The gut is a membrane, is a vesicle, is a gut!

The paper of Spiller *et al*¹ in this issue recalls an experiment we did in secondary school; it dealt with the forces of osmosis. We placed a fresh potato in a water bath, the potato was cored out to create a semipermeable layer between its interior space and the exterior bathing fluid. Fluids could be made to move into the potato, or out of it, depending on how much salt was added to one or other of the solutions. Thus the fundamental message of Spiller's work is that the human jejunum functions as a simple, semipermeable membrane; it is subject to the forces of osmotic pressure and of electrochemical concentration gradients. The jejunum being a generally leaky membrane² and lacking a potent electrical potential difference which could influence the movement of ions, behaves as did the potato. The proximal small bowel responds *in vivo*, to electrochemical gradients; it equilibrates freely with extra cellular fluid any major ion or other solute in the lumen. With respect to these properties the jejunum should be contrasted with the ileum and colon, where passive permeability is much less prominent.^{3,4} Such concepts help us to understand the 'gut functioning as a gut', but this intellectual approach considers the intestinal mucosa only as a single 'black box'. Although certain functions are carried out what are the mechanisms by which these are achieved and how can they be modified?

The science of epithelial transport moved its prime focus to the paradigm of the membrane and major contributions were made by the biophysical school introduced by Hans Ussing.⁵ This approach considered the epithelium as a more precise black box; it was an electrochemical resistance, across which the movement of charged particles could be quantified. Setting up a postage stamp of mucosa as the barrier between two closed chambers allowed electrical forces governing the transport of ions to be dissected further. When the electrical forces intrinsic to the membrane were negated by 'short circuit' technology, ions that move by forces other than electrochemical gradients that is to say 'actively', could be defined. This paradigm is still very useful: human tissues removed at surgery can be studied⁶ and, by imaginative use of pharmacological dodges, sufficient channels and ports can be recognised to satisfy even the most frustrated ancient mariner.⁷ An important new dimension was introduced when the intramural nervous tissues were jolted by an electrical shock (electrical field stimulation, EFS). Transport phenomena could be altered;⁸ EFS caused chloride ions to be secreted into the lumen and the prospect was raised that the nervous system within the gut (enteric nervous system, ENS) played a role in the control of these functions.

To dissect the gut's membrane further it became necessary to examine transport phenomena even more precisely at the level of the cell membrane. Vesicles of the plasmalemma of epithelial cells were prepared, so that their transport characteristics could be quantified and modified^{9,10} either on the brush border, or basolateral surfaces. Technology advanced even further;

now even smaller segments of a cell membrane can be studied as individual ionic channels.¹¹ This is the 'patch-clamp' technique, which knocks on the very doors by which water soluble solutes enter and leave the cell and can evaluate the role of specific molecular blockers of ion channels.

To return to the clinical world. Those who manage patients who absorb too little water from their intestines (or who may secrete fluid into the lumen) are all too conversant with the symptom of diarrhoea. Some may question where these seemingly esoteric *in vitro* models lead us, and although the question is not entirely inappropriate, it is facile; for the cellular (or membrane) mechanisms which modulate transport are the points at which these functions can be altered pharmacologically and at which potential benefits can ultimately be applied therapeutically.

Epitheliologists such as Diamond^{2,12} have considered the gut more as an integrated surface. In this sense then, the intestine is not just a series of ionic channels forming membranes which contain multiple channels, or a biophysical surface which can be short circuited and treated as a planar electrical resistance; neither is it a series of individual cells. It is a composite of absorptive and secretory cells, joined together by intercellular junctions which are not 'tight' but which function as 'shunts' for water and water-soluble solutes. Thus ionic channels and vesicles must be integrated into a functional epithelial surface.

The paper of Spiller, Jones, and Silk¹ bears on these issues. Studying the human jejunum, they conclude that the important determinant of whether sodium and water accumulates in the small bowel is the sodium content of the artificial diet. Because in Diamond's terms^{2,12} the jejunum is 'leaky', it is predictable that when the jejunal fluid is low in sodium, sodium will move from the extracellular fluid space into lumen. This phenomenon has been amply demonstrated by the studies of Fordtran.³ That amino acids are absorbed and do not constitute a driving force for fluid accumulation in the lumen is also not surprising.¹³ Likewise, glucose absorption may involve multiple, simultaneous mechanisms which may differ between species and vary according to the methods by which different tissues are studied.¹³ Cellular, indeed vesicular, mechanisms clearly exist for 'uphill' transport of glucose (and amino acids), and yet postprandially, when most of us are digesting and absorbing simple carbohydrates, amino acids and ions, the major driving forces are likely to be simple concentration gradients.

And so, coming back to the whole gut, two points need emphasis. The first relates to very practical considerations as to what needs to be replaced in patients with the short bowel syndrome. Some of these unfortunate persons do not absorb nutrients adequately and caloric deprivation is their major problem. In some the short gut is able to handle fat, carbohydrate and protein reasonably well,¹⁴ but they may suffer chronic fluid and electrolyte depletion.

The second question relates to how well can one equate data from jejunal perfusions of healthy volunteers to whole gut function in patients, when the distal bowel may be diseased, or has been resected. The 'leaky' jejunum may respond normally to the sodium and/or glucose composition of its contents by establishing net fluxes; but the intestine from oesophagus to rectum functions as an integrated tube. The present author's own work has described ileal feedback on the proximal gut;¹⁵ perhaps we should expect an integrated series of negative feedback controls at all levels. What is

therefore applicable to the healthy gut, may not be transposable to the short bowel of patients. What are the integrative roles of the distal small bowel and colon, in health, in disease, or when they are absent surgically? How important are the compensatory absorptive functions of the hind-gut?¹⁶ The answer to the issues raised in this title is clear, but as yet unresolved. The mammalian gut is at once an epithelial membrane, a biophysical resistance, and a combination of membrane vesicles and channels. It is also, at any one level, only a portion of a long, integrated tube, which functions as a large surface area with absorptive functions that change gradually from top to bottom.

Supported in part by Grants AM32121, AM34988 and RR585 from the National Institutes of Health, Bethesda, MD, USA.

SIDNEY PHILLIPS

*Director, Gastroenterology Unit,
Mayo Clinic and Medical School,
Rochester, MN 55905, USA.*

References

- 1 Spiller RC, Jones BJM, Silk DBA. Jejunal water and electrolyte absorption from two proprietary enteral feeds in man. Importance of sodium content. *Gut* 1987; **28**: 681–7.
- 2 Diamond JM. Tight and leaky junctions of epithelia : A perspective on kisses in the dark. *Fed Proc* 1974; **33**: 2220–4.
- 3 Fordtran JS, Reiter FC, Eivton MF, Soter N, Kinney J. Permeability characteristics of the human small intestine. *J Clin Invest* 1965; **44**: 1935–44.
- 4 Billich CO, Levitan R. Effects of sodium concentration and osmolality on water and electrolyte absorption from the intact human colon. *J Clin Invest* 1969; **48**: 1336–47.
- 5 Ussing HH, Kruhopper P, Hess-Thaysen J, Thorn NA. *The alkali metal ions in biology*. Berlin: Springer, 1960.
- 6 Sandle GI, Wells NK, Allis W, Binder HJ. Electrophysiology of the human colon: evidence of segmental heterogeneity. *Gut* 1986; **27**: 999–1005.
- 7 Powell DW. Intestinal water and electrolyte transport. In : Johnson LR, ed. *Physiology of the gastrointestinal tract*. New York: Raven Press, 1987.
- 8 Hubel KA. Intestinal nerves and ion transport: stimuli, reflexes and responses. *Ann J Physiol* 1985; **9**: 261–71.
- 9 Murer H, Hopfer V, Kinne R. Sodium/protein antiport in brush border membrane vesicles isolated from rat small intestine and kidney. *Biochemistry* 1976; **15**: 597–604.
- 10 Liedtke CM, Hopfer V. Mechanism of Cl⁻ translocation across the small intestinal brush border membrane. II. Demonstration of Cl⁻/OH⁻ exchange and Cl⁻ conductance. *Am J Physiol* 1982; **242**: 272–80.
- 11 DiStefano A, Wittner M, Schlatter E, Lang HJ, Englert H, Gregor R. Diphenylamine-2-carboxylate a blocker of the Cl⁻ conductive pathway in Cl⁻ transporting epithelia. *Pflug Archiv* 1985; **405** suppl. 1 S95-S100.
- 12 Diamond JM. The epithelial junction: budge, gate and fence. *The Physiologist* 1977; **20**: 10–18.
- 13 Hopfer V. Membrane transport mechanisms for hexoses and amino acids in the small intestine. In: Johnson LR ed. *Physiology of the gastrointestinal tract*. New York: Raven Press, 1987.
- 14 Woolf GM, Miller C, Kurian R, Jeejeebhoy KN. Nutritional absorption in short bowel syndrome. Evaluation of fluid, calorie and divalent cation requirements. *Dig Dis Sci* 1987; **32**: 8–15.
- 15 Spiller RC, Trotman IF, Higgins BE, *et al*. The ileal brake-inhibition of jejunal motility after ileal fat perfusion in man. *Gut* 1984; **25**: 365–74.
- 16 Debonigie JC, Phillips SF. Capacity of the human colon to absorb fluid. *Gastroenterology* 1978; **74**: 698–703.