GASTROINTESTINAL WATER AND ELECTROLYTES. IV. THE EQUILIBRATION OF DEUTERIUM OXIDE (D₂O) IN GASTROINTESTINAL CONTENTS AND THE PROPORTION OF TOTAL BODY WATER (T.B.W.) IN THE GASTROINTESTINAL TRACT [1]

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The concept of the anatomy of body water distribution as a two-compartment system consisting of intracellular and extracellular fluid has been shown to be inadequate (1–5). The heterogeneous nature of the extracellular fluid compartment has been established by previous studies on bone (2), dense connective tissue (6), and transcellular fluid (3–5). Cizek (3) has demonstrated that intraluminal gut water is a significant subdivision of body water in a number of species.

Neglecting the contribution of transcellular fluid to body water results in considerable errors in the derived normal values for body water compartments. Furthermore, transcellular fluid, if large enough in volume, must be considered as potentially important in determining the volume and osmolarity of plasma, interstitial and intracellular fluid by ion and water flux in or out of transcellular pools in response to metabolic stimuli.

In the preceding three papers of this series we reported the measured amount of sodium, potassium and chloride contained within the lumen of the gut in rabbits and in human subjects at post mortem (4, 5, 7). The present study is similar in design to these previous experiments and presents observations on a) the amount of intraluminal gastrointestinal water expressed as a fraction of total body water (T.B.W.) and the extent of deuterium oxide (D₂O) exchange equilibrium in gut contents in rabbits, and b) the amount of intraluminal water in man at post-mortem examination.

METHODS

A. Rabbits

Forty adult albino rabbits were studied in pairs consisting of a male and a non-gravid female. The animals were fasted and thirsted. All urine passed during the period of isotope equilibration was collected in a metabolism cage. This period varied from 2 to 5 hours. Each animal was injected intraperitoneally with 2 ml. of D₂O [5] from a calibrated syringe. At the end of the equilibration period each animal was anesthetized with 2 ml. of 2 per cent sodium pentobarbital injected into a dorsal ear vein and was then weighed to the nearest gram. A blood sample was obtained at this time by cardiac puncture through the intact chest wall with a syringe containing dry heparin. The syringe was capped and centrifuged immediately after collection, and the separated plasma was aspirated, sealed in a glass ampoule and stored in a freezer.

The gastrointestinal tract was removed in three segments by cutting between double ligatures placed at the cardia of the stomach, the pylorus, the ileocecal valve and at a position in the transverse colon where there was a transition point between semi-solid and solid stool pellets. After removal each segment was washed with distilled water, dried with towels and weighed to the nearest gram.

The contents of each segment were milked into one ligated end, a small incision was made, and an aliquot of contents was expressed into a dried test tube, which was quickly stoppered and centrifuged. The supernatant was then aspirated and sealed in a glass ampoule and stored in a freezer. Each segment was then opened longitudinally, and the remaining contents were evacuated into a clean container by gently stripping and then washing the mucosal surface with distilled water. The

TABLE I

Effect of equilibration time on measured total body water

Number of rabbits			Equilibration time (*hours*)	Body weight mean ± s.d.* (Kg.)	Total body water as % body wt. mean ± s.d.*	t Value	p Value†
Male	Female	Total					
5	5	10	2	2.46 ± .27	71.0 ± 7.0		
4	5	9	3	2.05 ± .25	75.1 ± 5.5	1.44	>0.1
5	5	10	4	2.16 ± .23	74.4 ± 3.5	1.29	>0.2
5	5	10	5	2.20 ± .20	72.0 ± 4.4	0.39	>0.5

* s.d. $= \sqrt{\dfrac{\Sigma(x - \bar{x})^2}{n - 1}}$.

† Compared with 2-hour value for T.B.W. in each instance.

evacuated contents were quantitatively transferred with multiple distilled water rinses into a graduated cylinder to which the remainder of the previously centrifuged aliquot was added. The diluted contents were thoroughly mixed, the volume recorded and an aliquot taken for determination of solids. The wall of each segment was dried and reweighed.

Ten-ml. aliquots of the diluted contents were pipetted in duplicate into tared weighing bottles. The solid content of each sample was estimated gravimetrically after drying at 105° C for 72 hours. All duplicates checked within 10 per cent.

The concentration of D_2O in blood was determined in duplicate by the falling-drop method (8). The maximal acceptable difference between duplicates was 0.006 volume per cent. Only single analyses were carried out on urine samples since less than 1 per cent of the tracer was excreted during the equilibration periods. The concentration of D_2O in intraluminal water was determined by mass spectrometer analysis (9).[6] Each of these analyses was done in duplicate, and all duplicates checked within 0.006 atom per cent D.

B. Human subjects

The gastrointestinal tracts were removed and the contents analyzed in 13 human subjects at autopsy. The technique of sample collection was described previously (4). Water content was estimated as described for the rabbits. Subjects selected for study had no gastrointestinal disease and minimal clinical abnormality of fluid and electrolyte metabolism. The body weight and height of each subject were measured. The appendix to the first report in this series (4) describes the pertinent clinical and pathological findings in these cases.

CALCULATIONS

Rabbits

Total body water was calculated from the well-known isotope dilution formula (1). The amount of tracer re-

[6] These analyses were performed by Mr. Brad Pearson under the direction of Dr. A. K. Solomon at the Biophysics Laboratory of the Harvard Medical School in Boston, for which we are most grateful.

tained was assumed to be the amount injected minus the amount excreted in the urine during the equilibration period. Isotope excretion varied between 0.1 per cent to 0.6 per cent of the injected D_2O. The maximum combined errors in this calculation are less than 5 per cent.

The volume of intraluminal water in each gut segment was calculated in the following manner:

a) *Weight of intraluminal contents =*
   Weight intact gut segment − Weight of segment wall

b) *Total solids in intraluminal contents =*
   (Volume diluted contents) (Weight solids in grams per ml.)

c) *Volume of intraluminal water =*
   Weight of intraluminal contents − Total solids in intraluminal contents

Accumulated errors in the final calculation are 10 per cent or less.

Completeness of D_2O exchange between plasma water and intraluminal water was determined from the ratio of D_2O concentration of intraluminal water to plasma water. This ratio is designated the specific activity ratio (S.A.R.) (2, 4).

When exchange is complete, S.A.R. is unity since the concentration of D_2O will be the same in both intraluminal water and plasma water. The value of S.A.R. is assumed to represent the fraction of gut water exchanged with extracellular water (2, 4).

Human subjects

Total body water was estimated in these subjects from data derived from D_2O dilution studies on normal subjects in this age group (10). The predicted T.B.W. was calculated, using the values 22.2 liters per square meter in males and 17.1 liters per square meter in females.

Volume of intraluminal water was calculated by the methods outlined above for the rabbit.

RESULTS

Rabbits

Uniform dispersal of a tracer theoretically occurs after an infinite period of time (11). A prac-

tical means for judging equilibrium of distribution, however, is to determine the time required for constant volumes of dilution, in this case T.B.W. The effect of the time allowed for equilibration on the apparent T.B.W. is summarized in Table I. Mean T.B.W. values at 3, 4 and 5 hours of equilibration are compared to the 2-hour values. No significant differences were found among these groups, nor was there a trend in either direction. Two hours is probably an adequate period for D_2O equilibration in this species.

Data on T.B.W. and "total" intraluminal gastrointestinal water [7] in animals matched carefully for weight, age and the period of isotope equilibration and compared on the basis of sex are tabulated in Table II. The differences in T.B.W. and the gut water content of male and female rabbits were not statistically significant.

The absolute magnitude of intraluminal water content and its isotope exchange characteristics in each segment of the tract are given in Tables III and IV.

The mean volume of intraluminal water, expressed as per cent of T.B.W., in the stomach,

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[7] "Total" intraluminal gastrointestinal water refers to water contained in the gut from the cardia of the stomach to the mid-transverse colon.

small intestine and large intestine is 4.1, 2.0 and 6.0 per cent, respectively (cf. Table III). The sum of these, or "total" intraluminal water, is 12.1 per cent of T.B.W. The coefficients of variation for these data are large, varying between 22 and 50 per cent, and reflect the considerable variation in the volume of intraluminal gut water found in different animals in spite of rigidly controlled experimental conditions.

The specific activity ratios of gut water to plasma water at 2, 3, 4 and 5 hours' equilibration for stomach, small intestine and large intestine are listed in Table IV. The p values in each instance refer to comparison of the measured S.A.R. with unity, the theoretical value for complete equilibration. Equilibration is complete in the large bowel segment at 2 hours. In the small intestine, equilibration is nearly complete at 2 hours, with an S.A.R. of 0.95 ± 0.05, and is complete at 3 hours, with an S.A.R. of 0.99 ± 0.03. There is a significantly slower rate of exchange of water in the stomach. The S.A.R. of ± 0.86 at 2 hours differs significantly from 1.00 (p < 0.001). At 3 hours only 93 per cent of water in the stomach has exchanged with plasma water, but at 4 hours complete exchange is demonstrated (S.A.R. = 0.98 ± 0.05).

TABLE II

The total body water and "total" intraluminal gastrointestinal water* of male versus female rabbits†

	Male	Female	t Value	p Value
Number	13	13		
Body weight in Kg. ± s.d.	2.15 ± .18	2.14 ± .16		
T.B.W. as % body weight ± s.d.	73.3 ± 2.6	74.8 ± 3.5	1.25	>0.2
"Total" G.I. water as % T.B.W.	11.6 ± 1.9	12.5 ± 3.2	0.82	>0.4

* "Total" intraluminal gastrointestinal water refers to water contained in the gut from the cardia of the stomach to the mid-transverse colon.
† Each pair of rabbits was matched for weight, age and period of isotope equilibration.

TABLE III

The intraluminal gastrointestinal water content in the rabbit

	Stomach			Small intestine			Cecum and proximal transverse colon			"Total" G.I.		
	(ml.)	(ml./Kg.)	(% T.B.W.)	(ml.)	(ml./Kg.)	(% T.B.W.)	(ml.)	(ml./Kg.)	(% T.B.W.)	(ml.)	(ml./Kg.)	(% T.B.W.)
Mean	65	30	4.1	31	18	2.0	93	44	6.0	189	90	12.1
s.d.	±15	±7	±0.9	±12	±9	±1.0	±22	±13	±1.6	±40	±24	±2.7
Coefficient of variation	23%	23%	22%	39%	50%	50%	24%	30%	27%	21%	27%	22%
Number of rabbits*	29	29	28	29	29	28	27	27	26	26	26	25

* All animals were allowed 3 to 5 hours of isotope equilibration and thirsted 3 to 5 hours as summarized in Table I.

TABLE IV

The equilibration of D_2O between plasma and gastrointestinal contents

Equili-bration time (hours)	Stomach				Small intestine				Cecum and transverse colon			
	No. of animals	S.A.R. mean ±s.d.	t*	p	No. of animals	S.A.R. mean ±s.d.	t*	p	No. of animals	S.A.R. mean ±s.d.	t*	p
2	10	0.86±.08	5.60	<0.001	9	0.95±.05	2.94	<0.02 >0.01	8	1.00±.09	0	1.0
3	9	0.93±.07	3.04	<0.02 >0.01	9	0.99±.03	1.00	>0.3	8	1.01±.04	.71	0.5
4	10	0.98±.05	1.25	>0.2	10	1.00±.03	0	1.0	10	1.01±.03	1.11	0.3
5	10	1.01±.02	1.67	>0.1	10	1.02±.03	2.22	>0.05 <0.10	10	1.01±.03	1.11	0.3

$$*t = \frac{1.00 - \bar{x}}{\frac{s.d.}{\sqrt{n}}}.$$

Human subjects

The volumes of measured intraluminal gastrointestinal water expressed in terms of predicted T.B.W. at post mortem in 13 human subjects are presented in Table V. "Total" gastrointestinal water comprised 1.4 per cent of the predicted T.B.W. The stomach, small intestine and the proximal half of the large intestine were found to contain an average of 0.4, 0.7 and 0.3 per cent of predicted T.B.W., respectively. "Total" intraluminal water content varied only from 0.5 to 2.2 per cent of T.B.W. In contrast, the intraluminal pool of the rabbit comprised 12 per cent of T.B.W.

DISCUSSION

The purpose of these experiments was to study the magnitude and exchange characteristics of intraluminal gastrointestinal water.

Total body water and the volume of intraluminal water in healthy animals might be expected to vary with body weight, age, sex and duration of fasting and thirsting. The animals studied were all young adults, each weighing about 2 Kg. Total body water was approximately 75 per cent of body weight in both male and female rabbits. The absence of a difference in T.B.W. between sexes contrasts with the significantly higher total body water content in males noted in studies on man (10). It is likely that these findings are explained by the fact that the female rabbits were all young nulliparous adults. Prepubertal human females have been shown not to differ from male subjects in body water content (10, 12). Cizek (3), in studies of somewhat larger and older rab-

bits, did find a significantly higher total body water in male than in female rabbits.

The volume of intraluminal water was not affected by the sex of the animal nor by fasting and thirsting up to 4 hours. The magnitude of this transcellular pool was approximately 12 per cent of T.B.W., which corresponds well with previous measurements (3) and represents a large fraction of the body water content of this species. This volume is comparable to one-half the volume of interstitial fluid or to twice the volume of plasma (13). The size of this subdivision of body water raises the possibility that it may contribute significantly to changes in plasma-interstitial fluid volumes induced by physiological or pathological influences. Furthermore, calculations of the distribution of water and ions which are based on a more simplified concept of the anatomy of body water, i.e., a two-compartment system, will be erroneous in proportion to the volume of transcellular fluid in the species under study.

The observation that the S.A.R. of gut water to plasma water reaches unity in all segments within 4 hours indicates that this transcellular pool of water is in exchange equilibrium with the remainder of T.B.W. D_2O exchange is fastest in large bowel contents, while slower exchange occurs in small bowel contents, and the slowest exchange occurs in stomach water. If this isotope penetrated stomach mucosa only and then passed down the intestinal tract, water in the large bowel should equilibrate last. Our data effectively exclude this possibility and suggest instead that water penetrates across the mucosa of the gut throughout the length of the tract. The delay of

TABLE V

Intraluminal gastrointestinal water content in the human studied post mortem

Sex	Pathological diagnosis	Post-mortem interval (hours)	Age (yrs.)	Body weight (Kg.)	Predicted T.B.W. (liters)	Stomach			Small intestine			Cecum and proximal transverse colon			"Total" G.I.		
						(ml.)	(ml./Kg.)	(% T.B.W.)	(ml.)	(ml./Kg.)	(% T.B.W.)	(ml.)	(ml./Kg.)	(% T.B.W.)	(ml.)	(ml./Kg.)	(% T.B.W.)
F-1	Recent myocardial infarction	6	77	35.0	22.4	51	1.5	0.2	100	2.9	0.5	13	0.4	0.1	164	4.8	0.8
M-2	Rheumatic heart disease with mitral stenosis	11	53	51.8	34.4	65	1.3	0.2	75	1.5	0.2	44	0.9	0.1	184	3.7	0.5
M-3	Hypertensive cardiovascular disease	22	51	43.6	29.7	233	5.4	0.8	335	7.7	1.1	33	0.8	0.1	601	13.9	2.0
F-4	Pituitary tumor	9	54	58.2	26.8	32	0.6	0.1	202	3.5	0.8	60	1.0	0.2	294	5.1	1.1
M-5	Squamous cell carcinoma of lung	7	64	43.6	29.7	233	5.4	0.8	151	3.5	0.8	13	0.3	0.1	397	9.2	1.7
F-6	Cerebral arteriosclerosis with encephalomalacia	6	56	58.2	26.8	132	2.3	0.5	60	1.0	0.2	178	3.1	0.7	370	6.4	1.4
F-7	Hypertensive and arteriosclerotic heart disease	22	68	63.4	28.0	11	0.2	0.1	234	3.7	0.8	80	1.3	0.3	325	5.2	1.2
M-8	Paralysis agitans and bronchopneumonia	16	69	63.2	37.7	64	1.0	0.2	349	5.5	0.9	430	6.8	1.1	843	13.3	2.2
F-9	Cerebral thrombosis	20	67	65.0	29.9	226	3.5	0.8	95	1.5	0.3	—	—	—	321	5.0	1.1
M-10	Dissecting aneurysm of ascending aorta	19	59	68.0	38.0	34	0.5	0.1	241	3.5	0.6	20	0.3	0.1	295	4.3	0.8
M-11	Recurrent myocardial infarction	16	72	64.5	38.0	97	1.5	0.3	352	5.5	0.9	15	0.2	0.1	464	7.2	1.3
M-12	Chromophobe adenoma of pituitary	7	50	70.0	37.3	170	2.4	0.5	220	3.1	0.6	107	1.5	0.3	497	7.0	1.4
M-13	Traumatic demyelinization of cervical spinal cord	12	76	54.5	38.6	181	3.5	0.5	345	6.3	0.9	7	0.1	0.1	533	9.9	1.5
	Mean:					118	2.2	0.4	206	3.8	0.7	83	1.4	0.3	407	7.4	1.4
	Range:					11–233	0.2–5.4	0.1–1.2	60–352	1.0–7.7	0.2–1.1	7–430	0.1–6.8	.0.1–1.1	164–843	3.6–13.8	0.5–2.2

TABLE VI

Summary of intraluminal gastrointestinal sodium, potassium, chloride, and water content in the rabbit

	Sodium		Potassium		Chloride		Water		Calculated concentration in intraluminal water*		
	M ±s.d. (mEq.)	M ±s.d. (% Na.)	M ±s.d. (mEq.)	M ±s.d. (% K.)	M ±s.d. (mEq.)	M ±s.d. (% Cl.)	M ±s.d. (ml.)	M ±s.d. (% T.B.W.)	Sodium (mEq./L.)	Potassium (mEq./L.)	Chloride (mEq./L.)
Stomach	0.8 ±0.4	0.9 ±0.4	0.7 ±0.3	0.7 ±0.3	8.7 ±3.4	11.7 ±4.4	65 ±15	4.1 ±0.9	12	11	134
Small intestine	3.1 ±1.1	3.2 ±1.2	1.2 ±0.4	1.2 ±0.4	1.8 ±0.4	2.5 ±0.7	31 ±12	2.0 ±1.0	100	39	58
Cecum and transverse colon	10.0 ±2.0	10.2 ±2.1	4.5 ±3.1	4.5 ±2.7	1.2 ±0.3	1.7 ±0.4	93 ±22	6.0 ±1.6	108	48	13
"Total" G.I. content	13.7 ±2.4	14.2 ±2.4	7.1 ±2.8	7.2 ±2.2	11.8 ±3.6	16.0 ±4.5	189 ±40	12.1 ±2.7			

* Calculated concentrations are derived by dividing intraluminal sodium, potassium, and chloride contents by intraluminal water content. Each quantity was determined in separate series of animals.

equilibration in stomach water, where 4 hours was required for distribution equilibrium compared with 1 and 2 hours for colon and small bowel, respectively, may be a result of at least three factors. The ratio of membrane surface area to intraluminal volume may be smaller in stomach than in either large or small bowel. The ratio of surface to volume has been proposed as the basis for D_2O exchange rates in other transcellular pools (14). The delay of equilibration of labelled water in small bowel contents compared to large bowel contents cannot, however, be explained on comparative ratios of surface area to volume. A second possible explanation is that mucosal blood flow, and consequently the rate of delivery of isotope in proportion to the volume of intraluminal water, may be highest in the large bowel and least in the stomach (15). Finally, active transport of water across gut mucosa may occur and account for some of these differences (16).

In the course of these studies it was noted that the contents of the cecum and the proximal transverse colon were semiliquid and that in the mid-transverse colon there was a sharp transition zone, 1 to 2 cm. in length, where the contents were transformed into hard, dry pellets of stool. This would suggest that the mucosa of the mid-transverse colon acts to conserve water efficiently.

Data from previous experiments in which the intraluminal content of sodium, potassium, and chloride were determined are summarized in

Table VI (4, 5, 7). The last three columns in Table VI show the calculated concentrations for each of these ions in intraluminal water of stomach, small bowel and large bowel. It is apparent from these values that the concentration of sodium, potassium and chloride maintained in intraluminal water bears no direct relation to the electrolyte structure of extracellular fluid. It would seem that their concentration and abundance in intraluminal water are determined by autonomous mechanisms in the gastrointestinal tract.

The presence of 14 per cent of Na_e, 7 per cent of K_e and 16 per cent of Cl_e in the contents of the gastrointestinal tract in rabbits has important implications in body partition studies where the normal anatomy of ion distribution or of ion shifts is measured (4, 5, 7). Calculating the extracellular fluid volume from a chloride space and assuming that all chloride exists in the same concentration as in plasma will lead to significant errors. Changes in the extracellular space inferred from changes in chloride concentration in plasma and external chloride balance may also be misleading since these calculations are based on the assumption that all, or nearly all, of the body chloride is in the plasma-interstitial fluid volume.

The volume of intraluminal water found in the gastrointestinal tract of man was a much smaller fraction of T.B.W. than in the rabbit. The significance of this species difference cannot be determined from our data since the observations on

human subjects must be evaluated cautiously for several reasons. Total body water was predicted from data on normal subjects; in contrast, accurate measurements were made in the rabbits. Significant migration of water from the gut may occur in critically ill patients. Post-mortem changes in intraluminal volume may have taken place during the 6 to 22 hours that elapsed between death and autopsy in these subjects. The measurements made in the human subjects consequently are not reliable, and further studies are needed to establish the amounts of intraluminal water and electrolytes in normal man.

SUMMARY

The volume of intraluminal gastrointestinal water was measured in rabbits and in human subjects studied post mortem. In rabbits this volume was referred to T.B.W. as determined by D_2O dilution. In man the intraluminal gut water was referred to predicted T.B.W. values.

Total body water averaged 75 per cent of the body weight in rabbits; 12 per cent of T.B.W. was contained in the lumen of the "total" gastrointestinal tract, with 4 per cent in the stomach, 2 per cent in the small intestine and 6 per cent in the large intestine. No significant difference between sexes was noted in either total body water or the volume of intraluminal gut water. Deuterium oxide equilibration was complete in large bowel water and nearly complete in small bowel water in 2 hours, but required 4 hours for completion in stomach water. The significance of delayed D_2O equilibration in stomach water compared with more distal segments of bowel was discussed with respect to the sites and mechanisms of D_2O exchange across gastrointestinal membranes.

The gastrointestinal tract of man at post-mortem examination contained approximately 1.5 per cent of the predicted T.B.W. The mean values were 0.4 per cent for stomach, 0.7 per cent for small bowel and 0.3 per cent for proximal large bowel. These values cannot be considered to represent the volume of intraluminal gut water to be found in the normal living human subject.

The amounts of intraluminal gut sodium, potassium, chloride and water in the rabbit are summarized in tabular form.

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