

TOTAL EXCHANGEABLE SODIUM, TOTAL EXCHANGEABLE
POTASSIUM, AND TOTAL BODY WATER IN EDEMA-
TOUS PATIENTS WITH CIRRHOSIS OF THE LIVER
AND CONGESTIVE HEART FAILURE¹

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The application of isotope-dilution methods to the study of body composition has provided accurate *in vivo* estimates of the amount of body sodium, potassium, chloride, water, and fat in normal human subjects of both sexes at many age levels (1-10). Similar studies in a variety of disease states have shown changes in body composition characterized by decreases in body fat, cell mass, and body potassium, and increases in body sodium and water, when these values are expressed on a body weight basis (11-16). While this pattern of change in composition is apparent in chronically ill or acutely stressed patients who are free of edema, it is particularly pronounced in edematous subjects (13, 14, 16-18). These studies, however, have not indicated whether there are changes in the proportions of body sodium, potassium, and water which are specific for a disease state. Recently, Farber and Soberman (19) noted that edematous patients with heart disease have less body water and a higher ratio of exchangeable sodium to body water than edematous patients with hepatic or renal disease. They suggested that heart failure invokes an increase in body sodium content out of proportion to the gain of extracellular water. Similar comparative stud-

ies with respect to body potassium have not yet been reported, although low values have been noted in chronically ill patients with and without edema (15, 16, 18, 20-23). The lack of a practical method for estimating body fat, however, makes it difficult to decide whether these findings represent a loss of cell mass or a decrease in the proportion of potassium to cell mass.

These studies need to be extended because of difficulties in quantitating and interpreting changes in body composition in edematous patients. It has recently been shown that equilibrium of isotope distribution may be delayed in edematous subjects (18). The variations of body composition with sex (5, 8, 16), age (5, 7, 8, 24, 25), nutrition (5, 7, 12, 16), and treatment (15, 19, 22, 26) make it important to assure that changes ascribed to a disease are not a reflection of some of these other factors.

The objectives of the present investigation were to compare total exchangeable sodium (Na_e), total exchangeable potassium (K_e), and total body water (T.B.W.) in patients with edema due to congestive heart failure and in patients with edema due to cirrhosis of the liver, to add information on differences in body composition in edematous and edema-free patients, and to clarify the interpretation of changes in body potassium content.

Sodium²⁴, K⁴² and D₂O were used as tracers in this study, and the findings are expressed as $Na_e/T.B.W.$, $K_e/T.B.W.$, Na_e/K_e , Na_e /"dry" body weight, and K_e /"dry" body weight, as well as the usual expressions per unit of body weight. The results failed to confirm a disproportional increase in body sodium or a higher ratio of body sodium to body water ($Na_e/T.B.W.$) in patients with congestive heart failure compared with patients with cirrhosis of the liver. However, distinct differences in body composition were found

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TABLE I
Clinical data—Males

Patient number	Age years	Body weight Kg.	Transudates			Remarks
			Ascites	Pleural effusion	Peripheral edema	
Group I. Cirrhosis of liver—edema						
2	50	67.3	+4	0	+1	icterus
3	47	80.0	+1	0	+1	icterus
6	51	41.8	+3	0	0	liver biopsy, portal cirrhosis
16	74	101.3	+4	0	+1	icterus; autopsy, portal cirrhosis
20	45	50.9	+2	0	0	esophageal varices
24	60	67.0	+3	0	0	
30	51	78.8	+3	0	0	liver biopsy, portal cirrhosis
66	48	55.5	+2	0	0	liver biopsy, portal cirrhosis
79	64	78.2	+3	0	+4	icterus
81	64	81.4	+4	0	+2	icterus
84	39	84.6	+2	0	+2	icterus
87	46	76.8	+2	0	0	icterus; hepatic coma
88	50	60.0	+2	0	+1	icterus
89	59	67.7	+3	0	+1	
91	42	64.0	+1	0	+1	icterus; liver biopsy, portal cirrhosis
92	45	60.0	+3	0	+2	icterus
Mean	52.2	69.7				
Range	39-74	50.9-101.3				
Group II. Congestive heart failure—edema						
1	64	64.1	0	+1	+1	hypertensive and arteriosclerotic heart disease
5	64	53.9	0	+1	+1	hypertensive and arteriosclerotic heart disease
10	66	119.5	+4	0	+4	arteriosclerotic heart disease
11	76	80.0	0	0	+2	hypertensive and arteriosclerotic heart disease
12	68	59.8	0	0	+1	arteriosclerotic heart disease
18	55	41.8	0	0	+1	cor pulmonale
25	67	47.7	0	0	+1	arteriosclerotic heart disease
26	58	75.8	0	+1	+3	hypertensive and arteriosclerotic heart disease
37	79	62.3	0	0	+1	hypertensive and arteriosclerotic heart disease
47	54	48.6	0	0	+2	hypertensive cardiovascular disease
51	84	56.4	0	0	+2	arteriosclerotic heart disease
61	71	58.0	0	0	+2	arteriosclerotic heart disease
75	66	53.6	0	0	+2	heart disease of unknown type
78	40	71.4	0	0	+2	hypertensive cardiovascular disease
90	60	53.2	+3	0	+4	hypertensive cardiovascular disease
93	74	65.9	+2	0	+2	arteriosclerotic heart disease
Mean	65.4	63.3				
Range	40-84	47.7-119.5				
Group III. Hospitalized "controls"—no edema						
4	68	86.9	0	0	0	benign gastric ulcer
9	45	69.2	0	0	0	duodenal ulcer
14	67	59.5	0	0	0	abscesses of wrist and elbow
15	72	59.3	0	0	0	cellulitis of arm and leg
31	69	48.0	0	0	0	pulmonary emphysema
34	90	43.6	0	0	0	generalized arteriosclerosis
41	73	60.5	0	0	0	cerebrovascular accident
45	74	57.0	0	0	0	anemia and purpura
49a	33	44.0	0	0	0	pulmonary tuberculosis
76	62	62.5	0	0	0	panhypopituitarism
Mean	65.3	59.1				
Range	33-90	43.6-86.9				
Group IV. Patients with heart disease—previously edematous						
21	60	59.8	0	0	0	cor pulmonale
42	71	44.8	0	0	0	cor pulmonale
52	70	50.9	0	0	0	heart disease of unknown type
Mean	67.3	51.8				
Range	60-71	44.8-59.8				

TABLE II
Clinical data—Females

Patient number	Age years	Body weight Kg.	Transudates			Remarks
			Ascites	Pleural effusion	Peripheral edema	
Group V. Cirrhosis of liver—edema						
19	28	39.6	+1	0	0	icterus
22	37	39.8	+1	0	0	icterus
35	43	51.8	+3	0	0	
44b	43	56.8	+3	0	0	icterus; liver biopsy, portal cirrhosis
50	39	65.7	+3	0	0	icterus; autopsy, portal cirrhosis
Mean	38	50.7				
Range	28–43	39.6–65.7				
Group VI. Congestive heart failure—edema						
7	67	85.0	0	0	+3	arteriosclerotic heart disease
23	51	55.2	0	0	+2	cor pulmonale
49b	86	51.8	0	0	+1	hypertensive and arteriosclerotic heart disease
80	82	63.6	0	0	+1	arteriosclerotic heart disease
Mean	72	63.9				
Range	51–86	51.8–85.0				
Group VII. Hospitalized “controls”—no edema						
40	78	41.4	0	0	0	cerebrovascular accident
39	28	36.4	0	0	0	adrenal insufficiency
72	77	43.2	0	0	0	subdural hematoma, postoperative
Mean	61	40.3				
Range	28–78	36.4–43.2				

between edematous and edema-free patients, and all patients differed significantly from normal subjects in all three categories of body composition.

SUBJECTS AND METHODS

Subjects. Fifty-seven patients were studied. They were divided into the following groups for purposes of comparison:

- Group I: Sixteen edematous males with cirrhosis of the liver.
- Group II: Sixteen edematous males with congestive heart failure.
- Group III: Ten nonedematous male hospitalized “controls.”
- Group IV: Three nonedematous males with heart disease who had been edematous.
- Group V: Five edematous females with cirrhosis of the liver.
- Group VI: Four edematous females with congestive heart failure.
- Group VII: Three nonedematous female hospitalized “controls.”

Only subjects in whom an unequivocal diagnosis could be made by clinical and laboratory criteria were included for study. All patients received the customary treatment for their disease up to the week of study. The period of hospitalization, duration of treatment and loss of

weight prior to the time of study were similar in the subjects with edema of cardiac and hepatic origin. The hospitalized “control” group consisted of patients without either heart disease or cirrhosis of the liver who had never been edematous. All patients were fed an analyzed diet containing 10 mEq. of sodium and 28 mEq. of potassium per 24 hours for at least one day prior to and the three days of study. Diuretics were withheld during the period of study. Food and fluid were withheld for the six hour period of D₂O equilibration.

Methods. All isotopes were administered intravenously from calibrated syringes. Three hundred μc. of K⁴² was administered in the afternoon of the first day of study. Thirty-six to 40 hours later, following a complete voiding, two consecutive spot urine specimens were collected over a three to six hour interval. Catheterization was used when necessary to ensure complete urine collection. At the time of the first spot urine collection, 45 to 100 ml. of 99.5 per cent D₂O was injected. Four and one-half and six hours later, venous blood was collected for deuterium, sodium, and potassium analyses; 150 μc. of Na²⁴ was then injected. Venous samples for Na²⁴ assay were collected 23 and 24 hours later.

The analytic procedures for chemical and radioactive assay have been described in detail (18). Potassium⁴² was counted with an end-window Geiger-Müller tube, and Na²⁴ with a well-type sodium iodide scintillation counter. Serum collected just prior to Na²⁴ injection was counted as a blank correction for residual K⁴² at the time of

radiosodium assay; this correction was less than 2 per cent in all cases. D₂O concentrations were determined in triplicate on each specimen by the falling drop method. Loss of D₂O was calculated as 0.16 per cent of the injected dose per hour (18).

Calculations. Standard formulas were used in calculating specific activities, Na_e, K_e, and T.B.W. (1). Zero time was taken to be the time at which the final equilibration samples for K_e and T.B.W. were obtained. "Dry" body weight was calculated by subtracting the measured T.B.W. from the patient's body weight at zero time. Back correction of the measured Na_e to zero time was accomplished by metabolic balance from the known diet and the urinary sodium excretion during the 24 hour period of Na²⁴ equilibration.

RESULTS

To avoid systematic influences on body composition because of age, sex and clinical status, the patients were grouped as listed in Tables I and II. The three primary groups for this study are the male subjects in Groups I, II and III. Tables III through VII list all the body composition data and the derived ratios of Na_e/T.B.W., Na_e/"dry" body weight, Na_e/K_e, K_e/T.B.W., and K_e/"dry" body weight. The statistical summary for the male subjects in Group I (cirrhosis of the liver with edema), Group II (congestive heart failure

with edema), and Group III (hospitalized "controls") is given in Table VIII.

Total body water

The mean values for T.B.W. as per cent of body weight for edematous males with cirrhosis of the liver and congestive heart failure were 58.6 and 62.9 per cent, respectively; these values were significantly greater than the mean of 54.6 per cent for male hospitalized "controls." The difference between the mean values in congestive heart failure and in cirrhosis of the liver is not statistically significant. Although the female subjects were few in number, the values for T.B.W. in those with heart failure average less than in those with cirrhosis of the liver (See Table VII). The three males with heart disease who were no longer edematous had the highest mean value for T.B.W. as per cent of body weight (See Table VI).

Total exchangeable sodium

In the edematous male patients with cirrhosis of the liver and those with congestive heart failure, mean values for Na_e/body weight were 54.1 mEq. per Kg. and 57.8 mEq. per Kg., respectively,

TABLE III
Group I—Body composition in male patients with cirrhosis of liver and edema

Patient number	Serum Na* mEq./L.	Serum K* mEq./L.	T.B.W. L.	T.B.W. Body wt. %	"Dry" body wt.† Kg.	Na _e mEq.	Na _e Body wt. mEq./Kg.	Na _e "Dry" body wt. mEq./Kg.	Na _e T.B.W. mEq./L.	K _e mEq.	K _e Body wt. mEq./Kg.	K _e "Dry" body wt. mEq./Kg.	K _e T.B.W. mEq./L.	Na _e /K _e mEq./mEq.
2	145.0	3.07	39.26	58.3	28.0	4,152	61.7	148.3	105.8	1,785	26.5	63.8	45.5	2.33
3	144.7	3.91	43.11	53.9	36.9	3,541	44.3	96.0	82.1	3,205	40.1	86.9	74.3	1.10
6	127.7	5.18	26.86	64.3	14.9	2,417	57.8	162.2	90.0	1,438	34.4	96.5	53.5	1.68
16	139.9	3.19	50.14	49.5	51.2	5,153	50.9	100.6	102.8	2,350	23.2	45.9	46.9	2.19
20	127.1	4.87	27.66	54.3	23.2	2,359	46.3	101.7	85.3	1,665	32.7	71.8	60.2	1.42
24	133.0	3.89	37.43	55.9	29.6	3,511	52.4	118.6	93.8	2,140	31.9	72.3	57.2	1.64
30	146.1	3.55	52.28	66.3	26.5	5,386	68.3	203.2	103.0	2,819	35.8	106.4	53.9	1.91
66	150.2	4.33	32.57	58.7	22.9	3,085	55.6	134.7	94.7	1,816	32.7	79.3	55.8	1.70
79	123.2	3.54	43.53	55.7	34.7	4,300	55.0	123.9	98.8	1,680	21.5	48.4	38.6	2.56
81	143.4	3.94	52.09	64.0	29.3	5,510	67.7	188.1	105.8	2,308	28.4	78.8	44.3	2.39
84	143.4	4.07	55.55	65.7	29.0	5,470	64.7	188.6	98.5	2,775	32.8	95.7	50.0	1.97
87	125.7	3.52	40.01	52.1	36.8	2,852	37.1	77.5	71.3	2,521	32.8	68.5	63.0	1.13
88	140.2	3.78	37.92	63.2	22.1	3,284	54.7	148.6	86.6	2,197	36.6	99.4	57.9	1.49
89	135.5	3.94	35.62	52.6	32.1	3,116	46.0	97.1	87.5	1,762	26.0	54.9	49.5	1.77
91	143.3	4.27	38.33	59.9	25.7	3,308	51.7	128.7	86.3	2,415	37.7	94.0	63.0	1.37
92	134.8	4.38	38.03	63.4	22.0	3,103	51.7	141.0	81.6	2,349	39.2	106.8	61.8	1.32
Mean	137.7	3.91	40.65	58.6	29.1	3,784	54.1	134.9	92.1	2,202	32.0	79.3	54.7	1.75
S.D.‡					±5.5		±8.6	±37.5	±10.0		±5.5	±20.0	±8.9	±0.45
Range	123.2- 150.2	3.07- 5.18	26.86- 56.12		14.9- 51.2	2,359- 5,510				1,665- 3,205				

* mEq. per liter of serum water.

† Body weight minus total body water.

$$‡ \text{S.D.} = \sqrt{\frac{\sum(x - \bar{x})^2}{n - 1}}$$

TABLE IV
Group II—Body composition in male patients with congestive heart failure and edema

Patient number	Serum Na* mEq./L.	Serum K* mEq./L.	T.B.W. L.	T.B.W. Body wt. %	"Dry" body wt.† Kg.	Na _o mEq.	Na _o Body wt. mEq./Kg.	Na _o "Dry" body wt. mEq./Kg.	Na _o T.B.W. mEq./L.	K _o mEq.	K _o Body wt. mEq./Kg.	K _o "Dry" body wt. mEq./Kg.	K _o T.B.W. mEq./L.	Na _o /K _o mEq./mEq.
1	154.5	4.55	34.05	53.1	30.0	3,122	48.7	104.1	91.7	2,454	38.3	81.8	72.1	1.27
5	141.8	4.61	33.78	62.7	20.1	3,189	59.2	158.7	94.4	1,963	36.4	97.7	58.1	1.62
10	148.0	4.74	69.64	58.3	49.9	6,983	58.4	139.9	100.3	3,293	27.6	66.0	47.3	2.12
11	146.7	4.16	39.85	49.8	40.1	3,812	47.7	95.1	95.7	2,681	33.5	66.9	67.3	1.42
12	129.2	4.88	35.00	58.5	24.8	2,359	39.4	95.1	67.4	2,599	43.5	104.7	74.3	0.91
18	146.9	4.69	24.89	59.5	16.9	1,953	46.7	115.6	78.5	1,862	44.5	110.2	74.8	1.05
25	146.2	4.13	30.91	64.8	16.8	3,113	65.3	185.3	100.7	1,665	34.9	99.1	53.9	1.87
26	137.0	6.45	49.52	65.3	26.3	5,116	67.5	194.5	103.3	2,772	36.6	105.4	56.0	1.85
37	145.1	4.65	32.41	52.0	29.9	2,971	47.7	99.4	91.7	1,986	31.9	66.4	61.3	1.50
47	137.6	4.52	31.57	65.0	17.0	3,046	62.7	179.2	96.5	1,750	36.0	102.9	55.4	1.74
51	119.5	4.74	36.78	65.2	19.6	3,385	60.0	172.7	92.0	1,424	25.2	72.7	38.7	2.38
61	122.6	4.96	39.99	68.9	18.0	3,451	59.5	191.7	86.3	2,048	35.3	113.8	51.2	1.69
75	125.3	5.88	38.87	72.5	14.7	3,659	68.3	248.9	94.1	1,699	31.7	115.6	43.7	2.15
78	139.9	3.34	50.36	70.5	21.0	3,702	51.8	176.3	73.5	3,723	52.1	177.3	73.9	0.99
90	138.5	4.25	36.34	68.3	16.9	3,733	70.2	220.9	102.7	1,571	29.5	93.0	43.2	2.38
93	144.0	3.37	47.21	71.6	18.7	4,770	72.4	255.1	101.0	1,928	29.3	103.1	40.8	2.47
Mean	138.9	4.62	39.45	62.9	23.8	3,648	57.8	164.5	91.9	2,214	35.4	98.5	57.0	1.71
S.D.				±7.0			±9.8	±49.5	±10.6		±6.9	±27.2	±12.6	±0.51
Range	122.6–154.5	3.34–6.45	24.89–69.64		14.7–49.9	1,953–6,983				1,424–3,723				

* mEq. per liter of serum water.
† Body weight minus total body water.

TABLE V
Group III—Body composition in male patients, hospitalized "controls"

Patient number	Serum Na* mEq./L.	Serum K* mEq./L.	T.B.W. L.	T.B.W. Body wt. %	"Dry" body wt.† Kg.	Na _o mEq.	Na _o Body wt. mEq./Kg.	Na _o "Dry" body wt. mEq./Kg.	Na _o T.B.W. mEq./L.	K _o mEq.	K _o Body wt. mEq./Kg.	K _o "Dry" body wt. mEq./Kg.	K _o T.B.W. mEq./L.	Na _o /K _o mEq./mEq.
4	146.3	4.41	43.79	50.4	43.1	3,511	40.4	81.5	80.2	3,427	39.4	79.5	78.3	1.03
9	147.7	3.94	37.81	54.6	31.4	3,040	43.9	96.8	80.4	3,126	45.2	99.6	82.7	0.97
14	146.3	4.32	30.15	50.7	29.3	2,624	44.1	89.6	87.0	2,040	34.3	69.6	67.7	1.28
15	145.1	4.59	32.34	54.5	27.0	2,646	44.6	98.0	81.8	2,112	35.6	78.2	65.3	1.25
31	145.3	5.21	27.83	58.0	20.2	2,257	47.0	111.7	81.1	2,105	43.9	104.2	75.6	1.07
34	143.6	4.37	25.21	57.8	18.4	2,287	52.5	124.3	90.7	1,491	34.2	81.0	59.1	1.53
41	132.2	4.45	29.85	49.3	30.6	2,446	40.4	79.9	81.9	1,805	29.8	59.0	60.5	1.36
45	128.7	5.10	32.12	56.4	24.9	2,707	47.5	108.7	84.3	1,996	35.0	80.2	62.1	1.36
49a	133.3	3.70	25.93	58.9	18.1	2,317	52.7	128.0	89.4	1,741	39.6	96.2	67.1	1.33
76	134.1	4.62	34.38	55.0	28.1	2,645	42.3	94.1	76.9	2,180	34.9	77.6	63.4	1.21
Mean	140.3	4.47	31.94	54.6	27.1	2,648	45.5	101.3	83.4	2,202	37.2	82.5	68.2	1.24
S.D.				±3.1			±4.1	±16.6	±4.5		±4.8	±13.9	±8.0	±0.17
Range	128.7–146.3	3.94–5.21	25.21–43.79		18.4–43.1	2,257–3,511				1,491–3,427				

* mEq. per liter of serum water.
† Body weight minus total body water.

TABLE VI
Group IV—Body composition in male patients with heart disease who were previously edematous

Patient number	Serum Na* mEq./L.	Serum K* mEq./L.	T.B.W. L.	T.B.W. Body wt. %	"Dry" body wt.† Kg.	Na _o mEq.	Na _o Body wt. mEq./Kg.	Na _o "Dry" body wt. mEq./Kg.	Na _o T.B.W. mEq./L.	K _o mEq.	K _o Body wt. mEq./Kg.	K _o "Dry" body wt. mEq./Kg.	K _o T.B.W. mEq./L.	Na _o /K _o mEq./mEq.
21	136.0	4.86	33.54	56.1	26.3	3,149	52.7	119.7	93.9	2,168	36.3	82.4	64.6	1.45
42	131.8	4.35	29.75	66.4	15.0	2,495	55.7	166.3	83.9	1,650	36.8	110.0	55.5	1.51
52	141.4	3.78	35.17	70.1	15.7	3,294	64.7	209.8	93.7	2,180	42.8	138.9	62.0	1.51
Mean	136.4	4.33	32.82	64.2	19.0	2,979	57.7	165.3	90.5	1,999	38.6	110.4	60.7	1.49
Range	131.8–141.4	3.78–4.86	29.75–35.17	56.1–70.1	15.0–26.3	2,495–3,294	52.7–64.7	119.7–209.8	83.9–93.9	1,650–2,180	36.3–42.8	82.4–138.9	55.5–64.6	1.45–1.51

* mEq. per liter of serum water.
† Body weight minus total body water.

both of which were significantly higher than the mean value of 45.5 mEq. per Kg. in the "control" group (Tables III, IV, V and VIII and Figure 1). These findings confirm the relationship between edema formation and increased body sodium content (18). There is, however, no statistically impressive difference in Na_e /body weight between Groups I and II (cirrhosis and heart failure) (See Table VIII).

Exchangeable sodium was expressed per unit of "dry" body weight to eliminate the contribution of edema water to weight, and the following mean values were obtained: "controls," 101.3 mEq. per Kg.; edematous male cirrhotics, 134.9 mEq. per Kg.; and edematous cardiatics, 164.5 mEq. per Kg. The values for each of the groups of edematous male patients differed significantly from those for the "controls." The Na_e /"dry" body weight was higher in the male edematous subjects with heart failure than in the edematous subjects with cirrhosis, but because of the large standard deviations, statistical significance was not achieved.

The ratio of Na_e to T.B.W. was calculated to evaluate whether there are disproportional changes in sodium content with edema formation in different diseases. The mean values for the ratio Na_e /T.B.W. were 83.4 mEq. per L. for "controls," 92.1 mEq. per L. for edematous male cirrhotics, and 91.9 mEq. per L. for edematous male cardiatics. The difference between the "control" group and the edematous groups is probably significant. There is no difference between edematous male cardiatics and cirrhotics (see Tables III, IV, V and VIII and Figure 1). This ratio is of the same magnitude in the edematous female subjects and in the nonedematous patients with heart disease as in the edematous male subjects (see Tables VI and VII).

Expressing body sodium in proportion to "dry" weight or to body water takes into account the effect of variations in absolute water content on relative body sodium content, but these ratios do not reflect the proportion of sodium to the fat-free mass of the body. The K_e , however, may be an approximate index of lean body mass even in these seriously ill subjects. The ratio of Na_e / K_e was

TABLE VII
Groups V, VI, VII—Body composition in female patients

Patient number	Serum Na^* mEq./L.	Serum K^* mEq./L.	T.B.W. L.	T.B.W. Body wt. %	"Dry" body wt.† Kg.	Na_e mEq.	Na_e Body wt. mEq./Kg.	Na_e "Dry" body wt. mEq./Kg.	Na_e T.B.W. mEq./L.	K_e mEq.	K_e Body wt. mEq./Kg.	K_e "Dry" body wt. mEq./Kg.	K_e T.B.W. mEq./L.	Na_e/K_e mEq./mEq.
Group V. Cirrhosis of liver—edema														
19	138.6	3.68	22.69	57.3	16.9	2,228	56.3	131.8	98.2	1,203	30.4	71.2	53.0	1.85
22	140.4	4.02	22.01	55.3	17.8	1,995	50.1	112.1	90.6	1,266	31.8	71.1	57.5	1.58
35	138.2	4.41	35.52	68.6	16.3	3,772	72.8	231.4	106.2	1,525	29.4	93.6	42.9	2.47
44b	130.7	3.90	32.55	57.3	24.2	2,941	51.8	121.5	90.4	1,683	29.6	69.5	51.7	1.74
50	138.7	3.24	36.00	54.8	29.7	3,376	51.4	113.7	93.8	2,133	32.5	71.8	59.3	1.58
Mean	137.3	3.85	29.75	58.7	21.0	2,862	56.5	142.1	95.8	1,562	30.7	75.4	52.9	1.84
Range	130.7– 140.4	3.68– 4.41	22.01– 36.00	54.8– 68.6	16.3– 29.7	1,995– 3,376	50.1– 72.8	112.1– 231.4	90.4– 106.2	1,203– 2,133	29.4– 32.5	69.5– 93.6	42.9– 59.3	1.58– 2.47
Group VI. Congestive heart failure—edema														
7	152.1	4.00	44.77	52.7	40.2	4,876	57.4	121.3	108.9	1,936	22.7	48.2	43.2	2.52
23	136.4	5.40	36.28	65.7	18.9	3,495	63.3	184.9	96.3	1,704	30.8	90.2	47.0	2.05
49b	140.7	2.83	30.26	58.4	21.5	3,176	61.3	147.7	105.0	1,245	24.0	57.9	41.1	2.55
80	122.2	4.88	23.99	37.7	39.0	1,957	30.7	50.2	81.6	1,164	18.3	29.8	48.5	1.68
Mean	137.9	4.28	33.82	53.6	29.9	3,376	53.2	126.0	98.0	1,512	24.0	56.5	45.0	2.20
Range	122.2– 152.1	2.83– 5.40	23.99– 44.77	37.7– 65.7	18.9– 40.2	1,957– 4,876	30.7– 63.3	50.2– 184.9	81.6– 108.9	1,164– 1,936	18.3– 30.8	29.8– 90.2	41.1– 48.5	1.68– 2.55
Group VII. Hospitalized "controls"—no edema														
40	143.0	3.62	22.20	53.6	19.2	2,146	51.8	111.8	96.7	1,218	29.4	63.4	54.9	1.76
39	137.6	4.10	17.97	49.4	18.4	1,228	33.7	66.7	68.3	1,358	37.3	73.8	75.6	0.90
72	134.9	4.06	25.95	60.1	17.2	2,110	48.8	122.7	81.3	1,667	38.5	96.9	64.2	1.27
Mean	138.5	3.93	22.04	54.4	18.3	1,828	44.8	100.4	82.1	1,414	35.1	78.0	64.9	1.31
Range	134.9– 143.0	3.62– 4.10	17.97– 25.95	49.4– 60.1	17.2– 19.2	1,228– 2,146	33.7– 51.8	66.7– 122.7	68.3– 96.7	1,218– 1,667	29.4– 38.5	63.4– 96.9	54.9– 75.6	0.90– 1.76

* mEq. per liter of serum water.

† Body weight minus total body water.

TABLE VIII

Statistical summary of body composition in edematous male patients with cirrhosis of the liver and congestive heart failure and in hospitalized "controls"

	Cirrhosis of liver Mean ± S.D.	Congestive heart failure Mean ± S.D.	Hospitalized "controls" Mean ± S.D.	Significance of differences						
				Cirrhosis vs. cardiacs		Cirrhosis vs. "controls"		Cardiacs vs. "controls"		
				t*	p	t†	p	t†	p	
Age (range)	52.2 (39-74)	65.4 (40-84)	65.3 (33-90)							
Body weight: Kg. (range)	69.7 (50.9-101.3)	63.3 (47.7-119.5)	59.1 (43.6-86.9)							
T.B.W. % body weight	58.6 ±5.5	62.9 ±7.0	54.6 ±3.1	1.93	>0.05	2.09	>0.02 <0.05	3.49	<0.01	
"Dry" body weight: Kg. (range)	29.1 (14.9-51.2)	23.8 (14.7-49.9)	27.1 (18.4-43.1)							
Na _e /body weight mEq./Kg.	54.1 ±8.6	57.8 ±9.8	45.5 ±4.1	1.13	>0.2	2.94	<0.01	3.74	<0.01	
Na _e /"dry" body weight mEq./Kg.	134.9 ±37.5	164.5 ±49.5	101.3 ±16.6	1.91	>0.05	2.66	<0.02	3.87	<0.01	
Na _e /T.B.W. mEq./L.	92.1 ±10.0	91.9 ±10.6	83.4 ±4.5	0.06	>0.5	2.58	<0.02	2.41	>0.02 <0.05	
K _e /body weight mEq./Kg.	32.0 ±5.5	35.4 ±6.9	37.2 ±4.8	1.54	>0.1	2.45	>0.02 <0.05	0.73	>0.4	
K _e /"dry" body weight mEq./Kg.	79.3 ±20.0	98.5 ±27.2	82.5 ±13.9	2.27	>0.02 <0.05	0.44	>0.5	1.71	>0.1	
K _e /T.B.W. mEq./L.	54.7 ±8.9	57.0 ±12.6	68.2 ±8.0	0.60	>0.5	3.92	<0.01	2.52	<0.02	
Na _e /K _e mEq./mEq.	1.75 ±0.45	1.71 ±0.51	1.24 ±0.17	0.24	>0.5	3.44	<0.01	2.81	<0.01	

$$* t = (\bar{x}_1 - \bar{x}_2) \sqrt{\frac{n(n-1)}{\sum(\bar{x}_1 - x_1)^2 + \sum(\bar{x}_2 - x_2)^2}} (S - 3).$$

$$† t = (\bar{x}_1 - \bar{x}_2) \sqrt{\frac{n_1 \cdot n_2 (n_1 + n_2 - 2)}{(n_1 + n_2) [\sum(\bar{x}_1 - x_1)^2 + \sum(\bar{x}_2 - x_2)^2]}} (S - 3).$$

therefore calculated for each subject. The following mean values for the ratio of Na_e/K_e were obtained: "controls," 1.24; male patients with edema and cirrhosis, 1.75; and edematous males with heart failure, 1.71. The values in the edematous patients differed significantly from those of the "control" group, but sodium content, when referred to an approximate measure of intracellular mass (K_e), was similar in edematous subjects regardless of type of disease (see Table VIII and Figure 1). In the three subjects with heart disease without edema the Na_e/K_e ratio was intermediate between the value for the edematous subjects and the value for the hospitalized "controls" (see Tables VI and VIII).

Total exchangeable potassium

The mean values for K_e/body weight for Groups I, II, and III (cirrhotics, cardiacs, and "controls") were 32.0, 35.4, and 37.2 mEq. per Kg., respectively. Only the difference between the "controls" and the edematous cirrhotics approaches statistical significance (0.05 > p > 0.02) (see Table VIII). Nor are there any significant differences in K_e per Kg. of "dry" body weight between the edematous male subjects and the hospitalized "controls." The higher value in the edematous male cardiacs compared with that in the edematous male cirrhotics is of borderline significance, and the female subjects show an opposite trend (see

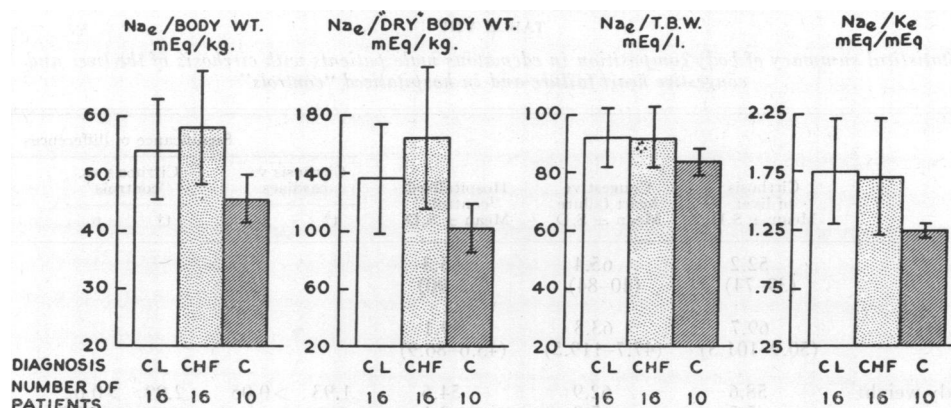


FIG. 1. COMPARISON OF Na_e IN EDEMATOUS MALE PATIENTS WITH CIRRHOSIS OF THE LIVER AND CONGESTIVE HEART FAILURE AND IN HOSPITALIZED "CONTROLS"

The mean Na_e is depicted by the height of the bar, and the length of the line is equal to twice the standard deviation. The Na_e is expressed as mEq. per Kg. of body weight, mEq. per Kg. of "dry" body weight, mEq. per L. of T.B.W., and mEq. per mEq. of K_e . CL stands for cirrhosis of the liver, CHF for congestive heart failure, and C for hospitalized "controls."

Tables VII and VIII). The values for K_e /"dry" body weight in the male subjects with heart disease but without edema also were high (see Table VI). Since the ratio of K_e to "dry" body weight reflects relative degrees of leanness as well as changes in potassium content, the latter findings probably indicate fat loss rather than conservation of potassium.

As one would expect, the ratio K_e /T.B.W. was significantly lower in patients with edema than in nonedematous subjects. The mean values for the K_e /T.B.W. ratio were 68.2 for "controls," 54.7 for edematous male cirrhotics, and 57.0 for edematous male cardiatics. The edematous groups differed significantly from the "controls," but not from each other (see Tables III, IV, V, and VIII and Figure 2). The results were the same in the female subjects (see Table VII). Indeed, these results reflect largely the diluting effect of overhydration on this ratio, and the reciprocal of this ratio (K_e /T.B.W.) is probably a fairly accurate measure of the magnitude of edema formation. The similarity of this ratio in Groups I and II probably indicates similar proportions of overhydration with respect to potassium content in these subjects.

DISCUSSION

Figures 1 and 2 depict the data on body composition in the three primary groups of patients. The Na_e /T.B.W. ratio in the edematous patients

with congestive heart failure is no different from that in the edematous patients with cirrhosis of the liver. The Na_e /body weight and the Na_e /"dry" body weight in edematous cardiatics exceed the corresponding value in the patients with liver disease, but the difference is not statistically convincing ($p > 0.05$). There are, furthermore, strikingly similar differences in K_e /body weight and K_e /"dry" body weight between these two groups (see Table VIII and Figure 2). Although the higher Na_e /body weight and K_e /body weight in the cardiatics might reflect changes in electrolyte content characteristic of these disease states, it is far likelier that the patients with liver disease had a higher percentage of body fat which diluted these parameters of body composition, *i.e.*, Na_e and K_e (see Table VIII). Edema formation appears, therefore, to be associated in these groups of subjects with similar changes in body composition, regardless of the type of disease. These results do not confirm the report of a lower body water content and a higher ratio of body sodium to body water in edematous subjects with heart disease than in edematous cirrhotics (19). Exchangeable sodium per Kg. of "dry" body weight and per L. of body water is high in subjects with heart failure rendered edema free (see Table VI). The T.B.W./body weight and the ratio of K_e to "dry" body weight are higher in these three subjects than in the "controls," while K_e /T.B.W. is slightly lower (see Tables VI and VIII), which is

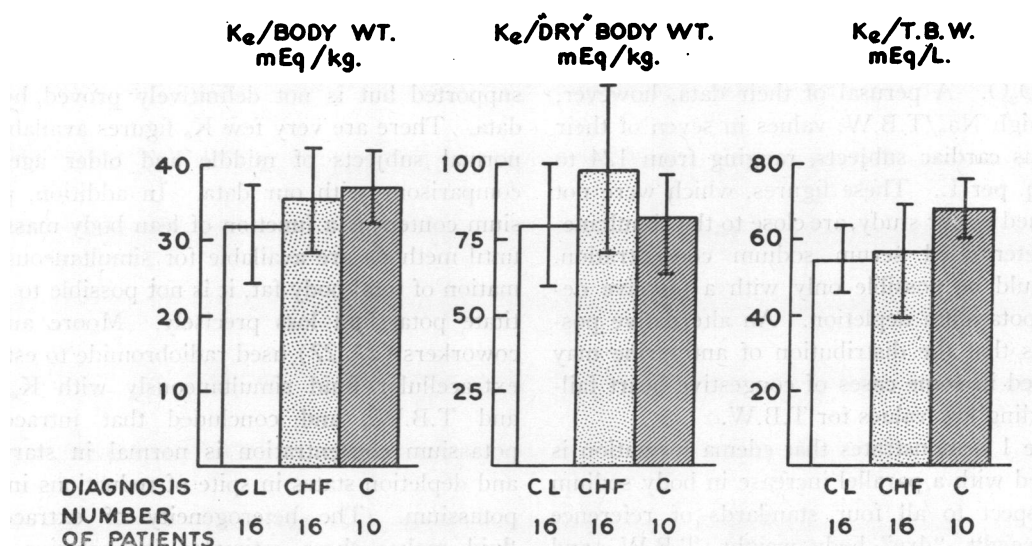


FIG. 2. COMPARISON OF K_e IN EDEMATOUS MALE PATIENTS WITH CIRRHOSIS OF THE LIVER AND CONGESTIVE HEART FAILURE AND IN HOSPITALIZED "CONTROLS"

The mean K_e is depicted by the height of the bar, and the length of the line is equal to twice the standard deviation. The K_e is expressed as mEq. per Kg. of body weight, mEq. per Kg. of "dry" body weight, and mEq. per L. of T.B.W. The diagnostic symbols are the same as in Figure 1.

consistent with the previous conclusion that greater depletion of body fat, rather than selective accumulation of sodium, is involved in the process of heart failure.

The differences in the results obtained by us and those reported by Farber and Soberman (19) deserve some analysis. The Na_e and T.B.W. data are summarized in Table IX. The results agree within 4 per cent except for the body water values and consequently the ratio of Na_e/T.B.W. in the groups with heart failure. These discrepancies could arise from differences in patient populations (*i.e.*, average fat content, influences of treatment, incidence of hyponatremia or amount of edema)

or in methods of measurement. All our subjects had been treated and had long standing congestive heart failure; as a result fat content may have been lower. There is little difference in the mean and variance with respect to serum sodium concentration in the two groups [see Table IV (19) and Table IV, this paper]. While differences in the amount of edema in the two groups could account for differences in T.B.W., this would not explain the discrepancy in the Na_e/T.B.W. ratio. Our results appear to be characteristic of the patient population with heart failure at this hospital since they are in agreement with those obtained previously (18). With respect to methods of

TABLE IX
Comparison of Na_e and total body water in patients with edema

Reference	Congestive heart failure				Cirrhosis of liver			
	Subjects no.	Na _e /body weight mEq./Kg.	T.B.W./body weight %	Na _e /T.B.W. mEq./L.	Subjects no.	Na _e /body weight mEq./Kg.	T.B.W./body weight %	Na _e /T.B.W. mEq./L.
(19)	50	59.9 ±11.0	55.5 ±7.5	108.2 ±12.0	16	56.2 ±9.3	61.0 ±7.2	90.3 ±11.6
This paper	16	57.8 ±9.8	62.9 ±7.0	91.9 ±10.6	16	54.1 ±8.6	58.6 ±5.5	92.1 ±10.0
% difference		-3.6	+12.5	-16.3		-3.8	-4.0	+2.0

measurement, Farber and Soberman used antipyrine to estimate body water after checking against D_2O . A perusal of their data, however, reveals high $Na_e/T.B.W.$ values in seven of their edematous cardiac subjects, ranging from 124 to 140 mEq. per L. These figures, which were not approached in our study, are close to the simultaneously determined serum sodium concentration. This would be possible only with a massive degree of potassium depletion. An alternative possibility is that the distribution of antipyrine may be delayed in some cases of congestive heart failure, yielding low values for T.B.W.

Figure 1 demonstrates that edema formation is associated with a parallel increase in body sodium with respect to all four standards of reference (body weight, "dry" body weight, T.B.W., and K_e), which confirms the findings in many previous studies (13, 14, 16, 18, 19, 26). Body potassium was no lower in the patients with edema than in the hospitalized "controls" when the diluting effect of edema water was eliminated. The values for K_e /body weight in these patients are in accord with those published previously (11, 15, 16, 20, 22, 23). Body potassium appeared to be abnormally low in all patient groups. The K_e /"dry" body weight in young adult males calculated from the data of Corsa, Olney, Steenburg, Ball, and Moore (2) is 129 ± 20 mEq. per Kg.⁶ and from the data of Ikkos, Ljunggren, Luft, and Sjögren (9) is 137 ± 31 mEq. per Kg.⁶ These figures are significantly higher than the values of 80 ± 20 mEq. per "dry" body weight⁷ in the male cirrhotics and 83 ± 14 mEq. per "dry" body weight⁷ in the male hospitalized "controls" (see Table VIII). The female patients all showed similar decreases in body potassium (see Table VII). The near normal values of 99 ± 27 mEq. per Kg. "dry" body weight in the edematous cardiacs and 110 ± 15 mEq. per Kg. "dry" body weight⁷ in the nonedematous cardiacs probably reflect more advanced degrees of fat depletion rather than greater conservation of body potassium. Since disease is generally attended by loss of body fat, these figures relating body potassium to water-free body mass probably underestimate the degree of potassium depletion in all of these groups.

⁶ Mean plus or minus one-fourth of range.

⁷ Mean plus or minus standard deviation.

The conclusion that there is depletion of body potassium with chronic or debilitating disease is supported but is not definitively proved by our data. There are very few K_e figures available for normal subjects of middle and older ages for comparisons with our data. In addition, potassium content is a function of lean body mass, and until methods are available for simultaneous estimation of total body fat, it is not possible to quantitate potassium loss precisely. Moore and his coworkers (23, 27) used radiobromide to estimate extracellular fluid simultaneously with K_e , Na_e and T.B.W., and concluded that intracellular potassium concentration is normal in starvation and depletion states in spite of reductions in body potassium. The heterogeneity of extracellular fluid makes these estimates inconclusive, however, since sodium and chloride are present in cells, transcellular fluid and dense connective tissues in varying quantities which have not yet been completely defined (28-32).

A clear distinction must be made between potassium depletion and potassium deficiency. The former refers to a decrease in potassium content per unit of lean body mass which may be an obligatory consequence of the disease process, since intracellular potassium accumulation is linked with cellular energy expenditure (32). In the latter case the cells are capable of accumulating potassium when it is provided in adequate quantities. Body composition studies alone do not, of course, enable one to make this distinction.

SUMMARY

Total exchangeable sodium, total exchangeable potassium and total body water were determined in nonedematous hospitalized "controls" and in edematous patients with cirrhosis of the liver and chronic congestive heart failure with the use of Na^{24} , K^{42} and D_2O as tracers.

Total body water expressed as per cent of body weight is increased in edematous subjects; it averaged 58.6, 62.9 and 54.6 per cent in male subjects with edema and cirrhosis and with edema and heart failure, and in "controls," respectively.

Edema formation is associated with an increase in Na_e by all criteria (per unit body weight, per unit "dry" body weight, per liter of body water and per mEq. of K_e). While the Na_e /"dry" body weight was highest in the edematous cardiac

group, no difference was found in the ratios of $Na_e/T.B.W.$ and Na_e/K_e between edematous cirrhotic and edematous cardiac subjects. Selective or disproportionate accumulation of sodium with heart disease beyond that associated with edema formation was not demonstrated.

Exchangeable potassium was decreased below normal standards when referred to either body weight or "dry" body weight in all groups of patients. There was no difference in body potassium between edematous and nonedematous subjects when referred to "dry" body weight. Edematous male cardiacs had the highest K_e /"dry" body weight, probably because total body fat was least in this group.

Limitations in interpretation of these data are discussed.

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REFERENCES

- Edelman, I. S., Olney, J. M., James, A. H., Brooks, L., and Moore, F. D. Body composition: Studies in the human being by the dilution principle. *Science* 1952, **115**, 447.
- Corsa, L., Jr., Olney, J. M., Jr., Steenburg, R. W., Ball, M. R., and Moore, F. D. The measurement of exchangeable potassium in man by isotope dilution. *J. clin. Invest.* 1950, **29**, 1280.
- Dunning, M. F., Steele, J. M., and Berger, E. Y. Measurement of total body chloride. *Proc. Soc. exp. Biol. (N. Y.)* 1951, **77**, 854.
- Aikawa, J. K., Harrell, G. T., and Eisenberg, B. The exchangeable potassium content of normal women. *J. clin. Invest.* 1952, **31**, 367.
- Edelman, I. S., Haley, H. B., Schloerb, P. R., Sheldon, D. B., Friis-Hansen, B. J., Stoll, G., and Moore, F. D. Further observations on total body water. I. Normal values throughout the life span. *Surg. Gynec. Obstet.* 1952, **95**, 1.
- Forbes, G. B., Reid, A., Bondurant, J., and Edtheridge, J. Estimation of total body chloride in young infants by radiobromide dilution. *Proc. Soc. exp. Biol. (N. Y.)* 1953, **83**, 871.
- Keys, A., and Brozek, J. Body fat in adult man. *Physiol. Rev.* 1953, **33**, 245.
- Edelman, I. S., James, A. H., Brooks, L., and Moore, F. D. Body sodium and potassium. IV. The normal total exchangeable sodium: Its measurement and magnitude. *Metabolism* 1954, **3**, 530.
- Ikkos, D., Ljunggren, H., Luft, R., and Sjögren, B. Content and distribution of potassium and chloride in adults. *Metabolism* 1955, **4**, 231.
- Friis-Hansen, B. Changes in body water compartments during growth. *Acta paediat. (Uppsala)* 1957, **46** (Suppl. 110), 1.
- Aikawa, J. K., Felts, J. H., Jr., Tyor, M. P., and Harrell, G. T. The exchangeable potassium content in disease states. *J. clin. Invest.* 1952, **31**, 743.
- Moore, F. D., Haley, H. B., Bering, E. A., Brooks, L., and Edelman, I. S. Further observations on total body water. II. Changes of body composition in disease. *Surg. Gynec. Obstet.* 1952, **95**, 155.
- Warner, G. F., Dobson, E. L., Rodgers, C. E., Johnston, M. E., and Pace, N. The measurement of total "sodium space" and total body sodium in normal individuals and in patients with cardiac edema. *Circulation* 1952, **5**, 915.
- Warner, G. F., Sweet, N. J., and Dobson, E. L. "Sodium space" and body sodium content, exchangeable with sodium²⁴ in normal individuals and patients with ascites. *Circulat. Res.* 1953, **1**, 486.
- Wilson, G. M., Edelman, I. S., Brooks, L., Myrden, J. A., Harken, D. E., and Moore, F. D. Metabolic changes associated with mitral valvuloplasty. *Circulation* 1954, **9**, 199.
- Moore, F. D., Edelman, I. S., Olney, J. M., James, A. H., Brooks, L., and Wilson, G. M. Body sodium and potassium. III. Inter-related trends in alimentary, renal and cardiovascular disease; lack of correlation between body stores and plasma concentration. *Metabolism* 1954, **3**, 334.
- Talso, P. J., Spafford, N., Ferenzi, G., and Jackson, H. O. Paradoxical hyponatremia associated with congestive heart failure and with cirrhosis of the liver. *Metabolism* 1956, **5**, 58.
- O'Meara, M. P., Birkenfeld, L. W., Gotch, F. A., and Edelman, I. S. The equilibration of radiosodium (Na^{24}), radiopotassium (K^{40}), and deuterium oxide (D_2O) in hydropic human subjects. *J. clin. Invest.* 1957, **36**, 784.
- Farber, S. J., and Soberman, R. J. Total body water and total exchangeable sodium in edematous states due to cardiac, renal or hepatic disease. *J. clin. Invest.* 1956, **35**, 779.
- Aikawa, J. K., Felts, J. H., Jr., and Harrell, G. T., Jr. Alterations in the body potassium content in cirrhosis of the liver. *Gastroenterology* 1953, **24**, 437.
- Blainey, J. D., Cooke, W. T., Quinton, A., and Scott, K. W. The measurement of total exchangeable potassium in man with particular reference to patients with steatorrhea. *Clin. Sci.* 1954, **13**, 165.
- Aikawa, J. K., and Fitz, R. H. Exchangeable potassium content of the body in congestive heart failure. Changes during treatment. *Circulation* 1956, **14**, 1093.
- Moore, F. D., McMurrey, J. D., Parker, H. V., and Magnus, I. C. Body composition; total body wa-

- ter and electrolytes; intravascular and extravascular phase volumes. *Metabolism* 1956, 5, 447.
24. Friis-Hansen, B. J., Holiday, M., Stapleton, T., and Wallace, W. M. Total body water in children. *Pediatrics* 1951, 7, 321.
 25. Forbes, G. B., and Perley, A. Estimation of total body sodium by isotopic dilution. I. Studies on young adults. *J. clin. Invest.* 1951, 30, 558.
 26. Aikawa, J. K., and Fitz, R. H. Alterations in exchangeable sodium content, "sodium" space and body weight during treatment of congestive failure. *Circulation* 1955, 12, 897.
 27. McMurrey, J. D., Davis, J. M., Boling, E. A., and Moore, F. D. The evaluation of body composition in surgical disease processes utilizing a method for the simultaneous determination of red blood cell volume, plasma volume, blood volume, total body water, extracellular water and total exchangeable chloride, sodium and potassium. *Surg. Forum* 1955, 6, 14.
 28. Nichols, G., Jr., Nichols, N., Weil, W. B., and Wallace, W. M. The direct measurement of the extracellular phase of tissues. *J. clin. Invest.* 1953, 32, 1299.
 29. Edelman, I. S., James, A. H., Baden, H., and Moore, F. D. Electrolyte composition of bone and the penetration of radiosodium and deuterium oxide into dog and human bone. *J. clin. Invest.* 1954, 33, 122.
 30. Edelman, I. S., and Sweet, N. J. Gastrointestinal water and electrolytes. I. The equilibration of radiosodium in gastrointestinal contents and the proportion of exchangeable sodium (Na_e) in the gastrointestinal tract. *J. clin. Invest.* 1956, 35, 502.
 31. Sweet, N. J., Nadell, J., and Edelman, I. S. Gastrointestinal water and electrolytes. III. The equilibration of radiobromide in gastrointestinal contents and the proportion of exchangeable chloride (Cl_e) in the gastrointestinal tract. *J. clin. Invest.* 1957, 36, 279.
 32. Conway, E. J. Nature and significance of concentration relations of potassium and sodium ions in skeletal muscle. *Physiol. Rev.* 1957, 37, 84.