Cholera—a clue to 'functional diarrhoea'?

Recent advances in the management of human cholera provide a striking example of the practical application of physiological principles and may have wider clinical significance. It has been found that glucose-electrolyte mixtures given by mouth or by gastric intubation greatly reduce the rate of intestinal loss of fluid and electrolytes\(^1,3,5\) and can be used to maintain fluid balance. In one series,\(^1\) the requirement for intravenous fluids was reduced by approximately 80\% in this way. This may prove to be of great value in situations where large quantities of sterile fluids are not available for parenteral use.

The exact cause of the massive diarrhoea of cholera is still unknown. The mucosal epithelium is not shed, but retains its normal morphological appearance as judged by light and electron microscopy both in man\(^4\) and in the experimental disease.\(^5\) There is no gross disturbance of permeability to macromolecules, because the protein content of the stools is always low.\(^6\) The jejunum is probably the major site of fluid loss, because the diarrhoea can be controlled by proximal aspiration of gut contents,\(^7\) and, in experimental canine cholera, the toxin has a greater effect on jejunum than on ileum and has little effect on the colon.\(^8\) The jejunal handling of fluid and electrolytes must, therefore, be disturbed in a very subtle way.

In the normal human jejunum the absorptions of sodium, water, and certain sugars are closely linked. The active transport of glucose against a concentration gradient depends upon the presence of sodium in the lumen,\(^9\) but this does not apply to glucose transport down a concentration gradient from lumen to blood.\(^10,11\) Conversely, the absorption of sodium and water is greatly stimulated by luminal glucose\(^12\) and galactose, but not by fructose.\(^13\) Since glucose and galactose share a common transport mechanism,\(^13\) this suggests that there is a link between carrier-mediated sugar transport and the net absorption of sodium and water. It is not known if glucose exerts its effect primarily on water or on sodium transport and there is conflicting evidence on this point.\(^14,15\) The clinical effects of glucose strongly suggest that the mechanism linking glucose transport to that of sodium and water is intact in cholera. Furthermore, galactose, but not fructose, is also capable of reducing the intestinal losses of fluid.\(^3\)

It has been suggested that the cholera toxin inhibits the sodium pump, because it reduces sodium transport by the isolated short-circuited frog skin.\(^6,16\) Recent studies using intestinal preparations do not support this view. For example, cholera toxin has no effect on the capacity of the isolated human ileum to transport sodium actively.\(^17\) It is difficult to extrapolate from this to the \textit{in vivo} situation, because, whereas glucose stimulates sodium transport by this preparation,\(^17\) it has no effect on ileal absorption of sodium and water in intact man.\(^14\) The active
transport of sugars is believed to depend on the integrity of the sodium pump and the maintenance of a low intracellular sodium concentration.18,19 The fact that glucose absorption is normal in experimental cholera20 would also suggest that the sodium pump is intact. However, this argument is not entirely valid, because glucose absorption by carrier-mediated diffusion is not sodium dependent, as already mentioned.10,11 Measurement of bidirectional sodium fluxes in experimental rabbit cholera indicates that glucose specifically stimulates the lumen to plasma flux, whereas the cholera toxin promotes flux in the opposite direction,21,22 but such clear-cut effects on sodium fluxes were not found in a canine experimental model.8 The effects of glucose and toxin appear to be separate and additive in the rabbit model but comparable studies in man have not been reported. Finally, the fact that stool losses in the human disease continue even if nothing is taken by mouth suggests that the primary disturbance is not a failure of sodium absorption from the lumen. All the evidence would indicate that the cholera toxin induces an abnormal movement of sodium and water from the plasma into the lumen.

Such a movement could result from filtration. There is some evidence that the permeability of the mucosal capillaries is altered23,24 but the findings are open to criticism.25 Calculations based on the properties of the permeability barrier in the normal human jejunum show that vascular hydrostatic pressure would not be capable of producing the massive fluid losses observed in cholera.26 This permeability must be increased, without allowing protein to enter the lumen and without interfering with several normal absorptive mechanisms. The alternative possibility is that sodium and water are secreted into the lumen by reversal of the normal direction of sodium pumping. This would have to be a non-electrogenic mechanism, ie, coupled to an anion, because the transmural potential difference is not reversed in experimental cholera in vivo.27

What are the possible wider applications of these findings? It seems unlikely that Vibrio cholerae is the only organism capable of producing these changes and epidemics of non-vibrio cholera have been reported.28 A staphylococcal toxin can impair sodium transport by the isolated toad bladder,29 and Shields has alluded to unpublished evidence that such a toxin can produce cholera-like effects on the gut mucosa.30 Certain laxatives interfere with intestinal transport of sodium and this may be the mechanism of their action.31 There may therefore be a variety of luminal factors, some of bacterial origin, which can affect sodium transport and produce diarrhoea, without giving rise to any easily detectable abnormality of the intestine. One wonders how many examples of unexplained ileostomy losses or severe ‘functional’ diarrhoea may be caused by mechanisms of this type. The methods used by workers in the study of cholera could certainly be exploited in the investigation of such patients.

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REFERENCES


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