Progress in Small-Bowel Physiology and Disease

SIMMY BANK, M.B., CH.B., M.R.C.P., I. N. MARKS, M.B., B.SC., F.R.C.P. AND B. NOVIS, M.B., CH.B., M.R.C.P.,
Gastro-intestinal Clinic and Department of Medicine, Groote Schuur Hospital and University of Cape Town

SUMMARY

There have been many interesting and exciting developments in the field of gastro-enterology in the past few years. Many of these advances have been due to technical skills in physiology, biochemistry and radiology, but newer diagnostic and therapeutic measures have also been introduced. The complex functions of the small bowel and especially the mucosal lining of the intestine, provide particular scope for detailed multidisciplinary research, clinical, paraclinical and scientific.

The present communication reflects our own brief selection of recent advances in the field of small-bowel physiology and disease and does not represent a comprehensive coverage of all the advances in the past decade.

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PHYSIOLOGY

The Intestinal Mucosal Epithelial Cell

The epithelial cell of the small-bowel mucosa is second only to bone-marrow cells in its rate of proliferation and turnover. It takes 48 - 96 hours for the epithelial cell to migrate from the base of the crypt of Lieberkühn to the apex of the villous and then to be extruded into the lumen. Because of this rapid activity, a number of authors have likened the epithelial cells to bone-marrow equivalents. Hence the mature columnar cell or enterocyte is found at the sides of the villi, and as the villous tip is reached the cell becomes somewhat more cuboidal before being extruded. At the base of the crypts, the cells tend to have a more open chromatin nucleus and may be megaloblastic, i.e. enteroblasts, and even normoblastic, i.e. enteronormoblasts. It is possible that all the cells are derived from a stem-cell at the depths of the crypt.

The proliferative kinetics of the cells have also been studied in detail. The normal proliferative cycle consists of a phase in which DNA is made before cell division, a premitotic, a mitotic and postmitotic phase. The genetic material of the cells is contained in the chromosomal DNA of the nucleus. Proliferating epithelial cells are normally seen only in the crypts. Abnormalities of proliferation and hence increased mitotic activity and a preponderance of enteroblasts may be seen in several disease states, notably gluten-induced enteropathy, vitamin B_{12} and folate deficiency and after cytotoxic administration. It is possible that the altered kinetics occurring in vitamin B_{12} and folate deficiency states may in themselves affect the absorptive capacity of the cells and result in steatorrhoea and malabsorption.

Cytochemical histochemistry of the epithelial cell has been a source of much recent research and the various enzymes, of fats, proteins and carbohydrates, the lysosomes, mitochondria, endoplasmic reticulum and Golgi apparatus in health and disease have been delineated, e.g. the mitochondria contain succinodehydrogenase, cytochrome oxidase and ATP and the endoplasmic reticulum a non-specific esterase and glucose-6-phosphatase.

The Brush Border of the Epithelial Cells

Electron-microscopic studies have long shown the presence of myriads of microvilli on the surface of each epithelial cell. Apart from their quite fantastic biochemical activity, these microvilli increase the absorptive surface of the intestinal mucosa tremendously. Recent evidence suggests that there might be micro-microvilli on the surface of the microvilli and the latter 'fuzzy' or 'filamentous' layer has been termed the glycocalyx because of its suspected mucopolysaccharide composition. If these findings are substantiated, then the absorptive or adsorptive surface of the mucosa would be further augmented by a million-fold. In fact, many digestive processes may start in the glycocalyx layer and it may serve as a barrier to foreign material or bacteria.

The digestive and absorptive capacity of enzymes situated within the microvilli might be regarded as the single most important and exciting advance in gastrointestinal physiology of the past decade. These minute structures, covered only by a membrane, contain the enzyme components which are finally required for the hydrolysis of carbohydrates and proteins and may play an important part in the entrapment of fat micelles before absorption at the epithelial cell level. Thus, the disaccharidases, lactase, maltase and sucrase hydrolyse lactose, maltose and sucrose at a microvillous level and there are at least 2 lactases (galactosidase) and 5 maltases. Similarly, amino-peptidase activity is localized to the microvilli and it appears that peptides of between 3 and 6 amino-acid residues are hydrolysed to free-amino-acids and dipeptides by these amino-oligopeptidases. Clearly, many diseases which affect the small bowel, should they affect the microvillous layer as well, would lead to severe disturbances of carbohydrate, fat and protein absorption and digestion. Perhaps a good example would be chronic intestinal ischaemia, as the microvilli represent the terminal area of blood supply of the mucosal surface. Although primary defects of amino-peptidase deficiency are not yet recognized (with the possible exception of enterokinase deficiency), there is little doubt of genetic or adaptive lactase and other disaccharidase deficiency. Studies carried out in this department have shown that it is possible to overload one's capacity to absorb disaccharides if the oral intake is grossly excessive or small bowel has been resected or diseased.

The Arteriovenous Arcade and the Lymphatics of the Villous

Close inspection of peroral jejunal biopsy specimens by dissecting microscopy reveals the beautiful arteriovenous arcade of the intestinal villous. The terminal arteriole of the arcade can be seen to be virtually continuous and in juxtaposition to the basement membrane connecting the individual epithelial cells. By virtue of this arrangement the vascular tree is aptly positioned to retrieve digested, absorbed and/or reconstituted materials such as short-chain fatty acids, monosaccharides, vitamins, electrolytes, etc., after traversing and leaving the epithelial cell, whatever the mechanism of extrusion from the cell may be (i.e. by diffusion, active transport, release from its transcellular carrier or reversed pinocytoses) and its ultimate transport to the liver.

The lymphatic system is more enigmatic. Electron-microscopic studies clearly delineate the lymphatic wall as consisting not only of a layer of endothelial cells but also of intercellular spaces and some smooth muscle. It is probable that chylomicrons leave the epithelial cells and enter the lymphatic through the intercellular space. The central lacteal engorges with fat and a combination of smooth-muscle activity and pumping action of the villi propels the lymph to submucosal lymphatics and ultimately to the cysterna chyle and venous system.

Small-Bowel Resection and Bypass, with Special Reference to Ileal Competence and Bile Salt Recirculation

Until recently, surgeons have been reluctant to accept the diarrhoeagenic or steatorrhoeagenic effect of resection of the ileocaecal valve and, more particularly, the terminal ileum. With increasing knowledge of the importance of the ileocaecal valve in preventing reflux bacterial contamination of the small bowel and the fundamental role of the lower ileum in bile salt, vitamin B_{12} and water absorption, it has become patently manifest that ileal resection or disease may leave in its wake a more serious malabsorptive state than more proximal jejunal resection or disease. As most dietary components are absorbed in the jejunum this paradoxical situation of 'ileal incompetent steatorrhoea' is probably due to the more rapid transit in the ileum, a lesser adaptive or compensatory mechanism in the jejunum and the decreased absorption of water and bile salts. Although the colon is the major site of water reabsorption after passage through the small bowel, it has been suggested that the last 10 - 30 cm of terminal ileum is equally important, particularly as the liquid intestinal residue may be held up in this area for a reasonable length of time before entering the colon. However, most attention has been focused on the importance of deficient bile salt recirculation and its effect on fat metabolism.

Bile salts have a superefficient enterohepatic circulation. Active transport of conjugated bile salts occurs in the ileum and this enters the enterohepatic circulation to be re-excreted in the bile. Less than 5% of the daily bile salt pool appears in the stool and there is some evidence that the ascending colon may further augment bile salt absorption. Interruption of the enterohepatic circulation by ileal disease or resection leads to decreased bile salt return to the liver, which compensates for the deficiency until its reserve is depleted. The glycine and taurine conjugates of the bile salts are particularly affected and subsequently, with time, fat digestion and absorption, which are so dependent on bile salts to form micelles in the upper bowel, are disturbed, leading to steatorrhoea. It has been shown that as little as 20% interruption of bile salt reabsorption from the ileum will eventually result in fat malabsorption. The increased load of bile salts in the colon leads to its own deleterious effects as bile salts are irritant and purgative. When the small-bowel resection or disease is limited in extent, steatorrhoea is the predominating result. However, when massive distal resection is done the cathartic effect predominates and a 'choleretic' type of diarrhoea occurs. Cholestyramine, a chelator of bile salts, has been used with reasonable success in the treatment of some of these patients. Bile salts may be tried but tend to be irritative and medium-chain triglycerides as replacement of ordinary fats are occasionally of benefit because of their easier absorption at the cellular level.

Compensatory Mechanisms after Bowel Resection

While the majority of patients after massive bowel resection do badly and suffer severely from intractable malabsorption, it is surprising how well the occasional patient with but 15 - 30 cm of remaining small bowel may cope with the deficiency. In our experience, it is usually the younger patients who are able to cope more readily with the 'short bowel syndrome' and the severity of symptoms tends to decrease with ensuing time after resection. We have for many years contemplated whether the remaining bowel may increase in size, either in width or length, or whether compensatory mechanisms in the mucosa may not occur. Repeated jejunal biopsies in this department on a 15-year-old boy with resection of all but 15 cm of jejunum, who has remained extremely well despite persistent steatorrhoea, appeared to have confirmed the possibility of histological and biochemical compensatory mechanisms. Histological examination of the mucosa with time showed an undoubted increase in the height of his villi and the size of the individual epithelial cells. Furthermore, repeated estimations of his jejunal disaccharidase activity showed increasing levels of lactase, maltase and sucrase activity to the highest values that we have encountered in this department even in normal controls. More recently, the Hammersmith group of workers have shown experimental data on the macroscopic and microscopic enlargement of remaining bowel after massive resection, and increased glucose absorption after massive resection in humans. Despite these compensatory mechanisms in the bowel most patients after bowel resection require a fat-restricted diet, replacement therapy, careful adjustment of their disaccharide intake and the substitution of medium-chain triglycerides for long-chain fats in their diet.

The Importance of Intestinal Bacteria

After years of indecision, it is now quite clear that the human small bowel normally contains a number of

bacteria (rarely more than 10^3 or 10^4/ml) which increase distally and after a meal. Streptococci, staphylococci, lactobacilli and fungi have been sampled from the proximal bowel and the distal ileum may contain bacteriodes, anaerobic lactobacilli and a few coliforms depending on the competence of the ileocaecal valve.

Symptoms appear when these bacteria proliferate and increase in number. While the causes of bacterial proliferation are legion, they may be divided broadly into 3 main groups: (*i*) intestinal dilatation and stagnation, e.g. blind loops, vagotomy, strictures, scleroderma, etc.; (*ii*) fistulae—gastrocolic or ileocolic; and (*iii*) decreased bacterial destruction—pernicious anaemia, atrophic gastritis, malnutrition, debility, total gastrectomy. In these conditions coliforms, bacteriodes, anaerobic lactobacilli and streptococci may reach concentrations of 10^6 - 10^9/ml and may result in two effects, namely, steatorrhoea and vitamin B_{12} deficiency.

Current concepts of the method of production of the steatorrhoea is based on the known effect of bacteria on bile salts, i.e. the deconjugation of conjugated bile salts to their unconjugated forms, namely free cholate, deoxycholate and lithocholate. Unconjugated bile salts are inefficient emulsifiers and result in poor micelle formation, thus producing defective fat absorption. It has also been suggested that they may be toxic to the mucosa but this is unproven.

The mechanism of the vitamin B_{12} deficiency with bacterial proliferation is unclear. The 3 current concepts are (*a*) *E. coli* requires vitamin B_{12} for active division or competes for the available vitamin B_{12} in the bowel; (*b*) that bacteria may be capable of uncoupling the IF-B_{12} complex; and (*c*) that bacterial endotoxin may damage the mucosa. The finding of a low serum vitamin B_{12} in the presence of a high serum folate level is characteristic of bacterial overgrowth as bacteria may synthesize folic acid.

A third effect of bacterial overgrowth is on protein metabolism. Tryptophan may be broken down to indolic compounds leading to a rise in urinary indican levels. Work in this department has shown high indican levels in malabsorption associated with bacterial overgrowth and normal levels in pancreatic steatorrhoea and kwashiorkor.

Whatever the mechanism, antibiotics and surgical correction of the lesions will improve the steatorrhoea and vitamin B_{12} absorption and will decrease the urinary indican excretion.

CLINICAL GASTRO-ENTEROLOGY

The clinical advances in small-bowel disease have been no less formidable than the experimental, but the two are inseparable. A few of the more important will be highlighted briefly.

Jejunal Mucosa

Total atrophy of the jejunal mucosal villi, so characteristic of gluten-induced enteropathy, may be found in a variety of secondary conditions including Whipple's disease, lymphomatous infiltration, radiation enteritis and bowel ischaemia. In coeliac disease it may take 3 - 4 months for the villi to regenerate after gluten restriction.

However, a number of British workers have found a 'flat' mucosa in a wide variety of skin diseases, carcinomas, pancreatitis, etc., in contradistinction to the rarity of such villous atrophy in Cape Town and probably South Africa. We have for many years felt that the population on both sides of the English Channel have a genetic or environmental vulnerability of their small-bowel mucosa or a very high incidence of subclinical coeliac disease, resulting in mucosal atrophy when the mucosa is challenged by diseases. The importance of establishing the state of the mucosa in any individual area is essential before any wild speculation is made: for example, partial villous atrophy would appear to be a 'normal' finding in Thailand and other tropical areas.

Protein-Losing Enteropathy

Protein may leak from the mucosa in many mucosal, submucosal and lymphatic diseases of the bowel and the patient presents with hypoalbuminaemic oedema. The methods of demonstrating the loss are relatively satisfactory and consist basically of injecting a radioactive labelled substance which will combine with albumin and measuring the faecal radioactivity. However, the loss is not confined to albumin and a corresponding loss of immunoglobulins IgG, IgA and IgM and lymphocytes may result in a severe depletion of immunological responses on the part of the patient. In addition, caeruloplasmin, fibrinogen, iron, copper and calcium may also be lost from the body. Treatment consists of removing a localized lesion if such is present or the substitution of medium-chain triglycerides for long-chain fats in the diet where lymphatic blockage is the cause.

Malignant Disease and Steatorrhoea

Recent evidence suggests that patients with long-continued malabsorption, particularly coeliac disease, may show splenic atrophy and defects in immunological competence, resulting eventually in the development of intestinal lymphoma and even more distant carcinomata. One of our patients with alpha chain disease of the bowel died with a gastric carcinoma.

On the other hand, abdominal lymphoma may present with steatorrhoea and in areas where coeliac disease is rare, as in Cape Town, a lymphoma should always be suspected. Although this type of lymphoma has been termed 'Mediterranean' because of its frequency in Middle Eastern countries, this term is a misnomer as we have seen 23 cases over 10 years in Cape Town; the majority had occurred in young Coloured patients. Survival may be prolonged but rarely exceeds 3 years after diagnosis.

OTHER DISEASES

Whipple's Disease

Previously termed 'intestinal lipodystrophy', this rare condition has now been shown to be due to, as Whipple originally suggested, an unusual bacillus. Considered to

be a lethal disease in the past, it is now completely curable with long-term antibiotic administration, i.e. for at least 1 year.

Crohn's Disease

The aetiology of regional enteritis is still unknown. Because of its possible immunological basis, azothioprine (Imuran) has been tried in severe cases. Although some good responses have been obtained, the results are far from spectacular and several deaths have been recorded when high loading doses were used. This form of therapy should not be undertaken lightly and should be reserved for otherwise non-responsive patients at a dose not exceeding 2 mg/kg.

Tuberculosis

Intestinal tuberculosis remains a common disease certain countries, South Africa included. In the b it is often indistinguishable from Crohn's disease an this regard a positive Mantoux test may be the only h ful diagnostic parameter other than histological proof

Eosinophilic Enteritis

This uncommon condition may be a diffuse or local involvement of the bowel with eosinophils and o occurs in allergic subjects. The diffuse variety may duce malabsorption and protein-losing enteropa Antihistaminics and steroids have been used with varia results.