THE EQUILIBRATION OF RADIOSODIUM (Na^{24}), RADIOPOTASSIUM (K^{42}), AND DEUTERIUM OXIDE (D_2O) IN HYDROPIC HUMAN SUBJECTS¹

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Isotope dilution methods have been described for the determination of total exchangeable sodium (Na_e) (1, 2), total exchangeable potassium (K_e) (3-5), and total body water (T.B.W.) (6-8) with Na^{24} , K^{42} and D_2O as tracers. The time required for equilibrium of distribution of each of the isotopes must be determined experimentally, since uniform mixing is an explicit assumption with these methods (9). In normal human subjects the times required for 95 to 100 per cent equilibration were found to be 12 to 20 hours for Na^{24} , 18 to 40 hours for K^{42} , and 2 to 3 hours for D_2O (1-7). The presence of abnormal fluid collections, however, may produce significant delays in diffusion equilibrium.

The present study was undertaken to determine the equilibration time of Na^{24} , K^{42} and D_2O in patients with edema or abnormal fluid collections. Equilibrium of distribution was evaluated by comparisons of specific activities between various body fluids and by determinations of apparent exchangeable quantities as a function of time.

METHODS

A total of 78 hydropic patients, 57 males and 21 females, was studied. Each subject received only one of the three isotopes. The group was divided into patients with congestive heart failure, designated as cardiacs, and those with hepatic cirrhosis and ascites, as well as a few with the nephrotic syndrome, designated as non-cardiacs. Subjects receiving Na^{24} or K^{42} were fed an analyzed diet, containing 10 mEq. of Na and 28 mEq. of K, for the 2 days preceding and the 2 days of the study.

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Those receiving D_2O were allowed only a dry, low-fat breakfast without fluids at the start of the 6 hours of the procedure and no food or fluids for the period of equilibration.

The isotopes were administered intravenously by calibrated syringe. Two hundred to 400 microcuries of Na^{24} was given to each of 23 patients, 12 cardiac and 11 non-cardiac. Approximately 300 microcuries of K^{42} was given to each of 26 patients, 14 cardiac and 12 non-cardiac. These quantities of isotope are somewhat higher than those ordinarily used in tracer studies because the objectives of the study required prolonged observations. The maximum radiation from Na^{24} was 0.6 r.e.p. and from K^{42} was 0.3 r.e.p. Although these are permissible radiation exposures for two-week periods, lower doses should be used when possible. Forty-five ml. of 99.5 per cent D_2O was given to each of 29 patients, 17 cardiac and 12 non-cardiac.

Venous blood was drawn at 8, 24, 32 and 48 hours following injection of isotonic Na^{24}Cl . One-ml. serum aliquots from 6 patients were dried and counted in triplicate with an end-window, sodium-iodide scintillation counter. The probable error of these measurements was ± 1 per cent. In the remaining patients Na^{24} assay was carried out in a well-type sodium-iodide scintillation counter, with a probable error of ± 1 per cent. Transudates were obtained from the thoracic or peritoneal cavities or subcutaneous spaces by aspiration with a needle and syringe simultaneously with venipuncture. The method of measuring radioactivity was the same for each pair of samples.

One- to 2-hour spot urine specimens were collected at 12, 24, 36 and 48 hours following injection of K^{42}Cl . Catheterization was used only when necessary to insure complete urine collection. The urine was concentrated to one-third its original volume by heat, and triplicate 1-ml. aliquots of each urine concentrate were dried and counted with an end-window Geiger-Müller tube with a probable error of ± 1.5 per cent. Serum and transudate specimens were obtained at the time that one or more of the spot urine specimens were collected. The protein in these samples was precipitated with 95 per cent ethanol in a ratio of 2 volumes of ethanol to 1 of sample. The supernatants were reduced in volume to approximately 12 ml., and aliquots were taken for assay of chemical potassium and radioactivity. Isotopic assay was performed in triplicate as described above for urine.

All chemical Na and K determinations were done in duplicate with a lithium internal standard flame photom-

TABLE I
THE APPARENT EXCHANGEABLE BODY SODIUM (Na_e) IN PATIENTS WITH EDEMA

Pt. No. Sex	Dx* Age yrs.	Na _e (mEq)				Na _e /Body Wt. (mEq./kgm.)				Na _e /Body Wt. as a Fraction of 32-hr. Value			
		8 hrs.	24 hrs.	32 hrs.	48 hrs.	8 hrs.	24 hrs.	32 hrs.	48 hrs.	8 hrs.	24 hrs.	32 hrs.	48 hrs.
A. CARDIACS													
1-M	HCVd 54	2510	2746	2793	2798	32.9	43.4	43.8	45.1	0.89	0.99	1.00	1.03
2-F	ASHd 50	5762	6059	6120	5804	67.8	69.8	70.1	65.8	0.97	1.00	1.00	0.94
3-F	ASHd 67	3814	3877	3991	4108	51.8	52.8	54.2	56.3	0.96	0.97	1.00	1.04
4-M	ASHd 52	3139	3114	3104	3102	55.7	56.1	56.8	57.7	0.98	0.99	1.00	1.02
5-M	RHD 56	2382	2386	2412	2442	46.6	46.7	47.4	48.0	0.98	0.99	1.00	1.01
6-M	RHD 53	4149	4340	4410	--	54.5	57.2	58.1	--	0.94	0.98	1.00	--
7-M	ASHd 73	3294	3465	3536	--	61.9	66.3	68.3	--	0.93	0.97	1.00	--
8-M	HCVd 51	5224	5869	5956	5872	54.9	62.4	63.3	63.0	0.87	0.99	1.00	1.00
9-M	ASHd 78	4869	5101	5214	5046	65.3	69.3	70.9	70.2	0.92	0.98	1.00	0.99
10-M	ASHd 73	3294	3426	3449	3506	52.8	56.1	55.6	56.8	0.95	1.01	1.00	1.02
11-F	RHD 50	2992	3025	3079	3083	47.0	47.6	48.7	48.8	0.97	0.98	1.00	1.00
12-M	ASHd 72	3888	4040	4067	4116	53.1	56.6	56.8	58.4	0.93	1.00	1.00	1.03
					Mean:	54.2	57.0	57.8	57.0	0.94	0.99	1.00	1.01
					±S.D.***:	±7.9	±8.7	±8.3	±6.8	±0.04	±0.01	--	±0.03
B. NON-CARDIACS													
13-M	CL 59	3895	4192	4341	4349	57.3	62.8	64.4	65.5	0.89	0.98	1.00	1.02
14-M	DG 61	2642	2774	2908	2819	46.6	49.7	51.7	50.8	0.90	0.96	1.00	0.98
15-M	CL 65	3973	4094	4209	4250	62.3	64.6	66.4	67.6	0.94	0.97	1.00	1.02
16-M	CL 52	5349	5732	5848	6051	81.4	87.2	89.0	92.1	0.91	0.98	1.00	1.03
17-M	CGNS 43	6870	7079	7036	--	83.3	85.8	85.3	--	0.98	1.01	1.00	--
18-M	CL 52	4838	6368	6324	6502	56.0	73.8	74.0	75.7	0.76	1.00	1.00	1.02
19-M	DG 66	4228	4504	4458	4607	59.2	63.6	62.9	66.0	0.94	1.01	1.00	1.05
20-M	CL 55	4397	4562	4607	4713	65.6	67.6	67.8	69.1	0.97	1.00	1.00	1.02
21-M	CL 52	4435	5159	4607	4814	48.2	56.8	50.6	53.2	0.95	1.12	1.00	1.04
22-M	CL 59	2940	3152	3184	3252	42.9	47.2	47.0	48.8	0.91	1.00	1.00	1.04
23-F	DG 55	4100	4112	4091	4088	71.3	71.5	72.2	72.2	0.99	0.99	1.00	1.00
					Mean:	61.3	66.4	66.5	66.1	0.92	1.00	1.00	1.02
					±S.D.***:	±13.3	±12.8	±13.4	±12.9	±0.06	±0.04	--	±0.02
Mean (combined):										0.93	0.99	1.00	1.02
±S.D. (combined):**										±0.05	±0.03	--	±0.03

* HCVd = hypertensive cardiovascular disease
ASHd = arteriosclerotic heart disease
RHD = rheumatic heart disease

CL = cirrhosis of liver
DG = diabetic glomerulosclerosis
CGNS = chronic glomerulonephritis, nephrotic stage

** Standard deviation = $\sqrt{\frac{\sum (x - \bar{x})^2}{n-1}}$

eter. A complete urine collection was obtained from each patient during each period of equilibration and analyzed for radioactivity as described. Each patient was weighed at the time of collection of each sample.

Venous blood was collected at 2, 3, 4.5 and 6 hours following injection of sterile 99.5 per cent D₂O containing 0.85 per cent NaCl. Simultaneous transudate specimens were obtained by aspiration at one or more of these times.

TABLE II
THE DISTRIBUTION OF RADIOSODIUM IN TRANSUDATES AND IN SERUM

	Pt. No.	Source of Fluid*	Ratio of Transudate S.A. to Serum S.A. (S.A.R.)		
			8 hrs.	24 hrs.	32 hrs.
CARDIACS	2	SC	0.73	0.96	1.00
	3	AF	--	1.00	1.01
	4	PF	1.01	1.03	--
	6	SC	--	--	1.01
	7	SC	--	--	1.02
	9	SC	0.76	--	--
	10	SC	--	1.00	--
	11	PF	1.03	--	1.01
NON-CARDIACS	13	AF	0.91	1.01	1.01
	14	SC	0.78	--	--
	15	AF	--	1.00	--
	16	SC	--	0.96	1.00
	17	SC	--	1.00	0.98
	18	AF	0.57	0.99	--
	19	SC	0.84	--	--
	20	AF	0.97	--	1.01
	21	AF	1.00	1.13	--
	22	AF	0.97	0.99	--
	Mean:		0.87	1.01	1.01
	S.D.:		± 0.14	± 0.04	± 0.01

*PF = pleural fluid

AF = ascitic fluid

SC = subcutaneous fluid

Deuterium concentrations were determined in duplicate by the falling drop method (8). Urines were collected and similarly analyzed. The loss of deuterium in the urine did not exceed 1 per cent of the injected dose. The coefficient of variation of replicate determinations of D_2O by this method was found to be 0.6 to 0.9 per cent in a concentration range of 0.10 to 0.20 volumes per cent.

Standard formulas were used in calculating specific activities and Na_e , K_e and T.B.W. (1-9). The total exchangeable quantities, Na_e , K_e and T.B.W., were corrected for isotope excretion in the urine. These corrections were used to calculate the amount of isotope retained at the end of each period allowed for equilibration. Specific activity ratios (S.A.R.) were calculated for transudate:serum in the case of Na^{24} , transudate:urine and urine:serum for K^{40} , and transudate:plasma for deuterium. These ratios were used as a measure of exchange equilibrium (10).

RESULTS

The values for consecutive Na_e determinations with equilibration periods extended to 48 hours are listed in Table I; the last four columns list the values for Na_e per kgm. of body weight, expressed as a fraction of the 32-hour value. The mean of this ratio was 0.99 ± 0.01 at 24 hours and 1.01 ± 0.03 at 48 hours for cardinals, and 1.00 ± 0.04 at

24 hours and 1.02 ± 0.02 at 48 hours for non-cardiac subjects. In neither series did the Na_e obtained at 24 hours differ significantly from the 48-hour value ($p > 0.05$ ⁵ for both cardiac and non-cardiac subjects). In 18 of 20 subjects, however, there was an increase in the Na_e /body weight at 48 hours as compared with 24 hours. Combining the two groups gives a mean value of 0.99 ± 0.03 at 24 hours and 1.02 ± 0.03 at 48 hours. The difference between these values does achieve statistical significance ($p < 0.02$). The apparent Na_e at 8 hours did differ significantly from the measurements made after longer equilibration periods.

Transudate:serum S.A.R.'s obtained in 18 patients had a mean value of 1.01 ± 0.04 and 1.01 ± 0.01 at 24 and 32 hours after injection, respectively (see Table II). The specific activity of transudates obtained 8 hours after Na^{24} injection, however, often was considerably lower than that of corresponding sera. These data indicate that

⁵ $P > 0.05$ indicates that the probability that these differences are due to chance is greater than 5 in 100. The probability "p" was derived from the "t" test.

TABLE III
THE APPARENT EXCHANGEABLE BODY POTASSIUM (K_e) IN PATIENTS WITH EDEMA

Pt. No.	Dx	Age yrs.	K _e (mEq.)				K _e /Body Wt. (mEq./kgm.)				K _e /Body Wt. as a Fraction of 36-hr. Value				
			12 hrs.	24 hrs.	36 hrs.	48 hrs.	12 hrs.	24 hrs.	36 hrs.	48 hrs.	12 hrs.	24 hrs.	36 hrs.	48 hrs.	
CARDIACS															
A. Males															
1K	ECVD	71	1214	1490	1493	1564	19.9	25.0	24.9	26.5	0.81	1.00	1.00	1.05	
2K	RHD	67	1688	1961	2259	2319	29.5	34.2	39.7	40.4	0.75	0.87	1.00	1.03	
3K	ECVD	69	1906	1999	2120	1957	19.8	20.6	21.8	20.3	0.92	0.94	1.00	0.93	
4K	ASHD	81	1212	1344	1369	1429	22.0	24.5	25.2	26.4	0.89	0.98	1.00	1.04	
5K	ASHD	64	1324	1588	1791	1780	19.4	23.7	27.9	28.2	0.74	0.89	1.00	1.01	
6K	ASHD	67	--	1737	2003	2018	--	29.4	34.1	35.2	--	0.85	1.00	1.00	
7K	RHD	24	2345	2720	3211	3326	23.1	26.9	31.9	32.7	0.73	0.85	1.00	1.03	
8K	ECVD	61	--	1424	1938	2025	--	18.5	25.2	26.6	--	0.74	1.00	1.05	
Mean:							22.3	25.4	28.8	29.5	0.81	0.89	1.00	1.02	
S.D.:							±3.8	±4.9	±5.7	±6.1	±0.08	±0.08	--	±0.04	
B. Females															
9K	ECVD	83	--	1350	1406	1303	--	25.2	26.4	25.1	--	0.96	1.00	0.96	
10K	ASHD	60	1090	1574	1928	1958	15.1	21.7	27.1	27.4	0.57	0.82	1.00	1.01	
11K	RHD	48	1580	1853	2049	2105	18.9	21.9	24.2	24.9	0.78	0.91	1.00	1.03	
12K	ASHD	67	923	1067	1344	1441	19.5	22.6	28.7	31.3	0.69	0.79	1.00	1.07	
Mean:							17.8	22.9	26.6	27.2	0.68	0.87	1.00	1.02	
CIRRHOSIS OF THE LIVER AND ASCITES															
A. Males															
13K		65	1130	1698	2146	2150	15.3	23.2	29.2	29.4	0.53	0.78	1.00	1.01	
14K		52	1203	1437	1574	1642	16.1	19.2	21.0	22.6	0.78	0.91	1.00	1.04	
15K		50	1436	2238	2318	2302	19.4	31.0	32.1	32.2	0.62	0.97	1.00	1.00	
16K		54	1507	1596	1613	1711	23.6	24.9	25.5	27.0	0.93	0.99	1.00	1.06	
17K		57	1615	1731	1796	1953	25.2	26.6	28.5	31.1	0.93	0.96	1.00	1.09	
18K		55	1635	1873	1920	2074	25.3	28.9	29.7	32.4	0.87	0.98	1.00	1.07	
19K		66	1553	1723	1831	1868	20.8	23.0	25.1	25.7	0.85	0.94	1.00	1.02	
20K		59	1371	1655	1884	--	25.2	30.2	34.8	--	0.73	0.88	1.00	--	
21K		74	1952	2267	2454	2552	16.8	19.5	21.2	22.2	0.80	0.92	1.00	1.04	
Mean:							20.9	25.2	27.5	27.9	0.78	0.93	1.00	1.04	
S.D.:							±4.0	±4.3	±4.7	±4.2	±0.14	±0.07	--	±0.03	
B. Females															
22K		36	1326	1462	1465	1592	24.2	26.7	26.5	28.7	0.91	1.00	1.00	1.09	
23K		38	1264	1450	1675	1642	20.7	23.6	27.9	26.9	0.75	0.87	1.00	0.96	
Mean:							22.5	25.2	27.2	27.8	0.83	0.93	1.00	1.02	
Mean (combined):												0.78	0.90	1.00	1.03
S.D. (combined):												±0.11	±0.07	--	±0.04

TABLE IV
 THE DISTRIBUTION OF RADIOPOTASSIUM IN TRANSUDATES, IN SERUM AND IN URINE

	Pt. No.	Ratio of Spot Urine S.A. to Serum S.A. (S.A.R.)		Source of Fluid*	Ratio of Transudate S.A. to Spot Urine S.A. (S.A.R.)			
		12 hrs.	24 hrs.		12 hrs.	24 hrs.	36 hrs.	48 hrs.
CARDIACS	1K	--	1.11	PF	1.09	--	0.93	--
	2K	--	--	AF	1.05	1.06	1.02	--
	3K	1.02	--	AF	1.04	0.98	0.90	--
	4K	--	0.90	AF	--	1.15	--	1.07
	5K	--	1.13	PF	0.93	1.01	0.93	0.93
	6K	--	0.92	PF	--	1.30	1.17	--
	7K	--	0.90	---	--	--	--	--
	8K	--	1.03	PF	--	--	0.99	0.96
	9K	--	0.97	PF	--	0.88	--	--
	9K	--	0.91	---	--	--	--	--
	10K	1.60	--	PF	0.88	0.98	--	1.11
	11K	--	1.00	AF	1.22	1.13	1.13	1.04
	12K	--	1.19	PF	--	--	1.04	1.00
NON-CARDIACS	YK	--	0.85	---	--	--	--	--
	13K	1.48	1.08	AF	0.99	1.12	1.12	1.04
	14K	--	1.12	AF	1.06	--	1.01	--
	15K	1.24	--	---	--	--	--	--
	16K	0.93	--	AF	1.01	0.96	--	--
	17K	1.07	--	AF	1.43	1.23	1.08	--
	18K	0.97	--	AF	1.23	1.01	1.01	--
	19K	--	0.94	AF	1.16	--	--	1.04
	20K	--	0.96	---	--	--	--	--
	21K	--	0.98	AF	--	1.04	1.07	0.96
	22K	1.04	--	AF	1.05	1.03	--	--
	23K	--	0.98	AF	--	--	1.16	1.02
	2K	--	1.01	AF	--	1.06	1.00	--
Mean:		1.11	1.00		1.09	1.06	1.04	1.02
S.D.:		+0.18	+0.09		+0.14	+0.11	+0.08	+0.06

*PF = pleural fluid
 AF = ascitic fluid
 SC = subcutaneous fluid

equilibration of Na^{24} is substantially complete at 24 hours in these hydropic patients. The values for Na_e per kgm. of body weight were considerably higher than normal, confirming previous reports of a positive correlation between edema and body sodium content (11-13).

The results of the K^{42} study are listed in Tables III and IV. The K_e values listed in Table III were calculated from spot urine specific activities. The apparent K_e per kgm. of body weight for the combined series, calculated as a fraction of the 36-hour value, was significantly smaller at 24 hours than either the 36- or 48-hour value ($p < 0.02$). In cardiac patients the mean K_e relative to the 36-hour value was 0.88 ± 0.08 at 24 hours and 1.02 ± 0.05 at 48 hours. In patients with cirrhosis of the liver and ascites, the corresponding values were 0.93 ± 0.07 at 24 hours and 1.04 ± 0.04 at 48 hours. The magnitude of the changes in K_e from 24 to 48 hours in both groups of subjects is too large to be ascribed to any possible contribution from dietary potassium.

Comparisons of simultaneous serum:urine specific activities were obtained to validate the use of urine samples as representative of K^{42} specific

activity in body fluids. The data listed in Table IV indicate that the specific activities are identical after 24 hours of isotope equilibration. The scatter in these data probably results from the lesser accuracy of serum assays because of the lower counting rates of these samples. The transudate:spot urine S.A.R. was high during the early part of the equilibration period and declined progressively to mean values of 1.04 ± 0.08 at 36 hours and 1.02 ± 0.06 at 48 hours. The combined mean values for relative K_e show only a 3 per cent rise between 36 and 48 hours. It appears, therefore, that K^{42} equilibrates almost completely between 36 and 48 hours in hydropic patients. It has been shown in normal man, in rabbits and in rats that about 40 hours are required for uniform tissue distribution of K^{42} , except for erythrocytes and brain (3, 14). The low values of K_e per kgm. of body weight in hydropic patients are in accord with previous studies (13, 15).

Tables V and VI list the results of studies on the equilibration of D_2O in patients with edema and ascites. The dilution of D_2O reached a plateau 3 to 6 hours after injection in both groups of patients (see Table V). The 6-hour T.B.W. dif-

TABLE V
THE APPARENT TOTAL BODY WATER (T.B.W.) IN PATIENTS WITH EDEMA

Pt. No.	Dx	Age yrs.	T.B.W. (liters)				T.B.W./Body Wt. (liters/kgm.)				T.B.W./Body Wt. as a Fraction of 4.5-hr. Value				
			2 hrs.	3 hrs.	4.5 hrs.	6 hrs.	2 hrs.	3 hrs.	4.5 hrs.	6 hrs.	2 hrs.	3 hrs.	4.5 hrs.	6 hrs.	
CARDIACS															
A. Males															
1D	ASHD	72	42.5	42.0	42.3	42.6	67.1	66.4	66.8	67.1	1.00	0.99	1.00	1.00	
2D	ASHD	55	43.1	42.7	43.1	42.2	62.4	61.8	62.3	61.1	1.00	0.99	1.00	0.98	
3D	ASHD	50	35.9	36.2	34.2	39.2	52.7	53.0	50.1	57.5	1.05	1.06	1.00	1.15	
4D	ASHD	82	37.7	38.7	39.3	39.6	65.4	67.0	68.1	68.6	0.96	0.98	1.00	1.01	
5D	ASHD	73	35.4	36.0	36.0	34.7	60.8	62.1	61.8	59.6	0.99	1.01	1.00	0.97	
6D	HCVD	47	45.3	44.4	45.6	43.3	49.1	48.0	49.4	47.1	0.99	0.97	1.00	0.95	
7D	HCVD	78	36.7	37.6	37.1	38.9	60.1	62.1	60.7	64.0	0.99	1.02	1.00	1.05	
8D	RHD	67	34.8	35.0	36.4	35.8	62.2	62.6	65.3	63.6	0.95	0.96	1.00	0.97	
9D	Unknown Etiology	54	25.4	26.2	26.3	26.0	60.1	62.7	63.5	63.7	0.95	0.99	1.00	1.00	
10D	ASHD	64	47.6	48.6	47.6	49.6	67.3	68.9	67.7	70.9	0.99	1.02	1.00	1.05	
11D	ASHD	61	--	59.9	60.1	--	--	77.2	77.4	--	--	1.00	1.00	--	
						Mean:	60.7	62.9	63.0	62.3	0.99	1.00	1.00	1.02	
						S.D.:	±5.7	±7.7	±7.9	±6.7	±0.03	±0.03	--	±0.06	
B. Females															
12D	RHD	75	30.2	30.6	30.2	30.4	76.1	77.1	76.0	76.5	1.00	1.01	1.00	1.01	
13D	ASHD	79	28.5	29.2	29.4	29.4	49.1	50.3	50.6	50.6	0.97	0.99	1.00	1.00	
14D	RHD	67	37.4	40.0	39.9	40.4	56.4	60.3	60.4	61.4	0.93	1.00	1.00	1.02	
15D	ASHD	70	23.7	38.7	41.1	41.4	43.2	70.5	74.8	75.4	0.58	0.94	1.00	1.01	
16D	ASHD	70	39.0	39.7	41.1	42.2	57.7	58.6	60.7	62.4	0.95	0.97	1.00	1.03	
17D	ASHD	71	--	66.3	65.9	66.3	--	68.7	68.2	68.6	--	1.01	1.00	1.01	
						Mean:	56.5	64.3	65.1	65.8	0.89	0.99	1.00	1.01	
						S.D.:	±12.4	±9.7	±9.5	±9.8	±0.17	±0.03	--	±0.01	
NON-CARDIACS															
A. Males															
18D	NS*	43	51.5	53.3	54.5	56.4	69.4	71.8	73.4	76.0	0.95	0.98	1.00	1.04	
19D	CL	56	37.3	37.1	37.5	37.8	61.6	61.3	61.8	62.4	1.00	0.99	1.00	1.01	
20D	CL	60	50.2	50.1	53.6	52.2	62.7	62.6	66.6	64.9	0.94	0.94	1.00	0.97	
21D	DG	66	38.7	38.0	39.3	39.2	61.7	60.6	62.5	62.8	0.99	0.97	1.00	1.00	
22D	Hem*	66	43.7	45.5	49.0	49.0	59.6	62.2	66.9	66.8	0.89	0.93	1.00	1.00	
23D	CL	55	--	37.4	38.0	38.0	--	64.2	65.1	65.2	--	0.99	1.00	1.00	
24D	Ans*	54	25.4	--	26.9	27.7	67.3	--	70.8	73.6	0.95	--	1.00	1.04	
25D	CL	57	36.2	36.2	36.8	37.7	57.4	57.2	58.6	60.1	0.98	0.98	1.00	1.03	
						Mean:	62.8	62.8	65.7	66.5	0.96	0.97	1.00	1.01	
						S.D.:	±4.2	±4.5	±4.8	±5.6	±0.04	±0.02	--	±0.02	
B. Females															
26D	CL	40	31.9	33.8	35.7	34.3	53.7	56.8	59.9	57.6	0.90	0.95	1.00	0.96	
27D	CL	55	33.8	34.8	34.2	33.9	60.0	62.6	61.5	61.0	0.98	1.02	1.00	0.99	
28D	CL	36	33.3	33.3	33.7	--	59.0	59.3	59.9	--	0.98	0.99	1.00	--	
29D	CL	53	32.6	32.6	--	--	50.0	50.0	--	--	--	--	--	--	
						Mean:	55.7	57.2	60.4	59.3	0.95	0.99	1.00	0.98	
											Mean (combined):	0.95	0.99	1.00	1.01
											S.D. (combined):	±0.09	±0.03	--	±0.04

* NS = Nephrotic Syndrome

Hem = Hemochromatosis

Ans = Anasarca, ? Nephrotic

TABLE VI
THE DISTRIBUTION OF D₂O IN TRANSUDATES AND IN SERUM

	Pt. No.	Source of Fluid*	Ratio of Transudate D ₂ O Concentration to Serum D ₂ O Concentration (S.A.R.)			
			2 hrs.	3 hrs.	4.5 hrs.	6 hrs.
CARDIACS	1D	PF	0.68	0.79	0.90	--
	2D	PF	0.92	0.98	--	--
	3D	PF	0.94	0.91	--	--
	4D	SC	0.46	0.59	0.71	--
	6D	SC	1.08	1.00	1.07	1.03
	7D	PF	--	--	0.83	0.94
	8D	AF	0.94	0.97	1.02	1.00
	9D	SC	--	--	0.83	0.93
	10D	PF	0.73	0.84	0.88	0.98
	11D	PF	--	--	0.99	--
	12D	PF	0.95	1.02	--	--
	14D	PF	0.56	--	--	--
	15D	PF	0.47	0.86	--	0.99
	17D	AF	--	1.01	1.01	--
NON-CARDIACS	18D	SC	0.77	0.92	--	--
	19D	AF	1.03	0.99	0.99	--
	21D	SC	0.31	--	--	0.95
	22D	AF	0.66	0.81	0.92	0.96
	23D	AF	--	0.89	1.01	1.01
	24D	AF	1.05	--	1.06	1.01
	25D	AF	--	0.84	0.93	0.97
	26D	AF	0.75	--	1.01	0.97
	27D	AF	1.03	1.06	1.07	--
	28D	AF	0.96	1.00	0.99	--
	29D	AF	--	0.98	--	--
Mean:			0.79	0.91	0.95	0.98
S.D.:			+0.23	+0.11	+0.09	+0.03

*PF = pleural fluid
AF = ascitic fluid
SC = subcutaneous fluid

ferred significantly from the 4.5-hour value in only one instance (patient 3D). The 6-hour T.B.W. value in this case was more than three standard deviations from the combined mean.

Equilibration of D₂O between transudates and serum averaged only 0.91 ± 0.11 at 3 hours. Equilibration in transudates was substantially complete at 6 hours (see Table VI). These data also indicate uniform equilibration in each case at 6 hours, since the range of S.A.R. values at this time was only 0.93 to 1.03. Although calculated T.B.W. showed little change between 3 and 6 hours, the distribution of D₂O in transudates indicates that 4.5 to 6 hours are required for D₂O equilibration in hydropic patients. Total body water expressed per kgm. of body weight is considerably higher in these subjects than in normal subjects of the same age and sex (7).

DISCUSSION

Isotope equilibration could be delayed for a number of reasons in patients with abnormal states of hydration. Diffusion equilibrium could be prolonged because of increased mean diffusion distances or because of decreased surface:volume

ratios in various regions of the body (16). In patients with cardiovascular disease and edema, blood flow per unit volume of tissue water might be reduced sufficiently to produce some delay in uniform distribution of isotope.

Two techniques were used in this study to evaluate equilibration of Na²⁴, K⁴², and D₂O in the presence of abnormal fluid collections. The apparent exchangeable quantity determined as a function of time was used as such a measure on the assumption that during short intervals (*i.e.*, 48 hours) there is little change in body composition. The partition of isotope between serum and transudates was a further check on distribution equilibrium. Since the standard error of the methods for determining either exchangeable quantities or S.A.R.'s approximates 1 per cent, agreement within 5 per cent between simultaneous or consecutive values has been taken as indicative of complete equilibration within 95 per cent confidence limits for any pair of values.

Radiosodium is almost uniformly distributed in its exchangeable mass in 12 to 20 hours in normal man (2, 17, 18). Exchangeable sodium does not include approximately 15 per cent of body

sodium which is sequestered in bone (10). There appears to be an additional 6 per cent of body sodium which exchanges slowly and does not reach a plateau until 96 hours after injection. This slowly exchanging fraction is probably a part of the exchangeable bone sodium pool (19). Because of safety requirements it is more prudent to use Na^{24} with its short half-life and short equilibration periods (*i.e.*, 24 hours) than to use Na^{22} and longer equilibration periods in human subjects. The data in Tables I and II indicate that radiosodium equilibration is almost complete after 24 hours in patients with edema either of cardiac or non-cardiac origin. There is a slight upward trend in relative Na_e from 24 to 48 hours, but to precisely the same extent as in normally hydrated subjects (19). Hemodynamic factors have little influence, since the patients with congestive heart failure did not differ from those with liver or kidney disease in this respect. Although the data were not reported, Miller and Wilson (18) stated that radiosodium exchange is not complete until 24 hours after injection in cases of pleural effusion. Our findings confirm this statement (see Tables I and II).

There have been no specific studies of K^{42} equilibration in hydropic subjects. Corsa, Olney, Steenburg, Ball, and Moore (3), on the basis of tissue studies in rabbits and in patients without edema, estimated that 95 per cent of body potassium exchange in 40 hours, with red cells, brain and bone constituting slowly exchanging pools. The data in Table IV demonstrate that the potassium in abnormal fluid collections reaches equilibrium with radiopotassium in 36 to 48 hours. Furthermore, the K_e values determined from spot urine specific activities reach plateau values between 36 and 48 hours (see Table III). These results indicate that the rate of potassium equilibration is approximately the same in edematous and normally hydrated subjects. The short half-life of K^{42} makes it impractical to extend the time allowed for equilibration beyond 40 to 48 hours. The finding of low K_e per kgm. of body weight in edematous subjects confirms similar observations based on shorter equilibration periods in previous reports (13, 15). It is not certain that there is a reduction in K_e in relation to lean body mass in patients with congestive heart failure or cirrhosis of the liver, since body water content is increased

in these subjects and body fat content may be reduced as well.

Four and one-half to 6 hours are required for uniform distribution of D_2O in transudates (see Table VI). Relative T.B.W. reaches a plateau at 3 hours (see Table V). Hurst, Schemm, and Vogel (20) found that in 4 of 20 hydropic patients the transudate:plasma DHO ratio did not reach 4 per cent agreement by 6 hours. Faller, Petty, Last, Pascale, and Bond (21) found that 9 of 14 hydropic patients required more than 6 hours for deuterium equilibration between serum and transudate. Indwelling needles were used for fluid collections in the latter study. Their results may have been influenced by stasis and inflammatory reaction induced by leaving needles in the tissues for many hours. In the subjects we studied D_2O distribution equilibrium occurred in 6 hours, even in the presence of massive fluid collections.

SUMMARY

The equilibration of Na^{24} , K^{42} and D_2O was studied in hydropic subjects. The equilibration of Na^{24} with the readily exchangeable sodium requires at least 24 hours, the equilibration of K^{42} requires 48 hours, and that of D_2O , 6 hours in these subjects. Approximately 94 per cent of exchangeable sodium, 95 per cent of exchangeable potassium and 100 per cent of total body water are measured with equilibration periods as detailed above.

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