Comment

THE TRANSMURAL ELECTRIC POTENTIAL AS A PARAMETER OF THE STRUCTURAL AND FUNCTIONAL INTEGRITY OF THE SMALL INTESTINE

While the plea of Geall and Summerskill (1969) for measurements of the electric potential difference across the alimentary tract in various disorders merits strong support, a degree of caution is needed in the interpretation of the data obtained from such studies in the small intestine. Geall and Summerskill implied by their title 'Electric-potential difference—a neglected parameter of gut integrity and function?' that the electric potential difference across the gut is, in fact, a useful index of the integrity of the gut and of its functions. Clearly, to be useful, any parameter of an organ's structural or functional integrity must be sensitive enough to indicate physio-pathological changes. In the case of the small intestine, the electrical activity across the epithelium can be simply characterized by Ohm's Law, *ie*, potential difference = current $\times$ resistance. Because this equation has three variables, situations may arise where the potential is constant yet the values of the current and resistance may vary considerably. The magnitude of the potential difference across the intestine is related to its ability to separate positive from negative ions. This separation can be accomplished either by hindering the diffusion or specifically accelerating the movement of one of the charged ions (*ie*, via an electrogenic ion pump). Although the mechanisms generating the potential difference across the small intestine are not yet completely defined (see reviews by Barry, 1967; Smyth, 1968; Schultz and Curran, 1968, for details) it is likely that under normal conditions of absorption *in vivo*, most of the potential is due to electrogenic ion pumps. Theoretically, it only needs the functioning of a few mucosal cells for an electric potential to be generated across the small intestine. In the extreme situation of the operation of only one normal mucosal cell in a functionally damaged area, a normal potential difference could be recorded provided that the rest of the damaged cells had a high enough resistance to compensate for the extremely low current (*ie*, ion transfer) across such cells. Because of the continuous replacement of mucosal cells from the crypts, diseased and malfunctioning areas of the small intestine often have a patchy distribution. It is rare to see every single cell of the small bowel similarly affected by a disease process or drug-induced change. This means that some areas of the mucosa could be functioning normally amidst the malfunctioning tissue and the distinct possibility of recording a normal potential difference is apparent. It is this feature that makes electric potential measurements a difficult parameter to interpret without the control measurement of resistance or current. A more sensitive index of intestinal ion transfer would be a measurement of the short circuit current, that is, the

amount of current needed to reduce the potential across the membrane to zero. This parameter, first used by Ussing and Zerahn (1951) to measure the active transfer of ions across the frog skin, has since been found to be a useful index of net ion transfer (Barry, 1967; Schultz and Curran, 1968). It is impossible, however to obtain an accurate measurement of this parameter *in vivo* (Rehm, 1968). Furthermore, as the resistance of an epithelium is obtained by dividing the current it generates by the potential developed it is obvious that we are only able to measure one of the three variables of Ohm's law across the small intestine *in vivo*. The question that arises is thus how sensitive will measurements of the transmural potential be as an index of intestinal malfunction? One way of answering this question is to create experimental conditions that affect intestinal structure and transfer and then record the electric potential difference across the intestine. If the change in potential is related to the changes in structure and function then clearly it is a useful measure of integrity; if, however, there are no or very small changes in its value then its use must be limited. Fortunately, there are a number of studies that have measured both the transintestinal potential difference and the absorption of solutes in a variety of experimental conditions.

Sacher, Saha, and Hare (1967) found that the electrical potential differences generated by the addition of actively transferred hexoses to the intestinal luminal fluid *in vivo* were similar in humans suffering from acute cholera and in normal control patients. No changes in electrical activity across the small intestine *in vitro* were found by Norris, Schultz, Curran, and Finkelstein (1967) who used a rabbit model of cholera. Leitch, Burrows, and Stolle (1967) found a poor correlation between electrical potentials and the accumulation, *in vivo*, of intestinal luminal fluid in cholera toxin-treated rabbits. Despite these observations, it is known that patients suffering from cholera have a massive diarrhoea (Sladen and Dawson, 1969).

Hypophysectomy is known to affect both the structure and functions of the alimentary tract. The effects of this endocrinopathy on intestinal functions have been recently reviewed in detail (Levin, 1969). In many species there is a striking atrophy of the intestinal mucous membrane both villous height and intestinal weight are reduced (Havivi, Havivi, and Levitan, 1968). It might be anticipated that a general depression of absorptive capacity would occur concomitant with this atrophy, if not due to the reduced efficiency of the transfer mechanisms of the mucosal cells *per se* then at least because of the reduction in their number. The results obtained by Finkelstein and Schachter (1962) show, in fact, that the transfer of a number of substances across intestine removed from hypophysectomized rats and incubated *in vitro* is differentially affected. While the transfers of calcium, iron, and proline were decreased by 50, 67, and 20 to 40% respectively, that of galactose was increased by 25 to 40%, and that of sodium was unaffected. Despite these changes in absorption no variation in the electric potential across the jejunal sacs was recorded.

Levin (1968) investigated the effects of 5-fluorouracil, a fluorinated pyrimidine that has antimitotic and protein synthesis-blocking actions on the structure and functions of the small intestine. After three days of treatment with the drug, the absorption of glucose, galactose, and fructose was reduced and the intestinal maltase activity was depressed. Fine structural changes in the mucosal cells of the small intestine were revealed by electron microscopy. A number of the mucosal cells were vacuolated, others had reduced numbers of microvilli in their brush borders and many of the lateral spaces between mucosal cells were distended. Despite these functional and structural abnormalities, neither the hexose nor the amino acid transfer potentials generated across the drug-affected intestine by addition of these solutes to the fluid bathing the everted jejunal sacs were significantly different from those obtained in control intestines.

Another example of the poor correlation between functional changes and the transmural potential difference is from a study by McKenney (1968) on the effects of irradiation on the small intestine. He measured the electrical potentials across the everted intestine incubated *in vitro*. Under normal conditions of incubation, McKenney reported that many of the intestines removed from the irradiated animals had potentials similar to those obtained across control intestines. It was only when he used incubating buffers containing a lowered sodium concentration or made hyperosmotic with mannitol that differences could be clearly distinguished between irradiated and control intestines. Yet despite this practically normal electrical potential it is known that hexose and propionate absorption, fluid transfer, and metabolism of the irradiated intestine are all reduced (Perris, Jervis, and Smyth, 1966; Perris, 1966).

Finally, the lack of correlation between the potential and the function even of the normal intestine *in situ* is shown by the observations of Schedl, Wilson, and Miller (1969). These authors found that the pattern of the transmucosal potential differences in the duodenum, jejunum, and ileum did not parallel the absorption rates of sodium or water which were greater in the more proximal intestinal segments. The authors came to the conclusion that there was no evident correlation between the potential difference and the ion movements they observed and that 'the pattern of transmural potential differences showed no correlation with absorption and secretion rates'.

Bearing in mind the above observations, it is clear that in a number of conditions that alter the absorptive capacity of the small intestine, measurements of the transmucosal electric potential do not appear to be a useful index of the degree of the functional impairment of the mucosal cells. Apparently there can be large changes in absorption and secretion without concomitant effects on the electric potential. Gasser succinctly summed this up in 1933 with the statement: 'You cannot determine a process from a potential!' It is thus important to stress that future investigators measuring the electrical potential should not interpret any lack of change in this parameter as diagnostic of the functional and structural integrity of the small intestine unless other

tests of the organ's absorptive and secretive functions are confirmatory.

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DR GEALL replies

Levin had documented evidence that in the small intestine certain agents which affect transport and structure do not alter electrical potential difference. The recent finding of normal potential differences in the jejunum in non-tropical sprue is further support for this view.¹ However,