Electric-potential difference—a neglected parameter of gut integrity and function?1

Electrophysiological measurements, already established as crucial to investigation or diagnosis in other fields, may be applied increasingly to the understanding of gastrointestinal function and disease through determinations of the electric-potential difference between the gastrointestinal mucosa and serosa. The electric-potential difference is the difference between the electric potentials of two standard non-polarizable electrodes in contact with solutions on either side of a membrane, the junction potential being eliminated. In vivo, this steady potential reflects several factors, including the maintained separation of ions, the concentrations of such ions on the two sides of the membrane, and tissue resistance1; it differs from small cyclic potentials generated in smooth muscle cells. Although the precise origin of transmural electric-potential difference in the gut, and the relative influences of the physico-chemical processes that modify it or are modified by it, are uncertain, the transmural electric-potential difference arises in the mucosal cells2, 3, 4, 5 and represents the algebraic sum of all the potential differences across both the luminal and the serosal membranes6. Striking regional differences in the electric-potential difference are found in the gastrointestinal tract, presumably because of the differing structures and functions of the mucosa at various anatomical sites. Whereas earlier studies of electric-potential difference in man yielded conflicting results, because of the use of the unabraded or variably abraded skin for the indifferent electrode, valid determinations of electric-potential difference can now be performed simply by placing the indifferent electrode in peripheral blood7, which has been shown to be equipotential with serosa6.

The electric-potential difference in the human stomach is relatively high, approximating 40 mv in the corpus and 20 mv in the antrum (mucosa negative to serosa)7, 8. Abrupt declines in the electric-potential difference occur when the sensing electrode is passed from the stomach to the oesophagus or duodenum, and these declines coincide with the gastrooesophageal or pyloroduodenal mucosal junctions; therefore, the electric-potential difference has been used to locate these regions for a variety of purposes7, 9, 10, 11, 12. Animal studies can be interpreted as showing that gastric electric-potential difference is probably generated by continuous secretion of chloride in excess of cations13, but a more direct relationship with sodium transport is not excluded14. An intact mucosa is probably essential for maintenance of normal electric-

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potential difference. Davenport and his colleagues\textsuperscript{15} showed that eugenol, which causes exfoliation of gastric epithelial cells, abolishes the normal barrier to diffusion of sodium and simultaneously reduces the electric-potential difference of the canine stomach. Anoxia and agents believed to be toxic to the gastric mucosa, including salicylates, alcohol, and bile, lead to a decrease in the electric-potential difference and disrupt the gastric mucosal barrier in man or animals\textsuperscript{5, 16, 17, 18, 19}. Patients with pernicious anaemia have reduced electric-potential difference in the body of the stomach\textsuperscript{20, 21}, but the electric-potential difference has yet to be evaluated in man in other conditions associated with disease or damage involving the mucosa. Interestingly, gastric electric-potential difference remains unchanged during standard procedures that stimulate gastric secretion in health, except for a trivial and temporary decrease at the onset of maximal betazole stimulation\textsuperscript{20, 22, 23}.

Relatively small transmural potential differences of 1 to 5 mv (mucosa negative) have been measured throughout the small intestine in several species, and no regional difference has been defined\textsuperscript{1}. A close relationship exists between electric-potential difference and the transport of electrically charged particles. Ussing and his associates\textsuperscript{24} first stressed that a knowledge of the magnitude and polarity of electric-potential difference is essential in determining whether ions move actively or passively, and the relationship has been validated extensively by studies of simple membranes\textsuperscript{25, 26}. Thus, electric-potential difference in the small intestine is modified by, or modifies, the movement of sodium and actively transported sugars or amino acids. Decreasing the intraluminal concentration of sodium leads to the reduction of, and then the reversal in, polarity of transmural electric-potential difference, the latter change having been interpreted as reflecting a preferential leak of cations as a result of negative charges on the mucosal pores\textsuperscript{27}. By contrast, glucose, other actively transported sugars, and amino acids cause a rapid increase in electric-potential difference that is unrelated to the metabolism of these compounds\textsuperscript{27, 28, 29, 30, 31, 32, 33}. These electrophysiological effects were once attributed solely to concomitant changes in sodium transport, but the short circuit currents exceed those expected from the measured sodium movement\textsuperscript{34}, and it now appears that the disparity may be accounted for by chloride secretion into the lumen\textsuperscript{35}. In healthy man and animals, potentials of about 5 mv (mucosa negative) have been found throughout the small intestine; these potentials also increase during glucose absorption and are reduced by low concentrations of sodium in the lumen\textsuperscript{27, 31, 32, 33, 34, 35, 36, 37, 38}. The degree to which the electric-potential difference is modified by disease of the small intestine, especially those associated with disorders of ionic transport, has yet to be explored.

The relatively large potential differences (40 to 60 mv, mucosa negative) measured in the colon in various animals and in man\textsuperscript{5, 31, 39, 40} are currently attributed to active sodium transport\textsuperscript{40}, but no data are available regarding specific mechanisms or the findings associated
with disease of the organ. Similarly, although potential differences of considerable magnitude have been recorded from the liver and pancreas in animals, and are modified by hepatic damage from carbon tetra-chloride\textsuperscript{41, 42} or by pancreatic exocrine secretion\textsuperscript{48} respectively, no basic or clinical correlations of these phenomena have been sought.

It is concluded that measurement of the electric-potential difference, already essential for investigation of ionic transport and sometimes helpful in identifying anatomical junctional zones in the gut, now deserves greater application in seeking correlations between disorders, of structure and function in gastrointestinal disease.

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