PROCEEDINGS OF THE NUTRITION SOCIETY

A Meeting of the Clinical Metabolism and Nutritional Support Group of the Nutrition Society and the British Association for Parenteral and Enteral Nutrition was held at the Clarendon Suite, Birmingham on 7/8 December 1994

The Sir David Cuthbertson Medal Lecture

Enteral-feeding-related diarrhoea: proposed causes and possible solutions

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The inscription that Sir David Cuthbertson chose for his coat of arms on receiving his knighthood in 1965 was 'Understand and nourish'. The 'understand' represented the goal of science and the 'nourish' represented the importance of nutrition. Such a motto underlies any nutritional-based research, and the work I have undertaken and which is the basis of the present lecture has been carried out very much with this philosophy in mind.

Diarrhoea complicating enteral feeding is an all too common clinical problem. Its incidence occurs in up to 30% of patients being fed on general medical and surgical wards (Heymsfield *et al.* 1979; Heibert *et al.* 1981; Cataldi-Betcher *et al.* 1983) and in up to 63% of patients in intensive care units (Kelly *et al.* 1983). In an average 500-bed hospital there will be at least thirty patients receiving nutritional support at any one time, of whom twenty-four will be being enterally fed. With an incidence of, for example, 20% there will be at least five patients at any one time troubled with diarrhoea. Enteral-feeding-related diarrhoea is, therefore, a very real and common clinical problem that affects every area of hospital and community-based patient care. At present its management is notoriously unsuccessful; we prescribe anti-diarrhoeal agents, such as loperamide or codeine phosphate, and we may try a fibre-containing diet. But if these are unsuccessful there is a tendency to shrug our shoulders and hope the patient and nursing staff can cope as well as possible.

Despite its frequent and ubiquitous occurrence relatively little attention has been paid to this problem at a research level. In the present lecture I will review what is known about its causes and pathogenesis, and describe the studies I and my colleagues have carried out at the Central Middlesex Hospital. Finally, I will discuss how this problem might be combated at a clinical level.

AETIOLOGY

Several causes have been proposed (Table 1), including concomitant antibiotic therapy, infected diets, hypoalbuminaemia, lactose intolerance and osmolality.

There is an undisputed association between enteral feeding, antibiotics and diarrhoea (Jones *et al.* 1983; Keohane *et al.* 1983, 1984; Bastow, 1986; Guenter *et al.* 1990). The incidence of diarrhoea in enterally-fed patients taking antibiotics far exceeds the incidence in normally-fed patients taking the same antibiotics (Keohane *et al.* 1984).

Table 1. *Proposed causes of enteral-feeding-related diarrhoea*

Concomitant antibiotic therapy
Infected diets
Diet osmolality
Lactose intolerance
Hypoalbuminaemia

Thus, there appears to be a synergistic relationship between enteral feeding and antibiotic treatment that accounts for the high incidence of diarrhoea (Silk, 1987). Many believe that the diarrhoeagenic nature of antibiotics arises from their toxic actions on normal intestinal flora, with subsequent bacterial overgrowth of undesirable strains (Levine & Lamont, 1982). There is also a strong association with *Clostridium difficile* and pseudomembranous colitis (Bartlett *et al.* 1978; George *et al.* 1978; Burdon *et al.* 1981; Grube *et al.* 1987). However, it must be acknowledged that *Clostridium difficile* toxin is positive in 20–30% of patients with antibiotic-associated diarrhoea but without pseudomembranous colitis (Bartlett, 1979; George *et al.* 1982).

An interesting and important observation is that antibiotic therapy decreases the concentration of faecal short-chain fatty acids (SCFA; Surawicz *et al.* 1989; Raimundo *et al.* 1990*b*). These are the breakdown products of fibre fermentation in the colon and their production is reliant on the commensal colonic bacterial flora. SCFA have several biological functions: they play an important role in maintaining the integrity of the colonic epithelium (Roediger, 1980), and in stimulating mucosal proliferation (Jacobs, 1983); they are also avidly absorbed in the colon (Cummings, 1981), and in so doing enhance water and electrolyte absorption (Roediger, 1980; Ruppin *et al.* 1980; Binder & Mehta, 1989; Holtug *et al.* 1992). By altering the bacterial flora antibiotics can alter the production of SCFA and thereby influence colonic fluid absorption. The importance of this effect will be further discussed later.

Infected diets, also, can cause diarrhoea (Casewell & Phillips, 1978; Pottecher *et al.* 1979; Casewell *et al.* 1981), although this is now less of a problem with commercially-prepared diets than with the old diets which required reconstitution in hospital kitchens. Nevertheless, diet reservoirs are an excellent medium for bacterial multiplication, and studies have shown contamination with just 10 colony-forming units (cfu) increasing to 10^5 cfu within only 8 h (Simmons, 1981). The source of infection can be staff handling when attaching the giving sets or, more commonly, the patients themselves with bacteria spreading retrogradely into the diet reservoir (Payne-James *et al.* 1992). Normally gastric acid is an effective physiological means of destroying bacteria infused in the diet. Many patients, however, especially those in the intensive care unit, are often and for no apparent reason on histamine receptor antagonists. These raise gastric juice to a harmless pH and, hence, unable to undertake this important protective function (du Moulin *et al.* 1982).

Hypoalbuminaemia, also, has been associated with enteral-feeding-related diarrhoea (Brinson & Kolts, 1987; Ford *et al.* 1987; Waitzberg *et al.* 1988). In animal studies there is intestinal mucosal oedema and secretion of fluid into the gut with consequent diarrhoea (Paving *et al.* 1974; Duffy *et al.* 1978; Brinson *et al.* 1989). This has yet to be demonstrated in the *in vivo* human situation.

Diet osmolality is still sadly quoted by many as a cause of tube-feeding diarrhoea and other gastrointestinal complications, and the reason for using starter regimens. Keohane *et al.* (1984) performed a definitive study demonstrating that osmolality is not responsible for enteral-feeding-related diarrhoea and that starter regimens serve only to deprive the patient of much-needed nutrients over the 1–3 d that the diet is introduced.

Lactose intolerance, also, is not relevant to enteral-feeding-related diarrhoea. Most people who are lactose intolerant do retain some degree of lactase activity, and the rate that an enteral diet is infused is, therefore, most unlikely to overwhelm this enzyme system (Keohane *et al.* 1983). This, however, is now of academic interest as commercially-prepared diets are now lactose-free.

Of the various proposed mechanisms for enteral-feeding-related diarrhoea discussed previously, only antibiotic therapy, infected diets and possibly hypoalbuminaemia stand up to critical analysis. However, despite careful attention to these factors enteral-feeding-related diarrhoea still occurs in approximately 15% of patients (D. B. A. Silk, personal communication); therefore, there must be some other factor or factors contributing to the pathogenesis of enteral-feeding-related diarrhoea.

SMALL INTESTINAL RESPONSES TO ENTERAL FEEDING

Wright *et al.* (1978) perfused the human duodenum *in vivo* with a nutrient mixture and found a secretion of water and electrolytes in the jejunum, which was separated from the duodenum by an occluding balloon. These results implied that a mediator or mediators were responsible for the distal secretory effect, and the most likely candidate was a hormonal mechanism. Further support of a hormonal involvement was provided by the demonstration of a jejunal secretion of water and electrolytes in response to the intravenous infusion of a physiological mixture of gastrin, secretin, cholecystokinin, glucagon and gastric inhibitory polypeptide, similar to that found in the normal postprandial state (Poitras *et al.* 1980). However, recently several studies have demonstrated a pro-absorptive response in the jejunum to a meal stimulus, that appears to be induced by nutrient osmolality (Sarr *et al.* 1980, 1981; McFadden *et al.* 1984; Bastidas *et al.* 1989, 1990; Yeo *et al.* 1990). These studies, therefore, appear to contradict Wright's results.

Because of the resulting uncertainty over the small intestinal responses to enteral feeding Raimundo *et al.* (1988, 1990a) carried out a series of *in vivo* human perfusion studies to investigate the small intestinal response to both intragastric and intraduodenal enteral feeding. Two variables were looked at: the motor activity of the small intestine; and the volume of fluid entering the caecum (colonic in-flow), indicating the overall water and electrolyte movement through the small intestine. During post-pyloric feeding the small intestinal motility appropriately converted to the normal postprandial pattern and the colonic in-flow volumes were increased from fasting levels (Raimundo *et al.* 1988). During intragastric feeding both motility and in-flow volumes remained similar to that observed during the fasting state (Raimundo *et al.* 1990a). The diet infusion rate during these studies was the same as that used to provide 8·4 MJ (2000 kcal) and 2 litres/24 h period, which is what most patients will receive on the ward, and only provides 250 kJ (60 kcal)/h. As the receptors controlling the small intestinal responses to diet appear to be located in the proximal small intestine (Sarr *et al.* 1980, 1981; McFadden *et al.* 1984; Bastidas *et al.* 1989, 1990; Yeo *et al.* 1990), this may explain why

diet infused directly into the duodenum is able to initiate the fed response, whereas the same rate of infusion into the stomach, which will gradually release its contents through the pylorus, is insufficient to initiate the normal postprandial responses.

Taking these studies altogether it would appear that the small intestine responds predictably to enteral feeding, both in terms of motility and fluid movement, irrespective of the site of diet infusion. What was, however, an interesting observation was that during studies of Raimundo *et al.* (1990*a*) those subjects being fed intragastrically invariably developed diarrhoea, despite the lack of any normal postprandial response, whereas those being fed intraduodenally did not develop diarrhoea. This led to the hypothesis that enteral-feeding-related diarrhoea may occur as a result of a disorder of colonic function.

COLONIC RESPONSES TO ENTERAL FEEDING

To examine the colonic response to enteral feeding two sets of experiments were carried out, one to look at colonic water and electrolyte transport and the second to look at the motility responses. A new technique of *in vivo* colonic perfusion was designed to enable assessment of water and electrolyte movement simultaneously in the ascending and distal colon in response to the intragastric and intraduodenal infusion of a standard polymeric enteral diet (Bowling *et al.* 1993*a*). The distal colonic motor activity was measured with an established technique using four water-perfused catheters inserted in the descending, proximal and distal sigmoid and in the rectum, and monitoring activity before and during enteral feeding (Rogers *et al.* 1989; Rogers & Misiewicz, 1989).

In all these studies two different strengths of a polymeric diet were infused either intragastrically or intraduodenally: a low-load diet infused at 1·4 ml/min (5·9 kJ/min; 8·75 mg N/min), and a high-load diet infused at 2·8 ml/min (17·6 kJ/min; 26·1 mg N/min). The low-load diet corresponded clinically to the administration of 2 litres (8·4 MJ) over 24 h, the same as that used in studies of Raimundo *et al.* (1990*a*). Catabolic patients or those being fed cyclically over 12–14 h/d, a common situation especially in the home setting, require higher dietary loads; the high-load diet in our studies corresponded to this type of feeding.

A marked secretion of water, Na^+ and Cl^- was demonstrated in the ascending colon during the intragastric infusion of the low- and high-load diets, and during the intraduodenal infusion of the high-load diet (Bowling *et al.* 1995*a*; Fig. 1). This secretion amounted to approximately 120 ml/h or, if equated over a 24 h period, almost 3 litres/d. In the distal colon there was an absorption during fasting and feeding in all the groups.

The distal colonic segmental motor activity was unchanged from fasting during the low-load-diet infusions (Raimundo *et al.* 1992), but during the high-load infusions there was a significant suppression of activity, occurring immediately the intragastric infusion was commenced, and within 3 h of the start of the intraduodenal infusion (Bowling *et al.* 1993*b*; Fig. 2).

POSSIBLE MECHANISMS OF THE COLONIC RESPONSE TO ENTERAL FEEDING

These studies are the first to examine the *in vivo* human colonic response to enteral feeding and have demonstrated a colonic secretion of water and electrolytes, predominantly in the ascending colon, during both intragastric and intraduodenal feeding; and a
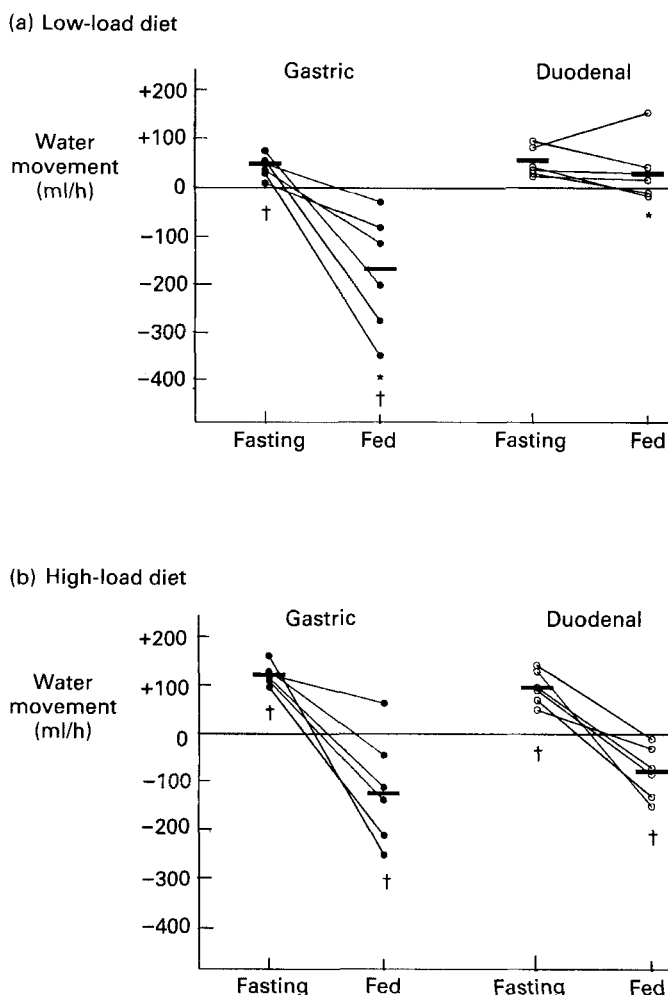
(a) Low-load diet

Gastric   Duodenal

Water movement (ml/h)

Fasting   Fed   Fasting   Fed

(b) High-load diet

Gastric   Duodenal

Water movement (ml/h)

Fasting   Fed   Fasting   Fed

Fig. 1. Water movement in the ascending colon after intragastric or intraduodenal infusion of a polymeric diet at (a) low load (1·4 ml/min; 5·9 kJ/min; 8·75 mg N/min) or (b) high load (2·8 ml/min; 17·6 kJ/min; 26·1 mg N/min). Each point represents one subject; —, medians. (●), Gastric feeding; (○), duodenal feeding; (+), net absorption; (−), net secretion. Medians for gastric feeding were significantly different from those for duodenal feeding: $*P<0.05$. Medians for fasted state were significantly different from those for the fed state: $†P<0.05$.

suppression of distal colonic segmental motor activity during both the high-load-diet infusions. The secretion amounted to an overall colonic load of up to 2·24 ml/min (in the high-load intragastric group) during a perfusion period of 6 h. If it is possible to extrapolate this over a 24 h period, the additional colonic volume would amount to 3·2 litres/d. This secretion, we feel, is of profound importance to the pathogenesis of enteral-feeding-related diarrhoea.

The normal absorptive capacity of the human colon has been shown to be 5700 ml/d (Debognie & Phillips, 1978), and from this information, therefore, it may be supposed
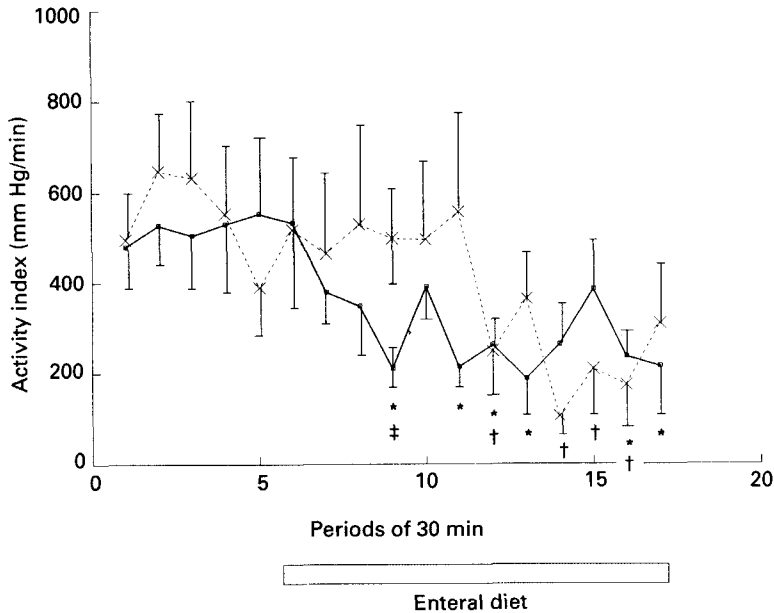
Fig. 2. Distal colonic segmental motor activity during high-load enteral feeding. Points are mean activity index values with their standard errors represented by vertical bars. (——), Gastric feeding; (– – –), duodenal feeding. Mean values for the fasting state were significantly different from those for the fed state for gastric group: *$P<0.05$, for the duodenal group: †$P<0.05$. Mean values for the gastric group were significantly different from those for the duodenal group: ‡$P<0.05$.

that the colon ought to be able to absorb this extra fluid. In this study the caecum of volunteers was intubated and fluid infused at rates sufficient to cause an increase in stool frequency and volume (Debognie & Phillips, 1978). The value of 5700 ml/d was derived from the volume of fluid required to cause diarrhoea (stool weight >200 g/d) plus the assumed caecal in-flow volumes and, therefore, reflected the absorptive capacity of the entire colon. In our studies the ascending colon, which in normal circumstances is the site of maximal fluid absorption, was secreting water and electrolytes and, therefore, the absorptive capacity of the colon would have been seriously impaired, such that an increased colonic load of 2·24 ml/min could cause diarrhoea. To compound matters, the suppression of segmental colonic motor activity, which will result in accelerated transit of colonic contents (Williams *et al.* 1984), will further diminish the absorptive capacity of the colon.

In our studies diarrhoea occurred more commonly when subjects were fed intra-gastrically with a high-load enteral diet. It is this group that had the greatest secretion and most profound suppression of motility. In the low-load groups, where motility remained unchanged from the fasting state and secretion only occurred in those fed intragastrically, diarrhoea was not observed. In the high-load duodenal group, where there was an overall secretion of 1 ml/min, predominantly in the ascending colon, and a delayed suppression of colonic motor activity, diarrhoea occurred in only one subject. Therefore, the clinical observations, i.e. the incidence of diarrhoea, are supported by the experimental results.
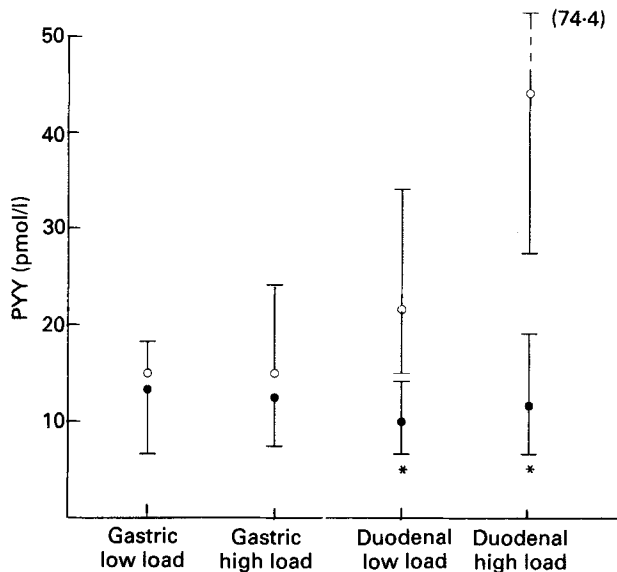
Fig. 3. Peptide YY (PYY) levels during perfusion studies. (●), Fasting; (○), fed. Values are medians and ranges represented by vertical bars. Median values for fasting state were significantly different from those for fed state: $*P<0.05$.

The most likely explanation for these colonic responses is some kind of neurohumoral response initiated from the proximal gastrointestinal tract during feeding. During all our studies serum was saved for estimation of various gastrointestinal hormones. One such hormone appears to be involved, peptide YY. In the human this hormone is found predominantly in the colon and terminal ileum (Tatemoto et al. 1988), and has been shown to inhibit intestinal secretion in animal in vitro and in vivo models (Okuno et al. 1992; Bilchik et al. 1993). In our studies peptide YY levels were significantly raised during intraduodenal feeding but remained unchanged from fasting during intragastric feeding (Bowling et al. 1995b; Fig. 3). What can be hypothesized is that during intraduodenal feeding the increase in peptide YY levels inhibits colonic secretion, but during intragastric feeding there is the loss of this negative feedback loop and, hence, the secretion is not inhibited. This clearly is not the whole story. To prevent the secretion the peptide YY must be inhibiting another secretory agent, presumably another hormone. We have also assayed vasoactive intestinal peptide (VIP), pancreatic glucagon and neurotensin, but none of these alters during enteral feeding.

FIBRE, SHORT-CHAIN FATTY ACIDS AND DIARRHOEA

In clinical practice many clinicians prescribe fibre-containing diets to patients with enteral-feeding-related diarrhoea (T. E. Bowling and D. B. A. Silk, unpublished results) because of the theoretical benefit on colonic water and electrolyte absorption. Fibre passes through the small intestine and is metabolized in the colon. Among the major products of fibre breakdown are SCFA acetate, propionate and butyrate which are
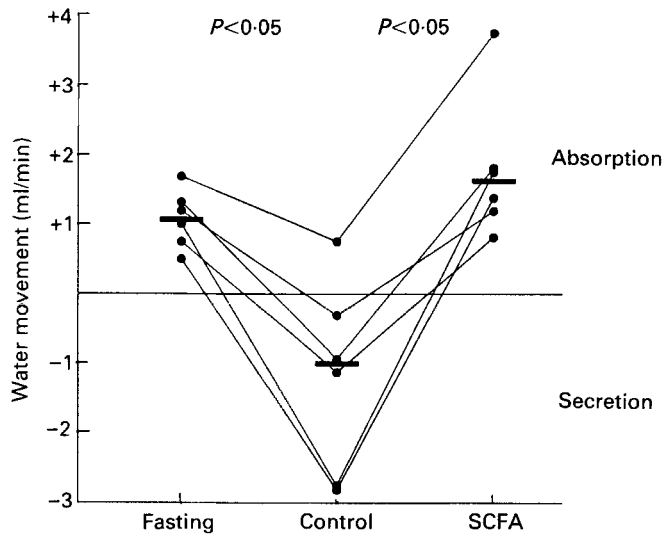
Fig. 4. Water movement in the ascending colon during intragastric feeding before and during the intracaecal infusion of short-chain fatty acids (SCFA).

produced in the large bowel by anaerobic fermentation of carbohydrates by endogenous bacteria (Cummings & Branch, 1986). Because one of the key roles of SCFA is the enhancement of colonic water and electrolyte absorption any mechanism that interferes with their production may have implications for colonic fluid movement. The effect of antibiotics on the colonic bacterial population and, hence, SCFA production is one proposed mechanism of antibiotic-induced diarrhoea. This theory also holds for the suggested benefit of fibre-containing enteral diets. Normal enteral diets contain no fibre source and, therefore, there will be little SCFA production in the colon. If a diet contains a fibre source that can increase colonic SCFA concentrations there will be a greater physiological weapon against the colonic secretion that occurs during enteral feeding. This has been the rationale for trying fibre-containing diets in patients with enteral-feeding-related diarrhoea, and evidence suggests this can be of benefit.

Our final study lends credence to this theory. We repeated the perfusion studies during intragastric feeding, but this time half-way through each study we infused a physiological SCFA solution directly into the caecum. Again, during the intragastric diet infusion there was an ascending colonic secretion, but when the SCFA solution was infused into the caecum this secretion was completely reversed to a net absorption (Bowling et al. 1993c; Fig. 4).

The study, therefore, demonstrates that colonic SCFA could play a key role in the prevention of enteral-feeding-related diarrhoea. Already, a number of clinical studies have been carried out to investigate whether fibre supplementation of enteral diets results in a decreased incidence of enteral-feeding-related diarrhoea (Hart & Dobb, 1988; Frankenfield & Beyer, 1989; Dobb & Towler, 1990; Guenter et al. 1990). All were carried out in intensive care units and none showed any benefit. Intensive care unit patients, however, are nearly always receiving antibiotic therapy and often histamine receptor antagonists and, hence, have other risk factors for developing diarrhoea. In

addition the fibre sources in the diets used in these studies are mainly insoluble and, therefore, do not get broken down to SCFA, so their lack of efficacy does not invalidate my suggestion of the possible beneficial effects of SCFA. What are now needed are randomized trials, comparing the effects of fibre- and non-fibre-containing enteral diets on the incidence of diarrhoea, that have been stratified for the existence of concomitant antibiotic therapy and other diarrhoeagenic risk factors.

SUMMARY

So to summarize the key points:
1. concomitant antibiotic therapy, infected diets and possibly hypoalbuminaemia can lead to enteral-feeding-related diarrhoea;
2. the small intestinal responses to both intragastric and intraduodenal enteral feeding are normal and predictable;
3. there is an ascending colonic secretion during enteral feeding which is more profound during intragastric feeding;
4. the suppression of distal colonic motor activity occurs only during high-load feeding and is probably a secondary phenomenon to the hormonal and secretory responses;
5. peptide YY appears to be intrinsically bound up with the causation of the secretory effect;
6. the secretory effect is abolished by intracaecal SCFA.

CLINICAL IMPLICATIONS

How does the present discussion and all the experimental findings affect and influence the clinical management of the patient with tube-feeding diarrhoea? The following steps show how I would manage such a patient:
1. review antibiotic therapy and stop if possible;
2. review histamine receptor antagonist therapy and stop if possible;
3. try loperamide and/or codeine phosphate;
4. consider a fibre-containing diet;
5. consider post-pyloric feeding.
Most patients should improve sufficiently on steps 1–3. Steps 4 and 5 are based on theoretical and anecdotal evidence, and clinical trial data are awaited. If, despite these steps, the diarrhoea is still difficult to manage then enteral feeding should be stopped and total parenteral feeding instituted.

There is still more work to be done to sort out this common problem. There are no controlled trials comparing pre- and post-pyloric feeding and the incidence of diarrhoea. Likewise, as already mentioned, there are no controlled trials examining the effect of fibre diets; we are currently undertaking such trials. It is an interesting concept that continuous intragastric feeding is not a physiological way of feeding, in that it does not resemble normal eating; whereas intraduodenal feeding is more physiological because it resembles the continual release of gastric contents through the pylorus. This may be the underlying reason for the abnormal colonic responses. The effects of bolus feeding on colonic secretion, therefore, need to be examined; again we are currently undertaking a trial. If this does not cause a secretory effect the whole technique of enteral feeding may

need revising. We also need to look more closely at fibre diets and ways of getting SCFA into the colon, possibly by pH release mechanisms.

A lot of ground has been covered in the last few years in understanding the pathogenesis of enteral-feeding-related diarrhoea, and the next few years should see much more progress and, it is hoped, successful means of combating it.

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