Progress report

Intestinal absorption in the 'contaminated small-bowel syndrome'

There has been a great upsurge of interest in human intestinal bacteria in the past few years with the increased accessibility of samples of small intestinal contents using various intubation procedures^{1,2,3,4,5} and improvements in bacteriological culture techniques⁶. The latter are especially relevant since, in the past, inadequate methods repeatedly failed to isolate anaerobic organisms such as *Bacteroides* and anaerobic *Lactobacilli*, which have important metabolic capacities. This increased interest in the intestinal flora has resulted in numerous papers about its place in health and disease^{2,7,8,9,10} and reviews concerning the importance of human intestinal bacteria have recently been published by Donaldson¹¹ and Tabaqchali¹². The present report will concentrate on the effects of the establishment of an abnormal bacterial flora on intestinal absorption.

Since an abnormal intestinal bacterial flora may become established in the absence of an intestinal blind loop, for example in cholangitis where the infected biliary tree acts as a reservoir for bacteria which contaminate the small bowel¹³ or in infants with the syndrome of temporary monosaccharide malabsorption^{14,15}, the term 'contaminated small-bowel syndrome' is used in the subsequent discussion rather than 'stagnant loop' or 'blind loop' syndrome which are the terms more commonly used.

Steatorrhea

Malabsorption of fat is a common and important clinical feature in patients with bacterial contamination of the small bowel. Several possible explanations for this disturbance have been investigated. It has been considered unlikely that morphological changes in the small intestine as a result of the altered bacterial flora could explain this absorptive defect. Although a moderate degree of infiltration of the lamina propria by inflammatory cells usually occurs the epithelium itself appears to be remarkably unaffected, and clinical^{16,17,18} and experimental¹⁹ studies using light microscopy have, with only rare exceptions^{20,21}, reported the appearance of the mucosa to be normal. A recent electron microscope investigation examined the ultra-structural appearances of the gut and the absorption of lipid in rats with an intestinal blind loop and supported the idea that the epithelium is structurally normal in this situation²². An electron microscope study in a single patient has also been reported to be normal²³. However, this opinion has recently been questioned by other investigators. Paulley²⁰ made extensive studies of the microscopic appearances of the upper gut in the presence of high bacterial counts and has demonstrated 'catarrhal inflammation' of the epithelium, a

finding apparently at variance with those of most previous workers. A more recent electron microscope study of rats with a jejunal blind loop by Gracey *et al*²⁴ has provided further evidence that there may be important ultrastructural changes in the epithelium in this syndrome. These animals showed a patchily distributed lesion characterized by vacuolation and swelling of microvilli and mitochondria of affected cells. These findings are of considerable interest, not only on account of their occurrence, but because they are almost identical to the changes caused by feeding small amounts of deconjugated bile salt to normal rats²⁵. As will be discussed later, alterations in bile salt metabolism are extremely important to our understanding of the contaminated small-bowel syndrome and it seems likely that the ultrastructural findings mentioned are related to the pathogenesis of the absorptive defects in this disorder. The electron microscope study of Gracey *et al*²⁴, was limited in its scope and it will be interesting to see if their findings are subsequently supported by others.

Some years ago impaired pancreatic function was suggested as a possible cause of steatorrhoea in this syndrome. Wirts and Goldstein²⁶ proposed that bacteria interfered with the activity of pancreatic lipase but since then lipolysis has been shown to be normal in clinical¹⁶ and experimental situations²⁷.

It now seems well established that the explanation for steatorrhoea in this syndrome rests with changes in bile salt metabolism, as originally suggested by Dawson and Isselbacher²⁸, who showed that unconjugated bile salts inhibit the uptake and esterification of fatty acids in everted sacs of rat jejunum. However, these effects were associated with considerable disruption of the tissue using that experimental technique and it is reasonable to suspect that at least some of the diverse and deleterious effects on the metabolism of the intestinal epithelium demonstrated in such experimental systems *in vitro* are due to nonspecific tissue damage²⁹. On the other hand, if a deconjugated bile salt, such as deoxycholate, is fed or infused into the duodenum for prolonged periods malabsorption of fat does not occur in rats³⁰ and gross histological damage to the intestinal epithelium is not produced³¹, although as mentioned above, ultrastructural changes may be present²⁵. By perfusing the small intestine with deoxycholate *in vivo* mild histological changes are induced³² but these are much less extensive than the gross changes following incubation with the same substance *in vitro*, such as shown initially by Dawson and Isselbacher²⁸. Studies in rats *in vivo* have shown no significant decrease in fatty acid entering the lymphatics in animals with cannulated lymph ducts³³ or in fatty acid uptake and esterification after perfusion of the gut with deoxycholate³⁴. Cheney *et al*³⁴ have related the differences between the effects shown *in vitro* and *in vivo* to the differences in the level of bile salt accumulated within the intestinal mucosa under these different experimental conditions. They showed levels *in vitro* six to ten times those found after studies *in vivo*. It thus seems likely that unconjugated bile salts are removed rapidly enough by the mesenteric circulation in the intact animal to prevent levels sufficient to cause tissue disruption being reached in the mucosa. How then, is bile salt deconjugation related to the production of steatorrhoea in the contaminated small-bowel syndrome? Normally conjugated bile salts when present in adequate concentrations (more than the critical micellar concentration) effect the dispersion of lipids in micelles before absorption. In dogs with experimental blind loops, steatorrhoea has been shown to be

corrected by feeding conjugated bile salts²⁷, a finding confirmed in a single patient with jejunal diverticulosis²³; and *in vivo*, as long as conjugated bile salts are present in amounts greater than the critical micellar concentration deoxycholate does not cause malabsorption of fat³⁴. This suggests that reduction in the level of conjugated bile salts rather than elevation in the level of their unconjugated counterparts is of prime importance in the production of steatorrhoea in this syndrome. It is possible that a further contribution towards steatorrhoea comes from impaired intracellular re-esterification of lipid since Dietschy²⁹ has showed such an effect in experimental animals fed or perfused with unconjugated bile salts *in vivo*. This inhibitory effect is modified by the addition of conjugated bile salts to the infusate, a finding which makes it difficult to assess the contribution of such a defect to the production of steatorrhoea in the contaminated small-bowel-syndrome. Anaerobic bacteria, such as *Bacteroides*, anaerobic *Lactobacilli*, and *Clostridia*, are particularly capable of deconjugating bile salts^{35,36} and such organisms occur in large numbers in the small intestinal contents of patients with this syndrome^{7,8}. While these organisms cause a significant increase in the level of unconjugated bile salts in these patients, a coincidental reduction of the level of conjugated salts to very low levels occurs²³ thus causing steatorrhoea. However, malabsorption of fat is not an invariable association of the contaminated small-bowel syndrome, for example in the presence of an isolated upper small intestinal lesion. In such instances normal fat absorption is maintained because the concentration of conjugated salts has not fallen below the critical micellar concentration²³.

Carbohydrate

Reports of impaired D-xylose tolerance tests in patients with the contaminated small-bowel syndrome have appeared for several years^{11,17,21,37}, and more recently the syndrome of temporary monosaccharide malabsorption in infancy has been documented^{14,15,38}. In this interesting disorder there is a self-limited but total inability to absorb all dietary monosaccharides in the presence of an abnormal small intestinal flora¹⁴. However, the mechanism of production of carbohydrate malabsorption in this situation has remained uncertain. It has been suggested that intraluminal consumption of sugar by bacteria might explain the apparent absorptive defect in adults with the contaminated small-bowel syndrome³⁹ but this explanation is not entirely satisfactory and there is considerable evidence to support the recent proposal²⁴ that the carbohydrate absorptive defect is due to changes in bile salt metabolism.

Goldstein *et al*³⁹ showed that aerobic intestinal bacteria isolated from their patients were able to utilize D-xylose *in vitro*, but, as they pointed out, this was really to be expected and had been known by bacteriologists for many years. However, their contention that this function of bacteria explained the apparent disappearance of the sugar in quantitative terms *in vivo* seems far from proven. In one patient with bacterial contamination of the small bowel, perfusion with a solution containing D-xylose showed a decrease in its intraluminal concentration which did not occur when the study was repeated after treatment with antibiotics had reduced the numbers of aerobic organisms present. However, this patient showed no improvement in absorption of D-xylose after treatment as judged by blood and urine levels follow-

ing a standard oral dose of this sugar. Bacterial utilization of D-xylose cannot completely explain its impaired absorption in such circumstances. Furthermore, Donaldson¹¹ has shown decreased absorption of D-xylose *in vivo* in rats with an upper small intestinal blind loop and has recently shown that the carbohydrate absorptive defect is not improved after washing the gut lumen free from bacteria (personal communication, 1970). These findings strongly suggest that the apparent relationship between intestinal bacteria and altered carbohydrate absorption is indirect and probably mediated by some other factor or factors.

What evidence is there that this absorptive defect may be adequately explained by alterations in bile salt metabolism? Deconjugated bile salts are known to interfere with intestinal sugar transport *in vitro*^{40,41} but until recently the results of these early experiments were open to the criticism that this effect might be due to nonspecific tissue damage by these substances in experimental systems *in vitro*²⁹. However, this criticism has now been overcome by experiments *in vitro* using a newly devised tissue-holding apparatus⁴² in which inhibition of intestinal sugar uptake by the small intestine in the presence of deoxycholate has been clearly shown to be acutely reversible⁴³. Subsequently, inhibition of intestinal sugar absorption by deconjugated bile salt has been demonstrated in perfusion experiments in rats *in vivo*⁴⁴ and the relevance of these findings to the present discussion is further supported by experiments in rats with a jejunal blind loop, the experimental counterpart of the contaminated small-bowel syndrome. In this experimental model a close relationship has been established between the degree of the abnormality of the anaerobic intestinal flora, the extent of bile salt deconjugation and the severity of impairment of intestinal sugar transport *in vitro* and *in vivo*²⁴. The precise mechanism by which deconjugated bile salts cause impaired intestinal sugar transport is still uncertain, but it is not simply an artefact due to tissue damage affecting the results of *in vitro* experiments, although ultrastructural changes may contribute to the absorptive defect in the intact animal²⁴. It seemed possible that the inhibitory effect of unconjugated bile salts might be mediated by depression of sodium-potassium dependent ATPase which is believed to be essential for the functioning of the sodium pump involved in intestinal transport of sugars. The effect of deoxycholate on sugar transport is reversible *in vitro* while depression of ATPase activity is not⁴⁵. The dissociation of these two effects of unconjugated bile salts precludes this suggested mechanism of inhibition of sugar transport. The demonstration that the inhibitory effect of deconjugated bile salt is mediated by competitive inhibition⁴³ suggests that bile salts have an important specific effect on intestinal sugar transport and further study of this phenomenon will add fundamental knowledge to our understanding of transport by the intestine.

Protein

Hypoproteinaemia frequently occurs in the contaminated small-bowel syndrome^{46,47}, and may be severe enough to produce a clinical picture resembling protein-calorie malnutrition⁴⁸ but its cause is not absolutely established. Although gastrointestinal protein loss has been documented in rats with a blind intestinal loop⁴⁹ it has been reported only once in a patient⁵⁰. On the other hand, bacterial degradation of dietary protein to substances no

longer available for protein synthesis by intestinal organisms such as *E. coli*, *Bacteroides*, and some strains of *Klebsiella*, appears to be more important⁵¹. Indican and indoles derived from bacterial metabolism of tryptophan appear in the urine of patients with bacterial contamination of the small bowel⁵² and this is used by some as a diagnostic test. The quantitative importance of bacterial breakdown of protein in this syndrome is, however, not known. An important study by Jones *et al*⁵³ showed detamination of protein may be another important mechanism leading to protein deficiency, at the same time producing ammonia which contributes to urea synthesis. In their study the metabolic changes were corrected by antibiotic treatment. A further possible mechanism requires consideration; deconjugated bile salts have previously been shown to inhibit amino acid transport by the small intestine *in vitro*⁴¹ and a similar effect on tyrosine transport has been shown in blind loop rats *in vitro*⁵⁴. Since the inhibitory effect of deconjugated bile salts on another group of water-soluble substances, namely monosaccharides, is important in this syndrome it is important that the relevance of this mechanism to impaired amino acid transport in this disorder is appropriately studied in the near future. We may then be in a position to assess the relative contributions of these several factors to overall protein deficiency in patients with the contaminated small-bowel syndrome.

Vitamin B₁₂

'Pernicious anaemia' was the first systemic abnormality to be recognized in patients with intestinal stasis⁵⁵ and it is now well known that macrocytic anaemia often occurs in this situation. This was initially thought to be due to the absorption of toxic substances from the stagnant intestinal contents. However, it has since been established that this form of megaloblastic anaemia is due to malabsorption and subsequent deficiency of vitamin B₁₂^{46,56}. The pathogenesis of this absorptive abnormality has remained in some doubt. While microorganisms are able to consume free vitamin B₁₂ *in vitro*⁵⁷ the previous binding of the vitamin to intrinsic factor prevents this uptake to a large extent⁵⁸. However, certain enteric organisms such as *Bacteroides* and *Enterobacteria* are still partly capable of binding the vitamin B₁₂-intrinsic factor complex *in vitro* and it has recently been shown that in patients with bacterial contamination of the small bowel following a small oral dose of intrinsic factor-bound ⁵⁷Co-vitamin B₁₂ a considerable amount of radioactivity (43-72%) is recoverable from ileal aspirates while in controls much less (less than 11%) was recovered⁵⁹. This indicates that in the contaminated small-bowel syndrome malabsorption of the vitamin occurs by bacterial binding of the vitamin B₁₂-intrinsic factor complex.

Other Substances

FOLIC ACID

Deficiency of folic acid has been reported in patients with jejunal diverticulosis⁴⁷ but appears to be a rare accompaniment of the contaminated small-bowel syndrome. Serum folate levels are often normal⁵⁶ or even more commonly are elevated, probably as a result of bacterial synthesis of folic acid like materials within the gut⁶⁰.

OTHER VITAMINS

Malabsorption of vitamin D probably occurs in some patients with the contaminated small-bowel syndrome although prolonged malabsorption of this vitamin and subsequent osteomalacia are uncommon⁴⁷. It is rather surprising that deficiencies of other fat-soluble vitamins, such as vitamin K, which depend on dispersion by normal intraluminal bile salts, apparently do not occur. This may be explained by the fact that intestinal bacteria are able to synthesize vitamin K and other essential substances, including riboflavin, biotin, and nicotinic acid^{1,61,62}. However, deficiency of nicotinic acid causing encephalopathy has been reported once (cited by Tabaqchali¹²), in this instance it was probably due to utilization of the vitamin by intestinal bacteria.

IRON

Iron deficiency may complicate the clinical and haematological features in patients with bacterial contamination of the small bowel. Sometimes this may be due to frank or occult bleeding in the presence of strictures and ulceration but the possibility that intestinal malabsorption of iron also occurs has not been thoroughly investigated and clearly needs further study.

WATER AND ELECTROLYTES

The possibility that impaired intestinal absorption of water and electrolytes occurs in the contaminated small-bowel syndrome has received little attention. Forth *et al*⁴⁰ recently showed that deconjugated bile salts caused impaired transport of water, sodium, and potassium by the jejunum *in vitro* and similar effects in the colon *in vitro* and when perfused *in vivo*. Mekhjian and his colleagues^{63,64} have also shown that bile salts have important effects on water and electrolyte transport in the human and the dog. In view of the serious disturbances in bile salt metabolism which occur in this syndrome it seems pertinent that these features are looked into in future studies.

Bacterial contamination of the upper gut results in a diverse spectrum of absorptive defects. Our understanding has increased considerably in the past few years and with the present level of interest in intestinal bacteria it seems likely that these additions to our knowledge will continue unabated. Many recent contributions have come from the demonstration of the effects of certain bacteria on bile salt metabolism; the possible effects of enteric organisms on other metabolic processes should receive close attention in the future. The results of these studies will be awaited with considerable interest over the next few years.

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