

# Small bowel review – Part I

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The small bowel has undergone intense study. Part I of this two-part review of the small bowel focuses on gastrointestinal peptides; intestinal infections and human immunodeficiency virus; drugs; intestinal growth – mucosal proliferation and differentiation; nucleic acids, nucleotides and nucleosides; vitamins and minerals; Whipple's disease; radiation; and early development.

**Key Words:** *Drugs, Review, Small bowel*

## Vue d'ensemble du grêle – 1<sup>re</sup> partie

**RÉSUMÉ :** L'intestin grêle a fait l'objet de recherches approfondies. La première partie de cette synthèse en deux volets sur l'intestin grêle s'attarde aux peptides gastro-intestinaux, aux infections intestinales associées au virus de l'immunodéficience humaine, aux traitements médicamenteux, à la croissance intestinale, à la prolifération et à la différenciation muqueuse, aux acides nucléiques, aux nucléotides et aux nucléosides, aux vitamines et aux minéraux, à la maladie de Whipple, à l'irradiation et au développement précoce.

The small bowel has undergone intense study. In part I of this two-part review of the small bowel, attention is paid to gastrointestinal peptides; intestinal infections and human immunodeficiency virus (HIV); drugs; intestinal growth – mucosal proliferation and differentiation; nucleic acids, nucleotides and nucleosides; vitamins and minerals; Whipple's disease; radiation; and early development.

### GASTROINTESTINAL PEPTIDES

In response to the presence of luminal contents, a series of complex intracellular signalling events occurs to release gastrointestinal peptides. Cholecystokinin (CCK) is secreted from the intestine in response to the ingestion of food, with an increased rate of transcription of CCK mRNA. Somatostatin inhibits dietary-stimulated CCK secretion and lowers intestinal CCK mRNA levels. Using a perfusion system with isolated intestinal mucosal cells, it has been shown that the neuropeptide bombesin stimulates CCK release but does not influence its mRNA level, consistent with a post-transcriptional mechanism (1). A long-acting somatostatin analogue, octreotide (SMS 201-995), is useful to close intestinal fistulae and to control diarrhea in a number of clinical settings. In patients with a permanent end jejunostomy who are on home parenteral nutrition, octreotide reduces fluid

losses and the use of amino acids for splanchnic protein synthesis, while increasing pancreatic enzyme synthesis and secretion, and suppressing the plasma levels of several gut hormones (2).

Peptide YY is released into the blood stream in response to intraluminal and neural stimuli. Peptide YY inhibits gastric emptying, pancreatic exocrine secretion and small intestinal as well as colonic motility. A receptor for neuropeptide Y has been identified in HT29 cells and may prove to be a useful cell culture model in which to study the regulated release of this peptide after meals (3).

Neurotensin is localized to specialized enteroendocrine cells of the adult small intestine. In response to the presence of intraluminal fat, neurotensin is released and facilitates the absorption of fatty acids, as well as stimulates pancreatic secretion, intestinal motility and mucosal growth. Neurotensin converts the myoelectric activity of the rat intestine from the fasted to the fed state and inhibits the peristaltic movement of chyme, thereby optimizing conditions for fat digestion. Neurotensin produces a transient myogenic relaxation followed by a neurogenic contraction involving the release of acetylcholine and substance P. Two receptor types mediate the contractile effect of neurotensin (4). Neurotensin/neuromedin expression is initially low in rat small in-

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testine but increases after birth, with increasing expression along the length of the small bowel.

Vasoactive intestinal polypeptide (VIP) is an inhibitory neurotransmitter in the enteric nervous system. Intravenous injection of VIP decreases gastric acid secretion and the intestinal absorption of alanine and water; these inhibitory effects are partially mediated by the vagus nerve (5). VIP is released locally as a neurotransmitter, and in combination with nitric oxide relaxes the gastrointestinal tract through a nonadrenergic noncholinergic pathway, with the predominant effect being the inhibition of gastrointestinal electrical activity (6).

Growth hormone and prolactin arise from a common ancestral gene, and both promote water and electrolyte transport as well as calcium absorption. Use of reverse transcription-polymerase chain reaction (RT-PCR) combined with Southern analysis has demonstrated intestinal receptors for a number of the peptide hormones in humans, rabbits, and fetal and adult rat intestine (7).

Calcitonin gene-related peptide relaxes intestinal smooth muscle; in the guinea pig this effect involves the generation of cAMP but not of cGMP (8). Neuromedin U is present in large amounts in the enteric nervous system, and stimulates the contraction of the human ileum. The neuromedin U gene has been cloned and sequenced (9).

Insulin and insulin-like growth factors I (IGF-I) and II (IGF-II) synergistically enhance epidermal growth factor (EGF)-stimulated proliferation of cultured enterocytes. EGF acts as a 'competence' factor, increasing the fraction of proliferating cells and thereby allowing IGF-I (a 'progression' factor) to act as a proliferative agent on the cycling cell population (10). Subcutaneous injection of IGF-I improves the abnormal mucosal structure and absorptive function, and reduces the bacterial translocation usually seen in transplanted small bowel (11). IGF activity is modulated by IGF binding proteins, of which six have been identified. The profile of IGF binding protein secretion changes with differentiation, and IGF-I together with EGF or transforming growth factor (TGF)- $\alpha$  stimulates different types of these binding proteins (12). TGF- $\beta$  inhibits enterocyte proliferation, and stimulates the migration and differentiation of intestinal epithelial cells (13).

Enterostatin, the amino-terminal pentapeptide of pancreatic procolipase, is released with colipase in the intestine by trypsin activity. Enterostatin is a powerful anorectic peptide important in the regulation of fat intake (14).

#### INTESTINAL INFECTIONS AND HIV

Enteric infection and gastrointestinal symptoms are common in AIDS patients. The definition of 'AIDS enteropathy' needs to be clarified (15). About 20% of patients with advanced HIV infection and chronic diarrhea, for which no cause is found after extensive initial investigations, subsequently have a possible cause of diarrhea identified on follow-up investigations; about half have resolution of the diarrhea over a mean follow-up of seven months and the remainder have 'pathogen-negative', persistent diarrhea (16).

The diarrhea in these pathogen-negative patients may be due to a novel and as yet unidentified organism, to autonomic neuropathy and bacterial overgrowth or to a flat mucosal lesion. The opportunistic pathogens seen most commonly in this setting include *Cryptosporidium* species, *Isospora belli* and *Enterocytozoon bieneusi*. *Cryptosporidium* is found in the stools of 10% to 20% of patients with AIDS-associated diarrhea and may range from mild to life-threatening. The intensity of intestinal infection with *cryptosporidium* varies from patient to patient, and the differences in symptomatology may relate to this variable number of organisms. The extent of abnormal lactulose/mannitol permeability and villus atrophy is correlated with the intensity of infection, whereas vitamin B<sub>12</sub> and D-xylose absorption are not correlated (17). Enteric cryptosporidiosis may result in abnormalities in the architecture of the intestine, the release of inflammatory metabolites and the production of an enterotoxic moiety by the parasite (18). Secretory immunoglobulin (Ig) A normally prevents the adherence of pathogens to the intestinal brush border membrane (BBM). Patients with AIDS and enteric cryptosporidiosis have increased fecal total IgA outputs and specific anticryptosporidium IgA levels, whereas increased total fecal IgM output and specific anticryptosporidium IgM co-pro-antibodies are increased only in cryptosporidium-infected patients (19). Interestingly, the development of pathogen-specific mucosal antibody responses in patients with AIDS and cryptosporidium fails to clear the parasite.

Bacterial colonization of the proximal intestine may also occur as the result of hypochlorhydria, disturbances of gastric emptying and intestinal motility due to HIV-induced autonomic neuropathy, and impaired local immunity arising from alterations in T lymphocyte subsets.

Using careful sampling under sterile conditions, gastric and/or duodenal bacterial colonization has been documented in 30% of HIV-positive patients, with all isolates being oral Gram-positive cocci or bacilli (20). Bacterial colonization is associated with higher mean fasting gastric pH, but there is no correlation between the presence of bacterial colonization and CD4+ cell counts.

Intestinal BBM activity of disaccharidases (measured by a urinary disaccharide ratio) is decreased in many HIV-positive patients and is more prevalent with advancing clinical stage of disease and decreasing CD4+ counts (21). RT-PCR analysis of mRNA from intestinal biopsies of HIV-infected patients revealed significant increases in the expression of the pro-inflammatory cytokines interleukin (IL)-1 $\beta$  and interferon-gamma, with reduced levels of IL-10. This result suggests that cytokine dysregulation is a possible factor in the pathogenesis of AIDS in the gastrointestinal tract (22).

Low vitamin B<sub>12</sub> levels in the blood are noted in 39% of HIV-infected patients with chronic diarrhea (23); in some this is due to reduced absorption of vitamin B<sub>12</sub> arising from an enteropathic process affecting both the proximal and the distal small bowel. Because of the high prevalence of vitamin B<sub>12</sub> deficiency in these individuals, it is reasonable to screen

for vitamin B<sub>12</sub> deficiency in all HIV-infected patients with chronic diarrhea.

In some individuals with AIDS enteropathy, HIV proteins have been identified in the lamina propria of the small bowel. Lipid accumulation may be observed at the basolateral membrane (BLM) and in the lamina propria, and may be associated with increased fecal fat excretion (24).

Mycobacterial infection is a newly recognized and major problem associated with the spread of AIDS. Abdominal tuberculosis (TB) may be suspected from abnormal barium studies. However, a definitive diagnosis may be obtained from percutaneous needle or peritoneal biopsy, or from biopsies at colonoscopy or surgery. Sonographic findings of abdominal TB include the presence of ascites, peritoneal thickening, peritoneal nodules, lymphadenopathy, cold abscesses and concentric bowel wall thickening with or without ulceration (25). PCR assay may be used on endoscopic biopsy samples to increase the ease of diagnosing intestinal TB (26). <sup>67</sup>Ga scintigraphy was shown to be abnormal in a middle-aged male with diarrhea associated with biopsy-proven yersinia and TB enterocolitis (27).

Rotavirus is a major cause of diarrhea worldwide. An organ culture method has been developed to demonstrate the reduction in activities of BBM enzymes produced by equine rotavirus infection (28). In the neonatal rat model of group B rotavirus infection there is reduced villous height, increased crypt depth and reduced sodium absorption; water is also secreted (29). Similar morphological changes occur in the rabbit model, but basal fluid absorption in these infected animals is unaltered. The increase in short-circuit current evoked by prostaglandin E<sub>2</sub> is less in rotavirus-infected tissues than in controls, and the apparent maximal transport rate for electrogenic glucose and alanine uptake is increased (30). These findings underscore the importance of selecting the appropriate animal model to delineate the mechanisms of rotavirus-associated diarrhea.

Pathogenic strains of *Escherichia coli* may be enterotoxigenic, enteroinvasive, enterohemorrhagic or enteropathogenic. Enteropathogenic *E coli* is a major cause of diarrhea in both developed and developing countries. Enteropathogenic *E coli* attachment to the BBM is by two stages, a 'nonintimate adherence' step and an 'intimate adherence' step. The *bfpA* gene encodes nonintimate adherence and the *eaeA* gene is responsible for intimate attachment. Attachment of enteropathogenic *E coli* is followed by increased intracellular calcium concentrations, activation of protein kinases and phosphorylation of several proteins including the myosin light chain. Many cytoskeletal proteins are redistributed to plaques, and a cup and pedestal are formed at the site where enteropathogenic *E coli* microcolonies adhere. T84 cell monolayer infection with enteropathogenic *E coli* results in decreased transepithelial electrical resistance, increased permeability to tight junction markers and sequestration of intracellular calcium stores (31).

A combination of methods (ultrastructural analysis, in situ hybridization, immunohistochemistry and, more recently, immunogold electron microscopy with co-localization of

nucleocapsid-like particles with gold-labelled antibody specific for measles virus nucleocapsid protein) has described the presence of measles infection in Crohn's disease patients (32). These exciting findings are controversial and await confirmation.

## DRUGS

Different approaches have been used to increase the absorption of poorly absorbed drugs, such as enhancing the absorption of a cyclosporine derivative by a novel emulsifier from milk fat globule membranes (33). This emulsifier has also been shown to increase the absorption of vitamin A, vitamin D<sub>3</sub>, insulin and EGF. Incorporation of a nonabsorbable sugar such as mannitol into a pharmaceutical formulation may lead to reduced bioavailability for drugs that are absorbed from the small intestine (34).

Intestinal absorption of peptide drugs has been reviewed (35). Peptides such as insulin or calcitonin are not well absorbed by the small intestine because of their luminal proteolytic digestion and poor permeation across the BBM. Various strategies have been used to increase peptide absorption, including the use of protease inhibitors, absorption enhancers and targeted delivery within liposomes, nanocapsules or microspheres (36). The incorporation of insulin into mixed micelles increases its enteral absorption in dogs (37), and the hypoglycemic effect of placing insulin into the colon is enhanced by coadministration of a protease inhibitor (38). The low bioavailability of certain proteins and peptides of therapeutic value may be enhanced by agents that increase absorption, eg, surfactants. However, some surfactants may cause intestinal damage (39).

The passage of macromolecules across the intestine of mice is increased after infection with enterotoxigenic *E coli* (40). In neonatal rats, intraperitoneal administration of cortisone reduces the uptake of bovine serum albumin whereas this does not occur when animals are given spermidine (41).

Administration of nonsteroidal anti-inflammatory drugs (NSAIDs) may cause damage to the stomach and the small and large intestines. Indomethacin given subcutaneously to mice leads to reduced small intestinal length and decreased villous height, and to intestinal dilation, subepithelial blebs and submucosal vascular dilation (42). Mice may represent a suitable animal model for the study of NSAID enteropathy. The increased permeability associated with the use of NSAIDs is due, in part, to the inhibited synthesis of cytoprotective prostaglandins, but neutrophils also play an important role in NSAID-induced intestinal injury (43). The early neutrophil-independent phase of indomethacin-induced enteropathy involves rapid cyclooxygenase inhibition, as well as both microvascular and smooth muscle changes (44).

Loperamide oxide is the prodrug of the effective antidiarrheal medication loperamide. Systemic absorption of the active drug is lower and more delayed than that after loperamide administration, potentially leading to more pronounced and longer lasting antisecretory effects (45).

## INTESTINAL GROWTH: MUCOSAL PROLIFERATION AND DIFFERENTIATION

There is coordinated control of cell growth and differentiation of the small intestine. The epithelial lining undergoes continuous and rapid removal; the intestinal epithelial cells migrate continuously from the proliferative to the functional compartments, where they are then extruded into the intestinal lumen at the villous tip. There are tightly regulated mechanisms to balance proliferative activity with functional capacity and the loss of mature cells from the villus (46). Regulation of cell death is an important contributor to the developmental process, and a novel suggestion has been made that apoptosis accounts for the bulk of cell loss in the gut and therefore may be a central feature in the regulation of cell number (47).

The signals regulating the growth of the small intestine are unknown and may include intraluminal pancreaticobiliary secretions and a variety of hormones and peptides such as gastrin, CCK, enteroglucagon, TGF- $\alpha$ , TGF- $\beta$ , platelet-derived growth factor and EGF. While gastrin may be trophic for the mucosa of the stomach, it does not promote the growth of the remainder of the gastrointestinal tract (48). Keratinocyte growth factor and its receptor are important for intestinal proliferation (49). Neurons may also influence intestinal morphology (50). Protein kinase C (PKC), a family of serine/threonine kinases, has an important role in the cessation of growth, differentiation and function of intestinal epithelial cells (51).

EGF administered by mouth or parenterally promotes mucosal growth in the small intestine. EGF becomes mitogenic after it binds to a glycoprotein receptor that induces phosphorylation, with activation of the EGF receptor kinase and phosphorylation of other cellular substrates that serve as intracellular second messengers. The EGF receptor is present in higher concentrations on the basolateral rather than on apical membranes, and only BLM stimulation with EGF increases tyrosine kinase activity and enhances the uptake of thymidine (52). How then does the high concentration of EGF in milk and saliva stimulate the growth of the intestine? Orally administered EGF is absorbed in suckling, but not in mature, rats. Because there are similar amounts of EGF-receptor abundance and similar localization in mature and immature animals, it is likely that the oral proliferative response to EGF is due to the greater mucosal permeability of the immature intestine (53).

Milk-derived IGF-I has an important role in the developmental regulation of the gastrointestinal tract of neonates. IGF-I binds to a single class of specific Caco-2 cell surface receptors, which increase in number with differentiation and are found on both sides of the enterocyte (54). This class of receptors is specific for IGF-I; the affinity of IGF-I to the receptor is four and 150 times greater than the affinity for IGF-II and insulin, respectively.

During sepsis in rats there is increased protein synthesis in the mucosa of the small intestine, with cellular proliferation being partly mediated by IL-1 (55). Many other cytokines in the inflamed mucosa may enhance epithelial proliferation,

including increased proliferation of Caco-2 cells in culture (56). Cytokines, eg, IL-1, IL-6, interferon and tumour necrosis factor, influence the expression of acute phase plasma proteins expressed in cultured human intestinal epithelial cell lines such as Caco-2 and T84 (57).

Enteral nutrition in the small intestine has been reviewed (58). Glutamine, the most abundant amino acid in the plasma, is released from skeletal muscle and used as the preferred fuel for enterocytes. In enterocytes, glutamine or glutamate is converted into citrulline, proline and ornithine. Ornithine aminotransferase is a key enzyme in the citrulline synthesis pathway in the small intestine. Activity of this enzyme in rats is increased by administration of a low protein diet and is suppressed by a high protein diet (59). Depletion of the body glutamine pool may increase intestinal permeability and facilitate bacterial translocation across the intestine. Glutamine is unstable and difficult to prepare for use in intravenous or supplementary oral solutions. However, administration of the stable dipeptide L-alanyl-L-glutamine stimulates crypt cell proliferation in the ileum and colon of the human intestine (60). This dipeptide may prove to be useful in total parenteral nutrition solutions when mucosal atrophy might otherwise lead to a breakdown of the intestinal barrier. When glutamine dipeptide supplementation was given to 12 intensive care unit patients, the unwanted increased intestinal permeability seen with the use of glutamine-free parenteral nutrition was avoided (61).

Activation of the respiratory burst in polymorphonuclear neutrophils increases the concentration of tissue oxygen-free radicals. Tissue damage results when the production of reactive oxygen species exceeds the capacity of antioxidant enzymes to detoxify these free radicals. There are three superoxide dismutases. Steroid treatment of IEC cells with dexamethasone reduces the manganese superoxide dismutase mRNA by a process that requires protein synthesis in addition to transcriptional regulation (62).

Abolition of amniotic fluid ingestion early in gestation in fetal sheep results in a profound growth retardation of the gastrointestinal tract (63). This growth retardation is progressive, becoming more pronounced as the period of absences of swallowing is increased. The effect is reversed if fetal swallowing is restored, even for relatively short periods.

## NUCLEIC ACIDS, NUCLEOTIDES AND NUCLEOSIDES

Ingested nucleic acids undergo hydrolysis in the intestine to yield nucleotides and nucleosides. Nucleotides are absorbed from the diet, salvaged from intracellular degradation or synthesized de novo from amino acids such as glutamine and sugars (glucose) (64). Human milk, but now cows' milk, is a good source of nucleotides for young infants, and it has been suggested that infant formulas should have sources of nucleotides added to duplicate human milk more closely (65). The gastrointestinal mucosa has a high rate of cellular proliferation and metabolic activity. Dietary nucleotides may be important nutrients for intestinal repair (66). The importance of human milk in the protection of the infant from infections

has been reviewed (67). The intestine has a very low capacity for *de novo* synthesis of nucleotides and therefore needs to 'salvage' exogenous nucleotides from the diet and endogenous nucleotides from the plasma.

Nucleosides are transported by Caco-2 cells and are metabolized during this process (68). The uptake of uridine is higher in suckling versus older rats due to a progressive decrease in the value of the maximal transport rate of the carrier-mediated process (69). There is a sodium-dependent active transport system for nucleosides in the intestine.

### VITAMINS AND MINERALS

Intestinal iron absorption involves three steps: uptake, intracellular transport across the enterocyte (in which ferritin and transferrin are important) and transfer of the iron across the BLM. Iron uptake is inversely proportional to body iron stores. Iron is absorbed intact and organic iron is absorbed much more efficiently than inorganic iron. Although absorbed poorly, inorganic iron accounts for a major portion of the iron absorbed from the diet because it is present in relatively large amounts. Premicellar taurocholate binds calcium ions with high affinity, forming soluble calcium-taurocholate complexes, whereas micellar taurocholate has low calcium ion binding properties. In a manner similar to how taurocholate binds calcium ions, iron is bound by taurocholate, and intestinal bile salt depletion inhibits iron absorption (70).

Transferrin, transferrin receptor and ferritin are the major proteins involved in the control of cellular iron metabolism. In patients with genetic hemochromatosis, the signal for ferritin H and L subunit mRNAs is lower in duodenal biopsy tissue compared with that from normal subjects or those with secondary hemochromatosis (71). In those with genetic hemochromatosis there is a diffuse/cytoplasmic pattern of iron staining, whereas a supernuclear/granular staining pattern is found in normal individuals or secondary hemochromatosis patients. The low accumulation of ferritin in biopsies of patients with genetic hemochromatosis is not necessarily caused by defective control of ferritin synthesis, but rather may be caused by low expression of ferritin mRNA and sustained activity of an unknown iron regulatory factor.

Riboflavin is a water-soluble vitamin. Protein kinase A (PKA) and PKC regulate a variety of membrane transport processes, and in Caco-2 cells an increase in intracellular cAMP levels down-regulates riboflavin intestinal uptake, possibly by influencing a PKA-mediated pathway (72).

Vitamin A is an essential fat-soluble vitamin. Retinoids are bound to cellular retinol-binding proteins (CRBP and CRBP II). Intestinal levels of CRBP II are influenced by lactation and vitamin A deficiency, and intestinal retinol uptake, retinyl ester synthesis and retinyl ester secretion are correlated with levels of CRBP and CRBP II in Caco-2 cells (73). Feeding rats a diet rich in long-chain triacylglycerols increases CRBP II mRNA and protein levels in rat intestine (74).

Calcium uptake is mediated by both a saturable and a

nonsaturable process. Nonsaturable calcium uptake may be competitively or noncompetitively inhibited by strontium or magnesium, respectively; the nonsaturable component may be increased by a positively charged polycation such as polyarginine, which decreases membrane fluidity (75).

A BLM is important in the active intestinal transport of calcium. Calcium pump mRNA levels are higher in young versus old animals, but in all age groups 1,25-dihydroxyl vitamin D (1,25[OH]<sub>2</sub>D), the biologically active metabolite of vitamin D, increases calcium pump mRNA levels (76). Vitamin D<sub>3</sub> is metabolized to 25-hydroxyl vitamin D<sub>3</sub> in the liver and to 1 $\alpha$ , 25-dihydroxyl vitamin D<sub>3</sub> in the kidney, which in turn binds to a cellular receptor (77). There are age-related decreases in serum 1,25(OH)<sub>2</sub>D levels, and the decline of intestinal calcium absorption with age may be partly due to this serum reduction of vitamin rather than to decreased responsiveness of the calcium pump to vitamin D. PKC, a phospholipid-dependent serine/threonine kinase, plays an important role in the signal transduction of many hormones and may play a role in the action of 1,25(OH)<sub>2</sub>D (78).

Many of the effects of 1,25(OH)<sub>2</sub>D are mediated by a vitamin D nuclear receptor that modulates gene transcription, but this biologically active form of vitamin D may also act by nongenomic mechanisms. Biologically active vitamin D increases the breakdown of membrane phosphoinositides, increases the intracellular calcium concentration, translocates PKC from the cytosolic to the particular fraction of Caco-2 cells and activates some – but not all – PKC isoforms (79).

The fractional absorption of zinc and copper is lower in diabetic compared with nondiabetic control rats; food consumption is higher and therefore the net absorption is greater, yet because of the higher urinary excretion of diabetic animals zinc and copper retention remains unchanged (80).

### WHIPPLE'S DISEASE

Whipple's disease is a chronic disorder of many organs, with presenting symptoms including weight loss, diarrhea/malabsorption, polyarthralgias, fever and central nervous system manifestations. Trimethoprim-sulfamethoxazole is superior to tetracycline in treating this multisystem disorder, with fewer treatment failures and less development of drug intolerance (81). Unfortunately, trimethoprim-sulfamethoxazole does not always prevent the development of cerebral manifestations.

### RADIATION

Abdominal radiation results in acute and/or chronic changes in the gastrointestinal tract, particularly to the radiosensitive small intestine. The acute effects of abdominal radiation usually subside within weeks, and late complications may develop insidiously over the following months to years. Studies in dogs have demonstrated that shortly after abdominal radiation to the ileum, morphological as well as transport abnormalities in the intestine result. Pretreatment with the radioprotective agent WR2721 improves the chance of the

animal's survival, reduces ileal morphological damage, and diminishes the malabsorption of water and electrolytes. Late radiation enteropathy may be a chronic debilitating disorder characterized by malabsorption, complications requiring surgery and substantial mortality.

Late radiation enteropathy is often associated with impaired motility of the proximal small intestine. Impaired fasting motility was found in 29% of patients, with 24% demonstrating an attenuated postprandial motor response (82). These motility changes may contribute to the observed malnutrition.

Models have been developed for estimating the risk of ulcer in the small intestine after localized single or fractionated applications of irradiation (83). Abnormalities in gastrointestinal function occur in over 70% of patients when studied two to 10 years following radiation treatment for seminoma of the testis (84). Radiation-associated alterations in the intestinal transport of salt and water may be due to changes in the enteric nervous system as well as in the mucosal immune system, with a reduction of tissue responsiveness to electrical field stimulation to prostaglandin E2 and theophylline. These effects correlate temporally with decreased mast cell and histamine levels (85).

### EARLY DEVELOPMENT

The expression and localization of each member of the glucose transporter family in the rat embryonal and fetal intestine varies with gestational age. GLUT2 is localized within the BLM of the enterocytes on day 18 and GLUT5 localized to the BBM after day 18 (86).

Neurotensin is a tridecapeptide found in the central nervous system and in the N cells of the distal small intestinal mucosa. Neurotensin stimulates growth of the small intestine

and reverses the small bowel mucosal atrophy associated with feeding rats an elemental diet. Neurotensin also augments intestinal regeneration after small bowel resection. Subcutaneous injection of neurotensin in the rat increases mucosal growth, crypt depth and villus height in older animals without changing BBM disaccharidases (87). This demonstrates that the proliferative potential of the small bowel mucosa is maintained with ageing.

The activity of the BBM disaccharidase lactase-phlorizin hydrolase (LPH) is high at birth and declines during weaning, whereas the activity of sucrase-isomaltase is undetectable at birth and increases rapidly as the diet is changed from milk to solid foods. During postnatal development LPH and sucrase-isomaltase biosynthesis appear to be regulated at the level of mRNA abundance, with a fall in LPH mRNA and increase in sucrase-isomaltase mRNA during weaning, which suggests that the primary mechanisms underlying the control of sucrase-isomaltase and LPH is transcriptional (88).

The parturition rise in endogenous cortisol secretion stimulates the prenatal expression of certain BBM enzymes in the pig small intestine. The effect of cortisol on the developing intestine is different for particular enzymes and intestinal regions (89). The infusion of cortisol into fetal pigs causes an increase in the activity of LPH, maltase-glucoamylase, aminopeptidase IV and aminopeptidase A in the proximal and middle intestine during the last 10 to 15 days before term; this increase correlates positively with the log<sub>10</sub> of plasma cortisol concentrations. The activities of sucrase-isomaltase and dipeptidyl peptidase IV are not affected by fetal age or exogenous cortisol. The mechanisms of these effects are unknown, and it is unclear whether glucocorticosteroids given to the pregnant or nursing mother will modify the ontogeny of the intestine.

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