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Research Article

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Effects of Sodium Concentration and Osmolality on Water and Electrolyte Absorption from the Intact Human Colon

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ABSTRACT The influence of sodium concentration and osmolality on net water and monovalent electrolyte absorption from or secretion into the intact human colon was studied in healthy volunteers.

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INTRODUCTION

The intact human colon absorbs sodium and water from isotonic sodium chloride solutions (1). The relationship between sodium and water absorption, however, has not been systematically studied in the human colon. In addition, no information is available on the movement of sodium and water into the large intestine when perfused with hypertonic solutions. The present experiments were done to determine the effects of osmolality and sodium concentration of colonic contents on the absorption of water and electrolytes from this organ.

METHODS

Subjects. Studies were performed on healthy male volunteers aged 22–63 yr. Informed consent was obtained in all instances.

Perfusions. Test solutions, containing 0.5 g/100 ml polyethylene glycol (PEG)[1] as a nonabsorbable volume marker, were infused into the ascending colon via a tube at a constant rate of 820–880 ml/hr by means of a peristaltic pump[2] using various methods described below. The test solution, after traversing the entire colon, was collected continuously in hourly aliquots (i.e. "a study period" or "n") via a size 26F rectal tube placed 6–8 inches above the anal sphincter. The colon was cleansed and a steady flow of perfusate from caecum to rectum was achieved before the studies as previously described (1). The concentrations of urea, glucose, mannitol, bicarbonatae, PEG, and electrolytes were measured. The perfusate was collected on ice and frozen at the end of each study period. Urine and blood samples were obtained for determination of osmolalities, urea, creatinine, and mannitol. The subjects fasted for 8–10 hr before each test but were maintained in good state of hydration by intravenous administration of 5% dextrose in water and 0.5% NaCl in equal parts (300–600 ml/hr).

[1] PEG: mean molecular weight 4000; obtained from City Chemical Corp., New York.

[2] Harvard Apparatus Co., Inc., Cambridge, Mass.

TABLE I

*Area and Length of 15 Human Colons as Measured at Necropsy**

	Cecum, area	Ascending and cecum		Transverse		Descending		Total colon	
		Length	Area	Length	Area	Length	Area	Length	Area
	cm²	*cm*	*cm²*	*cm*	*cm²*	*cm*	*cm²*	*cm*	*cm²*
Mean ±SD	57 ±24	29 ±7	270 ±91	46 ±10	281 ±97	59 ±15	297 ±83	133 ±19	875 ±261
Range	32–117	18–44	150–479	27–64	171–376	34–77	197–412	90–150	636–1613

* The colons of seven males and eight females, who had no signs of intestinal disease, were obtained at autopsy. The ages ranged from 15 to 77 yr (mean age: 57 yr; mean weight: 134 lbs.). The hepatic and splenic flexures were marked by a stitch *in situ*. After its removal from the body, the colon was opened longitudinally and transsected at the two flexures. Mesentery and gross fat were removed. The three parts were loosely spread on paper and the contours drawn. The area of each segment was measured in duplicate by a Compensating Polar Planimeter (No. 620015), Keuffel & Esser Co., New York). The upper border of the cecum was determined by a horizontal line drawn at the level of the ileocecal valve. The descending part of the colon included part of the rectum, as it was taken from as low in the pelvis as possible.

Intubations and type of experiments. A. A polyvinyl tube (1) with an infusion opening at the distal third was passed transintestinally as described by Blankenhorn, Hirsch, and Ahrens (2). The infusion site, marked with radiopaque tubing, was placed just distal to the ileocecal valve under fluoroscopic control and checked before and after all studies. Using this technique, the following solutions were perfused: (*1*) Isotonic solutions containing NaCl and mannitol in varying proportions; (*2*) Isotonic solutions containing Na(132–155 mEq/liter), K (6.3–16.0 mEq/liter), Cl (26–95 mEq/liter), and HCO_3 (55–155 mEq/liter); (*3*) Tyrode's solutions (3), isotonic solutions of NaCl, isotonic NaCl with 250 mg/100 ml glucose (with and without 250 mg/liter neomycin sulfate) and isotonic $NaHCO_3$; (*4*) hypertonic solutions of NaCl (189 and 200 mEq/liter); (*5*) hypertonic solutions of mannitols or urea, containing either 25 or 150 mEq/liter NaCl. Corresponding equiosmotic solutions of mannitol or urea were perfused on the same day in the same subject in alternating sequence.

B. An assembly of three polyvinyl tubes, each with a proximal opening (about 8 cm apart), was attached to a transintestinally passed polyvinyl tube and pulled back into the ascending colon. The lumen of the large intestine was occluded with a balloon containing 100–140 ml of air which covered the middle tube opening. Ileal effluent was then aspirated from the proximal tube which was located in the ileum proximal to the ileocecal valve, while different isotonic solutions, containing 0, 15, and 25 mEq/liter NaCl, respectively, and appropriate amounts of mannitol to make the solution isotonic, were infused through the distal tube opening located in the cecum. After a "steady state"[3] had been achieved, small volumes of perfusate (about 150 ml) were collected rectally and recirculated through the colon. Only three of such studies are reported, as in several others the position of the balloon was changed by peristalsis. In these three studies, complete occlusion of the ascending colon was verified by instillation of Bromsulphalein (BSP) proximal to the balloon.

C. A four-lumen tube assembly was placed into the ascending colon as described under B. Mannitol solutions of variable osmolality (288, 450, 600, 650, 800, and 1055 mOsm/kg), all containing 25 mEq/liter NaCl, were infused into the ascending colon and samples (35–50 ml/hr) were aspirated continuously at 10, 20, and 40 cm distally to the infusion site in addition to collections of the rectal effluent.

Analytical methods. PEG, Na, K, Cl, HCO_3, and osmolalities were measured as described (1). Mannitol was analyzed according to Corcoran and Page (4). Urea and glucose were determined by a Technicon AutoAnalyzer and BSP by colorimeter (5).

Definitions and calculations. Net changes of water and solutes were calculated from the concentration changes of PEG (1).

"Absorption" (+) denotes a net decrease and "secretion" = "filtration" (−) a net increase of luminal contents of water and solutes. "Mean osmotic pressure gradient" is the difference of the mean osmotic pressure of the perfusate and the serum osmolality (6). "Filtration coefficient" was calculated as the volume of water secreted into the lumen (ml/min) divided by the mean osmotic pressure gradient (mOsm/kg). The term "reflection coefficient" (7) is used for the quotient of the filtration coefficient of corresponding urea and mannitol perfusions (6).

Statistical methods. The data are presented as mean standard deviation and were analyzed by variance analysis.

Reproducibility. Hypertonic solutions (800 mOsm/kg), containing 150 mEq/liter NaCl and urea or mannitol, were perfused for 4–6 hr under conditions of steady state eight times in four different subjects (Intubation type A), (see Fig. 1). There were no significant differences in osmotic pressures and water filtration rates between the hourly collections on one day ($P > 0.05$) or on different days in the same individual ($P > 0.05$). On the other hand, differences between individuals were highly significant ($P < 0.01$). As the results were reproducible in the same subjects, the inter-subject variability cannot be attributed to vagaries of the perfusion technique. It is probably due to other factors such as differences in colonic surface area, transit time of test solutions, and intracolonic pressures.

Indeed, we found that the macroscopic mucosal surface area of 15 normal adult colons, measured at autopsy, varied greatly (Table I). BSP dilution studies, done in two subjects during steady-state perfusions, revealed colonic volumes of 773 and 490 ml respectively; assuming the colon to be a cylinder, the respective surface areas were 819 and 659 cm². The colonic transit times of the test solutions mea-

[3] The time during which rectally collected specimens contained a relatively steady PEG concentration (mean = 5%).

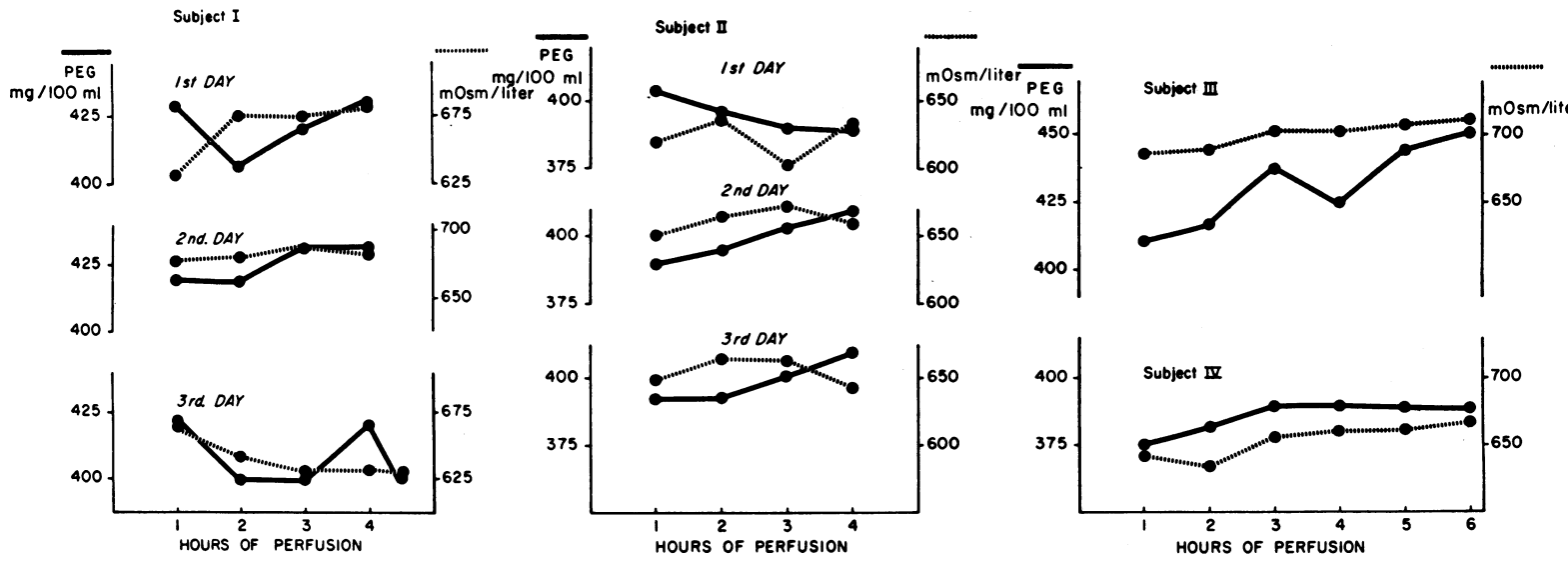

FIGURE 1 Reproducibility of the colonic perfusion technique using hypertonic solutions. The colon was perfused continuously with hypertonic urea or mannitol solutions (800 mOsm/kg), containing 500 mg/100 ml PEG as a volume marker. The rectal effluent was collected continuously for periods of 4–6 hr. The PEG concentrations and osmolalities of the hourly collected rectal effluents are plotted in the above graph. The solid lines are PEG concentrations; the dotted lines are osmolalities. No significant differences in water filtration rates or osmotic pressures were found between the hourly collections on the same day or different days in the same individuals. Data obtained in four subjects; two were studied on three different days.

TABLE II

Net Water and Electrolyte Movements in and out of the Colon as a Function of the Sodium Concentration of the Infusion Solutions (Mean ±SD)

Solution	Na concn of infused colon	Na concn of rectal effluent	n	Net water flow	Net Na change	Net Cl change	Net K change
	mEq/liter	*mEq/liter*		*ml/min*	*mEq/hr*	*mEq/hr*	*mEq/hr*
1	0	5.1 ±1.9	8	−0.9 ±0.5	−4.4 ±2.1	−1.6 ±1.6	−1.6 ±0.05
2	7.5	8.6 ±1.9	6	−0.2 ±0.4	−1.4 ±0.9	+2.9 ±1.6	−1.6 ±0.26
3	23.0	18.4 ±6.5	16	+0.07 ±0.6	+2.7 ±1.2	+8.1 ±5.4	−1.7 ±0.40
4	50.0	32.5 ±2.2	2	+0.8 ±0	+13.0 ±5.0	+19.0 ±2.8	−1.9 ±0.80
5	100.0	79.6 ±7.0	9	+1.7 ±0.9	+23.0 ±10.0	+31.0 ±9.0	−1.5 ±0.40
6	150.0	140.0 ±10.0	44	+2.8 ±1.0	+32.0 ±10.0	+48.0 ±13.0	−1.7 ±0.50
7	189.0 (360 mOsm/kg)	157.0 ±5.4	5	+1.6 ±0.7	+43.0 ±6.0	+59.0 ±4.0	−1.6 ±0.04
8	220.0	171.0 ±7.7	7	−0.8 ±0.6	+34.0 ±13.0	+42.0 ±13.9	−1.6 ±0.20

n = number of studies, each lasting 1 hr; (+) = absorption from the lumen; (−) = secretion into the lumen. Solutions 1–6 were made isotonic by the addition of mannitol. Solutions 7 and 8 were hypertonic.

sured during the perfusions in five subjects as the time from injection of a BSP bolus into the ascending colon to peak appearance of BSP in the rectal effluent (in 2- to 5-min rectal collections), varied from 12 to 40 min (mean: 24 ±10; n = 7). Intracolonic pressures, measured during the perfusion in four subjects by means of a water-filled open-tip tube located in the colon and connected to a Sanborn transducer, ranged from 4 to 8 mm Hg.

RESULTS

Colonic perfusions with isotonic solutions

The relation of electrolyte and water absorption. (See Methods, Intubation, type A/*1*.) Water absorption grossly paralleled the luminal concentration and absorption of Na and Cl. Cl absorption was always greater

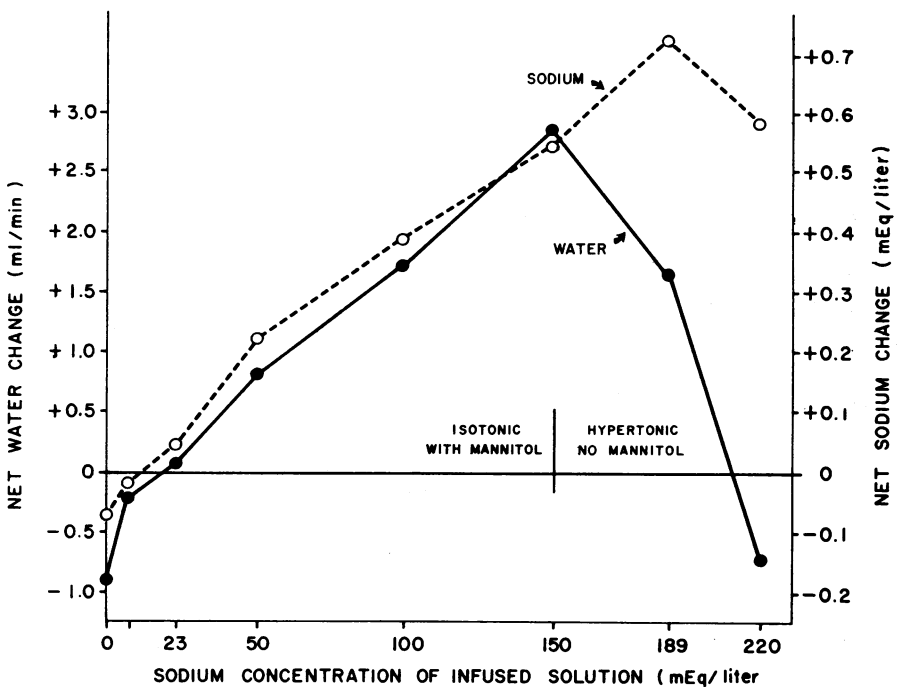

FIGURE 2 Net water and sodium movements in and out of the colon shown as a function of sodium concentration in the test solution. (+) = absorption from the lumen; (−) = secretion into the lumen. The solid line shows net water absorption or secretion and the dotted line net sodium absorption or secretion. Mean values are shown. The number of studies done are shown in Table II.

TABLE III

*Continuous Colonic Recirculation of Isotonic Test Solutions**

Subject	Duration of study	Water absorption	Isotonic test solution							
			Sodium		Chloride		Potassium		Bicarbonate	
			Infused	Recovered	Infused	Recovered	Infused	Recovered	Infused	Recovered
	hr	*ml/hr*	*mEq/liter*							
I	4.5	5.1	24	17.0	24.0	12.0	0	4.3	0	11.1
II	4.0	none	15	6.3	15.0	4.0	0	6.2	0	5.6
III	2.2	none	0	2.5	0.5	2.0	0	5.2	0	6.4

Ileal contamination was prevented by a balloon which effectively occluded the colonic lumen distal to the ileocaecal valve.
* Isotonic solutions contained mannitol and 25, 15, or 0 mEq/liter sodium chloride, respectively, and were continuously recirculated. Electrolyte concentrations (mEq/liter) of the infused test solutions and that of the last rectal collections are presented.

than that of Na, whereas K secretion appeared to be independent of water and NaCl absorption (Table II and Fig. 2).

Water absorption was maximal (2.8 ±1.0 ml/min; n = 44) from isotonic solutions of NaCl, decreased with declining luminal Na concentration, and ceased when the isotonic infusion solutions contained 22 mEq/liter NaCl. Some water secretion took place when the Na concentrations of the infusion solutions were 7.5 and 0 mEq/liter and 5 mEq/liter Cl. The K concentration remained constant when the perfusate contained 4 mEq/liter and 11.5 mEq/liter $KHCO_3$.

The factor of ileal contamination. (See Methods, Intubations, type B.) Recirculation of isotonic solutions of mannitol and 0, 15, and 25 mEq/liter of NaCl distal to a balloon effectively occluding the colonic lumen and preventing contamination by ileal effluent, resulted in a perfusate containing between 6.3 and 2.5 mEq/liter of Na and 4.0 and 2.0 of mEq/liter of Cl (Table III). Thus, Na, Cl, and water absorption ceased at a slightly lower Na and Cl concentration than in the first experiments (*cf.* Table II). These differences may reflect colonic contamination by ileal fasting contents; the 0.2–0.7 ml/min (mean: 0.56 ml/min) less water absorption found in the studies without balloon occlusion are similar to the value of 0.67 ml/min ileal fasting flow determined by Whalen, Harris, Geenen, and Soergel (8). Ileal fasting juice, aspirated from the distal ileum proximal to a balloon in two studies (10–20 ml/hr), contained 143 mEq/liter Na, 82 mEq/liter Cl, 6.9 mEq/liter K and 47 mEq/liter HCO_3 (mean values).

Equilibrium concentrations of univalent electrolytes.

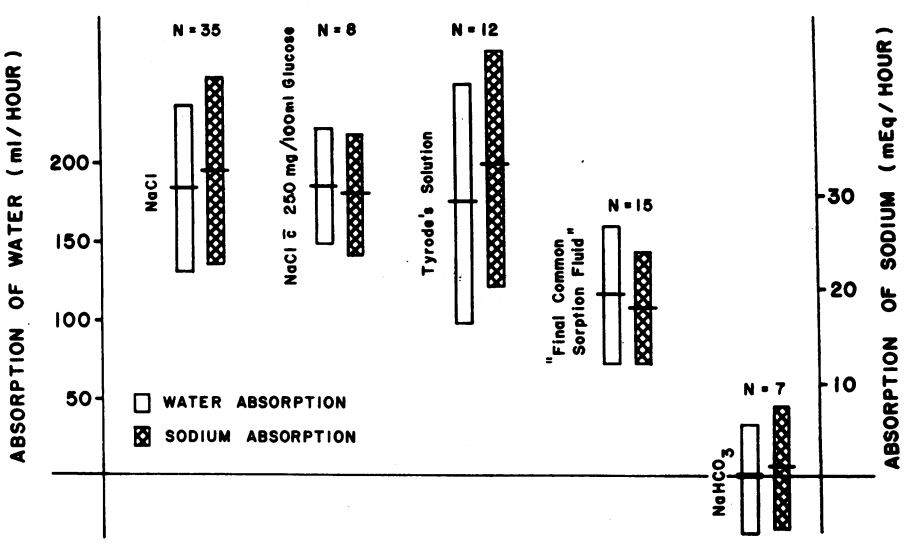

FIGURE 3 Net water and sodium absorption from different isotonic test solutions. The experimental conditions were identical in all studies. The different solutions were infused into the colon of the same subjects at random. "n" refers to the number of studies each lasting 1 hr (see text).

TABLE IV

Consecutive Perfusions of the Colon with Hypertonic Solutions of Urea and Mannitol Mean ±SD Are Shown

Study	U = urea, M = mannitol (in order of perfusion)	Mean osmotic pressure gradient	Volume change	Filtration coefficient	Reflection coefficient of urea
		mOsm/liter	*ml/min*	*ml/min per mOsm*	
A,* mean ±SD	U	447 ±20.4	3.19 ±1.05	0.00718 ±0.00248	1.03695 ±0.1212
	M	451 ±19.4	3.15 ±0.88	0.00701 ±0.00197	
B,‡ mean ±SD	U	288 ±19.1	4.53 ±1.31	0.01601 ±0.00582	1.0336 ±0.167
	M	290 ±13.5	4.27 ±1.06	0.01486 ±0.0134	

*A. (Studies in 7 subjects): Test solution contained 150 mEq/liter NaCl adjusted to 825 mOsm/liter by addition of urea or mannitol respectively.

‡ B. (Studies in 7 subjects): Test solution contained 25 mEq/liter NaCl adjusted to 650 mOsm/liter by addition of urea or mannitol respectively.

(See Methods, Intubation, type A/2.) The "final common sorption fluid" (9) was determined by perfusing isotonic solutions, containing Na, K, Cl, and HCO_3 in different proportions, in four subjects (27 study periods). By plotting the electrolyte concentrations of the rectal effluent against those of the infusion solutions and determining the regression lines (9), the following approximate equilibrium concentrations were obtained: Na, 139 mEq/liter; K, 12.9 mEq/liter; Cl, 50 mEq/liter; and HCO_3, 103 mEq/liter.

Recirculation of such solutions over prolonged periods of time (without balloons occluding the ileum) resulted in a continuous drop of the Cl concentrations and a rise of the HCO_3 concentrations in the perfusates in all four studies (e.g., in one subject the Cl dropped from 63 to 19 and HCO_3 rose from 95 to 117 mEq/liter over a period of 6 hr). This observation can be explained by a progressive accumulation of HCO_3-rich ileal fluid and displacement of more easily diffusable Cl from the colonic lumen.

Factors influencing Na and water absorption. (See Methods, Intubation, type A/3.) The absorption of Na and water from isotonic NaCl (n = 35), isotonic NaCl containing 250 mg/100 ml glucose (n = 8), and Tyrode's solutions (n = 12), was identical (see Fig. 3). Absorption of Na and water from isotonic $NaHCO_3$ (pH 8.2, n = 7) was significantly less ($P < 0.05$) than from isotonic NaCl solutions (pH 6.2–7.0). Absorption of Na and water from "final common sorption fluid" (n = 15), as described in the preceding paragraph, was intermediate between NaCl and $NaHCO_3$ solutions (Fig. 3). Neomycin sulfate (0.25 g/liter) did not effect Na and water absorption ($P > 0.01$, n = 10) (all statistical analyses refer to data obtained in the same subjects).

The recovery of glucose in the above perfusions was incomplete: 16.5 ±12.2 mg/100 ml glucose (n = 16, two subjects) disappeared from Tyrode's solution which initially contained 85–95 mg/100 ml glucose; 19.2 ±21.3 mg/100 ml glucose, (n = 16, three subjects) disappeared from isotonic 250 mg/100 ml glucose-NaCl solutions containing neomycin; and and 52.6 ±55 mg/100 ml (n = 5, two subjects) disappeared from 250 mg/100 ml glucose-NaCl solutions without neomycin. All glucose was recovered in 3 out of 10 separate perfusions (0.3 ±7.0 mg/100 ml, n = 8, three subjects).

Colonic perfusions with hypertonic solutions

Absorption from hypertonic NaCl solutions. (See Methods, Intubation, type A/4.) Studies with hypertonic NaCl solutions (389 and 420 mOsm/kg) showed that the human colon absorbs water from moderately hypertonic NaCl solutions (see Table II and Fig. 2). Water absorption ceased when the mean osmotic pressure and the mean Na concentration of the perfusate were approximately 350 mOsm/kg and 188 mEq/liter Na, respectively. It is noteworthy that Na absorption continued (34 ±13 mEq/hr), although water was secreted (− 0.8 ±0.6 ml/min) at the same time.

Effect of NaCl concentration in hypertonic mannitol solutions on filtration of water. (See Methods, Intubation, type A/5.) Significantly less water was filtered into hypertonic mannitol solutions containing 150 mEq/liter NaCl than into those containing 25 mEq/liter NaCl (see Table IV). The filtration coefficients were lower and the apparent Na and Cl concentrations of the filtrate were higher in the solutions containing 150 mEq/liter NaCl.

Comparison of water flow into hypertonic urea and mannitol solutions. (See Methods, Intubation, type A/5.) Net water flow into urea and mannitol solutions of equal osmolality and NaCl concentration was identical (see Table IV). The mean reflection coefficient for urea solutions was about 1.0 in both types of studies.

TABLE V

*Effect of Osmolality of the Test Solution on Water and Electrolyte Movements**

Osmolality of infusion solution	n‡	Net water movement	Filtration coefficient	Electrolyte concentration of the filtrate		
				Na	Cl	K
mOsm/kg		*ml/min*	*ml/min per mOsm*		*mEq/liter*	
450	4	−3.5 ±1.1	0.029 ±0.011	9.0	absorbed§	15.1 ±7.9
600	4	−4.2 ±0.9	0.019 ±0.004	25.2 ±3.8	3.6	20.6 ±7.8
650	7	−4.4 ±0.9	0.015 ±0.004	21.4 ±11.8	0.9	19.4 ±7.5
800	4	−5.5 ±0.8	0.013 ±0.013	36.1 ±15.0	20.7 ±16.2	22.5 ±9.1
1055	3	−7.2 ±2.7	0.014 ±0.074	49.9 ±2.9	25.2 ±12.0	15.1 ±5.2
825	7	−3.2 ±0.9	0.007 ±0.002	51.0	14.8	24.8 ±11.0

* All infusion solutions contained 25 mEq/liter NaCl except those with an osmolality of 825 mOsm/liter, which contained 150 mEq/liter NaCl. All solutions were made hypertonic by addition of mannitol. Studies with solutions of 450, 600, 800, and 1055 mOsm/kg were done in the same subjects. Filtration coefficients and electrolyte concentrations were calculated separately for each study and expressed as mean ±SD. If the direction of the individual electrolyte changes within one group differed, the mean concentration was calculated from the total water and electrolyte change within this group and SD has been omitted.

‡ n = number of studies.

§ At solutions of 450 mOsm/liter, Cl was absorbed at a rate of 2.2 ±6.1 mEq/hr, while water was secreted into the lumen at a rate of 209 ±66 ml/hr.

Absorption of urea and mannitol. (See Methods, Intubation, type A/5.) (*a*) The recovery of urea from perfused hypertonic urea solutions (mean urea concentration: 3460 ±198 mg/100 ml, n = 18, seven subjects) was 98.1% (mean urea deficit: 62 ±135 mg/100 ml).[4] (*b*) The urinary excretion of urea and creatinine was 8.6 ±6.0 mg/min (n = 8) and 1.25 ±0.05 mg/min (n = 5), respectively, during hypertonic mannitol perfusions and 9.2 ±5.0 mg/min (n = 8) and 1.26 ±0.34 mg/min (n = 7), respectively, during hypertonic urea perfusion. Urine flows during urea and mannitol perfusions were also comparable (3.1 ±1.9 ml/min (n = 7) and 3.0 ±1.9 ml/min (n = 9), respectively.

In the same studies, blood urea nitrogens and serum creatinines were 11.2 ±2.8 mg/100 ml and 0.71 ±0.08 mg/100 ml, respectively, after mannitol perfusion, but 13.2 ±2.1 mg/100 ml and 0.82 ±0.08 mg/100 ml, respectively, after urea perfusions. Differences between BUN values before and after urea perfusions were of borderline significance ($P = 0.05$); however, a parallel increase in serum creatinine values was noted. (*c*) The urea concentration in perfused isotonic and hypertonic mannitol solutions was not measurable by AutoAnalyzer (i.e. less than 0.6 mg/100 ml) in seven subjects (n = 10) and was 3.0 mg/100 ml (n = 2) in one subject. Ileal contamination was not excluded in these studies. For comparison, perfusion of a 30 cm segment of human jejunum with isotonic NaCl-glucose solutions at a rate of 14 ml/min yielded a urea level in the perfusate of 20.6 ±6.2 mg/100 ml (n = 11). Likewise, ileal fasting contents, aspirated in one healthy subject, contained 16 mg/100 ml urea. (*d*) The amount of mannitol excreted into the urine during perfusion with hypertonic mannitol solutions was 0.31% of the amount infused into the colon (51 perfusion hr in nine subjects).

Water and electrolyte movement in response to different osmotic gradients. (See Methods, Intubation, type C.) Mannitol solutions of 450, 600, 800, and 1055 mOsm/kg were perfused in the same four subjects, while solutions of 288 and 650 mOsm/kg were perfused in different subjects. All solutions contained 25 mEq/liter NaCl, as studies with isotonic solutions had shown that there was only minimal Na and water absorption at this concentration (see Fig. 2). Water secretion into the colonic lumen increased with rising osmolalities of the infused solutions (see Table V and Fig. 4). The secretion of Na and Cl increased out of proportion to that of water (Table V and Fig. 5). However, sodium and chloride entered the colonic lumen at a linearly related rate to that of water entrance when the lumen to

[4] In vitro tests, in which urea containing test solutions were exposed to perfusate or fresh stool at 38°C, showed nearly complete recovery of urea after 20 min (a time period corresponding to the colonic transit during the perfusion); more and more urea was lost after 1 and 2 hr. When urea solutions were perfused on 3 consecutive days for 6–8 hr daily, 42% urea disappeared in the first 1-hr collection of the 1st day; in the following samples of the 1st day, urease activity was decreasing rapidly and all urea was recovered on the 2nd and 3rd days. Bacteriologic studies on hypertonic perfusates showed a continuous decrease of bacterial count of the perfusate over the 3 perfusion days. For these reasons, all urea perfusions reported in this paper were done on the 2nd or 3rd perfusion days.

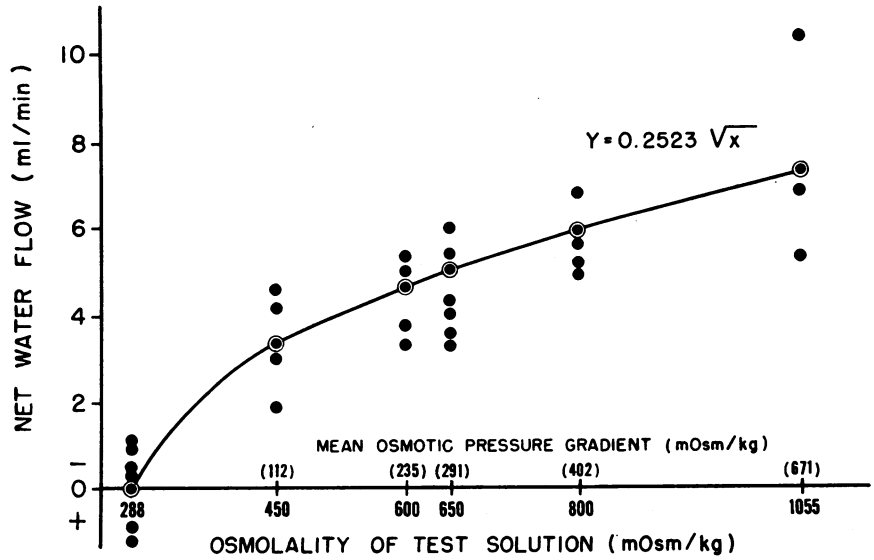

FIGURE 4 Net water flow into the colonic lumen as a function of osmolalities of the test solution. (−) = net water flow into the lumen (= secretion or filtration); (+) = net water flow out of the lumen (= absorption). Water flow is plotted against the osmolality of the test solution. The mean osmotic pressure gradient is also indicated.

blood osmotic gradient exceeded 150 mOsm/kg. No such relationship for potassium was apparent. The electrolyte concentrations of the osmotic filtrate, calculated for each study individually, are shown in Table V.

The perfused colon had a total length of 75–85 cm as measured by the tube segment from infusion site to rectum. 65% of the total decline of osmolalities of the test solution occurred over the first 10 cm ($n = 1$), 87% over 20 cm ($n = 15$), and 97% over 40 cm ($n = 15$) distal to the infusion site, regardless of the initial osmolality of the hypertonic solution.

An effective osmotic gradient between blood and lumen was maintained over the whole length of the study segment in all of these studies. The ratio of the osmotic gradient between rectal effluent and blood to that of infused fluid and blood was nearly constant and averaged 0.48 for an infusion solution of 450 mOsm/kg, 0.63 for 600 mOsm/kg, 0.65 for 800 mOsm/kg, and 0.63 for 1055 mOsm/kg.

DISCUSSION

Water movement across the colon. The present studies disclose some general characteristics of colonic absorption of water and electrolytes. The main forces influencing water movement across the colon seem to be osmotic gradients and sodium transport.

Net movement of water into the colon increased when the osmotic gradient between lumen and blood rose (Fig. 4). This relationship, when plotted, best conformed to a parabola (it could also be fitted to two straight lines with a greater slope for infusion solutions below 430 mOsm/kg than for hypertonic solutions). A similar relationship between water flow and osmotic gradients has previously been described in the canine stomach (10). Dilution of the hypertonic perfusate took place predominantly in the ascending colon, suggesting that this large bowel segment is more permeable than the rest of the colon, since macroscopic surface area measurements (Table I) showed no significant differences between ascending, transverse, and descending colon.

The test solution (luminal) NaCl concentration influenced water movement across the colonic mucosa from both iso- and hypertonic solutions. Water absorption from isotonic perfusates decreased with decreasing NaCl concentrations. Water secretion into hypertonic perfusates decreased with increasing NaCl concentrations, suggesting more effective reabsorption of the osmotic filtrate in the presence of higher NaCl concentrations. Water absorption from hypertonic solutions of NaCl continued until the mean osmolality of luminal fluid was 50 mOsm/kg above that of blood. This phenomenon has previously been observed in dog and rat large (11, 12) and small intestine (13, 14). A blood-to-lumen gradient of 50 mOsm/kg seems to just achieve an equilibrium between the two opposing forces of osmotic water secretion and Na-linked water absorption, as has been discussed by Curran and Solomon (15).

The great importance of Na transport in initiating water movement in the colon is stressed by the fact that

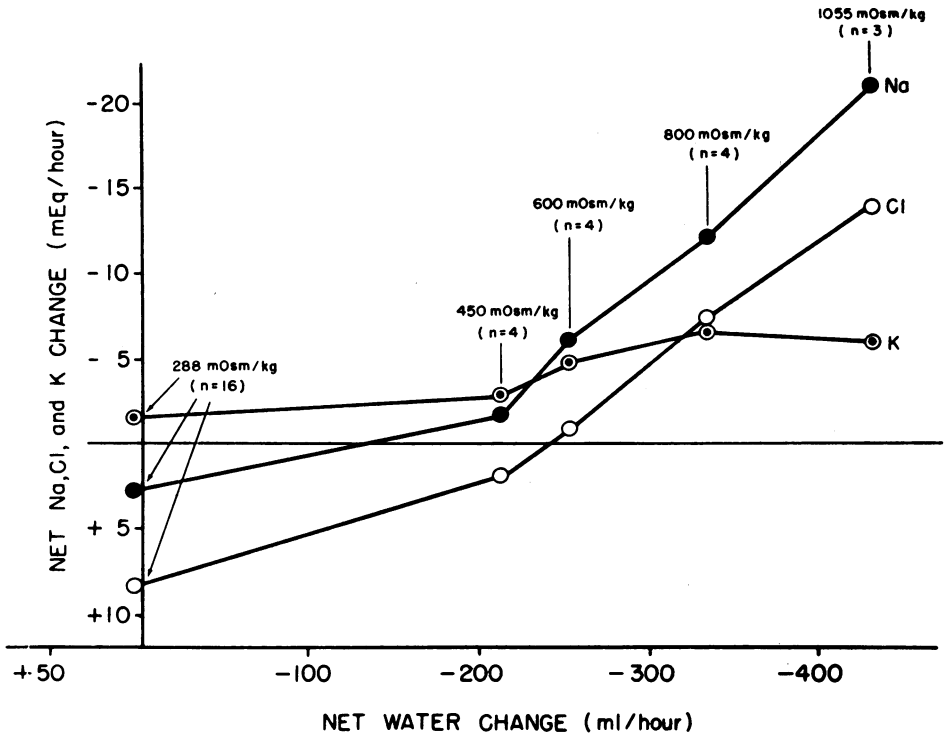

FIGURE 5 Net sodium, chloride, and potassium movements into or out of the colon expressed as a function of water flow. (+) = absorption from the lumen; (−) = secretion into the lumen (see text).

Na is the only substance for which active transport has been demonstrated in this organ (16–20). Unlike the small intestine, glucose is not actively (12) nor to any extent (21) absorbed from the colon and has only a minimal effect on water movement when added to the mucosal solution in the everted rat colon (12). In our studies, absorption of Na and water from the colon was not altered by addition of 85–250 mg/100 ml glucose to isotonic NaCl solutions. The disappearance of small amounts of glucose from the perfusates during these studies could well be accounted for by bacterial utilization. On the other hand, Na and water absorption were influenced by the anions in the test solution. Replacement of Cl by HCO_3 reduced water absorption to zero, probably because of poor mucosal permeability to the HCO_3 ion.

Electrolyte movement across the colon. Fluid absorbed from isotonic NaCl solutions had calculated Na and Cl concentrations of 190 and 286 mEq/liter, respectively. The absorption of a moderately hypertonic fluid would explain our observation that NaCl solutions of 285–290 mOsm/kg usually assumed a slightly lower osmolality (278–285 mOsm/kg) during colonic perfusions.

Fluid filtered into hypertonic test solutions generally had lower calculated Na and Cl concenrations than the absorbed fluid of nonisotonic test solutions. At lower lumen-to-blood osmotic gradients, water entered the lumen while Na and Cl were still absorbed (Figs. 2 and 5). Calculations of the apparent electrolyte concentrations in the filtered fluids showed a continuous rise of the Na and Cl concentrations with rising osmotic gradients, but a relative constancy of the K concentration (see Table V). At higher osmotic gradients (test solutions of 450–1055 mOsm/kg), Na and Cl entered the lumen in a linear relationship to that of water (Fig. 5). Water flow into the colon in this part of the graph was caused by the forces of hypertonicity, whereas they were strongly counteracted by opposing absorptive factors at lower osmotic gradients. If the relationship of filtered water and electrolytes is calculated for infusion solutions of an osmolality above 450 mOsm/kg, a constant Na and Cl concentration of approximately 86 mEq/liter is obtained in the filtrate, while the K concentration in this fluid decreased from 52.3 mEq/liter at 600 mOsm/kg to 33.3 mEq/liter at 800 mOsm/kg and to 14.9 mEq/liter at 1055 mOsm/kg. The electrolyte composition of the osmotically filtered fluid can probably not be explained by osmotic filtration and solvent drag alone; osmotic changes of the transmucosal elec-

trical potential (15, 22), alterations of the reabsorptive processes, as well as true secretion, have to be considered.

States of equilibrium between lumen and blood. No net movement of water or any of the monovalent electrolytes occurred when isotonic solutions of a nonabsorbable substance such as mannitol, containing mean values of 4 mEq/liter Na, 3 mEq/liter Cl, 11.5 mEq/liter K, and slightly more than 11 mEq/liter HCO_3 (end point not determined), were placed into the colon. Such a solution can be termed "steady-state solution," as it probably will not affect water and electrolyte balance of the body. Large gradients of Na and Cl between lumen and blood in the presence of a nonabsorbable substance ("univalent ion impoverishment" (23)) have previously been observed in the canine colon (24). Thus, the human colon absorbs Na against a lumen-to-blood gradient of 140 mEq/liter, whereas the human ileum maintains a Na gradient of 110 mEq/liter (25) and the human jejunum one of only 17 mEq/liter (25). The different equilibrium concentrations in the different intestinal regions are believed to be due to differences of intestinal pore size (25); a large lumen-to-blood gradients of Na and Cl are possible because the colon is a relatively tight structure which impedes "leakage" of absorbed Na and Cl into the lumen.

If solutions contain Na, K, Cl, and HCO_3 alone, a "final common sorption fluid" (9) similar to that previously found in canine colon (9) and containing approximately 139 mEq/liter Na, 12.9 mEq/liter K, 50 mEq/liter Cl, and 103 mEq/liter HCO_3, will be attained during colonic perfusions. Absorption of such a solution proceeds at a slower rate than that of isotonic NaCl, probably because of limited absorption of HCO_3.

The permeability of the colon. It has been stated in the past that "the colon is less permeable than the small intestine" (26). This view was supported by studies of mannitol diffusion from rat intestine (16). A quantitative comparison of the absorption from different intestinal regions remained difficult, however, because the mucosal surface areas of different parts of the gut were not comparable. When expressed per serosal length of perfused bowel segment, the absorption of water and electrolytes appeared to be more rapid from the small than from the large intestine in dog (27–29) and man (1, 8). However, when absorption was calculated in relation to the mucosal surface area which was estimated from both macroscopic and microscopic measurements, the rate of water absorption appeared greater in the colon than in the small intestine (27). The same difficulties in interpretataion are encountered when water filtration rates of upper and lower intestine are compared; for hypertonic solutions (800 mOsm/kg) containing mannitol and 140–150 mEq/liter NaCl, the filtration coefficient was 0.044 ml/min per mOsm in 20-cm segments of human jejunum (mean osmotic pressure gradient between 95 and 300 mOsm/kg (6) and only 0.0007 ml/min per mOsm for the total colon in the present studies (mean osmotic pressure gradient 455 mOsm/kg).

The principles underlying the determination of the reflection coefficient (7), as discussed by Fordtran et al. (6), are independent of mucosal surface area. The data obtained by this method in different intestinal regions, therefore, are comparable. Our results, taken together with those of Fordtran et al. (6), document the old suggestion that the permeability of the intestine decreases from jejunum to ileum to colon.

We found that hypertonic solutions of urea (molecular radius 2.3 A) are as effective in provoking water flow into the human colon as mannitol solutions (molecular radius 4.2 A) of the same osmolality. Mannitol has previously been used to measure the theoretic osmotic pressure (6, 10, 22), as it is not appreciably absorbed from the intestine (6, 15, 16, 30–32), a finding confirmed in our studies by measurement of urinary mannitol excretion during colonic perfusion with hypertonic mannitol solutions. As the effective osmotic pressure of urea solutions was identical to that of mannitol solutions, urea exerted its full theoretic osmotic pressure, i.e., the reflection coefficient (7) was equal to one. The equivalent pore radius of the human colon, therefore, has to be smaller than the molecular radius of urea; namely, less than 2.3 A. By the same method, the reflection coefficients and the pore radii were found to be 0.45 and 8 A respectively in the human jejunum and 0.8 and 5.0 A respectively in the human ileum (6). The low reflection coefficient in the jejunum reflects the observation that urea equilibrates freely between blood and jejunal contents (33–35). The maximal reflection coefficient in the colon, on the other hand, has to be interpreted as evidence that urea does not penetrate through the colonic mucosa.

This finding was confirmed by measuring other parameters of urea absorption in our experiments, such as urea recovery in the rectal effluent of both urea-containing and urea-free infusion solutions as well as blood urea nitrogen levels and urinary urea excretion during colonic perfusion with urea and mannitol. All these studies indicate that the permeability of the colon to urea is minimal at best. Studies on the metabolic complications after bilateral ureterosigmoidoscopy, however, suggested that some urea might be absorbed from the colon (36–38). Venous blood, draining the sigmoid, was found to contain more urea and ammonia than peripheral blood when urine was instilled into the rectum of dogs (38). When both ureters were implanted into the upper small intestine of dogs, the animals rap-

idly succumbed to uremia; when the ureters were implanted into the colon, however, they survived and only a transient postoperative rise of blood nitrogen was observed (39). A recent study of the colonic permeability to urea in heifers was interpreted as showing "diffusion of urea into the colonic lumen" (40). In these experiments, labeled urea was infused into the circulation and the cecal contents were collected through a cannula in the cecum. It seems, however, that the colonic contents may have been contaminated by urea-containing ileal fluid as the continuity of the intestine was preserved and the animals were not fasted. Thus, the reported animal studies remain inconclusive. If our conclusion that the human colon is almost impermeable to urea is correct, it would provide an explanation for the improvement of patients with hepatic coma after colonic exclusion and ileoproctostomy (41), as urea would no longer be available for bacterial degradation in the defunctionalized colon.

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