Potassium transport in the human small bowel

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SUMMARY Perfusion experiments in the small intestine of normal subjects and in the ileum of patients with ileostomies demonstrated that the distribution of potassium across the mucosa was compatible with a passive process for transport. In the jejunum potassium transport was shown to be markedly influenced by solvent drag and the jejunal mucosa appears to be more permeable to potassium than to sodium. This permeability was apparently unaffected by calcium in the lumen in concentrations of between 1·15 and 7·25 m-equiv/l. In the ileum potassium transport was influenced by changes in luminal sodium concentration and it is suggested that this is a passive consequence of the change in electrical potential which the change in sodium concentration induces. The electrical potential is thought to be a sodium diffusion potential. All the evidence thus points to a purely passive behaviour of the small intestine towards potassium.

While intestinal transport of sodium has been the subject of fairly intensive investigation less attention has been paid to potassium transport in the human small bowel. Indirect evidence suggests that potassium is distributed simply passively across the mucosa of the small bowel. Thus after a meal its concentration in luminal contents of jejunum and ileum is close to plasma concentrations (Fordtran and Locklear, 1966) and isotonic electrolyte solutions equilibrate in the lumen of the small bowel at a similar potassium concentration (Code, Phillips, and Swallow, 1966). Investigations suggest that potassium transport is a purely passive process in the rat (Gilman, Koelle, and Ritchie, 1963) and a similar conclusion was reached by Phillips and Summerskill (1967) on the basis of small-intestinal perfusion experiments in man. The present investigations were designed to confirm and extend these observations and to study some of the factors which influence transport of potassium.

Methods

Normal young adult volunteers formed the majority of the experimental subjects in these investigations. In addition, four patients who had had an ileostomy for ulcerative colitis or Crohn's disease of the large bowel, performed between one and six years before this investigation, were also studied. These patients were fit and well, had normal serum electrolyte

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concentrations, and the terminal ileum and ileostomy was normal so far as could be judged clinically. The nature of the tests was fully explained before patients were asked if they would take part.

Perfusion studies in the normal volunteers were performed using a triple-lumen tube technique (Cooper, Levitan, Fordtran, and Ingelfinger, 1966). This technique has been described in detail previously (Fordtran, Rector, and Carter, 1968) but briefly the test involves the constant infusion of test solutions into the lumen of the intestine and the sampling of luminal contents 10 and 40 cm distally. For the jejunal studies the infusion point was sited at the duodeno-jejunal junction and for the ileal studies at 200 cm from the teeth. The infusion rate was 10 ml/min for most of the jejunal studies. In the studies of the influence of water movement on potassium transport, in which solutions of varying tonicity were infused, it was necessary to modify the infusion and aspiration rates and the concentration of electrolytes in order to achieve constant mean flow rates and mean ionic concentrations in the test segment of jejunum. Thus, when a solution made hypertonic with mannitol was infused, water entered the lumen across the mucosa in answer to the osmotic gradient. This had the effect of increasing the flow rate through the test segment and of decreasing the concentration of solutes in the lumen. A hypotonic solution, from which water was rapidly absorbed, developed a decreased mean flow rate and an increased solute concentration. In order to pro-

duce similar flow rates and solute concentrations with these two solutions it was necessary to infuse the hypertonic solutions at a slower rate (8·0 ml/ min) and take samples at a faster rate from the proximal aspiration site (1·5 ml/min) than with the hypotonic solutions (14 ml/min and 1·0 ml/min respectively). To maintain similar mean potassium concentrations in the test segment the hypertonic solutions had a higher potassium concentration (8 m-equiv/l) than the hypotonic solutions (2·5 m-equiv/l). Using this technique, mean flow rates and electrolyte concentrations in the intestinal lumen were similar when either a hyper- or hypotonic solution was infused (Table I).

Solution	Mean Flow Rate (ml/min)	Mean Potassium Concentration (m-equiv/l)
Hypotonic	11·4	4·5
Isotonic	10·0	4·7
Hypertonic	10·7	5·25

Table I *Mean values for flow rate through the test segment of jejunum and for luminal potassium concentrations during perfusion with solutions of varying tonicity*[1]

[1]By changing the infusion rate and initial potassium concentrations, as described in the text, it was possible to achieve similar results with these three solutions.
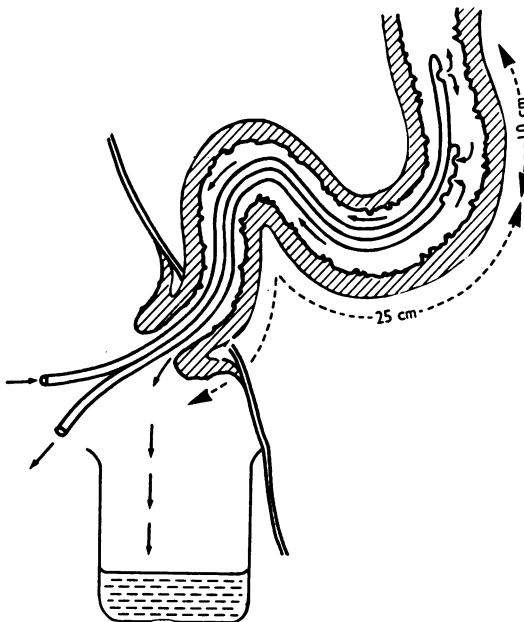

Fig. 1. *Double-lumen tube perfusion of the distal ileum through an ileostomy.*

The studies of distal ileum in the patients with ileostomies were performed using a double-lumen tube perfusion technique similar to that described by Wright, Cleveland, Tilson, and Herskovic (1969). The tube was made of two polyvinyl tubes loosely attached to each other and gently inserted through the ileostomy to a distance of 35 cm (Fig. 1). Test solutions were infused at a steady rate through the opening at the tip of the tube and intestinal contents were sampled 10 cm distal to this point through the second tube. This sample consisted partly of infusate and partly of intestinal fluid, which had mixed with it during passage down the intestine. The remainder of this perfusate passed down the last 25 cm of ileum and was collected in a disposable ileostomy bag. It was thus possible to measure electrolyte transport in the last 25 cm of ileum with this technique. Before perfusion studies were started an isotonic electrolyte solution was infused at 15 ml/min until the ileal washings leaving the ileostomy became clear. Test solutions were then infused at 9 ml/min for a 30-minute equilibration period and continued for a 40-min test period. On the basis of previous experience with triple-lumen tube perfusion experiments in normal subjects it was felt that these equilibration and collection period times would be sufficient to produce the necessary steady state conditions at this infusion rate. This was validated in two studies in which two consecutive perfusion experiments were performed, each of 40 minutes, after an initial 30-min equilibration period. The duplicate values for marker and potassium concentrations were very close to each other on both occasions. With an infusion solution containing 5 m-equiv/l potassium the potassium transport rates were +0·04 and −0·01 m-equiv/hour at a mean luminal potassium concentration of 4·7 m-equiv/l for both of the first pair of studies, and, with an infusion solution containing 10 m-equiv/l, transport rates were −0·22 and −0·20 at mean luminal potassium concentrations of 7·8 and 7·95 m-equiv/l respectively for the second pair. Samples of perfusate were taken at 1·5 ml/min from the aspiration tube with a syringe, by hand. The fluid leaving the ileostomy was also collected for 40 minutes but the timing of this collection was delayed by eight minutes from that for the aspirated sample. Preliminary investigation had suggested that the peak concentration of a bolus of infused bromsulphalein took eight minutes to pass down the 25 cm of ileum between the aspiration site and the ileostomy. Three different test solutions were infused consecutively during each investigation.

All infusion solutions contained 5 g/l of the poorly absorbable marker polyethylene glycol 4000 (PEG). Polyethylene glycol concentrations were measured

by the method of Hyden (1955), sodium and potassium by flame photometry, chloride with an EEL chloride meter, and total carbon dioxide content with a Natelson microgasometer. Osmolality was measured with an Osmette freezing point osmometer.

Results

JEJUNUM

Influence of potassium concentration on absorption

The influence of changes in luminal potassium concentration on net potassium transport rate was studied in four subjects. Solutions infused contained 100 m-equiv/l of sodium chloride, 30 m-equiv/l sodium bicarbonate, and 1, 5, or 10 m-equiv/l of potassium chloride. Small amounts of mannitol were added to the solutions with the lower potassium concentrations so that each solution had a similar osmolality of 280 mOsm/kg. The results, depicted in Figure 2, show that there is a linear relationship between mean luminal potassium concentration and net potassium transport rate. At concentrations greater than 3·5 to 4·0 m-equiv/l potassium was absorbed while at lower concentrations potassium was secreted into the lumen. There was no net potassium movement into or out of the lumen at this concentration which was similar to the serum potassium level of between 3·8 and 5·2 m-equiv/l in these subjects. These findings suggest that potassium may be distributed passively across the jejunal mucosa.

Influence of solvent drag

Sodium transport in the human jejunum has been shown to be markedly influenced by the direction and volume of water flowing across the mucosa (Fordtran *et al*, 1968). It was of interest then to study the influence of water movement on potassium transport. This was investigated in seven normal subjects in a series of experiments in which the potassium concentration in the lumen was held constant at a level similar to that in plasma while water was made to enter or leave the lumen across the mucosa by changing the osmotic pressure of the perfusate. Hypotonic solutions were made by reducing the concentration of electrolytes and hypertonic solutions by adding the non-absorbable mannitol. The results, shown in Figure 3, demonstrate that at a constant potassium concentration water movement had a marked influence on potassium transport. Thus potassium absorption was associated with water absorption and secretion with water secretion. When water movement was nil, net potassium movement also ceased. These findings suggest that

solvent drag is an important force in the passive transport of potassium in the jejunum.

Influence of calcium on potassium transport

Since it is known that calcium exerts an effect on the passive permeability of a number of biological membranes it was of some interest to study the influence of calcium, in different concentrations, on potassium transport. In 14 normal subjects electro-
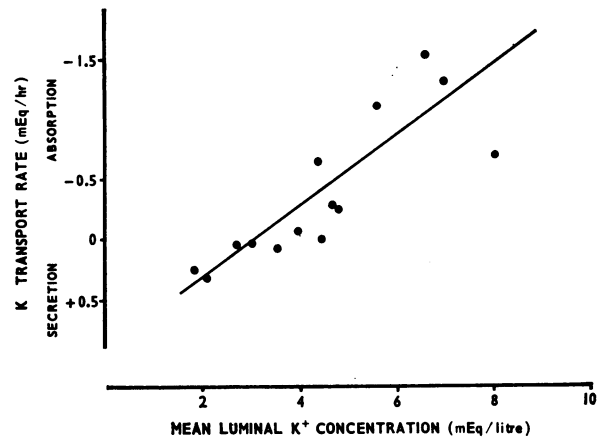

Fig. 2. *Jejunum. Relationship between potassium transport rates and the mean potassium concentration in the lumen.*
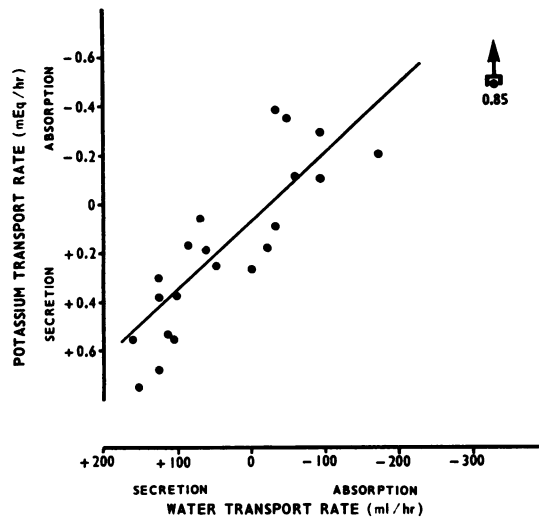

Fig. 3. *Jejunum. The influence of water movement on net potassium transport rates.*
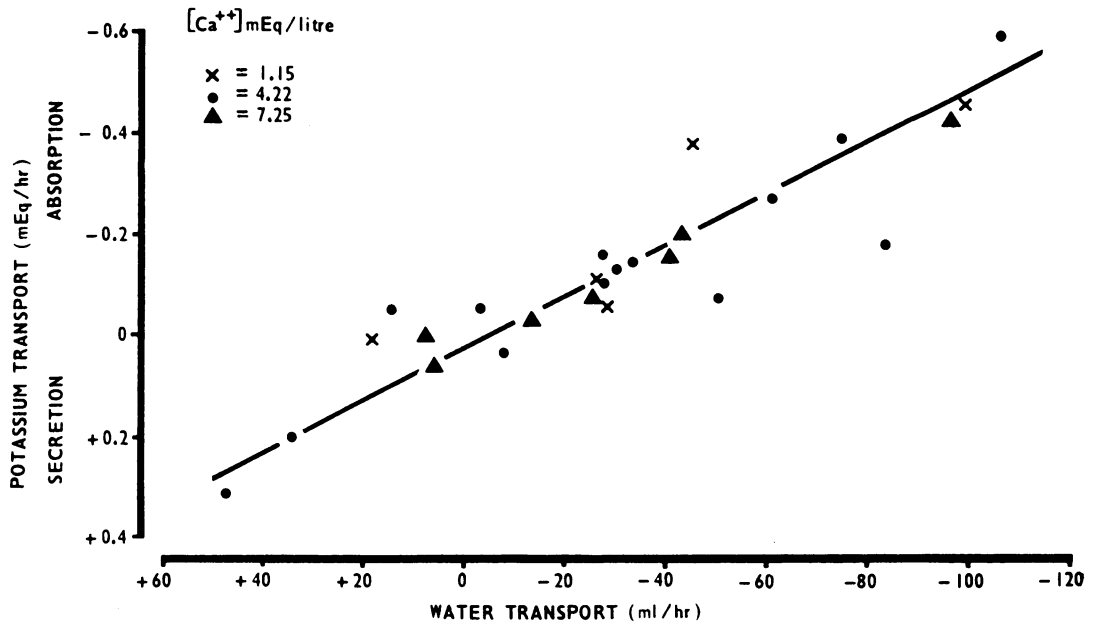
Fig. 4. *Jejunum. The relationship between net water and net potassium transport rates at three different intraluminal concentrations of calcium.*

lyte solutions containing 5 m-equiv/l potassium chloride, 130 or 135 m-equiv/l sodium chloride, and 1, 5, or 10 m-equiv/l of calcium chloride were infused at 4·5 ml/min into the jejunum. Absorption of potassium was variable in these studies but there was no evidence that changing the intraluminal calcium concentration altered potassium transport. When the mean intraluminal calcium concentrations were 1·15, 4·22, and 7·25 m-equiv/l potassium absorption rates were 0·187, 0·113, and 0·117 m-equiv/hour respectively and these were not significantly different from each other. Water movement in these studies varied from secretion of 47 ml/hour to absorption of 107 ml/hour but this variation was not related to changes in luminal calcium concentration or calcium transport rates. However, potassium movement bore a direct relationship to water movement (Figure 4). If potassium transport here is a passive process, as suggested by the results presented above, then the variation in potassium movement shown in Figure 4 is probably secondary to the variation in water movement. The finding that the slope of the line for this relationship is virtually identical for the studies performed at three different concentrations of calcium suggests that the permeability of the jejunal mucosa to potassium is also unaffected by changes of this order in luminal calcium concentration.

ILEUM

Slow perfusion

In 14 normal subjects the ileum was perfused with an electrolyte solution resembling plasma in composition. This solution was infused at the slow rate of 2·5 ml/minute so that changes in electrolyte concentration were made more obvious by prolongation of the contact time between mucosa and perfusate.

The initial concentration of potassium was 5 m-equiv/l and after passing down the 45 cm of ileum between the infusion site and the distal end of the test segment a mean concentration of 4·94 m-equiv/l was reached (Table II). Potassium was slowly absorbed from this solution at a mean rate of 0·14 m-equiv/hr/30 cm of ileum. This concentration is near to the concentration which was achieved when solutions were allowed to equilibrate in the lumen (Code *et al*, 1966). Since it is close to plasma concentrations this equilibrium value suggests that potassium is distributed across ileal mucosa by passive forces as in the jejunum.

Ileostomy perfusion

The influence of variation in luminal potassium concentration on potassium transport was investigated during perfusion of the distal ileum in four patients with ileostomies. All solutions had a similar

Test No.	Concentration of K+		K+ Absorption (−) or Secretion (+) (m-equiv/hr)
	Distal End of Test Segment	Mean	
1	5·65	5·43	−0·07
2	4·9	4·9	−0·09
3	5·2	5·2	−0·78
4	4·6	4·7	−0·08
5	4·8	4·85	−0·11
6	4·4	4·55	−0·18
7	4·6	4·7	−0·04
8	4·4	4·55	−0·15
9	4·4	4·5	−0·10
10	4·6	4·7	−0·23
11	6·55	6·0	−0·02
12	4·35	4·55	−0·06
13	5·1	4·92	−0·06
14	5·6	5·6	+0·01
Mean	4·94	4·94	−0·14

Table II *Concentration of potassium at the distal end of the ileal test segment and the mean concentration during slow perfusion of the ileum for 14 subjects and potassium transport rates*

Fig. 5

Fig. 6

sodium concentration of 135 m-equiv/l. The results of these studies, shown in Figure 5, demonstrate a linear relationship between potassium concentration and transport rate. As in the jejunum, potassium was neither absorbed nor secreted when the luminal potassium concentration was similar to plasma concentrations at 3·5 to 4·0 m-equiv/l.

This finding lends support to the suggestion that potassium is transported by passive forces in the illeum.

Influence of changing sodium concentration on potassium transport
Solutions containing potassium, 5 m-equiv/l, and sodium in a concentration of 25, 75, or 140 m/equiv/l, were infused into the ileum in a group of normal subjects. Isotonicity was maintained by the addition of mannitol to solutions with low sodium concentrations. In four experiments the electrical potential difference between lumen and abraded skin was measured during perfusion of these solutions and in seven experiments electrolyte transport rates were measured. The results, shown in Figure 6, reveal that as the luminal sodium concentration was lowered from a mean concentration of 124·4 to 27·4 m-equiv/l, potassium absorption increased from $0·21 \pm 0·04$ to $0·42 \pm 0·1$ m-equiv/hour (mean ± 1 SE). This increase just fails to reach statistical significance ($0·05 < P < 0·1$). The electrical potential difference increased as sodium concentration was reduced, the lumen becoming increasingly electropositive (Fig. 6). This change in PD, which is probably the result of a sodium diffusion potential (Turnberg, Bieberdorf, Morawski, and Fordtran, 1970), would tend to increase the passive absorption
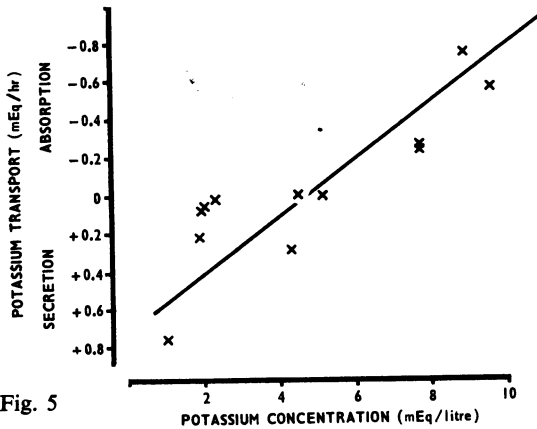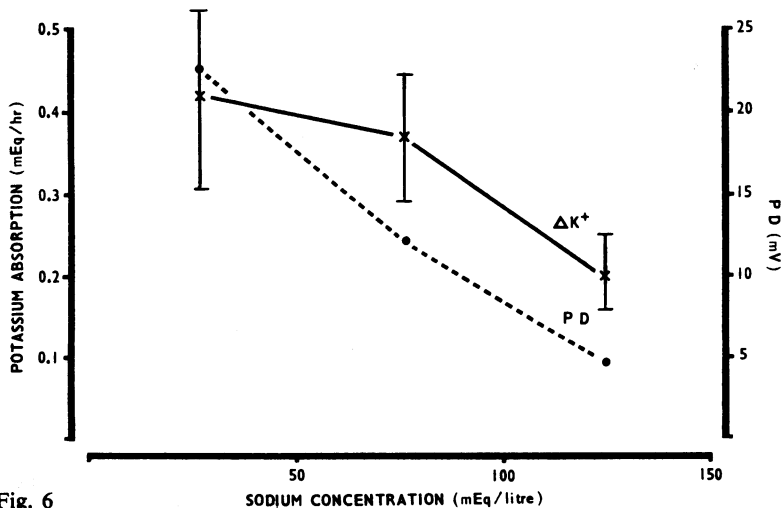
Fig. 5. *Ileum. Potassium transport rates at different mean intraluminal potassium concentrations in patients with ileostomies.*

Fig. 6. *Ileum. Mean net potassium transport rates (± 1 SEM) at different intraluminal concentrations of sodium, when potassium concentration was constant. Also shown are the mean values for the electrical PD at the different sodium concentrations.*

of potassium and may account for the observed increase in absorption.

Discussion

The finding that potassium is absorbed from the jejunum and ileum when the luminal concentration is higher than that in plasma and secreted when it is lower suggests that potassium traverses the mucosa according to the simple physical forces governing diffusion of ions.

Diffusion of potassium across the mucosa from the lumen would appear to be an adequate mechanism for its absorption since the concentration of potassium in ingested food is usually much higher than in plasma. Thus on theoretical grounds, too, there is no requirement for a special active transport process for potassium absorption.

The electrical potential will influence the distribution of ions across the mucosa, but it is unlikely that it affected potassium movement in these experiments since the PD was close to zero during perfusion with solutions similar to those used here (Turnberg, Fordtran, Carter, and Rector, 1970).

Phillips and Summerskill (1967) also concluded from the results of their perfusion experiments that potassium was transported passively in the human small intestine. However, interpretation of their data is complicated by their use of perfusion solutions in which potassium concentrations were varied reciprocally with sodium concentrations. At high potassium concentrations sodium concentrations were low and, as shown in the present studies in the ileum, potassium transport is influenced by the luminal sodium concentration, as well as by the potassium concentration. Reciprocal changes made in the concentration of both ions will have an additive effect on potassium transport, and the influence of each of these ionic concentration changes alone cannot be assessed. In those studies in which sodium and potassium concentrations were not far removed from plasma concentrations, where the predominant factor influencing potassium transport was the potassium concentration, their results are more readily interpreted as indicating a passive process for potassium transport. The present studies, in which the complicating influence of variation in sodium concentration was removed, confirm these conclusions.

The mechanism by which potassium absorption is enhanced by lowering the luminal sodium concentration is most likely to be through the change in electrical potential which this produces. At low sodium concentrations the lumen became more electropositive, probably as a result of a sodium diffusion potential (Turnberg *et al*, 1970). This change

would itself enhance the passive absorption of potassium ions.

Transport of potassium in the jejunum is shown here to be markedly influenced by the movement of water across the mucous membrane. Thus water moving from lumen to mucosa took potassium with it even in the absence of an electrochemical gradient which would make potassium diffuse across the membrane. Water flowing across the membrane is believed to take up small solutes in its stream and sweep them through 'pores' thought to exist in the membrane. This phenomenon of 'solvent drag' has been put forward as an important mechanism for sodium absorption in the human jejunum (Fordtran *et al*, 1968). The present results suggest that potassium movement is also markedly influenced by solvent drag.

Phillips and Summerskill (1967) suggested that potassium was not influenced by solvent drag in the jejunum but this conclusion was based on the results of experiments in which luminal potassium concentrations were 20 m-equiv/l. At this level diffusion of potassium out of the lumen will predominate and is likely to swamp any effect due to solvent drag. Conclusions made about solvent drag under these conditions are thus likely to be in error.

A numerical indication of the permeability of a membrane to an ion is given by its reflection coefficient (σ), and the smaller σ the greater the permeability. It is possible to calculate σ for potassium from the slope of the line relating potassium movement to water movement in Figure 3, using the formula $J_s = \bar{c}\,(1 - \sigma)J_w$ (Curran and Schultz, 1968) where J_s is the solute movement, J_w the water movement, and $\bar{c}$ the mean potassium concentration across the membrane. σ for potassium derived in this way is 0·38 which compares with the value of 0·45 for sodium calculated by Fordtran, Rector, Ewton, Soter, and Kinney (1965). Although the derivation of these values may be open to question they do suggest that the human jejunum is more permeable to potassium than to sodium. It is of interest in this respect that although the relative permeability of a membrane towards different ions depends on several factors (Diamond and Wright, 1969) the hydrated potassium ion is somewhat smaller than the hydrated sodium ion (Ussing, 1960).

Although the intracellular potassium concentration of human intestinal mucosal cells has not been measured it is likely that, as in other mammals, it is higher than plasma levels (Schultz, Fuisz, and Curran, 1966). The question arises then as to how potassium in the lumen is able to cross the mucosa so rapidly by solvent drag, when it is separated from plasma by a mucosal barrier containing a high

concentration of potassium. One possibility is that the pores through which the potassium equilibrates lie in the so-called tight junctions between the cells rather than in the cell membrane itself. Evidence in favour of a similar route for the rapid flux of potassium across rat colonic mucosa has been reported by Barnaby and Edmonds (1969), and similar suggestions have been made for the route for passive sodium movement across rat ileum and frog skin (Clarkson, 1967; Cereijido and Rotunno, 1968). An alternative explanation is that potassium may traverse the cell rapidly through a compartment which is separated from the bulk of the intracellular potassium.

In a variety of epithelia the permeability to different ions has been shown to be influenced considerably by the concentration of calcium in fluid bathing the mucosal surface. Thus, bathing toad bladder, frog skin, frog gastric mucosa, and rabbit gallbladder with a calcium-free medium increases their permeability to cations, while increasing the calcium concentration decreases their permeability (Hays, Singer, and Malamed, 1965; Curran and Gill, 1962; Sedar and Forte, 1964; Wright and Diamond, 1968). In the present investigations, changing the mean luminal calcium concentration from 1·15 to 7·25 m-equiv/l did not apparently alter potassium absorption rates nor did it clearly influence the relationship between potassium and water absorption. Thus, there was no evidence to suggest that permeability to potassium was affected by changes in calcium concentrations over the range normally found in the intestine after meals (Fordtran and Locklear, 1967). This does not exclude the possibility that mucosal permeability is influenced by calcium concentrations outside this range, and indeed it seems likely that if an extremely low calcium concentration could be achieved in the immediate vicinity of the mucosal cell surface then ion permeability would be changed. However, this phenomenon is unlikely to be observed *in vivo*.

Although open to criticism the assumption was made in the studies of patients with ileostomies that the terminal ileum in these subjects behaved as a normal ileum, at least towards potassium. In support of this assumption are the results of the slow perfusion studies of ileum in the normal subjects which fit in well with the conclusion, derived from the ileostomy perfusion experiments, that potassium is transported passively. While all the evidence presented here suggests that potassium transport is a purely passive process in the small intestine some observations suggest that this may not always be the case. Thus potassium concentrations in ileostomy effluent may reach levels much higher than in plasma in salt-depleted patients,

suggesting the possibility that active potassium secretion might occur under these conditions (Clarke, Hill, and Macbeth, 1967). However, the electrical PD across ileal mucosa has not been reported in these circumstances and the mechanism ior the high potassium concentrations cannot be ascribed with certainty.

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