of absorption of non-glyceride fat. Preliminary results with labelled sitosterol, however, indicate that, although both these levels of specificity might be important for the absorption of sitosterol, other factors as yet unknown are also operating.

REFERENCES

Borgström, B. (1964). *J. Lipid Res.* **5**, 522.
Borgström, B. (1965). *Biochim. biophys. Acta* **106**, 171.
Borgström, B., Lindhe, B.-A. & Wlodawer, P. (1958). *Proc. Soc. exp. Biol. Med.* **99**, 365.
Feldman, E. B. & Borgström, B. (1966*a*). *Biochim. biophys. Acta* **125**, 136.
Feldman, E. B. & Borgström, B. (1966*b*). *Biochim. biophys. Acta* **125**, 148.
Hofmann, A. F. (1963). *Biochem. J.* **89**, 57.
Hofmann, A. F. & Borgström, B. (1963). *Biochim. biophys. Acta* **70**, 317.
Hofmann, A. F. & Borgström, B. (1964). *J. clin. Invest.* **43**, 247.
Laurent, T. C. & Persson, H. (1966). *Biochim. biophys. Acta* **106**, 616.

16 *July, Second Session*

Chairman : PROFESSOR D. H. SMYTH, MD, *Department of Physiology and Medical Research Council Research Group on Intestinal Absorption, University of Sheffield*

Sodium chloride absorption by the small intestine and the relationships between salt transport and the absorption of water and some organic molecules

By D. S. PARSONS, *Department of Biochemistry, University of Oxford*

Ionic composition of contents of intestinal lumen

A feature of the luminal environment of the mucosal cells of the small intestine is that it normally contains sodium in a concentration which is approximately that in the plasma. Distilled water damages the mucosa of the small intestine (Reid, 1900; Dennis, 1940), and was indeed used by Waymouth Reid to poison intestinal segments during experiments on absorption. Under physiological conditions the mucosal cells of the small intestine never come in contact with plain water, water taken by mouth being considerably mixed with gastro-intestinal secretions before absorption. For example, when meals and liquids are consumed by human subjects, the contents of the duodenum and jejunum are rapidly diluted and sodium chloride is added (Reitmeier, Code & Orvis, 1957; Borgström, Dahlqvist, Lundh & Sjövall, 1957; Fordtran, Levitan, Bikerman, Burrows & Inglefinger, 1961; Hindle & Code, 1962).

There appear to be two causes for these phenomena. Firstly, the gastro-intestinal secretions provide a daily circulation of fluid and salt which considerably exceeds the dietary intake (Table 1). The entry of these secretions into the upper intestine will continually modify the composition of the contents. The second factor in modifying the composition of the gastro-intestinal contents is the occurrence of massive bidirectional fluxes of water and of electrolytes across the intestinal cells. The existence and magnitude of these fluxes was first demonstrated for dog intestine by the classical experiments of Visscher and his associates (cf. Visscher, Varco, Carr, Dean & Erickson, 1944; Visscher, Fetcher, Carr, Gregor, Bushey & Barker, 1944).

Table 1. *Estimates of quantities of water and solutes entering human intestine daily from gastro-intestinal secretions and diet (reproduced by permission from Carter, Coxon, Parsons & Thompson, 1959)*

	Volume	Concentration (mM $l.^{-1}$)			Solute load (mM 24 h^{-1})			
	(ml)	Na	K	Cl	Na	K	Cl	Ca
Saliva	1500	30	20	35	45	30	52	15
Gastric juice	3000	50	10	150	150	30	450	
Bile	500	160	5	50	80	3	25	
Pancreatic juice	2000	160	5	30	320	10	60	
Internal load	7000				595	73	587	15
Dietary intake	1500				170	65	110	22
Total load	8500				765	138	697	37
Dietary intake as % daily load	18				22	47	16	59

Such sorts of exchange also exist in the human intestine. In experiments on the normal human duodenum and jejunum, Code and his associates have found that the undirectional influx of water into the blood from the lumen is of the order of 20% of the luminal water per min, while that of sodium is some 10% of the luminal sodium per min (Code, 1965). Fordtran *et al.* (1961) have found that for segments of human jejunum 30 cm long and containing 100 ml of 150 mM NaCl/l. water the unidirectional fluxes observed over 10 min amounted to an influx, lumen to blood, of 80 ml water with a corresponding efflux, blood to lumen, of 55 ml yielding a net water absorption of 25 ml. For sodium, the unidirectional influx, lumen to blood was 9·1 mM, the efflux being 5·4 mM, so the net absorption was therefore 3·7 mM in 10 min.

Priestley (1915–16) suggested that, after water was ingested, salts moved from the blood into the gastro-intestinal lumen and it seems probable that this occurs during the initial entry of hypotonic fluid into the duodenum. Net entry of electrolyte through the mucosa into hypotonic solutions certainly occurs in dog and rat jejunum (Burns & Visscher, 1934–5; McHardy & Parsons, 1957).

Salt absorption

There is now clear evidence that the translocation of sodium from the lumen across the epithelial layer of the intestine is an 'active' process. In other words, the sodium movement can proceed against an electrochemical potential gradient and is dependent upon metabolic processes occurring within the absorbing cells. The evidence that the intestinal absorption of sodium can proceed independently of electrical and concentration gradients is as follows: with identical Ringer solutions bathing both sides of isolated segments of rat intestine, there is a net inward transport of sodium. This occurs although a potential difference exists across the whole wall, the fluid bathing the serosal surface being some 10 mV positive to that in the lumen. In rat intestine, net inward sodium movement can occur against an electrochemical gradient (Curran, 1960; Clarkson & Rothstein, 1960; Barry, Smyth & Wright, 1965).

The electrochemical potential gradient across the intestinal wall can be reduced

https://doi.org/10.1079/PNS19670010 Published online by Cambridge University Press

to zero by exposing the two faces of the tissues to identical bathing solutions and then clamping the transcellular potential difference to zero volts. Any single ionic species which is subject to independent active transport will then move more rapidly in one direction across the tissue than in the other and will contribute to the current which has to be passed through the voltage clamp circuit to maintain zero potential difference across the epithelium. This technique has been applied by Ussing & Andersen (1955) to the guinea-pig caecal mucous membrane where it was found that the net sodium influx was somewhat greater than the short-circuit current. Cooperstein & Hogben (1959) found that from the isolated intestine of the frog, the short-circuit current could almost, but not entirely, be attributed to sodium transport. Measurements of short-circuit current have been made on rabbit and rat intestine in vitro by various workers (Schultz & Zalusky, 1964*a*; Barry *et al.* 1965). Since in all these experiments there occurs an appreciable net transfer of sodium from the mucosal into the serosal solutions bathing the intestine, the sodium transport cannot simply be explained in terms of passive movements down electrochemical gradients existing across the tissue. In the rabbit ileum the sodium transport depends upon aerobic metabolism (Schultz & Zalusky, 1964*a*).

The question arises as to whether the inward chloride movement during salt absorption is 'active' or passive. The evidence is as yet incomplete and most experiments have been undertaken in ileal segments. In short-circuited preparations it is not usual to find any net chloride flux (Schultz, Zalusky & Gass, 1964) although a net flux of chloride from the serosa into the mucosal fluid has sometimes been observed (Clarkson & Toole, 1964).

There seems to be no doubt that some chloride is absorbed passively with the sodium, but it is possible that some is also absorbed in exchange for bicarbonate ions. During the absorption of saline solutions, acid–base changes occur across the intestinal wall. Saline solutions in the duodenum and jejunum of mammals become adjusted during absorption to pH values (*c.* 6·5) more acid than those in the ileum (pH *c.* 7·5). Bicarbonate rapidly disappears from rat jejunal contents, but enters those of the ileum during the absorption of bicarbonate-saline. In the hamster, bicarbonate secretion into the lumen occurs along the whole length of the small intestine (Parsons, 1956; Wilson & Kazyak, 1957). In rat jejunum the rate of net sodium absorption exceeds that of chloride while in the ileum the net chloride absorption may exceed that of the sodium. The movements of sodium and of chloride are therefore independent of each other to a certain extent and cannot entirely be tightly coupled.

The absorption of sodium and also of water is greatly influenced by the hydrogen ion concentration in the intestinal lumen, being reduced at increased hydrogen ion concentrations. From saline in rat jejunum, for example, the rate of absorption of sodium at pH 5 is but one-sixth of that found at pH 7 (McHardy & Parsons, 1957).

Water absorption

Since the pioneer experiments of Waymouth Reid (Reid, 1892) clear evidence has accumulated that water may be moved inwards across the mucosal cells against

a transmural osmotic gradient in vivo and in vitro. With rat jejunum in vitro, even when the contents of the lumen are 130 milliosmoles hypertonic with respect to the serosal fluid a net water flux from lumen to serosa occurs (Parsons & Wingate, 1961). This water movement against an osmotic or water activity gradient, although falling within the operational definition of active transport, appears to be secondary to the inward pumping solutes such as sodium chloride. In a tissue as complex as the intestinal wall in vitro, with no mesenteric circulation and in which the absorbed fluid and solutes have to pass through several membranes in parallel, it is possible that, by the establishment of local osmotic gradients, a local accumulation of solutes could have marked effects on water movements. In all instances where the problem has been examined, water transfer and solute transfer appear to be closely related

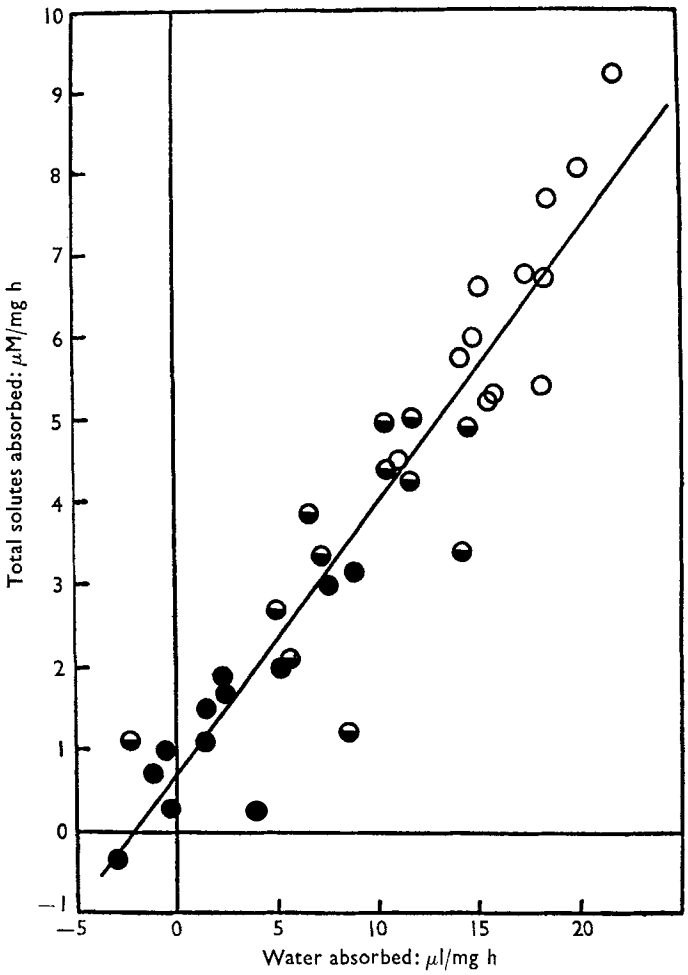

Fig. 1. The linear relation between total solutes absorbed and volume of water absorbed by rat jejunum in vitro. Fluid absorbed is approximately isotonic with that in lumen; slope of regression line 331 ± 20 m-osm $l.^{-1}$, concentration of solutes in lumen, approximately 340 m-osm $l.^{-1}$. (From McHardy & Parsons, 1957).

https://doi.org/10.1079/PNS19670010 Published online by Cambridge University Press

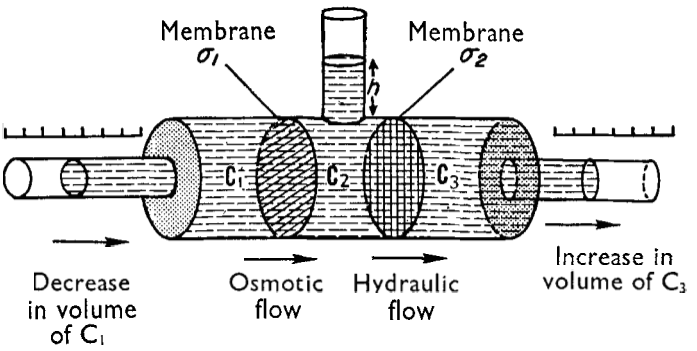

Fig. 2. Model system in which fluid flow is induced against an osmotic gradient. The three compartments C_1, C_2 and C_3 are separated by membranes which have different permeability properties.

Suppose fluid in all three compartments to contain sucrose solutions, that in C_1 being hypertonic to C_3 and that in C_2 hypertonic to C_1. The membrane separating C_1 and C_2 is impermeable to sucrose ($\sigma_1 \approx 1$) and with a high resistance to hydraulic flow. The membrane separating C_2 and C_3 is very permeable to sucrose ($\sigma_2 \rightarrow 0$) and with a low resistance to hydraulic flow. With the hydrostatic pressure in C_2 h cm above that in C_1 and C_3, there is a movement of water from C_1 through C_2 into C_3 and of solute from C_2 into C_3.

(Fig. 1) and no instance has been reported where water movement across the intestinal wall occurs from isotonic solutions in the absence of any solute movement (McHardy & Parsons, 1957; Curran, 1960; Clarkson & Rothstein, 1960; Parsons & Wingate, 1961; Barry *et al.* 1965).

Curran has suggested a model which can explain both the coupling of solute transport to volume flow and also the occurrence of net volume flow against a gradient of water activity. The model depends upon the accumulation of solute and the establishment of a positive hydrostatic pressure in a compartment which is bounded by two membranes possessing different permeability properties (Curran, 1960; Curran & McIntosh, 1962; Ogilvie, McIntosh & Curran, 1963). In this model, fluid flow is induced by the hydrostatic pressure and the flow can occur even against osmotic gradients existing across the whole system (Fig. 2). In intestine in vitro, solutes and water accumulate in the wall during absorption (Fisher & Parsons, 1949, 1953) and most of the water absorbed passes over into the serosal fluid under slight hydrostatic pressure via the lymphatics (Lee, 1961). Thus the conditions obtaining in the wall of intestine surviving in vitro can be closely related to the operational requirements for the model. It is to be pointed out that, in vivo, extensive solute accumulation is less likely in the presence of the mesenteric capillary circulation, and it is correspondingly more difficult to demonstrate the occurrence of water absorption against osmotic gradients in vivo. However, absorption of water from hypertonic solutions in dog colon in vivo has been shown to occur by Goldschmidt & Dayton (1919).

Although other mechanisms of water transport clearly cannot be excluded, the evidence now indicates that water transport across the epithelium must be very closely coupled to the absorption of sodium chloride and other solutes.

It will now be shown that it is likely that the transport of many of these other solutes is also directly dependent upon salt transport.

Coupling of sodium transport with solute transport

There is now a substantial body of evidence which suggests that there must be close coupling between the transport of sodium and the transport of certain sugars and of amino acids by the intestinal mucosa. The capacity of the small intestine to transport sugar against a concentration gradient in vitro depends upon the presence of sodium ions in the intestinal lumen (Riklis & Quastel, 1958; Csáky & Thale, 1960; Parsons & Wingate, 1961; Bihler & Crane, 1962; Crane, 1965). Sugar transport is inhibited by strophthin (ouabin), which itself is an inhibitor of sodium transport (Csáky, 1963; Schultz & Zalusky, 1964*b*).

As mentioned above, in rabbit ileum in vitro the short-circuit current is closely related to the net inward transport of sodium. In this tissue the magnitude of the current and hence of the sodium transport is increased when a sugar which is subjected to active transport is added to the mucosal fluid. The effect is still evident when a non-metabolized sugar is added so that it is not due to the stimulation of salt pumping by the addition of a metabolizable substrate (Schultz & Zalusky, 1964*b*) (Fig. 3). A similar effect appears when amino acids are present in the intestinal lumen. Schultz & Zalusky (1965) have shown that alanine, glycine, glutamate and other amino acids produce an increase in the short-circuit current when added to

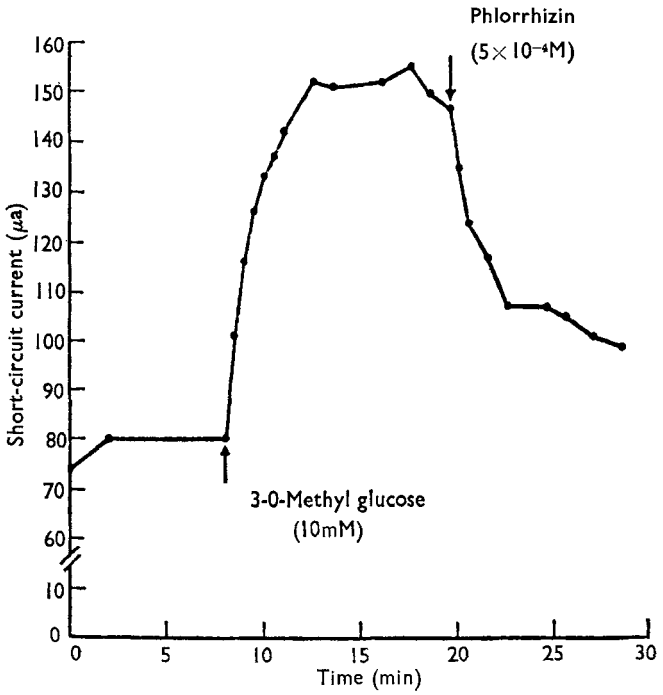

Fig. 3. Short-circuit current in isolated ileum of rabbit. The addition at 8 min of 10 mM 3-O-methyl glucose to fluid bathing the mucosal surface leads to an increase in the current. At 20 min the addition of phlorrhizin inhibits the short-circuit current. 3-O-Methyl glucose is a sugar which is subjected to 'active' transport, yet is not metabolized. Phlorrhizin is an inhibitor of 'active' sugar transport. In these experiments the short-circuit current is a measure of the 'active' sodium transport. (Reproduced from Schultz & Zalusky (1964*b*) by permission of Rockefeller Institute Press).

https://doi.org/10.1079/PNS19670010 Published online by Cambridge University Press

the mucosal fluid bathing the rabbit ileum. Bronk & Parsons (1966) have shown that when the sodium in the incubation medium is replaced by potassium, then the capacity of rings of rat intestine to accumulate a mixture of amino acids is abolished.

Systems for transcellular transport

Systems for the translocation of material across epithelial cells appear to be of two sorts. Both sorts of system depend for their function on the asymmetrical disposition of 'pumps' and 'leaks' in the two opposed cellular faces through which

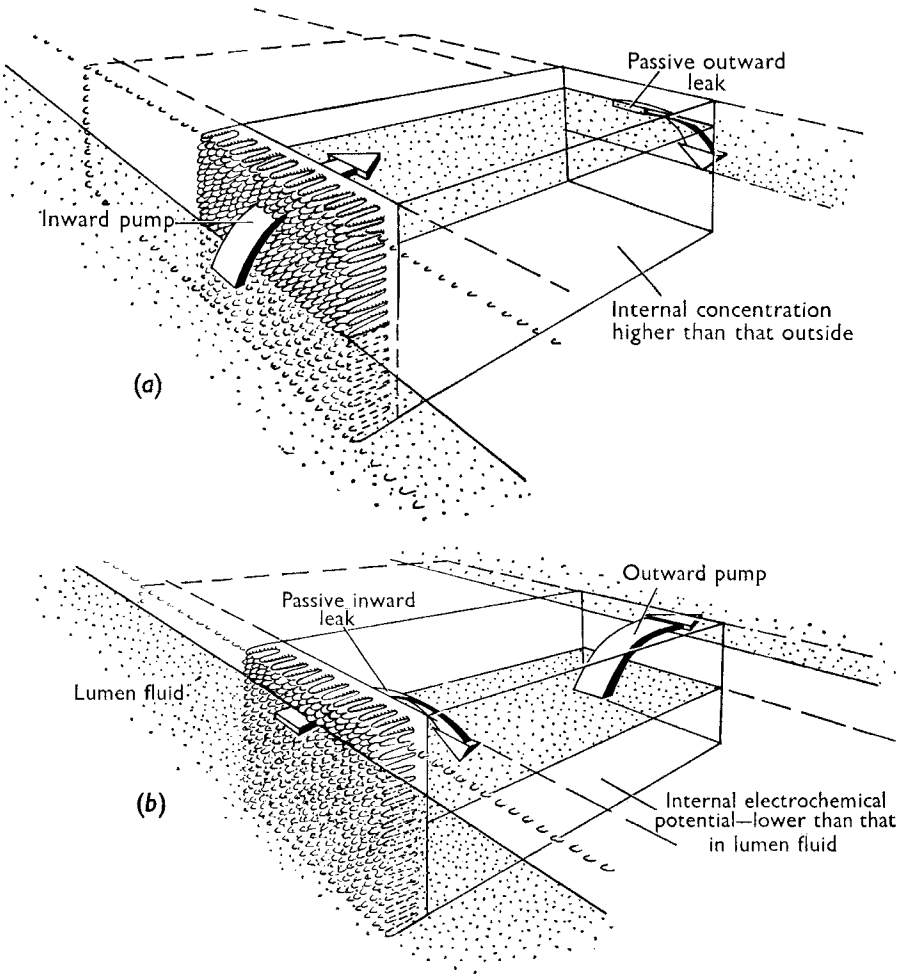

Fig. 4. Diagram showing two types of model asymmetrical intestinal mucosal cell.

(*a*) Model for sugars and amino acids. With an inwardly directed pump at the microvillus face of the cell, material is accumulated in the cell to leak out passively down the concentration gradient across the opposite far face.

(*b*) Model for sodium. By the functioning of an outwardly directed pump at the far face of the cell an electrochemical potential gradient is established across the microvillus face of the cell down which the substance moves passively into the cell.

For both models in the steady state, rate of pumping = rate of leaking.

https://doi.org/10.1079/PNS19670010 Published online by Cambridge University Press

transport occurs. In one sort, characteristic of the transport of amino acids and sugars, there is an accumulation of the substance inside the cell so that in the brush border of the intestinal cell there is required to be an entrance mechanism ('pump') with the capacity to move the substance across the concentration gradient. The substance thus accumulated can then move passively out of the cell down a concentration gradient ('leak') (Agar, Hird & Sidhu, 1954; Oxender & Christensen, 1959; Parsons, 1963; Kinter & Wilson, 1965). In the second sort of system, which is characteristic of the translocation of sodium across epithelial layers (Ussing, 1960) the intracellular electrochemical potential is maintained at a value which is less than those obtaining in the solutions between which transport is occurring. Thus work has to be done in moving the ion out of the cell across the far face; the energy for this 'pumping' process is presumably derived from the hydrolysis of adenosine triphosphate by the membrane-bound hydrolytic systems which recently have been so extensively investigated (cf. Skou, 1965). On the other hand, the ion which is subjected to transport can 'leak' passively into the cell down the electrochemical gradient existing across the face bordering the phase from which transport is occurring (Fig. 4).

The energetics of these systems are of interest. It should be noted that substantial amounts of energy are, in theory, available from the passive movement of ions down electrochemical gradients of physiological magnitude (Table 2). Provided a suitable method of coupling exists, this energy could be used to drive another substance such as an amino acid or a sugar up another concentration gradient (Table 3). It will be noted that for salt transport the existence of a passive 'leak' is postulated in the mucosal face of the cell, while for sugar and amino acid transport, the 'pumps' are required to be located in exactly the same region, namely the brush border.

There is rather good evidence that a coupling with sodium movement can provide energy for amino acid accumulation by ascites tumour cells (Eddy & Mulcahy, 1965) and by avian erythrocytes (Vidaver, 1964). With this sort of system operating in the

Table 2. *Energy released or absorbed by ions of molecules moving down or up electrochemical gradient specified. For positively charged ion, e.g. Na, calculations are on the basis that the ion is moved (e.g. Na out of a cell) up or down chemical concentration gradient of* 15:1 *(e.g.* 120 *mM* $l.^{-1}$ *extracellular,* 8 *mM* $l.^{-1}$ *intracellular); membrane potential,* C_1 *positive to* C_2. *Units, calories mole*$^{-1}$, 38°C, *calculated from* $\triangle G = nRT \ln [C_1/C_2] + nF \triangle \psi$

$\frac{C_1}{C_2}$	Unchanged molecule or $\triangle\psi = 0$	Membrane potential ($\triangle\psi$) mV						
		5	10	20	40	60	80	100
150	3090	1785	1899	2129	2587	3046	3505	3963
50	2413							
30	2097							
15	1670							
10	1420							
5	993							
2·5	565							
2·0	427							
1·1	59							

https://doi.org/10.1079/PNS19670010 Published online by Cambridge University Press

Table 3. *Maximum number of moles of a sugar (or neutral amino acid) which can be moved up the concentration gradient specified into a cell by energy derived from the movement of one mole of an ion moving into a cell down an electrochemical gradient with differing membrane potentials. Ionic concentration gradient,* 15 : 1 (*e.g.* 120 *mM* $l.^{-1}$ *extracellular,* 8 *mM* $l.^{-1}$ *intracellular*). *Membrane potential, exterior positive.*

Sugar concentration gradient: 1	Membrane potential $\triangle\psi$ mV						
	0	5	10	20	40	60	100
5·0	1·7	1·8	1·9	2·1	2·6	3·1	4·0
2·0	3·9	4·2	4·4	5·0	6·1	7·1	9·3
1·1	28	30	32	36	44	52	67

intestine, the energy for sugar and amino acid transport would be derived directly from ionic movements and hence only indirectly from hydrolysis of adenosine triphosphate. It also follows that if the processes of ion pumping are arrested, for example by placing the tissue in vitro in metabolically unfavourable conditions, movements of sugar and amino acids into the cell can still continue until the ionic battery is discharged and the electrochemical gradient of the ion across the cell membrane is reduced to zero. Thus amino acid accumulation can occur in rat intestine over periods of up to 8 min in the presence of dinitrophenol or of anoxia (Bronk & Parsons, 1966).

Conclusion

It is concluded that a basic mechanism exists in the small intestine for the transport of sodium chloride; this primary process of transport is itself entirely dependent on the cellular metabolism and upon the operation of a functionally asymmetrical cell. Important secondary consequences of this primary process are the transport of other solutes such as amino acids and sugars and of water from the lumen across the mucosal cells.

REFERENCES

Agar, W. T., Hird, F. J. R. & Sidhu, G. S. (1954). *Biochim. biophys. Acta* **14**, 80.
Barry, R. J. C., Smyth, D. H. & Wright, E. M. (1965). *J. Physiol., Lond.* **181**, 410.
Bihler, I. & Crane, R. K. (1962). *Biochim. biophys. Acta* **59**, 78.
Borgström, B., Dahlqvist, A., Lundh, G. & Sjövall, J. (1957). *J. clin. Invest.* **36**, 1521.
Bronk, J. R. & Parsons, D. S. (1966). *J. Physiol., Lond.* **184**, 950.
Burns, H. S. & Visscher, M. B. (1934–5). *Am. J. Physiol.* **110**, 490.
Carter, C. W., Coxon, R. V., Parsons, D. S. & Thompson, R. H. S. (1959). *Biochemistry in Relation to Medicine.* Ch. 10 and p. 246. London: Longmans, Green & Co.
Clarkson, T. W. & Rothstein, A. (1960). *Am. J. Physiol.* **199**, 898.
Clarkson, T. W. & Toole, S. R. (1964). *Am. J. Physiol.* **206**, 658.
Code, C. F. (1965). *Proceedings of the Cholera Research Symposium*, p. 87. Washington: U.S. Department of Health, Education and Welfare.
Cooperstein, I. L. & Hogben, C. A. M. (1959). *J. gen. Physiol.* **42**, 461.
Crane, R. K. (1965). *Fedn Proc. Fedn Am. Socs exp. Biol.* **24**, 1000.
Csáky, T. Z. (1963). *Biochim. biophys. Acta* **74**, 160.
Csáky, T. Z. & Thale, M. (1960). *J. Physiol., Lond.* **151**, 59.
Curran, P. F. (1960). *J. gen. Physiol.* **43**, 1137.
Curran, P. F. & McIntosh, J. R. (1962). *Nature, Lond.* **193**, 347.
Dennis, C. (1940). *Am. J. Physiol.* **129**, 171.
Eddy, A. A. & Mulcahy, M. (1965). *Biochem. J.* **96**, 76P.

Fisher, R. B. & Parsons, D. S. (1949). *J. Physiol., Lond.* **110**, 36.
Fisher, R. B. & Parsons, D. S. (1953). *J. Physiol., Lond.* **119**, 210.
Fordtran, J. S., Levitan, R., Bikerman, V., Burrows, B. A. & Inglefinger, F. J. (1961). *Trans. Ass. Am. Physns* **74**, 195.
Goldschmidt, S. & Dayton, A. B. (1919). *Am. J. Physiol.* **48**, 433.
Hindle, E. W. & Code, C. F. (1962). *Am. J. Physiol.* **203**, 215.
Kinter, W. B. & Wilson, T. H. (1965). *J. Cell Biol.* **25**, 19.
Lee, J. S. (1961). *Am. J. Physiol.* **200**, 979.
McHardy, G. J. R. & Parsons, D. S. (1957). *Q. Jl exp. Physiol.* **42**, 33.
Ogilvie, J. T., McIntosh, J. R. & Curran, P. F. (1963). *Biochim. biophys. Acta* **66**, 441.
Oxender, D. L. & Christensen, H. N. (1959). *J. biol. Chem.* **234**, 2321.
Parsons, D. S. (1956). *Q. Jl exp. Physiol.* **41**, 410.
Parsons, D. S. (1963). *Nature, Lond.* **197**, 1303.
Parsons, D. S. & Wingate, D. L. (1961). *Biochim. biophys. Acta* **46**, 170.
Priestley, J. G. (1915–16). *J. Physiol., Lond.* **50**, 304.
Reid, E. W. (1892). *Br. med. J.* i, 1133.
Reid, E. W. (1900). *Phil. Trans. R. Soc.* Ser. B, **102**, 211.
Reitmeier, R. J., Code, C. F. & Orvis, A. L. (1957). *J. appl. Physiol.* **10**, 256.
Riklis, E. & Quastel, J. H. (1958). *Can. J. Biochem. Physiol.* **36**, 347.
Schultz, S. G. & Zalusky, R. (1964*a*). *J. gen. Physiol.* **47**, 567.
Schultz, S. G. & Zalusky, R. (1964*b*). *J. gen. Physiol.* **47**, 1043.
Schultz, S. G. & Zalusky, R. (1965). *Nature, Lond.* **205**, 292.
Schultz, S. G., Zalusky, R. & Gass, A. E. Jr (1964). *J. gen. Physiol.* **48**, 375.
Skou, J. C. (1965). *Physiol. Rev.* **45**, 596.
Ussing, H. H. (1960). *Alkaline Metal Ions in Biology, Handbuch der Experimentallen Pharmakologie.* Vol. 13, p. 1. Berlin: Springer.
Ussing, H. H. & Andersen, B. (1955). *Proc. int. Congr. Biochem.* III. *Brussels*, p. 434.
Vidaver, G. A. (1964). *Biochemistry* **3**, 803.
Visscher, M. B., Fetcher, E. S. Jr, Carr, C. W., Gregor, H. P., Bushey, M. S. & Barker, D. E. (1944). *Am. J. Physiol.* **142**, 550.
Visscher, M. B., Varco, R. H., Carr, C. W., Dean, R. B. & Erickson, D. (1944). *Am. J. Physiol.* **141**, 488.
Wilson, T. H. & Kazyak, L. (1957). *Biochim. biophys. Acta* **24**, 124.

Absorption of vitamin B_{12} from the intestine

By G. H. Spray, *Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford*

In a limited space only a brief outline can be given of knowledge about the absorption of vitamin B_{12}. The size of the problem is shown by the review by Glass (1963), which covers over 300 pages and contains over 1500 references. Later developments have been summarized by Donaldson (1964) and Herbert (1965).

Historical and general aspects

Over 30 years ago Castle and his collaborators showed that patients with Addisonian pernicious anaemia, the classical disease in man due to deficiency of vitamin B_{12}, did not respond when they ate beef. If, before it was given to the patients, the beef was eaten by a normal man and was recovered from his stomach and incubated, or was incubated with normal human gastric juice, most patients showed increased formation of red blood cells (Castle, 1929; Castle & Townsend, 1929). It was suggested that an extrinsic (food) factor reacted with an intrinsic (gastric) factor in the normal stomach to form material with 'a marked hematopoietic effect' (Castle, Townsend & Heath, 1930). The defect in pernicious anaemia was failure to secrete intrinsic factor.