JCI The Journal of Clinical Investigation

The mechanisms of sodium absorption in the human small intestine

John S. Fordtran, … , Floyd C. Rector Jr., Norman W. Carter

J Clin Invest. 1968;47(4):884-900. https://doi.org/10.1172/JCI105781.

Research Article

The present studies were designed to characterize sodium transport in the jejunum and ileum of humans with respect to the effects of water flow, sodium concentration, addition of glucose and galactose, and variations in aniomic composition of luminal fluid. In the ileum, sodium absorption occurred against very steep electrochemical gradients (110 mEq/liter, 5-15 mv), was unaffected by the rate or direction of water flow, and was not stimulated by addition of glucose, galactose, or bicarbonate. These findings led to the conclusion that there is an efficiently active sodium transport across a membrane that is relatively impermeable to sodium. In contrast, jejunal sodium (chloride) absorption can take place against only the modest concentration gradient of 13 mEq/liter, was dramatically influenced by water movement, and was stimulated by addition of glucose, galactose, and bicarbonate. The stimulatory effect of glucose and galactose was evident even when net water movement was inhibited to zero by mannitol. These observations led to the conclusion that a small fraction of jejunal sodium absorption was mediated by active transport coupled either to active absorption of bicarbonate or active secretion of hydrogen ions. The major part of sodium absorption, i.e. sodium chloride absorption, appeared to be mediated by a process of bulk flow of solution along osmotic pressure gradients. The stimulatory effect of glucose and galactose, even at zero […]

Find the latest version:

https://jci.me/105781/pdf

The Mechanisms of Sodium Absorption in the Human Small Intestine

JOHN S. FORDTRAN, FLOYD C. RECTOR, JR., and NORMAN W. CARTER

From the Department of Internal Medicine, The University of Texas Southwestern Medical School at Dallas, Dallas, Texas

ABSTRACT The present studies were designed to characterize sodium transport in the jejunum and ileum of humans with respect to the effects of water flow, sodium concentration, addition of glucose and galactose, and variations in anionic composition of luminal fluid. In the ileum, sodium absorption occurred against very steep electrochemical gradients (110 mEq/liter, 5–15 mv), was unaffected by the rate or direction of water flow, and was not stimulated by addition of glucose, galactose, or bicarbonate. These findings led to the conclusion that there is an efficiently active sodium transport across a membrane that is relatively impermeable to sodium. In contrast, jejunal sodium (chloride) absorption can take place against only the modest concentration gradient of 13 mEq/liter, was dramatically influenced by water movement, and was stimulated by addition of glucose, galactose, and bicarbonate. The stimulatory effect of glucose and galactose was evident even when net water movement was inhibited to zero by mannitol. These observations led to the conclusion that a small fraction of jejunal sodium absorption was mediated by active transport coupled either to active absorption of bicarbonate or active secretion of hydrogen ions. The major part of sodium absorption, i.e. sodium chloride absorption, appeared to be mediated by a process of bulk flow of solution along osmotic pressure gradients. The stimulatory effect of glucose and galactose, even at zero water flow, was explained by a model in which the active transport of monosaccharide generates a local osmotic force for the absorption of solution (NaCl and water) from the jejunal lumen, which, in the presence of mannitol, is counterbalanced by a reverse flow of pure solvent (H_2O) through a parallel set of channels which are impermeable to sodium. Support for the model was obtained by the demonstration that glucose and bicarbonate stimulated the absorption of the nonactively transported solute urea even when net water flow was maintained at zero by addition of mannitol to luminal contents.

INTRODUCTION

In the process of absorbing salt and water in the small intestine, sodium can be moved against both an electrical and a chemical concentration gradient (1, 2). This has led to the conclusion that the primary mechanism is the active pumping of sodium from lumen to interstitium with secondary movement of the anion and water. The observation that the addition of actively transported sugars (including the nonmetabolizable 3-methyl-glucose) and amino acids accelerates sodium transport has led to the conclusion that active monosaccharide and amino acid transport is coupled to and is able to stimulate the sodium pump (3–5). The role of passive processes has not been clearly defined, but it is generally assumed that passive leak of sodium tends to dissipate the gradients generated by the sodium pump and thus reduce its efficiency.

The characteristics of the sodium absorptive process do not appear to be the same in all segments of the small intestine, at least in some animal species. In early studies, Visscher found that isotonic saline solutions were rapidly absorbed in

Address requests for reprints to Dr. John S. Fordtran, Department of Internal Medicine, The University of Texas Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Tex. 75235.

Received for publication 10 July 1967 and in revised form 20 November 1967.

the ileum but not in the jejunum or duodenum of the dog (6). These differences were confirmed and extended by McHardy and Parsons (7) and by Hindle and Code (8), but in man, isotonic saline is absorbed at approximately the same rate in the jejunum and ileum (9, 10). However, this finding that the absorption rate of sodium chloride in the upper and lower human small intestine is the same does not necessarily mean that the characteristics of the transport processes are also the same. Previous studies in our laboratory on the permeability of the jejunum and ileum suggest that forces that influence passive movement of salt and water might play a major role in the jejunum and only a minor role in the ileum (11, 12).

The present studies were designed to characterize sodium transport in the jejunum and ileum of humans with respect to: (*a*) bulk water flow, (*b*) sodium concentration gradients, (*c*) addition of glucose and galactose, and (*d*) variations in anionic composition of luminal fluid. In addition, the effect of glucose and bicarobonate on the potential difference between intestinal lumen and skin was determined, and the effect of lumen osmolality on net water movement was measured.

METHODS

Normal male and female subjects between the ages of 21 and 65 yr were studied by a perfusion technique developed by Ingelfinger and co-workers. The small bowel was intubated with a triple-lumen tube under fluoroscopic control. Test solutions containing a nonabsorbable marker, polyethylene glycol, were infused at a constant rate (8, 9, 12, or 16 ml/min, depending on the experiment) through the most proximal tube, and the perfusate was collected through the two distal tubes 10 and 35 or 40 cm beyond the infusion point. Net water and electrolyte movement in the test segment (between the two collecting-sites) were determined by methods previously described (11–13). Jejunal studies were carried out when the infusion point was at the ligament of Treitz, and ileal studies when the infusion point was 225 cm from the incisor teeth. Mean solute concentration in the test segment was computed by arithmetically averaging the concentrations of solute in the fluid collected from each end of the segment. Practically identical results were obtained with logarithmic averages because the difference in solute concentration in fluid collected from the two collection sites was generally small. Mean osmolality in the test segment was calculated by plotting the osmolality of fluid obtained from the proximal and distal ends of the test segment on semilogarithmic paper and taking the midpoint value (see reference 11 for a validation of this method).

In many of these experiments net water movement was systematically varied in three consecutive test periods by varying the amount of mannitol added to the infused test solutions. For instance, one test solution might consist of a slightly hypotonic (260 mOsm/kg) electrolyte solution without mannitol. Rapid water absorption in the test segment would occur with this solution. The second solution might contain, in addition to electrolytes, 50 mM mannitol, and under these circumstances net water movement in the test segment would be near zero. Finally, the third solution would contain, in addition to electrolytes, 150 mM mannitol, and this solution would elicit rapid secretion of water into the test segment. Whereas the magnitude and direction of net water flow was easily controlled in this fashion, special precautions had to be taken in order to insure equal mean flow rates within the test segment. If, for instance, the same electrolyte solution was infused at the same rate once with and once without added mannitol, mean flow rate in the test segment would be higher with the mannitol-containing solution which elicited secretion, than with the non-mannitol-containing solution which was absorbed. This problem was solved by varying the rate at which the test solution was infused into the intestine and by varying the rate of collection from the proximal collecting tube. Specifically, the rate of infusion was slower, and the rate of collection via the proximal tube was higher when secretion, rather than absorption, was anticipated within the test segment. Another methodologic problem presented by such experiments was that of maintaining equal mean sodium concentrations within the test segment. If sodium concentrations were equal in two test solutions, one with and one without mannitol, the mean concentration within the test segment would be lower with the test solution that contained mannitol, rather than with the test soluion without mannitol, since with mannitol the volume of intestinal contents increases and without mannitol the volume of the intestinal contents decreases. This problem was solved by varying the concentration of sodium in the test solutions. Specifically, test solutions containing mannitol had a higher concentration of sodium than those without mannitol.

In designing a series of experiments, the composition of test solutions and the infusion rates necessary to accomplish any particular mean sodium concentration and mean flow rate were calculated from the data on filtration coefficients and reflection coefficients for sodium chloride in the human intestine that were previously published from this laboratory (11). The experimental conditions necessary to achieve the desired flow rates and sodium concentrations within the test segment were then confirmed by preliminary studies. For instance, in one set of studies the effect of water movement on sodium absorption was studied. It was decided to keep mean sodium concentration in the test segment at approximately 125 mEq/liter L and to have mean flow rates within the test segment of about 11 ml/min. The test solutions, infusion rates, and the rate of sampling from the proximal collecting tube in one subject are presented in Table I. It is evident that approximately equal mean flow rates and mean sodium concentrations in the test segment

TABLE I

Experiment 210. Example of Technique Used to Maintain Approximately Equal Flow Rate and Sodium Concentration in Test Segment when the Rate and Direction of Water Flow are Changing

Test solution infused	Rate of infusion	Rate of sampling proximal tube	Flow rates			Sodium concentration		
			Entering segment	Leaving segment	Mean	Entering segment	Leaving segment	Mean
	ml/min	*ml/min*		*ml/min*			*mEq/liter*	
NaCl, 110 *mmoles/liter*	16	1.9	12.6	10.1	11.3	117.5	127.7	123
NaCl, 140 *mmoles/liter* Mannitol, 65 *mmoles/liter*	10	2.0	10.9	10.6	10.8	123.0	126.2	124
NaCl, 175 *mmoles/liter* Mannitol, 165 *mmoles/liter*	9	3.5	11.1	14.8	12.9	134.5	118.5	127

were obtained, even though the test solutions that were actually infused and the infusion rates were quite different. This is typical of these experiments, and these results were not the best of the group. In analyzing five such triple studies, the average mean flow rate and the average sodium concentration for the three study periods were almost identical.

Potential difference between skin and intestinal lumen was measured with an intraenteric electrode that was attached to the perfusion tube midway between the proximal and distal collection sites. The intraenteric electrode was constructed from a one-half inch piece of glass tubing which had an approximately 2-mm O.D. An asbestos wick was fused into one end of the glass; the glass tubing was then ground off to allow a constant but slow leak of its internal contents (3 M potassium chloride) through the asbestos wick. The resistance of the electrode was ultimately set at approximately 7–14,000 ohms by alternately grinding and testing the resistance of such an electrode against a calomel half-cell. A silver silver chloride wire was then cemented (with epoxy resin) into the glass tubing, which previously had been filled with 3 M potassium chloride. A 300 cm peiece of enameled copper wire enclosed in polyvinyl tubing was soldered to the silver silver choride electrode. A portion of the polyvinyl tubing which covered the copper wire was slipped down over the glass tubing which contained the asbestos wick in such a way that only the end surface containing the asbestos wick was exposed to enteric contents. The other end of the copper wire was attached to the high impedance side of a Keithley 610A eletrometer (Keithley Instruments, Cleveland, Ohio). Before actual use of this electrode system in an experiment, the potential between the glass electrode and the reference electrode (see below) was tested in a variety of solutions; only those glass electrodes which gave a potential difference of less than 5 mv in normal saline, 0.5 M sodium bicarbonate, and 5% glucose were used.

The reference for this system was a Beckman skin electrode. Before applying the skin electrode, the skin was vigorously scrubbed with alcohol to remove lipid material, and three needle pricks were made in the skin at the site where the electrode was to be attached. Beckman electrode paste was used to apply the skin electrode. At the start of an experiment a small amount of paste was allowed to extend from under the skin electrode, and the glass–asbestos wick electrode was inserted into this paste. Any potential difference between the two electrodes was eliminated by means of a "bucking potential." After this procedure, the subject then swallowed the tube assembly containing the asbestos glass electrode, and measurements of potential difference between skin and gut were determined. Since the electrical resistance of these electrodes was low, it was not necessary to utilize a copper-screened room for these experiments. Fluctuations in potential difference were very small (less than 1 mv).

Electrolyte, sugar, and polyethylene glycol concentrations were measured with previously described techniques (11, 12). Urea was measured by a urease technique using a Conway microdiffusion apparatus (14).

When results of these experiments are given as a mean value, as in Figs. 3 and 4 and Tables II and III, the number of subjects studied and 2 SE of the mean are indicated on the figures or in the tables. When each result is plotted individually, as in Figs. 1, 2 (top part), 5, 6, 7, and 9, each symbol represents a single observation in one subject. Since an attempt was made to study each subject with three different test solutions, the number of different subjects actually studied for a given experiment may be roughly estimated by dividing the number of symbols by three. Occasionally a test was unsuccessful (wrong solution prepared, tube moved during the experiment, tube that became plugged with mucus and failed to drain, etc.), and hence the number of observations reported is not always an exact multiple of three. When data were collected to determine the effect of monosaccharides or bicarbonate on sodium, urea, and water transport (Figs. 4, 5, 7, and 9 and Tables II and III), the order of study (with and without sugars or bicarbonate) among the different subjects was randomized. However, subjects did not always return for their second series of tests, and the number of subjects actually studied with and without glucose or bicarbonate was not necessarily the same. The greatest discrepancy for this is shown in Fig. 5A, wherein we attempted to study 16 patients with and without glucose. All 16 subjects were studied with glucose, however one of the three test solutions for one subject was prepared incorrectly, therefore the total

number of observations was 47. 13 of these same subjects were sutdied without glucose, for a total of 39 observations; three subjects, studied first with glucose, did not return for their second study.

RESULTS

Effect of water movement on sodium absorption. The effect of the magnitude and direction of water movement (manipulated by mannitol concentration in the test solution) on sodium (chloride) absorption was compared in the jejunum and ileum when mean sodium concentration and mean flow rate in the test segment were approximately 110 mEq/liter and 10 ml/min, respectively. This concentration of sodium was selected because it approximates the sodium concentration in intestinal fluid after normal meals (15). As shown in Fig. 1, sodium absorption in the jejunum and ileum differed markedly. When net water movement across the intestinal wall was zero, sodium was secreted in the jejunum down a chemical concentration gradient, whereas in the ileum sodium was absorbed against its concentration gradient. More importantly, however, bulk movement of water had a dramatic effect on sodium transport in the jejunum but not in the ileum. Sodium absorption was more or less constant in the ileum regardless of whether water was absorbed or secreted into the intestinal lumen. In the jejunum the movement of water into the intestinal lumen enhanced sodium secretion, whereas absorption of water diminished sodium secretion and eventually promoted net sodium absorption against a concentration gradient.

Effect of sodium concentration. Since net water movement has such a marked influence on sodium absorption in the jejunum, the concentration gradient against which sodium transport can occur in this area of the gut must be measured under carefully controlled conditions with respect to water movement. It is impossible to measure this limiting concentration gradient simply by studying solutions with progressively lower sodium concentrations (keeping osmolality constant by some inert solute such as mannitol), since these different test solutions evoke different rates and directions of water movement, which, in turn, affect sodium absorption. In order to establish the chemical concentration gradient against which sodium can be absorbed in the jejunum, the rate of sodium movement when water movement was zero was determined for a number of different luminal sodium concentrations. Sodium movement (positive values = secretion or gain to lumen, negative values = absorption or loss from lumen) at zero water flow was + 4.8 mEq/hr per 30 cm when sodium concentration was 112 mEq/liter (Fig. 1, corrected from 4.0 mEq/hr per 25 cm), + 1.2 mEq/hr per 30 cm when sodium concentration was 123 mEq/liter (Fig. 5), − 0.2 mEq/hr per 30 cm when sodium concentration was 127 mEq/liter (Fig. 2), and − 3.5 mEq/hr per 30 cm when luminal sodium concentration was 140 mEq/liter (Fig. 2). As shown in Fig. 2, by plotting these measured values for sodium movement at zero water flow against luminal sodium concentration, it was determined that sodium movement was zero at zero water flow when luminal sodium concentration was 127 mEq/liter. When luminal sodium concentration was less than this value, sodium was secreted, and when luminal sodium concentration was higher than 127 mEq/liter, sodium was absorbed. Thus, sodium as the chloride salt can be absorbed against a gradient of only 13 mEq/liter in the human jejunum, assuming plasma sodium concentration to be 140 mEq/liter. In addition to establishing the gradient against which sodium can be absorbed in the jejunum, these data demon-

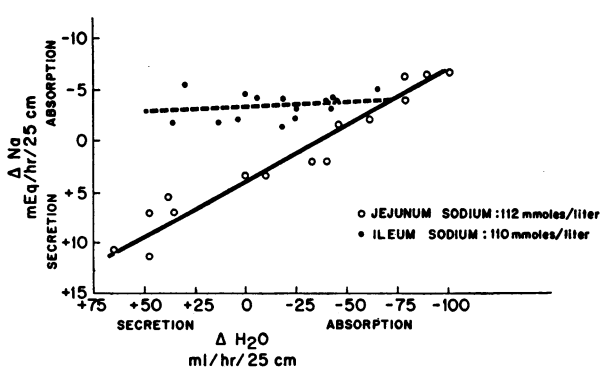

FIGURE 1 Effect of water flow on sodium (chloride) movement in jejunum and ileum. The sodium concentration in the test segment was 112 mM ± 2.3 in the jejunal and 110 mM ± 1.5 in the ileal studies. Regression lines are calculated by the method of least squares. Positive values indicate net secretion (gain to the lumen) and negative values indicate absorption (loss from the lumen).

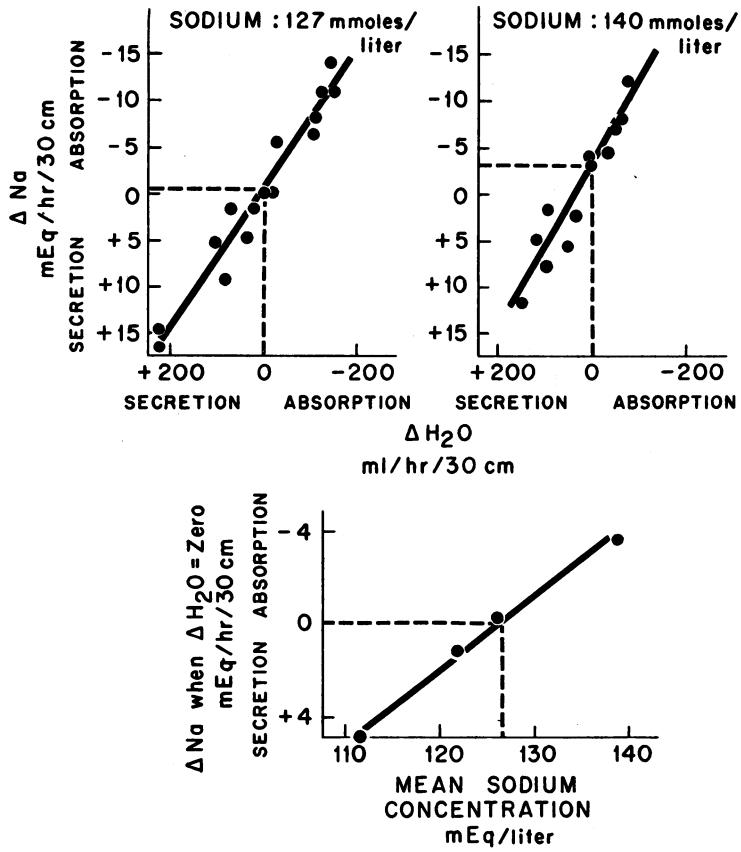

FIGURE 2 Sodium movement at zero water flow for different luminal sodium (chloride) concentrations. The studies in the upper part of the diagram were carried out with a luminal sodium concentration of 127 and 140 mEq/liter. For each concentration the rate of sodium movement is plotted against the rate of water movement. Regression lines are by the method of least squares. The rate and direction of sodium movement at zero water flow is calculated (dotted lines), and plotted in the lower part of the diagram as a function of luminal sodium concentration. The other two points are calculated from the data in Figs. 1 (for 112 mEq/liter) and 5 (for 123 mEq/liter). Note that sodium absorption is zero at zero water flow when luminal sodium (chloride) concentration is 127 mEq/liter.

strate that sodium as the chloride salt can be absorbed from the jejunum in the absence of water flow, glucose, or bicarbonate, but only when luminal concentration is nearly equal to that of plasma.

Measurement of the gradient against which sodium can be absorbed in the ileum was relatively simple, because sodium and mannitol concentrations can be reciprocally varied without much change in water movement, and because water movement exerts a relatively small effect on sodium movement, as shown in Fig. 1. Sodium absorption was therefore measured when mean sodium chloride concentration in the test segment was 124 (nine studies), 75 (11 studies), 36 (13 studies), and 16 mEq/liter (five studies). All test solutions were made isotonic to plasma by adding appropriate amounts of mannitol and all contained 30 mM glucose (see below for effect of glucose).

The results of these ileal experiments are shown in Fig. 3, and it is evident that ileal sodium absorption does not cease until the luminal concentration is less than 30 mEq/liter, i.e., the ileal mechanism for sodium absorption can operate against a gradient of about 110 mEq/liter. Sodium absorption reached near maximum rates when its concentration was 75 mEq/liter, and increased only slightly when concentration was raised above this level. Thus, the sodium absorptive mechanism exhibits some evidence of saturation kinetics. Chloride absorption was also measured in these experiments and, as shown in Fig. 3, chloride was absorbed even when mean chloride concentration in the test segment was as low as 16 mEq/liter, indicating that this anion can be absorbed against a gradient of at least 84 mEq/liter (assuming normal plasma chloride levels of 100 mEq/liter). Furthermore, the absorption of chloride is a linear function of chloride concentration, with no evidence of saturation phenomena within the range of chloride concentrations studied.

Effect of glucose and galactose on sodium absorption. Previous *in vitro* and *in vivo* studies in animals have shown that glucose stimulates sodium absorption; it has also been shown that glu-

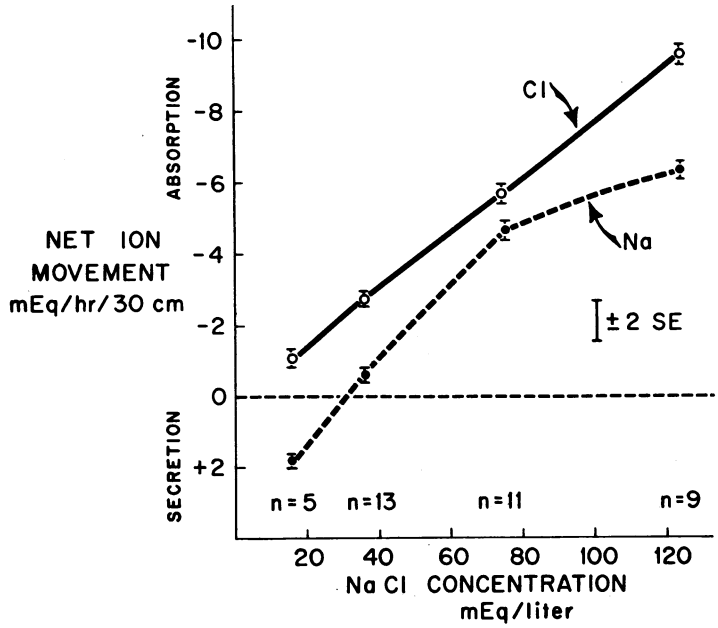

FIGURE 3 Effect of luminal NaCl concentration on sodium and chloride movement in the ileum. The number of studies at each concentration is indicated.

cose in luminal fluid stimulates sodium absorption in the human jejunum (2). The number of studies carried out in the human ileum has been too few to determine whether or not glucose stimulates sodium absorption in this area, although most animal studies showing an effect of glucose were actually carried out in the lower small bowel.

In the present experiments, mean sodium and chloride concentrations in the test segment were maintained at approximately 110 mEq/liter. Infused test solutions contained either zero, 25, or 105 mM glucose in the jejunal studies, and either zero, 15, or 90 mM glucose in the ileal studies. Mannitol was added in amounts necessary to keep the sum of glucose and mannitol concentrations equal in each solution. The effect of mean glucose concentration in the test segment and of glucose absorption rate on sodium movement in the jejunum and ileum is shown in Fig. 4. In the jejunum, glucose absorption had a markedly stimulatory effect on sodium absorption, whereas in the ileum the glucose concentration in the test segment and the rate of glucose absorption had no significant effect on sodium absorption. Although data on water movement are not recorded in Fig. 4, glucose stimulated water absorption in both the upper and lower small bowel.

The mechanism of the stimulatory effect of glucose on sodium absorption in the jejunum is not clear from these data. Two major possibilities are that glucose stimulates active sodium absorption per se, or that the active transport of glucose stimulates water movement, which, in turn, promotes the passive absorption of sodium. In order to evaluate these two possibilities, the absorption rate of sodium in the presence and absence of glucose was studied at varying rates and directions of water movement, while sodium concentration was maintained at a constant level. In this way, two regression lines could be obtained, one with and one without glucose. Since sodium concentration was constant, the effect of glucose on sodium absorption, independent of water movement, could be ascertained. Subjects were studied with three test solutions, designed to produce different rates of water movement, on 2 separate days, 1 day with

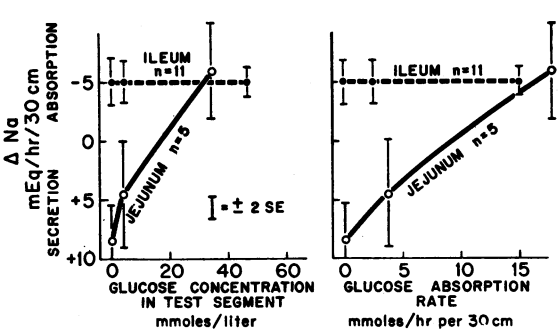

FIGURE 4 Effect of glucose concentration and absorption rate on sodium movement when sodium (chloride) concentration was 110 mM ± 2.6.

glucose, and 1 day without. The order of test days (with or without glucose) was randomized.

In one set (five subjects) of studies 50 mM glucose was added to the test solution on the test day that glucose was present. Absorption of glucose was rapid, so that the mean glucose concentration in the test segment was only 7.7 mmoles/liter. The regression line with glucose was slightly higher with than without, but the differences were not significantly different statistically.

A second set of studies was carried out using from 70 to 90 mM glucose in the test solutions (depending on the infusion rate, etc., as described in Methods). Under these conditions, the glucose concentration in fluid aspirated from the proximal tube averaged 40 mmoles/liter, and mean glucose concentration in the test segment averaged 24.2. As shown in Fig. 5A, glucose clearly raised the regression line, so that for any given rate of net water movement, glucose stimulated sodium absorption in the jejunum. For instance, when water flow was zero, sodium was secreted at a rate of 1.8 mEq/hr per 30 cm without glucose, but absorbed at a rate of 4 mEq/hr per 30 cm in the presence of glucose. Similar studies were carried out in the ileum, and as shown in Fig. 5D, glucose does not significantly enhance sodium absorption when water flow is zero.

To see if an actively transported, but poorly metabolized, sugar would have a similar effect on jejunal sodium absorption, studies with and without galactose were carried out. As shown in 5B, galactose also stimulates jejunal sodium absorption at any given rate of water movement. When net water movement was zero, sodium movement was approximately zero in the absence of galactose and absorbed at a rate of approximately 4.5 mEq/hr per 30 cm in the presence of galactose. In the ileum, galactose had no statistically significant effect on sodium transport ($P > 0.3$),

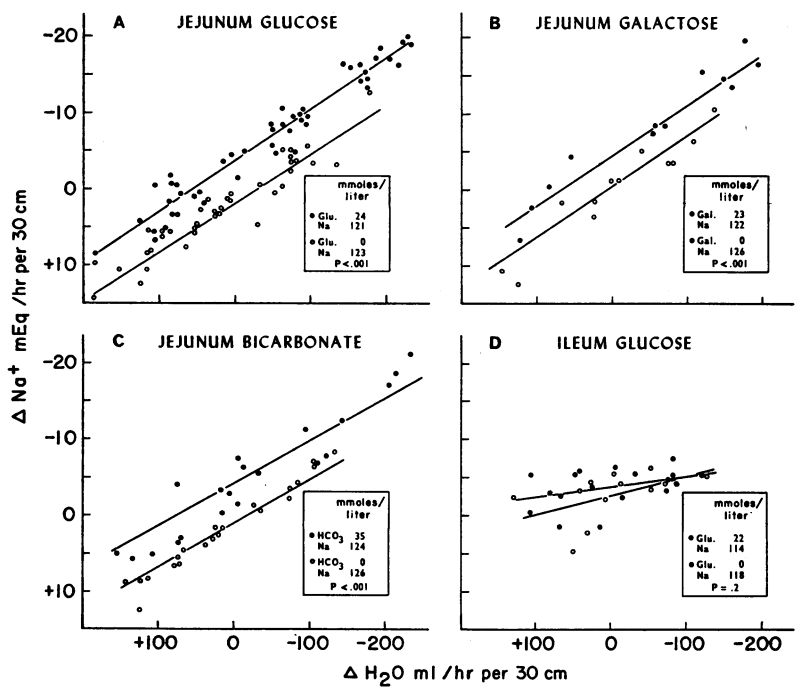

FIGURE 5 Effect of glucose, galactose, and bicarbonate on sodium movement in the jejunum, and effect of glucose on sodium movement in the ileum, at varying rates of water movement. The sodium and glucose concentration and mean flow rate in the test segment were the same regardless of the rate or direction of water movement (see Methods). The rate of sugar absorption in the studies with sugar was 19.3, 18.2, and 9.3 mmoles/hr per 30 cm in *A*, *B*, and *D*, respectively. The rate of bicarbonate absorption from the solutions containing bicarbonate in C was 12.4 mmoles/hr per 30 cm. The *P* values are calculated at zero water flow.

TABLE II

Effect of Galactose on Sodium and Water Movements in the Ileum (Results are Mean ± 2 SE of 12 Studies at each Galactose Concentration)

Galactose concentration in test segment	Galactose absorption	Mean [Na^+] in test segment	Na^+ absorption	H_2O absorption
mmoles/liter	*mmoles/hr per 30 cm*	*mEq/liter*	*mEq/hr per 30 cm*	*ml/hr per 30 cm*
0	0	108±1.4	2.5±2.2	13±16
35.1±4.0	9.9±2.2	108±0.6	3.1±1.4	28±13
57.6±6.6	14.4±3.2	108±1.2	3.8±1.8	36±11

although this sugar stimulates water absorption rate in the ileum, as shown in Table II.

Effect of Anion. Data in rats by McHardy and Parsons (7) and in humans by Malawer [1] have shown that jejunal sodium absorption is higher from solutions containing bicarbonate than from pure sodium chloride solutions, but the effect of these anions on sodium absorption has apparently not been studied in the human ileum.

Measurements of jejunal sodium absorption from test solutions containing 140 mEq/liter of sodium, 5 mEq/liter of potassium, and no glucose are shown in Table III. When infused test solutions contained chloride as the only anion, the mean bicarbonate concentration in the test segment was 2.1 mEq/liter, and sodium absorption was 3.4 mEq/hr per 30 cm. When infused test solutions contained 30 mEq/liter of bicarbonate, mean bicarbonate concentration in the test segment was 15.6 mEq/liter and sodium absorption increased to 4.9 mEq/hr per 30 cm. Finally, when infused test solutions contained 70 mEq/liter of bicarbonate, mean luminal bicarbonate concentration was 29.8 mEq/liter and sodium absorption rose to 9.7 mEq/hr per 30 cm. These studies therefore confirm the observation that bicarbonate in jejunal contents stimulates sodium absorption in this area of the small bowel. Water absorption was also stimulated by bicarbonate. In contrast, sodium and water absorption in the ileum were unaffected by bicarbonate concentration or the direction and rate of bicarbonate and chloride movement, as also shown in Table III.

These experiments, in which chloride and bicarbonate concentrations in the test solutions were reciprocally varied, also demonstrate that bicarbonate is preferentially absorbed in the jejunum, whereas chloride is preferentially absorbed in the ileum. For instance, in the jejunum, bicarbonate absorption exceeded that of chloride even when luminal bicarbonate concentration was less than that of plasma and chloride concentration exceeded that of plasma (Table III, row 2). Furthermore, bicarbonate, but not chloride, is absorbed against a concentration gradient in the jejunum. On the other hand, in the ileum, chloride is absorbed against steep concentration gradients (Table III and Fig. 3). Although not demonstrated here, previous studies have suggested that in association with ileal chloride absorption, there is a secretion of bicarbonate (16).

In order to study the stimulatory effect of bicarbonate on jejunal sodium absorption in greater detail, the effect of bicarbonate on jejunal sodium transport at different rates of water flow was measured. Seven subjects were studied with three

[1] Malawer, S. J. Unpublished observations.

TABLE III

Effect of Variations in Bicarbonate and Chloride Concentrations (mEq/liter) on Electrolyte Movement (mEq/hr per 30 cm) and Water Absorption (ml/hr per 30 cm) in the Jejunum and Ileum (Mean Values ± 2 SE of Mean are Given. A Minus Sign Denotes Absorption, a Positive Sign Secretion)

Mean [HCO_3^-] in test segment	HCO_3^- movement	Mean [Cl^-] in test segment	Cl^- movement	Mean [Na^+] in test segment	Na^+ movement	H_2O movement
Jejunal studies, *n = 18*						
2.1±0.4	+0.4±0.2	137 ±1.4	−4.9±1.4	138±0.7	−3.4±1.3	−31±19
15.6±2.2	−4.7±2.1	124 ±0.2	−2.7±1.8	137±0.5	−4.9±1.6	−38±24
29.8±3.6	−12.5±1.8	104 ±5.3	+0.7±3.3	138±0.6	−9.7±2.4	−76±36
Ileal studies, *n = 12*						
8.2±1.3	+2.5±0.5	100 ±2.0	−6.4±1.2	111±2.3	−4.6±1.2	−48±15
48.3±1.8	−2.9±1.1	61.2±1.8	−1.3±0.6	112±0.9	−5.0±1.6	−52±20

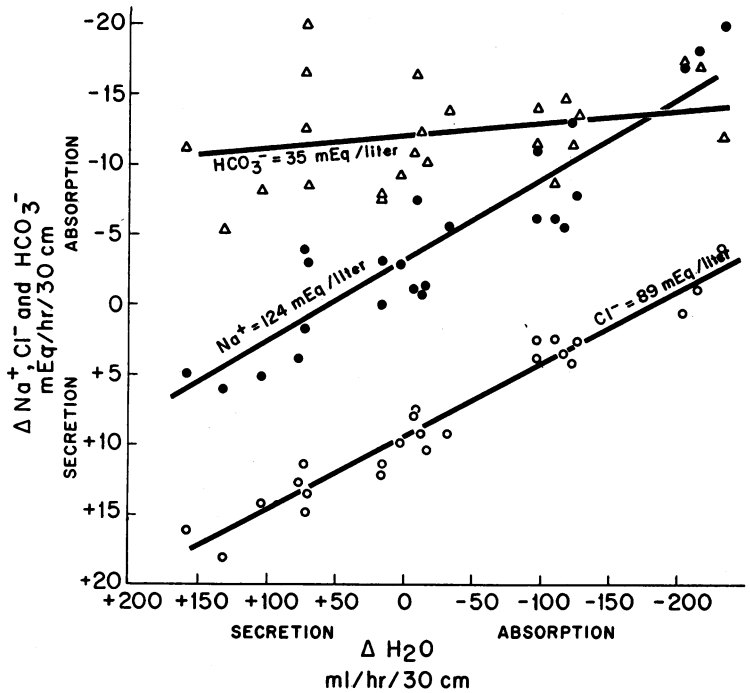

FIGURE 6 Effect of water flow on sodium, chloride, and bicarbonate movement in the jejunum when luminal concentration of these ions was constant at the specified value, regardless of the rate or direction of water movement.

test solutions on 2 separate days, 1 day when mean bicarbonate concentration in the test segment was 35 mmoles/liter, the other day with no bicarbonate. Water movement was manipulated by the amount of mannitol added to the three test solutions. Results are shown in Fig. 5C. At every level of water movement, sodium absorption was greater in the presence of bicarbonate than in its absence. Thus, the addition of bicarbonate to jejunal contents had much the same effect on sodium absorption as glucose: both enhance net sodium absorption independent of any effect on over-all net water movement.

In the jejunal studies just reported, on the test day when luminal contents contained 35 mM bicarbonate, the concentrations of bicarbonate, sodium, and chloride were constant no matter what the direction or rate of water movement. Consequently, these studies also demonstrated the relative degree to which the jejunal movement of these ions is affected by water flow. It is evident in Fig. 6 that whereas sodium and chloride movement are flow-dependent, bicarbonate absorption is relatively independent of water movement. Bicarbonate absorption was almost as high when water absorption was rapid as when net secretion of water into the jejunal lumen was occurring. It is also evident in Fig. 6 that at every level of water flow the absorption of sodium was greater than that of chloride; the difference represents that sodium absorbed in association with bicarbonate. The relatively constant difference between sodium and chloride at different water flows indicates that the sodium absorbed as sodium bicarbonate is flow-independent, and only that portion absorbed as sodium chloride is influenced by water movement.

Effect of glucose and bicarbonate on urea absorption. The data just presented have demonstrated that both glucose and bicarbonate enhance the absorption rate of sodium from the jejunum, even when water movement is zero. To examine the specificity of this enhancement, the effect of glucose and bicarbonate on the movement of a passively absorbed, noncharged solute was investigated. We chose to study urea, since our previous experiments showed that urea and sodium chloride have approximately the same reflection coefficient in the jejunum (11) and since all the data so far reported on urea absorption suggest that there is no active intestinal transport for this solute (17).

Our results with urea are shown in Fig. 7. In the jejunum we found that both glucose and bicarbonate stimulate urea absorption. For instance, as shown in Fig. 7A, at zero water movement in the absence of glucose there was a modest secre-

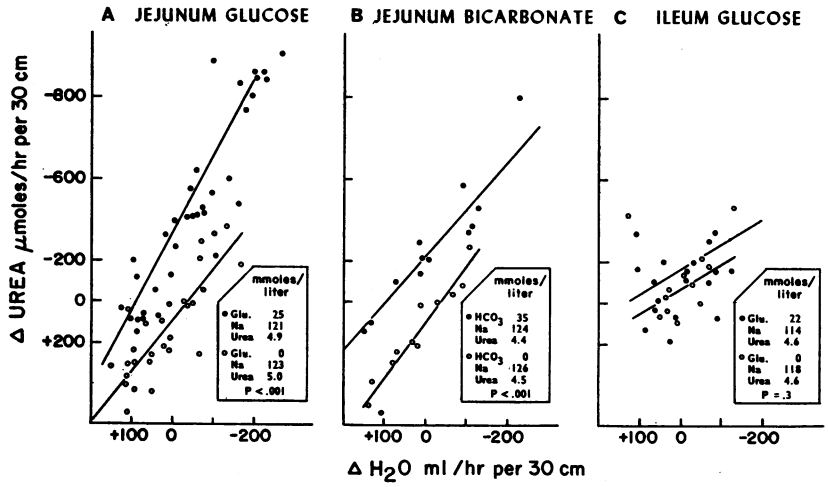

FIGURE 7 Effect of glucose on urea movement in the jejunum (A) and ileum (C) at varying rates of water movement, and of bicarbonate on urea movement in the jejunum (*B*). Mean plasma urea was 4.9 mmoles/liter in these subjects. The *P* values are calculated at zero water flow.

tion of urea into the lumen, whereas in the presence of glucose there was a significant absorption of urea. Bicarbonate had a similar effect, as shown in Fig. 7B. Since the concentration of urea in the luminal fluid and plasma were the same in these experiments, this net absorption of urea at zero water movement cannot be attributed to diffusion down a concentration gradient.

In the ileum, glucose did not significantly enhance urea absorption ($P = 0.3$), as shown in Fig. 7C.

Potential difference (PD). Results of a typical experiment are shown in Fig. 8. The top part of the figure gives results obtained in the jejunum, the lower part the results in the ileum. In the esophagus the PD was approximately −2 mv, in

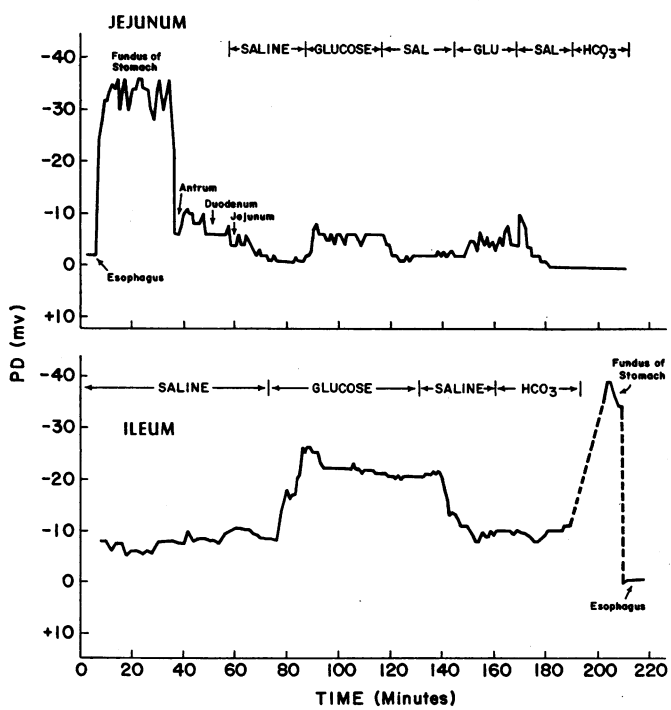

FIGURE 8 Potential difference (lumen to skin) during perfusion with saline, saline with glucose, and saline–bicarbonate solutions. Positive and negative values are in reference to the intestinal lumen.

TABLE IV

Potential Difference between Intestinal Lumen and Skin (Mean of Five Studies)

Jejunum			Ileum		
	PD			PD	
Solution perfused*	Mean	Range	Solution perfused*	Mean	Range
120 mM NaCl 20 mM Mannitol	+0.6	[(+10)−(−10)]	110 mM NaCl 60 mM Mannitol	−5	[(0)−(−8)]
140 mM NaCl 70 mM Glucose	−4	[(+4)−(−15)]	110 mM NaCl 60 mM Glucose	−15	[(−9)−(−22)]
50 mM NaCl 70 mM $NaHCO_3$ 35 mM Mannitol	+1	[(+11)−(−9)]	50 mM NaCl 60 mM $NaHCO_3$ 60 mM Mannitol	−5	[(+1)−(−8)]

* All solutions had 5 mM KCl and were infused at a rate of 12 ml/min.

the stomach fundus it was −34 mv, and in the stomach antrum it was from −8 to −6 mv. Upon entering the duodenum the PD fell to approximately −6 mv and during perfusion of the jejunum with a sodium chloride solution (Table IV) the PD fell to −1 mv. Addition of glucose caused the PD to become more negative, increasing to −6 mv. By alternating saline and saline–glucose solutions it was demonstrated that these PD changes were reproducible. Finally, the substitution of bicarbonate for chloride had no effect on PD. As shown in the bottom part of Fig. 8, the PD in the ileum during saline infusion was −8 mv. The addition of glucose had a definite and sustained effect, increasing the PD to approximately −22 mv. As in the jejunum, bicarbonate had no effect on PD. When the electrode was removed, the PD was −39 mv in the fundus of the stomach and zero in the esophagus.

Four other similar studies were performed, with the perfusion solutions given in Table IV. These solutions were chosen so that water absorption rate would be approximately zero and sodium concentration was constant at the midpoint of the test segment (where PD was measured). All of the infused solutions contained 5 mEq/liter of potassium. By using these solutions, diffusion potentials and streaming potentials were minimized. The results of the PD measurements are summarized in Table IV. In the jejunum, the average PD was +0.6 mv during saline perfusion and −4 mv in the presence of glucose. Substitution of bicarbonate for chloride in the saline perfusions had no effect on PD. In the ileum the average PD during saline perfusion was −5 mv, and glucose caused the PD to become more negative, the average value being −15 mv. Substitution of bicarbonate for chloride had no effect on ileal PD.

Effect of osmolality on water movement, with and without glucose and bicarbonate. Many of the studies carried out in these experiments involved manipulation of water movement in the presence or absence of glucose or bicarbonate, while sodium concentration was maintained at a constant level. As already explained, the water movement was varied by manipulating the osmolality (with mannitol) within the test segment. It was possible therefore from these studies to ascertain the effect of osmolality on water flow, in the presence or absence of glucose or bicarbonate while sodium concentration was constant. The results in the jejunum with and without glucose are shown in Fig. 9A and demonstrate several points. First, water movement is linearly related to osmolality within the test segment. Second, when sodium concentration is approximately 120 mmoles/liter, the osmolality of fluid within the test segment that is associated with zero water flow is 290 mOsm/kg when glucose is absent, and 320 mOsm/kg in the presence of 24.2 mM glucose. Thus, in the absence of actively transported sugars the jejunum cannot absorb water from 120 mM sodium chloride solutions against an osmotic pressure gradient, whereas in the presence of 24 mM

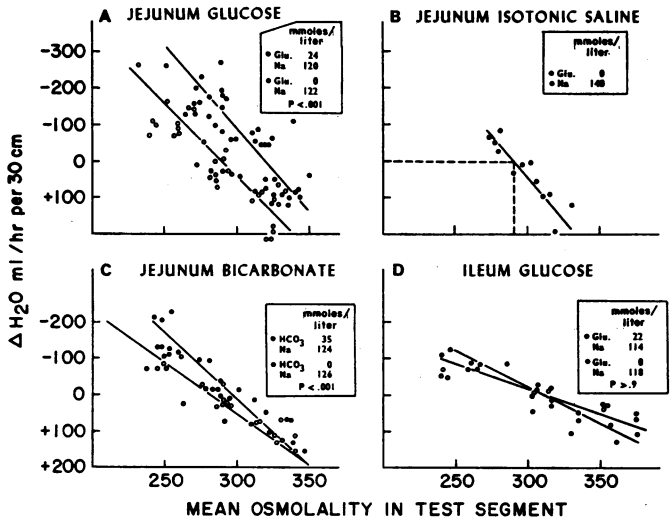

FIGURE 9 Effect of osmolality on jejunal and ileal water movement. In A the effect of glucose with 120 mM sodium chloride in the jejunum is shown; in B the effect of osmolality on jejunal water flow is shown for a luminal solution of 140 mM sodium chloride; in C the effect of bicarbonate is shown; and in D the effect of glucose with 114 mM sodium chloride in the ileum is shown. The *P* values are calculated at zero osmotic pressure gradient, assumed to be 290 mOsm/kg.

glucose, water is absorbed from such solutions against an osmotic pressure gradient of 30 mOsm/kg (assuming plasma osmolality of 290 mOsm/kg). Data presented in Fig. 9B demonstrate that when the jejunal contents contain 140 mM sodium chloride, zero water flow is associated with a lumen osmolality of 290 mOsm/kg. Thus, even when luminal contents contain sodium (chloride) in the same concentration as plasma, the jejunum cannot absorb water against an osmotic pressure gradient in the absence of glucose.

As shown in Fig. 9C, when the jejunal test segment contained 34.8 mM bicarbonate, the osmolality of luminal fluid associated with zero water flow was 297 mOsm/kg. The sodium chloride control studies for this series of observations revealed an osmolality of 283 mOsm/kg at zero water flow, and this value is significantly different from the value with bicarbonate. Thus, although the difference from control studies was small, the substitution of bicarbonate for chloride does appear to promote water absorption against a slight osmotic pressure gradient.

As shown in Fig. 9D, the osmolality of ileal contents associated with zero water flow when luminal fluid contained 114–118 mEq/liter of sodium chloride was 312 mOsm/kg. The addition of glucose did not change the gradient against which the ileum absorbed water.

DISCUSSION

Previous studies have shown that the rate of absorption of sodium and water from isotonic saline solutions is approximately the same in the human jejunum and ileum. Although this suggests that the absorptive processes are similar, the present studies show marked differences in four important respects: sodium absorption in the jejunum can occur against only slight concentration gradients, is markedly influenced by net water flow, and is stimulated by the addition of actively transported sugars and by bicarbonate; whereas in the ileum, sodium absorption occurs against steep concentration gradients, and is not influenced by water flow, nor by the addition of sugars or bicarbonate.

Ileum. In the ileum sodium can be absorbed against large concentration gradients and against a potential difference of 5–15 mv, which suggests an active transport process for sodium. The ability of the ileum to transport against such steep gradients suggests also that the membrane has a low permeability for sodium chloride with little back leak. This is substantiated by the fact that sodium movement in the ileum is not influenced by bulk water flow, and by our previous studies showing a high reflection coefficient for sodium chloride in the ileum (11).

The finding that reciprocal variations in chloride and bicarbonate concentrations do not influence the rate of sodium absorption or the potential difference in the ileum may appear surprising in view of the fact that chloride is absorbed in preference to bicarbonate in this part of the small intestine. It might have been expected, therefore, that sodium chloride absorption would proceed more

rapidly than sodium bicarbonate absorption. However, the fact that chloride was absorbed more rapidly than sodium suggests that much of the ileal chloride absorption may have occurred via an ion exchange mechanism with bicarbonate, and, as such, be unrelated to net movement of sodium. Although our data do not establish the presence of such an anion carrier, a number of previous observations are compatible with such a mechanism. For instance, Bucher, Flynn, and Robinson showed that saline test solutions instilled into the balloon-isolated ileum equilibrated with an alkaline pH, a high concentration of bicarbonate, and a low chloride concentration (16). Furthermore, ileal contents after a normal meal have a lower chloride concentration and a higher pH than plasma (15). In addition, a preliminary study by Hubel in the rat ileum has shown that bicarbonate secretion occurs only if chloride is present in ileal contents (18); this dependency of bicarbonate secretion on luminal chloride is also consistent with an anion exchange carrier in ileal membranes. These observations, plus those reported in the present paper, are therefore compatible with the hypothesis that chloride is absorbed in the ileum in exchange for secreted bicarbonate in a manner unrelated to sodium transport.

The addition of glucose or galactose to luminal contents did not stimulate the rate of sodium absorption in the ileum, although glucose did increase the negative potential difference between intestinal lumen and skin. An increase in potential difference without a change in sodium absorption rate might be explained by an alteration of mucosal permeability. Another possible explanation is that sodium transport might be stimulated by glucose but causes no increase in net sodium absorption, because the potential difference increases and thereby increases the back leak of sodium. The latter suggestion, i.e. a coupling of sodium and glucose transport, would be most compatible with the conclusions of other workers who have used in vitro preparations (3–5).

A final observation about ileal absorption is that water from 110 mM sodium chloride solutions can be absorbed against an adverse osmotic pressure gradient of approximately 20 mOsm/kg. Similar observations have previously been made in experimental animals, and the most generally accepted explanation of this phenomenon is that proposed by Curran in which sodium is actively transported into some small poorly mixed third compartment (1). The fact that glucose did not enhance either the osmotic gradient against which water absorption occurs or net sodium absorption is compatible with the hypothesis that active sodium transport is the main driving force for establishing a hypertonic solution within the middle compartment of the Curran model.

Jejunum. In marked contrast to the ileum, the jejunum is capable of absorbing sodium chloride against only a slight electrochemical gradient (13 mEq/liter, 0 mv). Moreover, bulk water flow has a marked effect on sodium movement, and absorption of sodium and the gradient against which sodium absorption can occur is enhanced by substitution of bicarbonate for chloride and by addition of glucose or galactose to luminal contents (Fig. 5).

The finding that water flow has a marked effect on sodium movement in the jejunum is consistent with our previous studies on the reflection coefficient of sodium chloride in the small intestine. Using the equations of Kedem and Katchalsky (19), it can be shown that the ability of bulk water flow to influence solute movement is directly related to the reflection coefficient of the solute in question. The quantity of solute (J_s) movement induced by bulk flow of water (J_w) is given by the expression: $J_s = \bar{C}(1 - \sigma)J_w$, in which $\bar{C}$ is the mean concentration of the solute across the membrane and σ is the Staverman reflection coefficient. It is seen from this equation that, the lower the reflection coefficient the greater the effect of bulk water flow on solute movement. Previously we reported that the reflection coefficient of sodium chloride in the jejunum was 0.5, whereas in the ileum it approached 1.0 (11). These values are therefore consistent with the present studies showing that water flow has a major effect on sodium transport in the jejunum and a negligible effect on sodium transport in the ileum. An independent measurement of the reflection coefficient of sodium chloride from the present data yields a value of 0.92 for the ileum (Figs. 1 and 5D) and an average value of 0.4 for the jejunum (Figs. 1, 2, 5, 6, and 7).[2] The finding

[2] The slopes of the curves in Figs. 1, 2, 5, 6, and 7 give the value of J_s/J_w. Dividing this value by the mean so-

that bulk water flow has such a pronounced effect on jejunal sodium movement suggests that passive processes for sodium absorption may be very important in the jejunum.

The observation that substitution of bicarbonate for chloride enhances sodium absorption suggests several possibilities. If sodium were absorbed by an active process while its associated anion moved passively along electrochemical gradients, then the absorption rate of sodium would be dependent on the permeance of the anions in luminal fluid. One possibility, therefore, is that the jejunal mucosa is more permeable to bicarbonate than to chloride. However, the direction and rate of water movement influence the movement of sodium chloride much more than the movement of sodium bicarbonate (Fig. 6). This indicates that the reflection coefficient for sodium bicarbonate is much higher than that for sodium chloride, and excludes freer permeability of bicarbonate as the mechanism by which bicarbonate enhances sodium absorption. As a matter of fact, it seems highly unlikely that bicarbonate is absorbed in the jejunum by passive processes. The steep concentration gradient against which bicarbonate is absorbed (down to luminal concentrations of about 4 mEq/liter, Table IV) cannot be explained by transmucosal potential difference, since this would require a potential difference of approximately −50 mv. Potentials of this magnitude have never been reported across the small intestine of any animal species (2), and a recent study in Soergel's laboratory (20) and our own results (Table IV) indicate that the maximum potential difference across the jejunal mucosa is of the order of from −4 to −16 mv. These observations therefore suggest that bicarbonate absorption is mediated by some active process. Bicarbonate absorption by an active process could stimulate sodium absorption in several ways. For instance, active absorption of bicarbonate might increase sodium absorption by creating favorable or decreasing unfavorable electrical gradients across the mucosa, and thereby decrease the electrochemical gradient against which sodium is absorbed at any given luminal concentration of sodium. Our PD measurements are against such a mechanism, since the PD did not change when bicarbonate was added to saline solutions. Alternatively, active hydrogen secretion (which would react with bicarbonate to form carbonic acid, which in turn would decompose to H_2O and CO_2 with diffusion of the latter across the mucosa) might influence sodium absorption electrically as just described, or by a direct coupling of hydrogen secretion and sodium absorption, which previously has been suggested in the rat jejunum by Parsons (21). The failure of the PD to change suggests direct coupling between hydrogen secretion and sodium absorption.[3] If the rate of hydrogen secretion were affected by the hydrogen ion concentration of jejunal fluid, raising the bicarbonate concentration of luminal contents would increase hydrogen secretion, and, thereby, increase the rate of sodium reabsorption.

The marked influence of water movement on sodium movement and the ability to absorb sodium against only small electrochemical gradients raise the possibility that only that portion of sodium transport linked to hydrogen secretion is actively absorbed (as the bicarbonate salt), whereas the greater fraction of sodium is absorbed passively as sodium chloride. The small sodium concentration gradient sustained across the jejunal mucosa (13 mEq/liter, Fig. 2), according to this view, would be a consequence of sodium–hydrogen exchange, which would maintain a low luminal bicarbonate concentration and keep total anion concentration in luminal fluid lower than that in plasma. The absorption of sodium from isotonic sodium chloride solutions containing no bicarbonate would simply represent diffusion of sodium chloride down chemical concentration gradients (lumen chloride 140, plasma 100). Since sodium chloride has a lower reflection coefficient than sodium bicarbonate, it would be more sensitive to the movement of water than sodium bicarbonate.

The addition of either glucose or the poorly metabolized but actively transported galactose stimulated net sodium absorption in the jejunum and increased the transmucosal PD slightly. This is in contrast to the ileum where these sugars had no effect on net sodium transport, but did cause a significant increase in PD. It has been suggested that the stimulatory effect of the actively transported sugars and amino acids is due to a direct coupling of their active transport process to the

dium concentration across the intestinal wall gives $(1-\sigma)$.

[3] A neutral pump transporting sodium and bicarbonate is an alternative possibility.

sodium pump (3–5). If this were the mechanism of action, it would have been expected that the addition of glucose and galactose, which were transported rapidly in both the jejunum and ileum, would have stimulated sodium absorption in both areas of the small intestine. In view of the fact that glucose and galactose stimulate sodium absorption only in those areas of the intestine where bulk water flow influences sodium movement, it is attractive to propose that the active transport of these sugars does not stimulate an active sodium pump directly, but, instead, generates an osmotic flow of water which, in turn, enhances sodium absorption. Two observations are, however, difficult to fit into this model. First, in the experiments shown in Fig. 5, the addition of either glucose or galactose stimulates sodium absorption at any level of water flow; even when net water movement was zero, a stimulatory effect on sodium absorption was noted. Second, these experiments were designed with a small limiting sodium concentration gradient of approximately 15 mEq/liter, so that in the absence of sugar there would be little net sodium movement at zero water movement. Thus, the ability of added sugars to stimulate sodium absorption at zero water absorption indicates that the ability to absorb sodium against concentration gradients has been enhanced.

It is still possible, however, to explain the stimulatory effect of sugars on jejunal sodium absorption, even at zero water movement, by a primary effect on water flow, without invoking a direct coupling of sugar transport to an active sodium pump. The model for such a mechanism involves a fluid circuit in which salt solution moves through one set of aqueous channels, while pure solvent moves in a reverse parallel fashion through a second set of channels. This is similar to the fluid circuit theory originally proposed by Peters and Visscher (22) and more recently by Kruger and Bresler (23). The principal feature of such a system to explain our observations is that active glucose absorption generates a local osmotic gradient which results in bulk flow of salt and water across a permeable membrane. Now, in order to counterbalance the water movement generated by glucose transport, it is necessary to add mannitol to the luminal fluid. The mannitol, however, exerts its osmotic effect, not only across the permeable membrane, but also across a second set of aqueous channels which are visualized as being permeable only to water, so that reentry of sodium into the gut lumen is restricted. When mannitol has been raised sufficiently to reduce water flow to zero, there is still a positive absorption of salt and water through the permeable portion of the membrane, balanced by a backflow of water into the lumen through the impermeable portion of the membrane—in other words, a fluid circuit. In such a model, therefore, glucose would stimulate sodium absorption at zero net water movement, and, in addition, would increase the concentration gradient against which sodium can be absorbed.

The data presented in this paper on urea absorption argue strongly for the presence of a fluid circuit across the jejunal mucosa. First, glucose was shown to enhance urea absorption at zero net water flow. This is in favor of the fluid circuit model, but could conceivably be explained by coupling of active glucose and active urea transport (even though all the data so far reported on urea absorption suggest that this solute is absorbed passively). However, bicarbonate also stimulates urea absorption at zero net water movement, and it is extremely difficult to visualize how both glucose and bicarbonate transport could be coupled to active urea transport. We believe, therefore, that the enhancement of urea absorption by glucose and bicarbonate can best be explained by the presence of a fluid circuit mechanism in jejunal mucosa.

Although we consider these urea experiments to strongly suggest the presence of a fluid circuit across the jejunal mucosa that is activated by glucose transport in the presence of a poorly absorbable solute (such as mannitol), our data do not necessarily prove that this is the mechanism by which glucose stimulates sodium absorption. It is possible that active sodium transport stimulated by glucose, rather than glucose transport itself, is generating the fluid circuit postulated to explain the urea data. On the other hand, it should be recalled that the definition of active transport is movement of a substance that cannot be explained on the basis of electrochemical gradients or solvent drag. Ordinarily, solvent drag is considered inoperative if net water flow is zero, but in the presence of a fluid circuit system as described above, solvent drag force may be operative even when net water flow is zero. Thus, enhancement of sodium absorption in the jejunum against a concentration gradient at zero water flow by glucose cannot be used as a criterion for stimulation

of active sodium transport. This does not, of course, mean that active transport does not exist, but it does mean that the criteria for active transport in the human jejunum cannot be met.

A model which explains many features of jejunal transport is illustrated in Fig. 10. In this model a fraction of luminal sodium is absorbed by being coupled in some way with active bicarbonate transport (probably via a sodium–hydrogen exchange). In addition, glucose is actively transported across the jejunal mucosa. Either the actively transported glucose or bicarbonate is deposited into the intercellular space generating local osmotic gradients. The tight junction between the cells is assumed to be highly permeable to water, sodium chloride, and urea, but relatively impermeable to glucose and to sodium bicarbonate. (Whereas anatomical studies have shown that this junction is completely fused [24], it is thought to have a low electrical resistance in some epithelial membranes [25], and has been suggested as the site of a shunt pathway for sodium ions in the frog skin [26]). Consequently, a solution of sodium chloride and urea flows across the tight junction from lumen into the intercellular space in response to osmotic gradients created by glucose and bicarbonate transport. In contrast to the tight junction, a part of the cell membrane proper is assumed to be relatively impermeable to sodium chloride and urea, as well as to glucose and mannitol. Therefore, when mannitol is added to luminal fluid to counteract the stimulatory effect of glucose and bicarbonate on bulk flow, its effect will be exerted not only across the tight junction, but also across the cell membrane, inducing a flow of water from interstitial space into the lumen. Thus, at zero net water flow there is still a positive absorption of water (and sodium and urea) through the permeable membrane, balanced by a backflow of water into the lumen through the impermeable membrane.

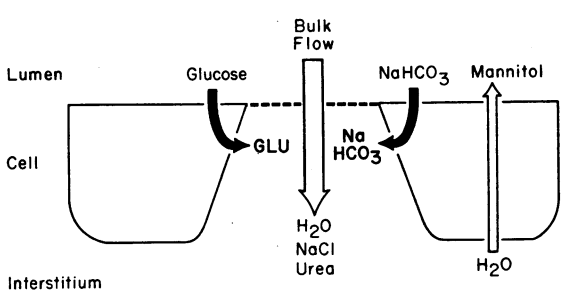

FIGURE 10 A model to illustrate how a fluid circuit system might enhance sodium and urea absorption at zero net water flow. In order to achieve reverse flow of H_2O, it is necessary that one of the compartments across which mannital exerts its effect must be isolated osmatically from the compartments in which glucose and sodium bicarbonate are accumulated. This may be in different regions of the same cell, as shown in this figure, or in different cells of the mucosa.

It should be emphasized that we have no data to support this specific type of fluid circuit system. Another possibility is that the movement of solution and water occurs across membranes of two different cell types, rather than across two different membranes of the same cell.

An additional feature of jejunal absorption which is explained by a fluid circuit system of the type described in Fig. 10 is the movement of water against an osmotic pressure gradient. In the absence of glucose or bicarbonate there is no water absorption against an osmotic pressure gradient. However, in the presence of glucose, water can be absorbed against osmotic pressure gradients of approximately 30 mOsm/kg, and in the presence of bicarbonate against a gradient of about 10 mOsm/kg. These results suggest that the active transport of glucose and bicarbonate into the poorly mixed third compartment of this modified Curran model is the mechanism responsible for absorption of water against osmotic pressure gradients.

ACKNOWLEDGMENTS

The authors express their appreciation to Stephen Morawski, Charlotte Douglas, Mary Jane Benton, and Carolyn Arnold for their contribution to these studies and to the preparation of the manuscript.

This paper was supported by research grant AM-06506 from the National Institutes of Health.

REFERENCES

1. Curran, F. P. 1965. Ion transport in intestine and its coupling to other transport processes. *Federation Proc.* **24**: 993.
2. Fordtran, J. S., and J. M. Dietschy. 1966. Water and electrolyte movement in the intestine. *Gastroenterology.* **50**: 263.
3. Schultz, S. G., and R. Zalusky. 1964. Ion transport in isolated rabbit ileum. II. The interaction between active sodium and active sugar transport. *J. Gen. Physiol.* **47**: 1043.
4. Schultz, S. G., P. F. Curran, R. A. Chez, and R. E. Fuisz. 1967. Alanine and sodium fluxes across mucosal border of rabbit ileum *J. Gen. Physiol.* **50**: 1241.

5. Curran, P. F., S. G. Schultz, R. A. Chez, and R. E. Fuisz. 1967. Kinetic relations of the Na-amino acid interaction at the mucosal border of intestine. *J. Gen. Physiol.* **50**: 1261.
6. Visscher, M. B. 1957. Transport of water and electrolyte across intestinal epithelia. *In* Metabolic Aspects of Transport Across Cell Membranes. Q. R. Murphy, editor. University of Wisconsin Press, Madison. 57.
7. McHardy, G. J. R., and D. S. Parsons. 1957. The absorption of water and salt from the small intestine of the rat. *Quart. J. Exptl. Physiol.* **42**: 33.
8. Hindle, W., and C. F. Code. 1962. Some differences between duodenal and ileal sorption. *Am. J. Physiol.* **203**: 215.
9. Fordtran, J. S., R. Levitan, V. Bikerman, B. A. Burrows, and F. J. Ingelfinger. 1961. The kinetics of water absorption in the human intestine. *Trans. Assoc. Am. Physicians.* **74**: 195.
10. Whalen, G. E., J. A. Harris, J. E. Geenen, and K. Soergel. 1966. Sodium and water absorption from the human small intestine The accuracy of the perfusion method. *Gastroenterology.* **51**: 975.
11. Fordtran, J. S., F. C. Rector, Jr., M. F. Ewton, N. Soter, and J. Kinney. 1965. Permeability characteristics of the human small intestine. *J. Clin. Invest.* **44**: 1935
12. Fordtran, J. S., F. C. Rector, T. W. Locklear, and M. F. Ewton. 1967. Water and solute movement in the small intestine of patients with sprue. *J. Clin. Invest.* **46**: 287.
13. Fordtran, J. S. 1966. Marker perfusion techniques for measuring intestinal absorption in man. *Gastroenterology.* **51**: 1089.
14. Conway, E. J. 1957. Microdiffusion Analysis and Volumetric Error. C. Lockwood, London.
15. Fordtran, J. S., and T. W. Locklear. 1966. Ionic constituents and osmolality of gastric and small-intestinal fluids after eating. *Am. J. Digest. Diseases.* **11**: 503.
16. Bucher, G. R., J. C. Flynn, and C. S. Robinson. 1944. The action of the human small intestine in altering the composition of physiologic saline. *J. Biol. Chem.* **155**: 305.
17. Wilson, T. H. 1962. Intestinal Absorption. W. B. Saunders Co., Philadelphia.
18. Hubel, K. A. 1966. Ileal bicarbonate secretion and its dependency on intraluminal chloride. *Proc. Central Soc. Clin. Res.* **39**: 37. (Abstr.)
19. Kedem, O., and A. Katchalsky. 1961. A physical interpretation of the phenomenological coefficients of membrane permeability. *J. Gen. Physiol.* **45**: 143.
20. Gustke, R. F., G. E. Whalen, J. E. Geenen, and K. H. Soergel. 1967. Mucosal potential difference in the intact human small intestine. *Gastroenterology.* **52**: 1134. (Abstr.)
21. Parsons, D. S. 1956. The absorption of bicarbonate-saline solutions by the small intestine of the white rat. *Quart. J. Exptl. Physiol.* **41**: 410.
22. Peters, H. C., and M. B. Visscher. 1939. On the mechanism of active absorption from the intestine. *J. Cell. Comp. Physiol.* **13**: 51.
23. Kruger, S., and E. H. Bresler. 1965. The absorption of solutions from dog ileum. *Federation Proc.* **24**: 589. (Abstr.)
24. Farquhar, M. G., and G. E. Palade. 1963. Junctional complexes in various epithelia. *J. Cell Biol.* **17**: 375.
25. Windhager, E. E., E. L. Boulpaep, and G. Biebisch. 1966. Electrophysiological studies on single nephrons. Proc. 3rd Intern. Cong. *Nephron.* **1**: 35.
26. Ussing, H. H., and E. E. Windhager. 1964. Nature of shunt path and active sodium transport through frog skin epithelium. *Acta Physiol. Scand.* **61**: 484.