3	5.25	90.6	31.5	7.41	37	109	280.3	261.0
48b	134.6	3.67		27.1	7.52	13	100	241.0	230.8
63	145.7	4.37	96.5	26.4	7.45	9	121	266.0	256.0
64	125.5	3.80	76.6	32.0	7.54	16	295	250.0	228.0
59	134.1	5.55	86.1	28.6	7.59	42	137	268.0	245.0
				Gastrointestinal disease					
4	147.3	4.44	100.7	29.0	7.46	23	103	277.6	263.7
9	148.7	3.97	106.2	24.0	7.46	33	149	282.8	262.7
44a	116.2	6.32	89.7	11.5	7.31	39	150	239.0	216.8
46	155.0	4.69		15.7		128	127	320.0	267.2
				Neurological disease					
40	143.9	3.65	113.7	25.9	7.44	30	91	278.0	262.2
41	133.1	4.48	116.8	23.4	7.42	13	127	256.7	245.0
65	131.3	4.78	80.0	24.5	7.55	30	139	254.0	235.0
68	192.5					238	367	450.0	345.0
72	135.8	4.09	92.0	30.4	7.50	15	95	258.0	247.3
77	158.1	2.28	103.8	34.1	7.47	34	100	301.7	284.0
83	161.5	3.97				34	102	317.0	304.2
34	144.5	4.40	101.5	26.8	7.39	36	136	286.5	266.0
				Miscellaneous					
14	147.3	4.35	103.7	28.1	7.41	16	83	278.7	268.4
15	146.1	4.62	106.1	25.8	7.41	27	100	280.9	265.7
32	148.3	4.02	97.1	34.3	7.35			283.7	
39	138.5	4.13	111.4	22.8	7.44	20	95	262.0	249.6
45	129.5	5.14	94.9	22.4	7.43	24	98	252.9	238.9
52	142.3	3.80		33.2	7.55	25	105	263.0	248.0
55	154.6	3.50	98.9	31.7	7.45	30	90	292.0	276.0
70	119.7	4.48	87.6	17.5	7.58	9	78	224.0	216.5
76	135.0	4.65				23	83	262.0	249.2
54	132.3	5.63		18.7	7.43	61	103	273.0	245.0
69	123.3	6.87	87.3	22.0	7.52	14	97	236.0	225.6
Mean	140.1	4.40	96.4	25.0	7.44	45.3	120	276.6	254.5
Range	108.9–192.5	2.28–7.00	72.6–125.6	8.1–40.4	7.19–7.59	9–238	66–502	224.0–450.0	202.5–345.0

and potassium were measured in dilutions of urine and serum with a lithium internal-standard flame photometer. Serum water was determined gravimetrically by drying 1 ml. aliquots, delivered from calibrated pipettes, at 104° C. for 72 hours. Serum chloride (Cl_s) was estimated by electrometric titration (21), plasma glucose by colorimetry (22) and plasma nonprotein nitrogen (NPN) by a modification of the Folin-Wu method (23). Total CO_2 content of arterial plasma was determined by the manometric method of Van Slyke (24). Arterial blood pH was measured at 37° C. with a Beckman model G pH meter, calibrated with buffer standards prepared from high purity salts provided by the National Bureau of Standards. All chemical determinations were done in duplicate or triplicate.

Calculations, statistics, and analytical error. Standard formulas were used in calculating specific activities, Na_e, K_e and T.B.W., including the appropriate corrections for isotope excretion in the urine (25–27). The measured Na_e was back corrected to the time of determinations of K_e and T.B.W. by metabolic balance for sodium during the period of Na^{24} equilibration. This correction was applied to provide simultaneous estimates of Na_e, K_e and T.B.W. since Na_e was measured 24 hours after measurement of K_e and T.B.W.

The osmotic contributions of glucose and NPN were

TABLE III

Summary of laboratory data: Body composition

Patient	Na_e	Na_e/Body wt.	K_e	K_e/Body wt.	T.B.W.	T.B.W./Body wt.	$\frac{Na_e + K_e}{T.B.W.}$
			Heart disease				
no.	*mEq.*	*mEq./Kg.*	*mEq.*	*mEq./Kg.*	*L.*	*%*	*mEq./L.*
1	3,122	48.7	2,454	38.3	34.1	53.1	163.8
5	3,189	59.2	1,963	36.5	33.8	62.7	152.5
7	4,876	57.4	1,936	22.8	44.8	52.7	152.2
10	6,983	58.4	3,293	27.6	69.6	58.3	147.6
11	3,812	47.7	2,681	33.5	39.9	50.3	162.9
12	2,359	39.5	2,599	43.5	35.0	58.5	141.7
18	1,953	46.7	1,862	44.5	24.9	59.5	153.3
21	3,149	52.7	2,168	36.3	33.5	56.1	158.5
23	3,486	63.2	1,704	30.9	36.3	65.7	143.1
25	3,051	64.2	1,665	34.9	30.9	64.8	154.6
26	5,116	67.5	2,772	36.6	49.5	65.9	159.3
27	2,880	47.3	1,639	26.9			
36	2,230	57.8	1,279	33.1	23.6	61.2	148.5
37	2,971	47.7	1,986	31.9	32.4	52.0	150.6
42	2,495	55.7	1,650	36.9	29.8	66.5	139.3
47	3,046	62.7	1,750	36.0	31.6	65.0	151.9
49b	3,176	61.3	1,245	24.0	30.3	58.4	146.1
51	3,385	60.0	1,424	25.2	36.8	65.2	130.8
53	3,734	75.0	1,211	24.3	37.6	75.4	131.6
61	3,451	59.5	2,048	35.3	40.0	68.9	137.5
75	3,659	68.2	1,699	31.7	38.9	72.5	137.8
78	3,702	51.9	3,723	52.1	50.4	70.5	147.5
80	1,957	30.8	1,164	18.3	24.0	37.7	130.1
80a	6,400	74.1	2,213	25.6	60.6	70.1	142.3
82	3,105	29.9	3,021	29.0	39.2	37.7	156.5
90	3,733	70.2	1,571	29.5	36.3	68.3	146.0
93	4,770	72.4	1,937	29.3	47.2	71.6	142.1
94			1,804	32.4	39.2	70.4	
56	2,227	31.8	2,227	31.8	28.5	40.8	156.1
57	3,447	39.8	4,222	48.9	45.6	52.7	168.1
58	2,180	38.7	2,063	36.8	27.9	49.7	152.0
67a	2,363	38.8	2,281	37.5	29.2	48.0	158.2
94a	2,276	41.4	1,882	34.2	27.9	50.8	148.8
			Liver disease				
2	4,152	61.7	1,785	26.5	39.3	58.3	151.2
3	3,541	45.1	3,205	40.1	44.5	55.6	151.7
6	2,417	57.9	1,438	34.4	26.9	64.3	143.5
8	2,906	77.1	1,044	27.7			
13	3,327	37.6	2,889	32.7			
16	5,153	50.9	2,350	23.2	50.1	49.5	149.6
19	2,228	56.3	1,203	30.4	22.7	57.4	151.2
20	2,359	46.3	1,665	32.7	27.7	54.2	145.5
22	1,995	50.2	1,266	31.8	22.0	55.3	148.2
24	3,511	52.4	2,140	31.9	37.4	55.4	151.0
29	2,716	32.9	2,265	27.5	32.5	39.4	153.2
30	5,386	68.4	2,819	35.8	52.3	66.3	156.9
35	3,772	72.8	1,525	29.4	35.5	68.6	149.1
38	4,236	79.3	2,624	33.1	45.0	56.8	152.3
43	3,337	29.7	3,637	32.3	45.4	40.4	153.6
44b	2,941	51.8	1,683	29.6	32.6	57.3	142.1
48a							
50	3,376	51.4	2,133	32.5	36.0	54.8	153.0
60			1,665	29.9	23.7	42.6	
66	3,085	55.6	1,816	32.7	32.6	58.7	150.5
67							
71			1,504		38.1		
73			1,802	31.2	32.7	56.7	
79	4,300	55.0	1,680	21.5	43.5	55.7	137.3
81	5,510	67.7	2,308	28.4	52.1	64.0	150.1
84	5,470	64.7	2,775	32.8	55.6	65.7	148.4
86	2,943	44.4	2,487	37.5			
87	2,852	37.1	2,521	32.8	40.0	52.1	134.3
88	3,284	54.7	2,197	36.6	37.9	63.2	144.5
89	3,116	46.0	1,762	26.0	35.6	52.6	137.2
91	3,308	51.7	2,415	37.7	38.3	59.9	149.3
92	3,103	51.7	2,349	39.2	38.0	63.4	143.4

TABLE III—*Continued*

Patient	Na_e	Na_e/Body wt.	K_e	K_e/Body wt.	T.B.W.	T.B.W./Body wt.	$\frac{Na_e + K_e}{T.B.W.}$
			Kidney disease				
no.	*mEq.*	*mEq./Kg.*	*mEq.*	*mEq./Kg.*	*L.*	*%*	*mEq./L.*
17	4,899	70.8	2,510	35.5	47.6	67.3	155.7
28	2,874	60.2	2,017	42.3	31.5	65.9	155.4
33	2,839	55.5	1,671	32.7	36.0	70.4	125.3
62	5,062	72.6	2,884	41.3	56.4	80.8	140.8
74	2,247	56.2	1,595	39.9	25.4	63.5	151.2
			Lung disease				
31	2,257	47.1	2,105	43.9	27.8	58.0	156.7
48b	2,411	46.1	1,771	33.9	29.3	56.0	142.7
63	2,479	48.3	2,035	39.7	29.8	58.0	151.6
64	3,602	69.2	1,569	30.1	37.0	71.2	139.8
59			2,196	36.5	38.7	64.6	
			Gastrointestinal disease				
4	3,511	40.6	3,427	39.4	43.8	50.4	158.4
9	3,040	43.9	3,126	45.2	37.8	54.6	163.1
44a			1,313	33.0	25.2	63.2	
46	3,451	76.8	1,608	35.8	31.3	69.6	160.8
			Neurological disease				
40	2,146	51.9	1,218	29.5	22.2	53.7	151.5
41	2,446	40.5	1,805	29.9	29.9	49.4	142.4
65	2,752		2,404		34.8		148.3
68							
72	2,110	48.8	1,667	38.6	26.0	60.1	145.6
77	2,867	73.3	1,097	28.1	25.5	65.2	155.4
83	3,103	80.3	1,291	33.3	25.1	65.0	175.1
34	2,287	52.5	1,491	34.2	25.2	57.8	149.9
			Miscellaneous				
14	2,624	44.1	2,040	34.3	30.2	50.7	154.7
15	2,646	44.6	2,112	35.6	32.3	55.1	147.1
32	5,247	31.2	5,444	32.4	69.8	41.5	153.3
39	1,228	33.8	1,358	37.4	18.0	49.4	143.9
45	2,707	47.5	1,996	35.0	32.1	56.4	146.4
52	3,294	64.7	2,180	42.8	35.2	69.1	155.6
55	2,710	50.6	2,504	46.7	33.8	63.0	154.4
70	2,479	40.1	2,039	33.0	35.6	57.6	126.9
76	2,645	42.3	2,180	34.9	34.4	55.0	140.3
54	3,782	59.2	3,006	47.0	46.1	72.1	147.4
69	2,037	43.4	1,611	33.7	27.0	56.6	135.2
Mean	3,263	53.2	2,099	33.9	36.1	58.9	148.6
Range	1,228–6,983	29.7–80.3	1,044–5,444	18.3–52.1	18.0–69.8	37.7–80.8	125.3–175.1

evaluated by measuring the freezing point depression of standard solutions of glucose and urea. The observed depression of freezing point was directly proportional to the molar concentrations up to 500 mg. per 100 ml. of glucose and 300 mg. per 100 ml. of urea. The "corrected" serum osmolarity (π'_s) in mOsm. per liter was therefore calculated as:

$$\pi'_s = \pi_s - \frac{G_p}{18} - \frac{NPN_p}{2.8}, \qquad 1)$$

where π_s is the measured serum osmolarity, G_p is the plasma glucose concentration in mg. per 100 ml. and NPN_p is the plasma NPN concentration in mg. per 100 ml. The factor 1/2.8 is derived from the mean nitrogen content of NPN (28) and is based on the assumptions that, like urea, the other components of NPN have an activity coefficient of 1.0 at physiological concentrations and that the relative amounts of each constituent of NPN are constant, regardless of absolute values. The "corrected" serum sodium concentration (Na'_s), expressed as mEq. per liter of serum water, is calculated from the measured serum sodium concentration and serum water content, since spuriously low serum sodium concentrations may be recorded when the lipid or lipoprotein content of serum is large (29).

Conventional statistical equations were used to calculate standard deviation (σ), correlation coefficient (r) and sample standard deviation from regression ($S_{y.x}$) (30). The regression equations were obtained by the method of

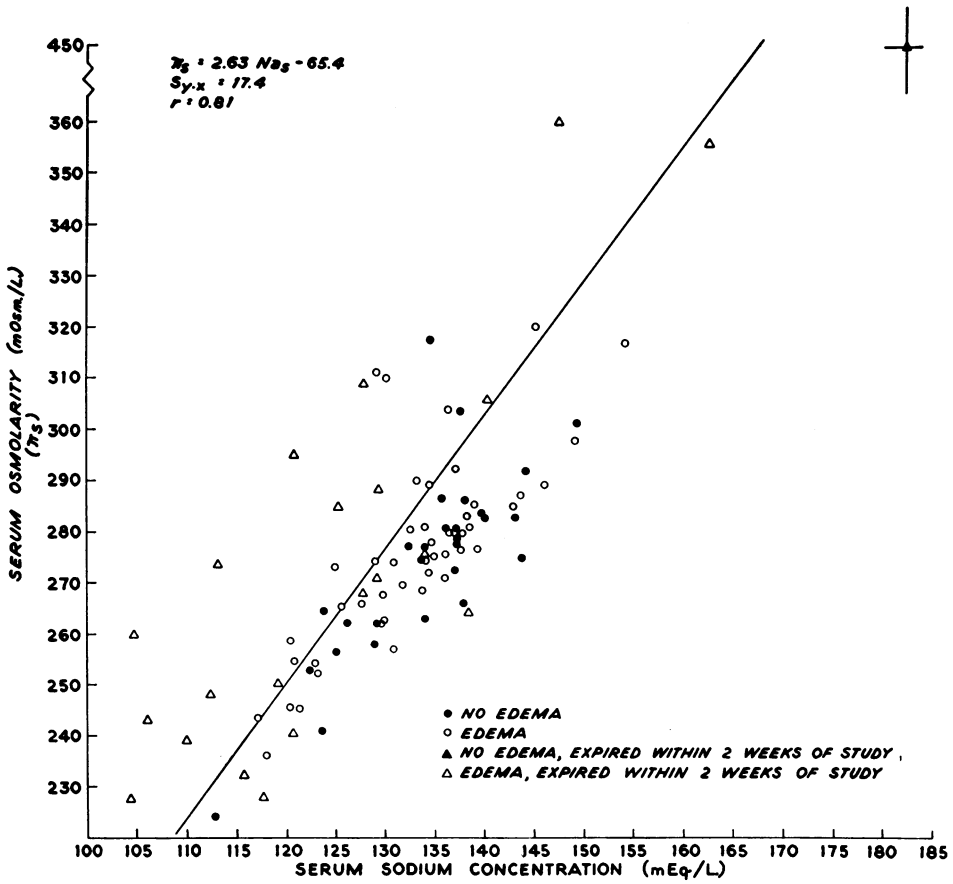

FIG. 1. THE RELATION BETWEEN SERUM OSMOLARITY AND SERUM SODIUM CONCENTRATION

The statistical data were calculated as described in the text. The regression is assumed to be linear.

least squares, and the probability (p) of a correlation coefficient being obtained by chance was evaluated by the t test (30). Some of the correlations encountered were very high. The possibility was therefore considered that these very high correlations might represent perfect relationships masked only by errors of measurement. This possibility was explored in the highly significant regression relations by correcting the correlation coefficients for attenuation (31). The correlation coefficient corrected for attenuation is an estimate of the correlation between two variables free of errors of measurement. The formula for this correction is:

$$r'_{y.x} = \frac{r}{\sqrt{r_{y.y} \cdot r_{x.x}}}, \qquad 2)$$

where $r'_{y.x}$ is the amended correlation coefficient, r is the correlation coefficient computed from the data and:

$$r_{y.y} = 1 - \frac{\sigma^2_{y.m}}{\sigma^2_y} \qquad 3)$$

$$r_{x.x} = 1 - \frac{\sigma^2_{x.m}}{\sigma^2_x} \qquad 4)$$

$_{y.m}$ is the standard deviation of reproducibility of measurement of the y parameter and $_{x.m}$ is the standard deviation of reproducibility of measurement of the x parameter. $_y$ and $_x$ are the standard deviations of the observed values. To compute $_{x.m}$ for the parameter of the form (a + b)/c, the following formula was used:

$$\sigma^2_{x.m} = \left[\frac{\sigma^2_{a.m} + \sigma^2_{b.m} + \bar{x}^2 \cdot \sigma^2_{c.m}}{\bar{c}^2}\right], \qquad 5)$$

where x = (a + b)/c. This formula assumes that the errors of determination in a, b, and c are unrelated to one another, which is a reasonable assumption.

Errors of measurement were evaluated from n number of observations on pooled specimens or by serial estimations in given subjects. The standard deviations of reproducibility were as follows: $\sigma_{Na'_s.m}$ = 1.05 mEq. per liter (n = 21); $\sigma_{\pi'_s.m}$ = 1.44 mOsm. per liter (n = 16); $\sigma_{Na_e.m}$ = 65 mEq. (n = 20); $\sigma_{K_e.m}$ = 57 mEq. (n = 23); $\sigma_{T.B.W.m}$ = 0.71 liter (n = 28). $\sigma_{Na_e.m}$, $\sigma_{K_e.m}$ and $\sigma_{T.B.W.m}$ were calculated from previously established values using the standard formula $\sigma^2_m = \frac{\Sigma d^2}{2n}$ (19). These estimates are slightly lower than previously published values (32, 33).

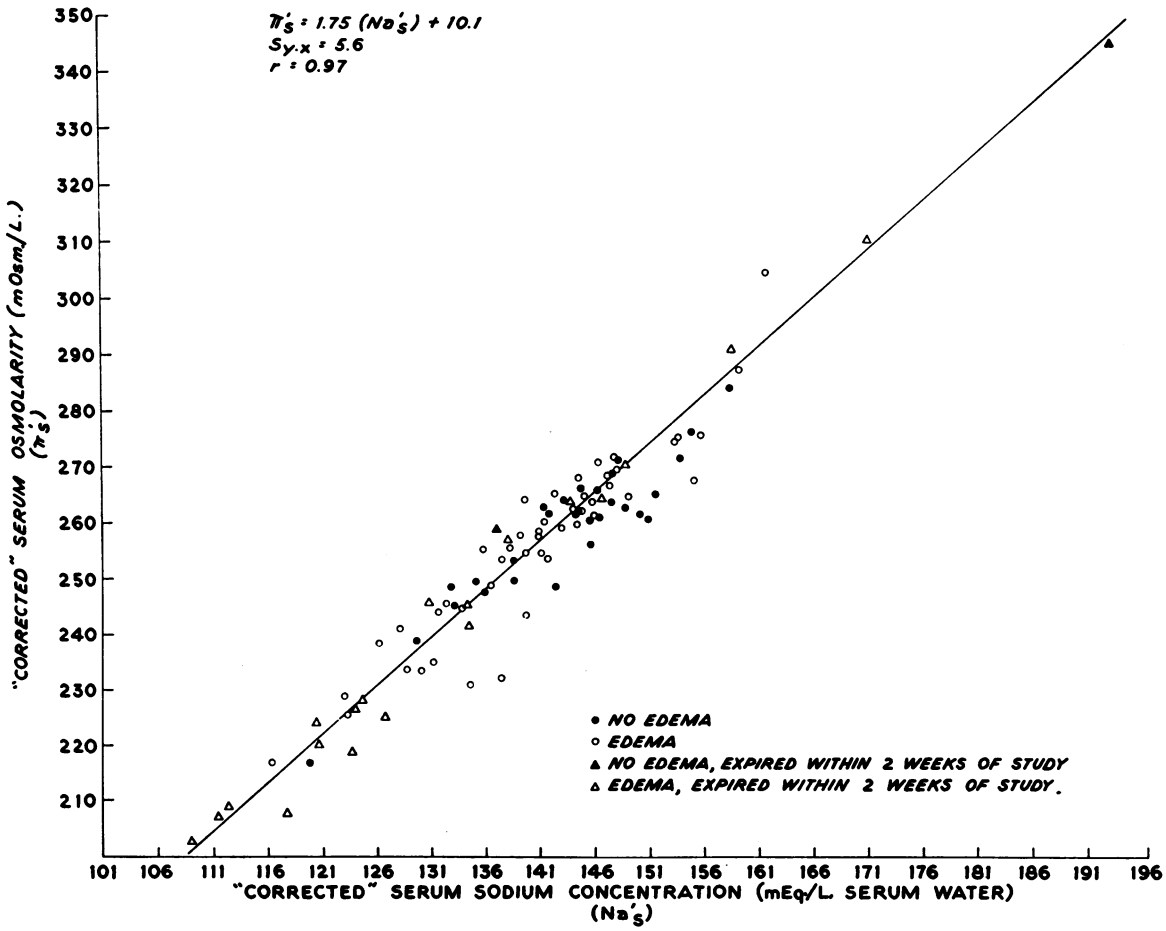

FIG. 2. THE RELATION BETWEEN "CORRECTED" SERUM OSMOLARITY AND THE "CORRECTED" SERUM SODIUM CONCENTRATION

The regression is assumed to be linear. See text for calculations of "corrected" serum osmolarity and "corrected" serum sodium concentration.

RESULTS

The data obtained in this study are listed in Tables II and III. The heterogeneity of the subjects is indicated by the wide range of values: Na'_s varied from 108.9 to 192.5 mEq. per liter of serum water, K'_s from 2.28 to 7.00 mEq. per liter of serum water, Cl_s from 72.6 to 125.6 mEq. per liter, $(HCO_3)_p$ from 8.1 to 40.4 mEq. per liter, arterial blood pH from 7.19 to 7.59 units, NPN from 9 to 238 mg. per 100 ml. of plasma, and glucose from 66 to 502 mg. per 100 ml. of plasma.

Serum osmolarity and serum sodium concentration

The total osmotic pressure of any fluid is the sum of the partial pressures of solute and may be expressed as equivalent osmotic concentrations or milliosmols. Sodium, the principal extracellular cation, must influence serum osmolarity considerably. Its quantitative contribution is depicted in Figure 1. While the correlation coefficient of the regression of total serum osmolarity with respect to serum sodium is highly significant ($r = 0.81$, $p < 0.001$), the large sample standard deviation from regression ($S_{y.x} = 17.4$ mOsm. per liter) indicates that other substances probably contribute significantly to π_s. The value of the amended correlation coefficient r' (0.82) indicates that errors of measurement contributed little to the observed scatter. These data corroborate the findings reported by Talso, Spafford, Ferenzi and Jackson in patients with congestive heart failure and cir-

rhosis of the liver (34). The estimated contributions of plasma NPN and plasma glucose to serum osmotic activity were subtracted to evaluate the separate relationship of Na'_s to π'_s; this is demonstrated in Figure 2. The correlation coefficient of this relationship, r = 0.97 (see Table IV and Figure 2), shows the primary dependence of π'_s on Na'_s, as has long been assumed (35). The data in patients who died within two weeks of study did not differ from those in the remaining patients. This is in contrast to the findings of Rubin, Braveman, Dexter, Vanamee and Roberts (36), who noted hyperosmolarity of plasma in critically ill patients in excess of measured solute concentration. The data in Figure 2 indicate a linear dependence of serum osmolarity on the concentration of sodium in serum water when corrections are made for the osmotic contributions of NPN and glucose. Total serum osmolarity (π_s), therefore, is given by:

$$\pi_s = 1.75\ Na'_s + 0.0556\ G_p + 0.357\ NPN_p + 10.1 \quad 6)$$

with an amended correlation coefficient, r' = 0.98, and a sample standard deviation from regression, $S_{y.x}$ = 5.6 mOsm. per liter. The values of the intercept of 10.1 mOsm. per liter and of $S_{y.x}$ of 5.6 mOsm. per liter can be attributed to the osmotic contributions and variations in concentrations of the salts of K^+ (~ 7.0 mOsm. per liter), Ca^{++} (~ 1.5 mOsm. per liter), Mg^{++} (~ 0.5 mOsm. per liter) and of trace substances (~ 1.0 to 3.0 mOsm. per liter) (37).

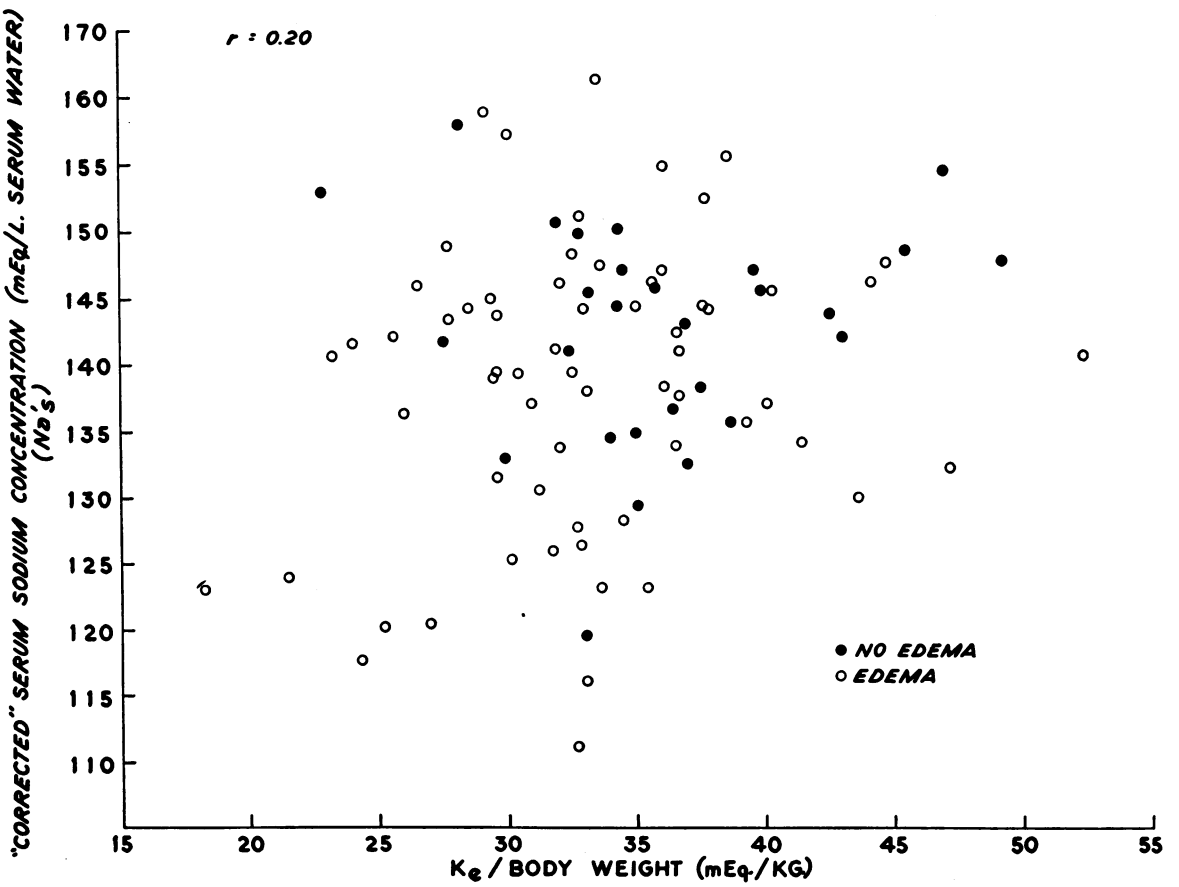

FIG. 3. THE RELATION BETWEEN THE "CORRECTED" SERUM SODIUM CONCENTRATION AND TOTAL EXCHANGEABLE POTASSIUM

The correlation is equally minor for both edematous and nonedematous subjects and does not justify calculation of a regression equation.

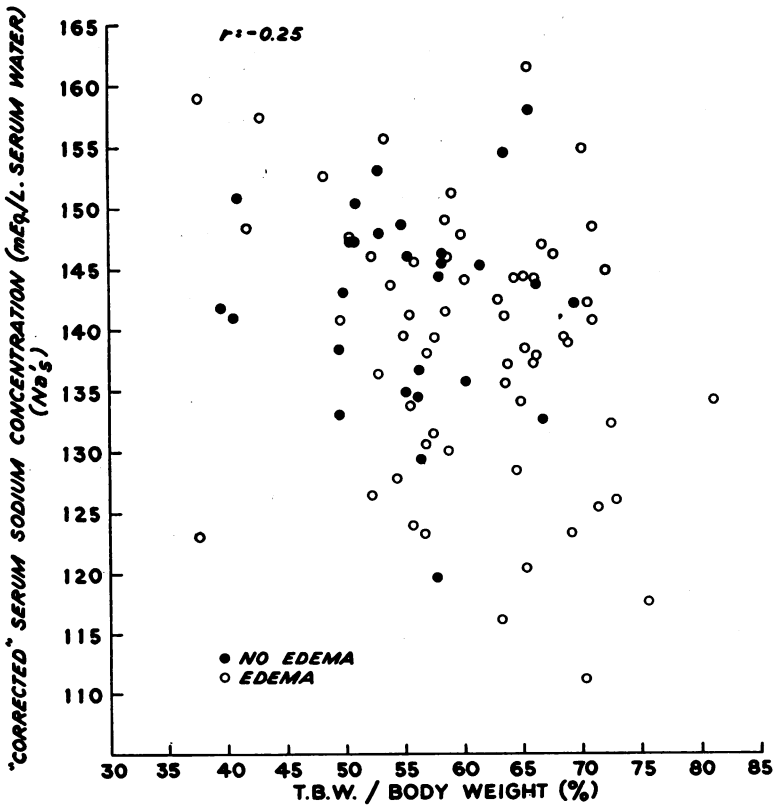

FIG. 4. THE RELATION BETWEEN "CORRECTED" SERUM SODIUM CONCENTRATION AND TOTAL BODY WATER

Neither the edematous nor the nonedematous patients shows a correlation great enough for calculation of a regression equation.

Serum sodium concentration and body composition

Variations in serum sodium concentration often parallel variations in sodium balance, but we found no correlation between Na'_s and Na_e/body weight ($r = 0.003$). This confirms many similar studies in the past (1–4, 6). The negative result, however, does not explain the known effects of alterations in sodium balance on Na_s.

Potassium balance modifies the level of Na_s, but as shown in Figure 3 the correlation between Na'_s and K_e/body weight ($r = 0.20$) is minor. Therefore, differences in body potassium alone would not account appreciably for the variations in Na_s in this group of subjects.

Figure 4 is a scattergraph of Na'_s as a function of total body water expressed as per cent of body weight. The coefficient, $r = -0.25$, indicates a minor negative correlation. Variations in body fat in these subjects may account in part for the poor correlation with either K_e or T.B.W. Further analysis of these relationships requires measurement of body fat.

The concept of "dilution hyponatremia" suggests that retention of water in excess of sodium may account for the poor correlation of Na'_s with either Na_e alone or T.B.W. alone. The relationship between Na'_s and the ratio Na_e/T.B.W. is shown in Figure 5. The coefficient, $r = 0.27$, indicates only minimal correlation of Na'_s with the ratio of body sodium to body water.

Since an inverse relation between retention of water and serum sodium concentration has been noted during periods of negative potassium balance, Na'_s may be related to the ratio of K_e to T.B.W. Figure 6 is a plot of Na'_s and the ratio K_e/T.B.W., which shows a modest correlation ($r = 0.40$). The choice of coordinates probably does not conceal any closer correlations since log-

log plots of Na'_s to Na_e/T.B.W. and to K_e/T.B.W. are equally disappointing.

The partial correlation of Na'_s with Na_e/T.B.W. and with K_e/T.B.W., as well as the evidence that body sodium, body potassium and body water affect Na_s, suggests that osmotic adjustments between body fluids may determine the relationship of Na_s to body composition (7, 11, 38–41). The precise correlation between Na'_s and π'_s may be paralleled by a similar correlation between intracellular osmolarity and intracellular K^+ concentration. The ratio $(Na_e + K_e)$/T.B.W., therefore, may be a primary determinant of Na'_s, provided that water is passively distributed across cell membranes. This hypothesis is tested in Figure 7. The high degree of correlation between Na'_s and $(Na_e + K_e)$/T.B.W. is obvious and in striking contrast to the lesser correlation of Na'_s to the separate elements in this ratio. The coefficient $r = 0.83$ is especially impressive since there must be a propagation of methodological errors in calculating this ratio. Figure 8 demonstrates the same high degree of correlation between π'_s and $(Na_e + K_e)$/T.B.W., and Table IV lists the statistical data describing these relations. The likelihood that these findings are chance phenomena is extremely small. Indeed, the correlation coefficents [$r = 0.83$ and $r' = 0.92$ for Na'_s versus $(Na_e + K_e)$/T.B.W., and $r = 0.82$ and $r' = 0.91$ for π'_s versus $(Na_e + K_e)$/T.B.W.] suggest that Na_e, K_e and T.B.W. are the primary determinants of Na'_s. The standard deviations from regression for the parameters Na'_s, $(Na_e + K_e)$/T.B.W. and π'_s, $(Na_e + K_e)$/T.B.W. were 5.6 mEq. per liter and 10.2 mOsm. per liter, respectively (see Table IV). These variations from regression are partly, if not wholly, a reflection of methodological errors since the standard deviation of reproducibility of

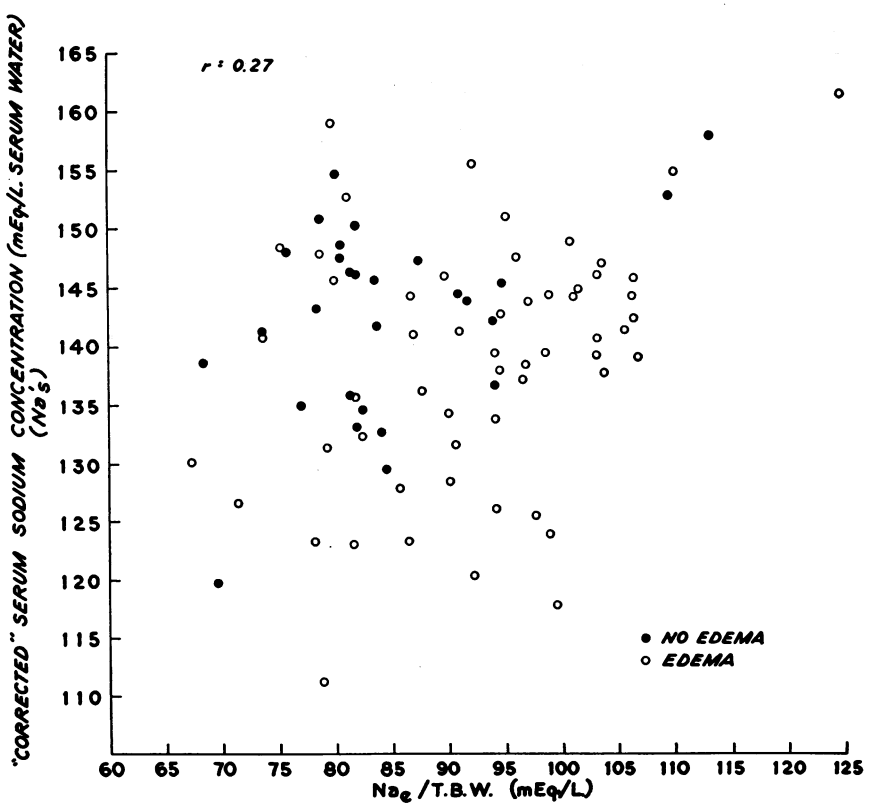

FIG. 5. THE RELATION BETWEEN "CORRECTED" SERUM SODIUM CONCENTRATION AND THE RATIO OF TOTAL EXCHANGEABLE SODIUM TO TOTAL BODY WATER

The correlation is quite limited for both edematous and nonedematous patients and a regression equation is not justified.

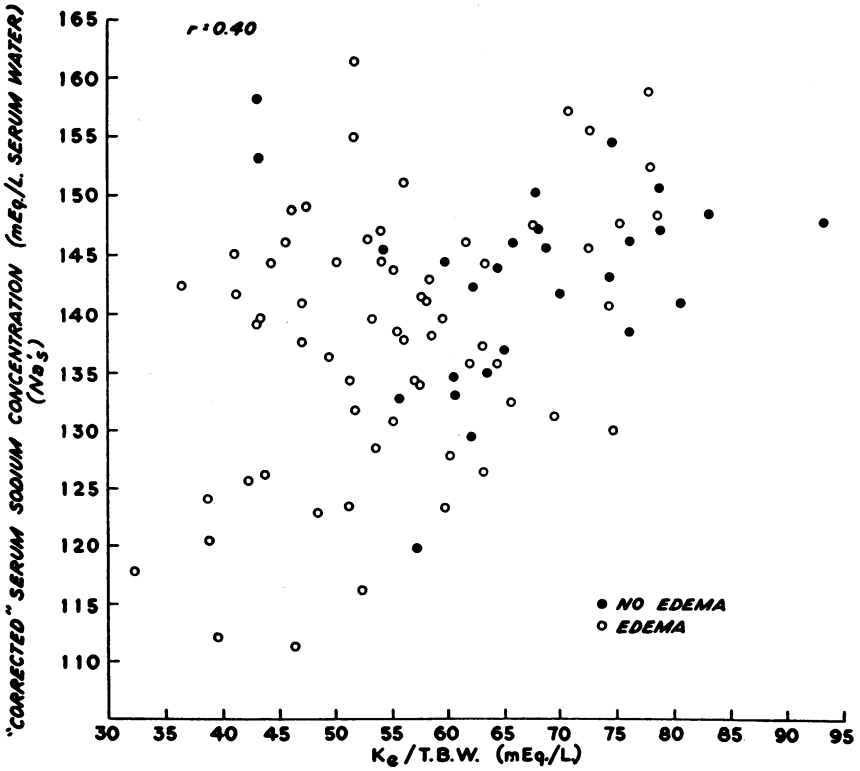

FIG. 6. THE RELATION BETWEEN "CORRECTED" SERUM SODIUM CONCENTRATION AND THE RATIO OF TOTAL EXCHANGEABLE POTASSIUM TO TOTAL BODY WATER

Although there is a modest correlation, neither the edematous nor the nonedematous patients fall into a precise relation.

TABLE IV

Summary of statistical relationships between serum sodium concentration, serum osmolarity and body composition

Parameters	Regression equation	Standard deviation from regression $S_{y.x}$	Correlation r	t	p	r'
Serum osmolarity Serum sodium concentration	$\pi_s = 2.63\ Na_s - 65.4$	17.4	0.81	23.1	<0.001	0.82
"Corrected" serum osmolarity "Corrected" serum sodium concentration	$\pi'_s = 1.75\ Na'_s + 10.1$	5.6	0.97	121	<0.001	0.98
"Corrected" serum sodium concentration $(Na_e + K_e)$/T.B.W.	$Na'_s = 1.11 \frac{(Na_e + K_e)}{T.B.W.} - 25.6$	5.6	0.83	24.4	<0.001	0.92
"Corrected" serum osmolarity $(Na_e + K_e)$/T.B.W.	$\pi'_s = 2.09 \frac{(Na_e + K_e)}{T.B.W.} - 56.7$	10.2	0.82	19.8	<0.001	0.91

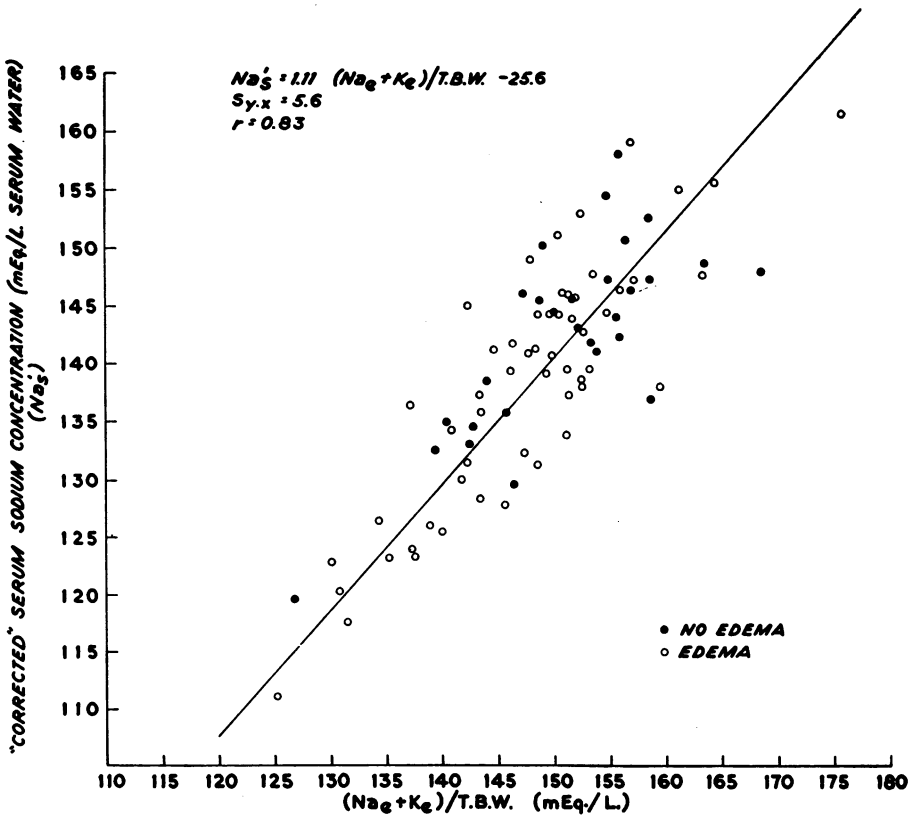

FIG. 7. THE RELATION BETWEEN SERUM SODIUM CONCENTRATION AND THE RATIO OF $(Na_e + K_e)$/TOTAL BODY WATER

The statistical data were calculated as described in the text. The regression is assumed to be linear. The presence or absence of edema does not appear to affect the regression relation.

the ratio $(Na_e + K_e)$/T.B.W. estimated from individual reproducibility of each component is 3.8 mEq. per liter.

The regression relation between Na'_s and $(Na_e + K_e)$/T.B.W. and between π'_s and $(Na_e + K_e)$/T.B.W., despite the high correlations, may include two or more populations. At least two sets of circumstances may alter the quantitative dependence of Na'_s or π'_s on $(Na_e + K_e)$/T.B.W.: *a*) acid-base disturbances and *b*) osmotic inequalities between cells and extracellular fluid (ECF). Bone sodium consists of exchangeable and nonexchangeable fractions, and most of the exchangeable bone sodium is osmotically inactive (15). Since acidosis will considerably reduce bone sodium content (17, 42), acid-base disturbances may shift the relationship between Na'_s and body composition. Figure 9 depicts the distribution of Na'_s versus $(Na_e + K_e)$/T.B.W. in subjects with arterial pH < 7.36 and in a second group with arterial pH > 7.48. Although the observations are too few to allow definite conclusions, there is no apparent deviation or variation from the general regression equation, and most of the data fall within ± 1 $S_{y.x}$. The quantitative relation between Na'_s and $(Na_e + K_e)$/T.B.W., therefore, appears to be independent of arterial pH. Osmotic inequalities among body fluids may influence this relation. Hyperglycemia particularly, and to a lesser extent azotemia, may be associated with transient or possibly even sustained osmotic differences across cell membranes (38, 41). Accordingly, Figure 10 shows the relation of Na'_s to $(Na_e + K_e)$/T.B.W. in patients with NPN > 50 mg. per 100 ml. of plasma or with glucose > 130 mg. per 100 ml. of plasma. There is no apparent deviation from the general regression equation, and no separation into different populations.

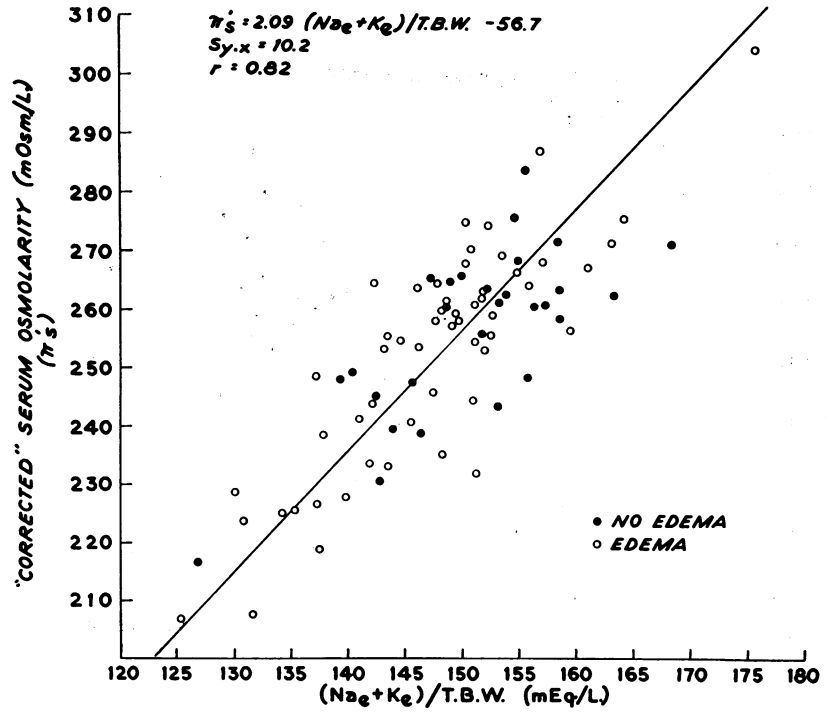

FIG. 8. THE RELATION BETWEEN THE "CORRECTED" SERUM OSMOLARITY AND THE RATIO OF $(NA_e + K_e)$/TOTAL BODY WATER

The statistical data were calculated as described in the text. The presence or absence of edema does not appear to affect the regression relation.

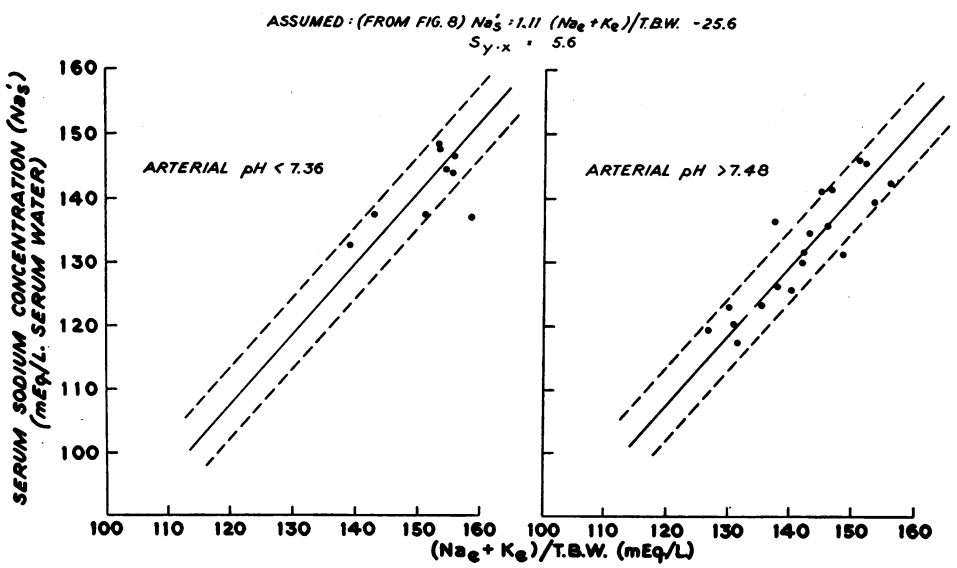

FIG. 9. THE RELATION OF NA'_s AND $(NA_e + K_e)$/TOTAL BODY WATER IN PATIENTS WITH ACIDOSIS (pH < 7.36) OR ALKALOSIS (pH > 7.48)

The regression line is taken from the relation depicted in Figure 8. Each broken line is one standard deviation from regression.

TABLE V

Serial studies of serum sodium concentration, serum osmolarity and body composition

	1st study	2nd study	Δ	1st study	2nd study	Δ	1st study	2nd study	Δ
Patient, *no.*	28	33		70	76		47a	53	
Diagnosis	chronic glomerulonephritis			panhypopituitarism			hypertension and congestive heart failure		
Clinical status	no edema	2+ edema		no edema	no edema		2+ edema	2+ edema	
Date	3/21/56	4/26/56		1/8/57	2/19/57		8/30/56	10/19/56	
Body weight, *Kg.*	47.6	51.1	+3.5	61.8	62.5	+0.7	48.6	49.8	+1.2
π'_s, *mOsm./L.* of serum water	261.6	207.0	−54.6	216.5	249.2	+32.7	256.4	208.0	−48.4
Na'_s, *mEq./L.* of serum water	144.0	111.2	−32.8	119.7	135.0	+15.3	138.5	117.6	−20.9
Na_e, *mEq.*	2,874	2,839	−35	2,497	2,645	+166	3,046	3,734	+688
K_e, *mEq.*	2,017	1,671	−346	2,039	2,180	+141	1,750	1,211	−539
T.B.W., *L.*	31.5	36.0	+4.5	35.6	34.4	−1.2	31.6	37.6	+6.0
$\frac{Na_e + K_e}{T.B.W.}$, *mEq./L.*	155.4	125.3	−30.1	126.9	140.3	+13.4	151.9	131.6	−20.3

The data summarized above indicate that Na'_s predominantly reflects the ratio of $(Na_e + K_e)$/T.B.W. and that this correlation is independent of differences in the pH of extracellular fluid or in glucose or NPN concentrations. The regression equation of this relation has a slope of 1.11 (see Table IV) and implies almost a 1:1 correspondence between changes in $(Na_e + K_e)$/T.B.W. and changes in Na'_s. The equation relating serial differences in Na'_s and $(Na_e + K_e)$/T.B.W. is:

$$Na_{s.1} - Na_{s.2} = 1.11\,[(Na_e + K_e)/T.B.W.]_1 - 1.11\,[(Na_e + K_e)/T.B.W.]_2$$

or,

$$\Delta Na'_s = 1.11\Delta[(Na_e + K_e)/T.B.W.]. \quad 7)$$

In three instances serial observations were made. The results, summarized in Table V, confirm the prediction of proportional changes between Na'_s and $(Na_e + K_e)$/T.B.W. independent of the presence or absence of edema. The proportionality to changes in π'_s is also obvious. These data confirm the report of Deming and Gerbode (11) on the synchronous changes in Na_s and sodium, potassium and water balance in patients after mitral valvulotomy and of Wynn (39) in similar studies. Wilson, Edelman, Brooks, Myrden, Harken and Moore (4) made serial observations of Na_s, Na_e, K_e and T.B.W. in patients before and after mitral valve surgery. When analyzed in terms of serial differences between successive observations, their data, combined with the values from Table V, demonstrate the same close correlation between ΔNa_s and $\Delta(Na_e + K_e)$/T.B.W. (see Figure 11). The slope, 0.83, and the intercept, 0.1, are in excellent agreement with the derived prediction (Equation 7), considering that in the earlier study (4) Na_s is expressed per liter of serum and that K_e was determined at 24 hours and T.B.W. at 3 hours. There is little doubt, therefore, that both among individuals and in any one individual, Na'_s is strongly dependent on $(Na_e + K_e)$/T.B.W.

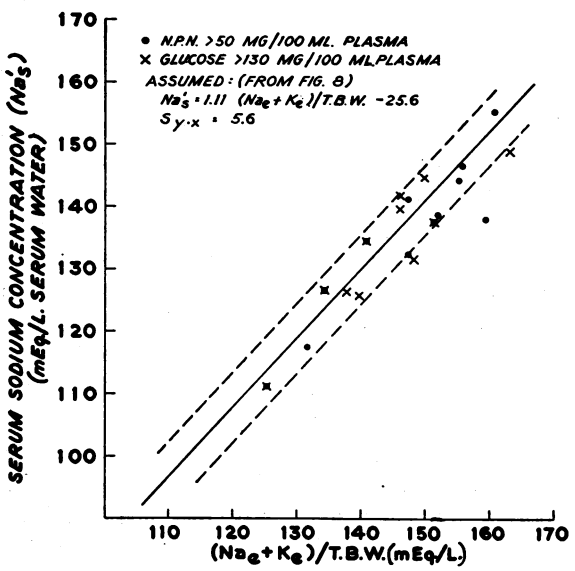

FIG. 10. THE RELATION OF Na'_s TO $(Na_e + K_e)$/TOTAL BODY WATER IN PATIENTS WITH AZOTEMIA OR HYPERGLYCEMIA

The regression line is taken from the relation depicted in Figure 8. Each broken line is one standard deviation from regression.

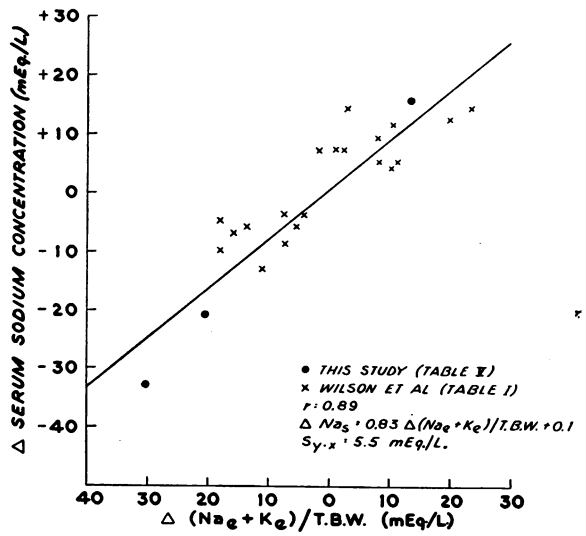

FIG. 11. SERIAL DIFFERENCES IN SERUM SODIUM CONCENTRATION AND THE RATIO (Na$_e$ + K$_e$)/TOTAL BODY WATER

The data from Wilson and co-workers (4) are successive observations where the change in Na$_s$ exceeded 3 mEq. per liter. The regression equation was calculated on the assumption of a linear relationship.

DISCUSSION

Figure 2 shows a linear regression of π'_s on Na'$_s$ over a concentration range of Na'$_s$ from 108.9 to 192.5 mEq. per liter of serum water. The slope, $\lambda = 1.75$, indicates that there is little or no binding of sodium in serum. Multivalent anions, such as phosphates, sulfates, organic anions and serum proteins, provide some electrochemical but lesser osmotic equivalence for sodium in serum, so that probably little or no difference exists between the activity and concentration of sodium salts in serum when referred to aqueous NaCl standards. Glucose and NPN contribute to total serum osmolarity in proportion to their concentrations. These observations confirm the findings of Leaf, Chatillon, Wrong and Tuttle (38), and account for the apparent discrepancies between π_s and Na$_s$ reported by Talso and associates (34) and by Rubin and associates (36). The general equation relating π_s, Na$_s$, glucose and NPN appears to hold for the full range of clinical variations and without regard to the seriousness of illness (see under Results). The residual osmotic activity ($\sim$ 10 mOsm. per liter), which is given by the zero intercept of Equation 6, furthermore, can be reasonably assigned to the known amounts of other salts and trace substances in serum (37).

The data demonstrate poor correlations between Na'$_s$ and Na$_e$, K$_e$, T.B.W., Na$_e$/T.B.W. and K$_e$/T.B.W. (see under Results and Figures 3 through 6). The linear correlation between Na'$_s$ and (Na$_e$ + K$_e$)/T.B.W. ($r = 0.83$, $r' = 0.92$) accounts for the reported effects of each of these components of body composition on Na$_s$ (1–12, 14, 34, 38, 39). That Na'$_s$ is a reflection of the ratio of the sum of exchangeable monovalent cation (Na$_e$ + K$_e$) to T.B.W. is confirmed by the approximately 1 : 1 correlation between sequential changes in Na'$_s$ and (Na$_e$ + K$_e$)/T.B.W. in the same individual (see Table V and Figure 11).

In 1944, Elkinton, Winkler and Danowski (43), using Na$_s$ as the primary index of ECF osmolarity, tested the hypothesis of body fluid iso-osmolarity by comparing the sum of sodium balance (b.Na) and potassium balance (b.K) with the change in total osmotically active base. The expression they derived relating total base balance to changes in Na$_s$ and in T.B.W. is:

$$(\text{b.Na} + \text{b.K}) = \text{T.B.W.}_1\,(0.95\,\text{Na}_{s.1} + 10) - \text{T.B.W.}_2\,(0.95\,\text{Na}_{s.2} + 10). \quad 8)$$

Despite very good correlations between observed and predicted base balances, the authors concluded that a significant and variable fraction of cell base is osmotically inactive. Deming and Gerbode (11) showed that the change in serum sodium concentration correlated closely with net change in sodium and potassium balance per unit change in body water. Recently, Wynn (39) compared the observed and predicted changes in serum cation concentration and found that the formulation of Elkinton and associates (43) predicts such changes within the limits of experimental error. These findings agree with ours since, assuming that sodium and potassium balance are equal to ΔNa$_e$ and ΔK$_e$, Equation 8 is equivalent to Equation 7 except for minor details.

Variations in extracellular pH, glucose or NPN concentrations appear to have no influence on the character of the correlation between Na$_s$ and Na$_e$, K$_e$ and T.B.W. (see Figures 9 and 10). These data do not exclude the possibility that factors other than Na$_e$, K$_e$ and T.B.W. alter Na$_s$. To demonstrate the existence of such factors, however, it would be necessary to show changes in

Na'_s independent of changes in the ratio $(Na_e + K_e)/T.B.W.$ The concept of internal redistribution or "shifts" in electrolytes, so often invoked to explain changes in Na_s in disease states, needs to be re-examined since no evidence for the existence of such shifts without simultaneous changes in the amounts of sodium, potassium or water in the body is apparent in our data or in those referred to above (11, 39).

The relationships between π'_s, Na'_s and $(Na_e + K_e)/T.B.W.$ are compatible with the concept of a passive distribution of water across cell membranes in proportion to solute activity. The possibility of parallel changes in intracellular and extracellular osmolarity with either a constant ratio or a constant difference between phases is not definitively excluded, but seems unlikely. Current evidence indicates that there are no sustained osmotic gradients across cell membranes, although transient gradients occur almost continuously as a result of cellular metabolic activity and absorption of ingested solute and water (8, 38, 39, 40, 44–47). The influence of potassium on Na_s is presumably a reflection of its contribution to intracellular osmolarity. The zero intercept of the regression equation for Na'_s versus $(Na_e + K_e)/T.B.W.$ is a negative constant ($-$ 25.6 mEq. per liter), which probably is a measure of the quantity of osmotically inactive exchangeable sodium and potassium per unit of body water. Since body water in this group of subjects averaged 36.1 liters (see Table III), the estimated osmotically inactive Na + K is approximately 920 mEq. Osmotically inactive exchangeable bone sodium, which is about 750 mEq., probably accounts for almost all of this quantity (15). The calculated ratio of osmotically inactive to total exchangeable potassium, therefore, is less than 10 per cent (*i.e.*, $\sim 170/2099$), which suggests that there is little or no discrepancy between exchangeable and osmotically active potassium. However, this calculation is valid only if Na_s and $(Na_e + K_e)/T.B.W.$ are linearly related over the entire range of their possible values.

Figures 7, 9 and 10 indicate that Na'_s reflects the proportion of $(Na_e + K_e)$ to T.B.W. This observation provides a rational basis for the classification of hyponatremic and hypernatremic states. Hyponatremia may reflect either *a*) primary sodium deficit, *b*) primary potassium deficit, *c*) primary water excess or *d*) combinations of these. Conversely, hypernatremia may reflect either *a*) primary sodium excess, *b*) primary potassium excess, *c*) primary water deficit or *d*) combinations of these. Hyponatremia in patients with gastrointestinal fluid loss probably results from loss of sodium and potassium (16, 48, 49). Hyponatremia in edematous subjects, on the other hand, appears to be a consequence of the loss of potassium and gain of water, as exemplified by Patients 28 and 47a in Table V. This pattern is also prominent in postoperative hyponatremia; in all but 2 of the 11 patients studied by Wilson and associates, (4) the postoperative fall in Na_s was associated with a rise in Na_e, a fall in K_e, and a rise in T.B.W. Hypernatremia has not yet been studied in terms of these components of body composition, but relative or absolute body water depletion is probably its most frequent cause. Diabetes insipidus and water deprivation are two classical examples of this state. Primary excess of potassium is probably not involved in the pathogenesis of hypernatremia, inasmuch as no instance of an abnormally high body potassium content as a consequence of disease has been reported (1, 18). However, reversal of hyponatremia by potassium-loading in patients who presumably were potassium-depleted has been observed (12), and this strategem promises to be valuable in the treatment of this disturbance in edematous subjects (7).

The correction of the hyponatremia presumed to result from sodium depletion is usually based on the formula:

$$\text{Na deficit} = (140 - Na_s)\text{T.B.W.} \qquad 9)$$

This equation, which is supported by clinical experience, is based on the assumption that isotonic conditions prevail throughout body water (7). Wolf and McDowell (40) emphasized that this formula assumes that T.B.W. is unchanged by therapy and revised Equation 9 to include the effect of changes in T.B.W.

$$\text{Na deficit} = (140 - Na_s)\,\text{T.B.W.}_1 + (\Delta H_2O)\,140, \qquad 10)$$

where $\text{T.B.W.}_2 - \text{T.B.W.}_1 = \Delta H_2O$. By substituting and rearranging terms their equation may

be expressed:

$$\text{Na deficit} = 140\,\text{T.B.W.}_2 - \text{Na}_s\,\text{T.B.W.}_1. \quad 11)$$

Both Equations 9 and 10 are special cases of the general regression equation derived in Figure 8. There are, in fact, three equations which may be derived from the general relation between Na_s and body composition (see Equation 7). This equation can be simplified if it is assumed that either *a*) T.B.W. is unchanged by therapy (T.B.W._c) or *b*) K_e is unchanged by therapy ($K_{e.c}$), or *c*) both T.B.W. and K_e remain constant. These three assumptions each lead to separate modifications of Equation 7. The general relation expressed in Equation 7 may be written:

$$\text{Na}_{s.2} - \text{Na}_{s.1} = 1.11 \times \left[\frac{\text{Na}_{e.2} + \text{K}_{e.2}}{\text{T.B.W.}_2} - \frac{\text{Na}_{e.1} + \text{K}_{e.1}}{\text{T.B.W.}_1}\right]$$

a) For the special case where T.B.W. is constant and both Na_e and K_e change as a result of therapy, the equation becomes:

$$\text{Na}_{e.2} - \text{Na}_{e.1} = [140 - \text{Na}_{s.1}]\text{T.B.W.}/1.11 - [\text{K}_{e.2} - \text{K}_{e.1}]. \quad 12)$$

b) For the special case where K_e is constant but Na_e and T.B.W. are altered by therapy:

$$\text{Na}_{e.2} - \text{Na}_{e.1} = [140\,\text{T.B.W.}_2 - \text{Na}_{s.1}\,\text{T.B.W.}_1 + \Delta\text{H}_2\text{O}\cdot 25.6]\,1/11. \quad 13)$$

c) Finally, for the special case where only Na_e is variable but $K_{e.2} = K_{e.1}$ and $\text{T.B.W.}_2 = \text{T.B.W.}_1$:

$$\text{Na}_{e.2} - \text{Na}_{e.1} - (140 - \text{Na}_{s.1})\,\text{T.B.W.}_c/1.11. \quad 14)$$

Equations 14 and 9 are identical, except for the factor 1/1.11, if the sodium deficit is equated with ΔNa_e. The Wolf-McDowell formulation, Equation 11, is similar to Equation 13, except for the term $\Delta H_2O \cdot 25.6$, which appears as a consequence of the difference between total exchangeable cation and total osmotically active cation. A similar set of equations may also be derived from Equation 8. Our data, therefore, provide an experimental basis for the formulas used in clinical manipulations and demonstrate the coordinated influence of the three major components of body composition on serum sodium concentration.

SUMMARY

The relationships between serum sodium concentration (Na_s), serum osmolarity (π_s), total exchangeable sodium (Na_e), total exchangeable potassium (K_e) and total body water (T.B.W.) were explored by simultaneous measurements in a heterogeneous group of chronically ill patients.

Serum osmolarity correlates closely with serum sodium concentration expressed as mEq. per liter of serum water (Na'_s) when appropriate corrections are made for the osmotic contributions of glucose and nonprotein nitrogen (NPN). Serum sodium concentration is only partially or poorly correlated with total exchangeable sodium/body weight, total exchangeable potassium/body weight, total body water/body weight, total exchangeable sodium/total body water and total exchangeable potassium/total body water. A high degree of correlation, however, exists between serum sodium concentration (Na'_s) or "corrected" serum osmolarity (π'_s) and the ratio $(Na_e + K_e)$/T.B.W. This relation is confirmed by the high correlation between the simultaneous serial differences in Na'_s and $(Na_e + K_e)$/T.B.W. The regression of Na'_s on this ratio appears to be independent of arterial pH, plasma glucose or plasma NPN concentrations.

The implications of these data with respect to osmotic gradients in various components of body water and to evaluation of osmotic activity of body potassium are explored. Body water appears to be passively distributed in proportion to osmotic activity, and all or almost all of body potassium is osmotically active.

A classification scheme for hyponatremia and hypernatremia is presented, and equations for estimating sodium deficits are derived.

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