Small bowel review: Part II

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ABR Thomson, G Wild. Small bowel review: Part II. Can J Gastroenterol 1997;11(7):607-618. Significant advances have been made in the study of the small bowel. Part II of this two-part review of the small bowel examines the early development and later ageing of the small bowel; the effect of diabetes, alcohol, radiation and HIV on the small bowel; enteral and parenteral nutrition; the brush border membrane and enterocyte proliferation; and peptide hormones (including transforming growth factors, motilin, peptide YY and cholecystokinin).

Key Words: *Alcohol, Brush border membrane, Diabetes, HIV, Parenteral nutrition, Peptide hormones, Radiation, Small bowel*

Vue d'ensemble sur l'intestin grêle : partie II

RÉSUMÉ : Des progrès significatifs ont été accomplis dans l'étude du grêle. La partie II de ce bilan en deux volets sur l'intestin grêle se penche sur les premiers stades du développement et sur le vieillissement de l'intestin grêle; sur l'effet du diabète, de l'alcool, des radiations et du VIH; sur la nutrition entérale et parentérale; sur la bordure en brosse et la prolifération des entérocytes, des hormones peptidiques (y compris les facteurs de croissance transformant la motiline, le peptide YY et la cholécystokinine) et sur la maladie au VIH.

Significant advances have been made in the study of the small bowel. In part II of this review of the small bowel, emphasis is placed on the early development and later ageing of the small bowel; the effect of diabetes, alcohol, radiation and HIV on the small bowel; enteral and parenteral nutrition; the brush border membrane (BBM) and enterocyte proliferation; and peptide hormones (including transforming growth factors [TGFs], motilin, peptide YY [PYY] and cholecystokinin [CCK])

EARLY DEVELOPMENT AND LATER AGEING

Despite its rapid proliferation, the gut epithelium maintains precise spatial differentiation in the crypt-to-villus tip or 'vertical' axis, and in the duodenal-to-colonic or 'horizontal' axis. When the four predominant epithelial cell types emerge from the proliferating progenitor cell zone of the crypts they acquire the differentiated phenotype and express a variety of gene products along the vertical and horizontal axes. For example, villus-associated enterocytes but not crypt epithelial cells express the liver fatty acid binding protein and apolipoprotein (APO) A-IV. However, the preferential accumulation of liver fatty acid binding protein and APO A-IV mRNA in villus base enterocytes is not observed in intestinal isografts (1). This suggests that the program of differentiation is encoded in fetal endoderm and mesenchyme, and that substances contained in the intestinal lumen play an important modulatory role in generating spatial differentiation during ontogeny.

During its life in utero, the fetus is supplied with most of its substrate needs by the placenta. The healthy fetus swallows large amounts of fluid, which consists of a mixture of amniotic fluid, lung liquid and oral/nasal secretions. Ingestion of this fluid in utero may be an important regulator of prenatal gastrointestinal tract development. In the presence of congenital defects, such as esophageal or intestinal atresia (both of which restrict access of the swallowed fluid to the gastrointestinal tract), there may be impaired function of the intestine. Ligating the fetal sheep esophagus results in mor-

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Received for publication February 17, 1997. Accepted June 26, 1997

phological changes in the intestine, which partially regress if the initial esophageal obstruction is relieved (2). Thus, it is likely that tissue or nutritional growth factors present in swallowed fluid may be involved in the regulation of intestinal development before birth.

Neurotensin is a tridecapeptide found mainly in the central nervous system and discrete enteroendocrine cells (N-cells) located with greatest abundance in the distal gut mucosa. The functions of neurotensin include stimulation of pancreatic secretion, stimulation of motility as well as inhibition of small bowel and gastric motility, and stimulation of the growth of the small intestine (3). Neurotensin may reverse the small bowel mucosal atrophy associated with feeding an elemental diet, and neurotensin augments intestinal regeneration after small bowel resection. When aged rats are given neurotensin, there is an increase in crypt depth and villous height, without alterations in the specific activities of BBM sucrase or maltase (4). This suggests that the potential of the aged small intestine to respond to trophic stimuli is maintained.

Proliferation of intraepithelial cells isolated from mature rats may be enhanced more by bacterial antigens when the intraepithelial leukocytes (IELs) are obtained from older versus younger rats (5). The mucosal or secretory immune response in the gastrointestinal tract is compromised by ageing, and this immunosenescence reflects deficits in the differentiation and/or migration (homing) of immunoglobulin A immunoblasts to the intestinal lamina propria, and the initiation and/or regulation of local antibody production (6).

The ratio of urinary lactulose:mannitol after oral administration of these sugars is a reproducible measure of small intestinal mucosal integrity, and this ratio is increased in diseases where the small intestinal mucosal integrity is disrupted. Mannitol is absorbed transcellularly through aqueous pores in the cell membrane, whereas lactulose is absorbed paracellularly. The lactulose:mannitol ratio does not change with increasing age (7). This suggests that the intestine does not become more 'leaky' with advancing years.

Decreased absorption of glucose, amino acids, cholesterol and calcium have been reported in association with ageing. The intestinal unstirred water layer may influence nutrient uptake, but the jejunal acidic microclimate layer is slightly thinner in senescent rats than in young adult rats (8); this is not an increased diffusion barrier responsible for age-related reduction in nutrient absorption. Clearly, there must be other mechanisms responsible for the reduced absorption that occurs with ageing. These mechanisms remain to be defined.

DIABETES

The small intestine of animals with experimental diabetes responds with hyperplasia and hypertrophy. The intestine may be heavier with taller villi, longer crypts, and increased DNA content as well as protein:DNA ratios. Diabetes diminishes vasoactive intestinal polypeptide (VIP) tissue concentrations and release from intestinal myenteric nerves, and insulin restores VIP concentrations (9). In streptozotocin-diabetic rats, a combination of insulin and an aldose reductase inhibitor returns cell numbers towards normal but does not influence the increased enterocyte size, or the number or area of microvilli per cell (10). Gastrointestinal dysfunction is common in diabetics, with as many as three of four patients complaining of nausea, vomiting, diarrhea, constipation, early satiety or dysphagia. A neuropathy of the myenteric plexus or the extramural nerves that regulate gastrointestinal movements has been implicated as a cause of many of these symptoms. Erythromycin is a macrolide antibiotic that produces a prokinetic effect on the stomach and duodenum, and stimulates the motility of the proximal gut by its actions on motilin receptors. In diabetic male subjects, erythromycin decreases the oral-to-cecal transit time (11). This suggests that erythromycin may be a useful prokinetic drug in diabetic subjects.

Clinical learning point: Gastrointestinal dysfunction is common in diabetics, and erythromycin may be a useful prokinetic agent in these patients.

Microangiopathy is common in diabetics, and regional bloodflow is altered in early diabetes. Hyperemia has been described in several tissues such as retina, glomeruli, skeletal muscle and small intestine. Gastrointestinal hyperemia is due at least in part to the increased demands of a hypertrophic mucosa and possibly to an increased vascular sensitivity to nitric oxide, and is mediated primarily by endogenous prostaglandins (12).

Calcium is malabsorbed in diabetics due to reduced saturable and nonsaturable components of uptake, and this, in turn, is associated with a lower serum concentration of 1,25-dihydroxycholecalciferol (13). Fractional absorption of zinc and copper is lower in diabetic rats, but net absorption is higher and is associated with higher urinary excretion. The result is that zinc and copper retention remains unchanged (14).

ALCOHOL

Nutrients interrupt the interdigestive motility cycle and induce a pattern of irregular contractile activity that mimics the postprandial form. The duration and specific motor characteristics of these responses to luminal nutrients vary with the caloric load and the nature of the nutrients. Ethanol is a major source of calories in people who drink alcoholic beverages regularly, and ethanol has nutritional characteristics of both fats and carbohydrates. Ethanol may slow gastric emptying and interrupt the interdigestive cycle. Intraluminal perfusion of the jejunum of canine intestine delays the phase III component of the interdigestive cycle (15). Both ethanol and ischemia/reperfusion produce an independent increase in the myeloperoxidase (MPO) activity in the small intestine. However, when ethanol is given before the onset of ischemia the MPO activity is increased further (16).

Clinical learning point: Ethanol may potentiate ischemic injury to the gut.

The cytoskeleton is important for enterocyte function at birth, and cytoskeletal integrity is a prerequisite for many normal cell functions. Long term exposure to ethanol in utero in the rat results in postnatal growth retardation, as well as causing severe dysfunction of the cytoskeleton of the developing intestinal epithelium (17). Exposure of the intestinal mucosa to ethanol causes morphological injuries and modifies BBM activities. After three months of 30% ethanol ingestion in rats the specific activities of maltase, lactase and sucrase are decreased in the ileum, but after five months of ethanol consumption these disaccharidase activities return to normal. This suggests an adaptive response to prolonged alcohol exposure (18).

Clinical learning point: Ethanol causes damage to the intestine, but over time the intestine may adapt to minimize the lost function, even when checked alcohol consumption continues.

Enprostil, a monomethylated prostaglandin E_2 analogue, protects intestinal epithelial cell lines IRD 98 and IEC 17 against ethanol injury (19). Prostaglandins may result in 'adaptive cytoprotection' of the intestinal mucosa. Adaptive cytoprotection refers to endogenous prostaglandin stimulation at the site of irritation, and direct cytoprotection involving reinforcement of mucosal resistance or administration of synthetic prostaglandins, which have a longer duration of action than natural prostaglandins.

RADIATION DAMAGE

Radiation-induced injuries to the intestine are dose dependent and may also be time dependent (20). Radiation enteritis has acute and chronic phases, and in experimental animals, radiation-induced gastrointestinal inflammation has been observed in the initial hours following exposure. Two hours after radiation of the rat jejunum, there is an increase in MPO and an increase in prostaglandin E_2 synthesis, together with altered responsiveness of the jejunal mucosal-submucosal vasculature (21). These changes in function may reflect the onset of an acute inflammatory response and appear to have cyclooxygenase-dependent and -independent components. Fractionated irradiation alters the contractile activity of the small intestine and colon. In the canine intestine, fractionated radiation changes gut regulatory peptides such as VIP, substance P, PYY and motilin. Fractionated radiation may play a role in changes in cholinergic enzyme activity (22). In randomly selected patients who had been treated for stage I seminoma of the testis two to 10 years previously, at least one parameter of gastrointestinal function was abnormal in 11 of 15 patients (23).

Clinical learning point: Late effects of abdominal radiation are common.

The pathogenesis of intestinal radiation syndrome remains controversial. The formation of free radicals during exposure to radiation has been proposed as being important. The radioprotective agent WR2721 improves seven-day survival in radiated dogs, and also improves mucosal integrity and absorption (24). The potential clinical usefulness of radioprotective agents to reduce the frequency or severity of irradiation injury to the intestine in humans remains unknown.

ENTERAL AND PARENTERAL NUTRITION

Enteral feeding represents primary therapy that benefits the outcome of critically ill patients, and recommendations have been formulated for tube feeding of enteral nutrition (25,26). Long term survival for patients with intestinal failure requiring home parenteral nutrition has been reported – under 40 years of age, start of home parenteral nutrition after 1987 and the presence of chronic intestinal obstruction are independent variables associated with decreased risk of death (27).

Severe malabsorption is observed after extensive small bowel intestinal resection. With time, patients progressively improve their ability to maintain nutrition orally. This adaptation is believed to be caused by growth and increased absorption efficiency of the remaining small bowel mucosa. Practical management of short bowel syndrome has been reviewed (28). When the small bowel is anastomosed to the remaining colon, the colon receives an increased amount of fermentable substrates, mainly carbohydrates. Despite fast transit time, patients with a short bowel and a colon remaining in continuity ferment more lactulose and hexoses, and have a higher activity of beta-galactosidase in their stools than do nonadapted normal subjects (29). This hyperfermentation is associated with efficient removal of extra short chain fatty acids (SCFAs) from fecal water.

Following massive intestinal resection in rats, the bethanacol-stimulated tonic stress response and phasic contractile activity of circular smooth muscle are reduced, concomitant with altered intestinal transit (30). Gastroduodenal emptying is delayed with decreased intestinal flow rate (31). Modular tube feeds and a commercially available enteral formula enriched with omega-3 fatty acids, arginine and yeast may result in decreased infections in burn and postoperative cancer patients but not in critically ill patients (32). The effects of SCFAs on gut morphology and function have been reviewed (33). The SCFAs acetate, propionate and butyrate are formed from bacterial fermentation of fibre. Dietary fibre consumption increases substrate oxidation by isolated colonocytes but not by distal small intestinal enterocytes (34). PYY has a trophic effect on the intestine in rats given total parenteral nutrition (TPN) and may offer a means by which the mucosal atrophy associated with TPN can be modulated (35). Also, TPN is associated with reduced numbers of gut-associated lymphoid tissue, and this can be prevented by feeding a complex enteral diet (36).

The lumenal administration of epidermal growth factor (EGF) in combination with protease inhibitors may reverse the gut atrophy associated with parenteral nutrition (37). EGF leads to an increase in *c-fos*, *c-jun* and *junB* gene expres-

sion, and pretreatment with somatostatin followed by EGF results in an inhibition of the EGF-induced increases in proto-oncogene expression in IEC-6 cells (38). Intestinal resection initiates a series of growth-related events in the remaining mucosa within 12 h, even in the absence of nutrient intake (39). Increased basal and postprandial levels of gastrin, CCK, glucose-dependent insulinotropic peptide (GIP), PYY and enteroglucagon are seen one month after massive small bowel resection in the dog (40). Concentrations of enteroglucagon, GIP and PYY remained high for six months after resection.

Efforts have been made to increase surgically the intestinal surface area in patients with short bowel syndrome by using the Bianchi procedure. However, intestinal lengthening actually impairs the nutritional status and intestinal absorption following massive resection in dogs. This is due possibly to motor disruption and hypergastrinemia, as well as to decreased enteroglucagon and increased somatostatin levels (41). Insulin-like growth factor (IGF)-I enhances the mucosal hyperplasia that normally occurs after massive small bowel resection. Miniosmotic pump infusion of growth hormone (GH) in rats after jejunal ileal resection allows for faster growth without a change in the hyperplasia that normally occurs after small bowel resection and without a change in IGF-I or IGF-binding protein (42,43). After jejunectomy, a rapid and sustained increase in the abundance of proglucagon mRNA occurs in the residual ileum and is accompanied by increases in plasma intestinal proglucagon-derived peptides. In rats with a massive small bowel resection, plasma enteroglucagon and glucagon-peptide-I levels are increased but are unaffected by inhibitors of ornithine decarboxylase (ODC) activity (44).

Forty-eight hours after intestinal resection in the rat, APO A-IV and intestinal fatty acid binding protein (I-FABP) mRNA levels are increased in remnant ileum, but after one week I-FABP mRNA levels have returned towards normal (45). Thus, the enterocyte can respond acutely to a loss of small bowel surface area by increasing expression of several genes, but this compensatory enterocytic response appears to be spatially and temporarily regulated.

Arginine becomes an essential amino acid during periods of growth and catabolic states. Both arginine and ornithine are precursors of nitric oxide and polyamines, respectively. Supplementation of enteral diets with ornithine or ornithine alpha-ketoglutarate may improve intestinal mucosal barrier function (46). ODC is the first rate-limiting enzyme in polyamine biosynthesis and catalyzes the conversion of ornithine to putrescine. An increase in ODC activity is one of the earliest biochemical events associated with the induction of cell proliferation. The activities of ODC and tyrosine kinase increase during the process of cell division. Tyrosine kinase modulates ODC activity during mucosal proliferation, as well as in mucosal hyperplasia associated with diabetes in rats (47). Asparagine stimulates ODC activity in IEC-6 cells, and the increased ODC mRNA levels result partly from a delay in the rate of degradation of ODC mRNA (48). This raises the possibility that luminal amino acids may stimulate gut mucosal growth in association with their ability to regulate ODC gene expression.

BBM AND ENTEROCYTE PROLIFERATION

Membrane surface: Intestinal enterocytes are coated with a 0.1 to 0.5 mm-thick glycocalyx layer composed of fine filaments that radiate from the tips of the brush border microvilli. The glycocalyx is comprised of the carbohydrate extensions of major membrane glycoproteins. These are anchored entirely in a membrane microdomain at the tip of the microvilli, suggesting that mature enterocytes are hyperpolarized epithelial cells (49).

The modulation of intestinal epithelial brush border digestive enzyme activity is central to the mucosal adaptation that occurs with refeeding after fasting, as well as to the adaptation that occurs with development, while intestinal epithelial cell motility is critical for mucosal healing. Differentiation of the intestinal epithelial cell is affected by lumenal nutrients and matrix proteins, while cell motility is stimulated by growth factors such as EGF and TGF-β. Differentiation is modulated by the extracellular matrix across which migration occurs. Modulation of protein kinase C by a phorbol ester in Caco-2 cells alters the expression of alkaline phosphatase but not that of cell migration (50).

The amount and relative distribution of intralumenal pancreatic biliary secretions may affect BBM enzyme activity, mucosal morphology, and adaptive responses to intestinal resection or transposition. Exocrine pancreatic insufficiency increases crypt cell proliferation in the distal small intestine (51). Pancreatitis-associated protein (PAP) I and III genes are expressed constitutively in the small intestine of rats (52).

P-glycoprotein is a multidrug transporter in the intestinal epithelium, and enterocytes of the ileum may be more actively involved in the P-glycoprotein-mediated transport of xenobiotics into the intestinal lumen (53).

The process of vesicle trafficking to plasma membrane domains is tightly regulated to provide for specific targeting of proteins to discrete cellular domains. To this end, the family of Rab small guanosine triphosphate-binding proteins plays an important role in the regulation of membrane trafficking. Rab2 expression is enriched in epithelial cells and is distributed in apically oriented vesicle populations (54). Changes in the concentration of free intracellular calcium are widely recognized as controlling a variety of functions in almost all cell types that have been examined. There may be synergism or 'cross-talk' between the calcium and the cyclic adenosine monophosphate (cAMP) signalling pathways, which regulate the extent of secretory responses (55).

It has been assumed that the intestinal dysfunction associated with villous atrophy (including diarrhea, malabsorption and impaired barrier function) is due to a decrease in the number of epithelial cells and, therefore, to a decrease in absorptive surface area. However, the individual enterocyte may also be changed, with villous atrophy being associated with an increase in lactase and a decrease in intestinal alkaline phosphatase gene expression. Through differential clon-

ing methods, when expression is altered with villous atrophy, a novel intestine-specific cDNA, which may play a role in the processes of intestinal epithelial growth and differentiation, has been identified (56).

Trefoil peptides are small proteins that are expressed by mucin-producing goblet cells and are distinguished by a unique six-cysteine motif called a 'P' domain. This results in the formation of three intrachain loops within the small peptide due to disulfide bond formation. Trefoil peptides are expressed in the intestinal goblet cells, where they may have a facilitating role in healing mucosal sites of injury. The rat intestinal trefoil factor gene has been cloned, and studies of the 5′-flanking region of the intestinal trefoil factor gene demonstrate the presence of *cis*-regulatory elements capable of directing goblet cell-specific expression (57).

The human intestinal trefoil factor has been characterized (58). In a human colonic adenocarcinoma cell line (Colony-29) basolateral EGF stimulates a predominately prostaglandin-dependent increase in chloride secretion that is enhanced by basolateral intestinal trefoil factor (ITF). These two peptides may interact in normal and in damaged mucosa to alter the local apical solute and fluid environment (59). There are trefoil binding sites in the gastrointestinal tract, and human spasmolytic polypeptide (hSP) may have affinity for the mucosal recombinant rat ITF (60).

Differentiation along the crypt-villous axis in adult rats follows a pattern similar to neonatal maturation as far as protein and carbohydrate composition, and food protein binding (61). Stimulation in jejunal protein synthesis by feeding is greater in young versus older suckling pigs, and this enhanced stimulation of protein synthesis is associated with elevated circulating concentrations of insulin but not of amino acids or IGF-I (62).

There are site- and species-related variations in membraneous epithelial cell surface glycoconjugate expression. These may reflect the local microorganism populations and, therefore, may have implications if orally delivered vaccines and drugs are to be targeted to these M-cells via their surface glycoconjugates (63). Lectins and glycoproteins of plant or animal origin have the ability to bind specific carbohydrate residues of cell glycoconjugates. Diet and gut microflora alter the lectin-binding patterns of intestinal mucins in rats (64). Dietary changes are influential in modifying the amount and proportion of mucins in the small intestine, and of the microbial flora in the large intestine (65,66). Intestinal epithelial cells form a barrier to many luminal irritants, and this barrier recovers within hours when disrupted by a superficial epithelial injury. Epithelial restitution is accomplished by epithelial cell migration that reseals the wound area without any cell proliferation, especially during the initial step of healing. The roles of eicosanoids and the gastrointestinal tract have been reviewed (67). Intestinal epithelial restitution is accelerated by several growth factors including TGF-α, EGF, TGF-β and hepatocyte growth factor. Endogenous prostaglandins play an important role in regulating intestinal epithelial restitution (68).

PROLIFERATION

Two IGFs, IGF-I and IGF-II, stimulate cell proliferation by the same type I IGF receptor, which is a tyrosine kinase. IGF-II is considered the predominate fetal IGF, whereas IGF-I predominates postnatally. EGF also has a trophic effect on the intestine and uses a distinct tyrosine kinase receptor. Both the EGF and IGF receptors share some common signal transduction pathways. EGF potently and rapidly induces *c-fos* and *c-jun* mRNAs, whereas IGF-I modestly increases *c-fos* but not *c-jun* mRNAs (69). These distinct effects of the two growth factors on intracellular signal transduction and gene expression may contribute to synergistic effects on DNA synthesis when they are added in combination to IEC-6 cells. TGF-β and EGF are potent stimulators of small intestinal crypts in the mouse, as is IGF-I (70).

A novel confocal microscopic technique has been used to investigate small intestinal epithelial cell proliferation in children. By means of noninvasive optical sectioning through microdisected crypts, high resolution, three dimensional data were obtained, enabling mitotic figures to be mapped accurately relative to the architecture of individual intact crypts. Crypt cell division occurs with an equal probability in health and in disease, and increased crypt cell production rates are caused largely by a change in crypt size rather than by a change in cell cycle time or crypt growth fraction (71).

Clinical learning point: The confocal microscopic technique has shown that the increased crypt cell production rates that occur in some diseases are not caused by a change in cell cycle time on crypt growth fraction, as has always been considered to be the case, but are caused instead by a change in crypt size.

Raw kidney bean-based diets reduce the growth rate of animals and induce reversible and polyamine-dependent hyperplastic growth of the small intestine. The factor responsible for this is the lectin phytohemagglutinin (PHA), which is present in raw kidney beans. PHA resists degradation by both proteolytic enzymes and bacteria, and keeps its biological activity during its passage along the intestine. Dietary PHA influences the size, metabolism and function of the entire digestive tract by lengthening the tissue and thickening the gut wall, as well as by increasing the number of crypt cells (72).

H_2 antagonists retard tumour growth in some animal models and prolong survival in patients with some types of cancer. An increase in ODC activity is one of the earliest biochemical events associated with the induction of cell proliferation, and inhibition of ODC activity prevents growth responses in a number of tissues. ODC is the initial rate-limiting enzyme in polyamine biosynthesis and has been studied extensively in IEC-6 cells (a line of normal rate intestinal crypt cells). Cimetidine inhibits the increase in ODC activity in the mucosa stimulated by pentagastrin and EGF but not by refeeding (73). An H_1-receptor antagonist

also inhibits increased ODC activity, but ODC mRNA levels are not inhibited by an H_2-receptor antagonist. This suggests that cimetidine acts nonspecifically to inhibit cell proliferation, at least partly through decreasing polyamine biosynthesis.

Clinical learning point: H_1- and H_2-receptor antagonists may inhibit tumour growth by reducing ODC activity.

Epithelial continuity is re-established in two phases. First, epithelial cells adjacent to or just beneath the injured surface migrate into the wound to cover the denuded area, a process that has been called epithelial restitution. This process does not require cell proliferation and occurs within minutes to hours. Second, epithelial cell proliferation and maturation take place to replenish the decreased cell pool. Acute epithelial injury in the rat small intestine in vivo is associated with expanded expression of TGF-α and TGF-β(74).

PEPTIDE HORMONES

TGFs and EGFs: TGF-α and pancreatic secretory trypsin inhibitor may be important in maintaining mucosal integrity (75). TGF-α binds to and activates the EGF receptor. Coexpression of the TGF-α and EGF receptor is associated with a transformed phenotype in a variety of carcinomas of both intestinal and extraintestinal tissues. Caco-2 cells are an intestinal epithelial cell line derived from a human colonic adenocarcinoma, and proliferation of Caco-2 is driven by autocrine stimulation of EGF receptors by TGF-α (76).

EGF is the prototype member of a family of growth factors sharing extensive structural and functional homology. EGF binds to a 170-kDa plasma membrane receptor on targeted cells, subsequently stimulating intrinsic tyrosine kinase activity. The activation of tyrosine phosphorylation is a necessary component of this signal-transduction pathway. EGF affects the mucosal integrity of the gastrointestinal tract, and saliva-derived EGF may be absorbed from the mouth and gastrointestinal tract (77). In humans, salivary EGF is derived from the parotid and submandibular glands. Lumenal exposure to EGF prevents starvation-induced mucosal atrophy of the small bowel but does not enhance the mucosal growth associated with refeeding (78). The potential of the oral administration of EGF to prevent intestinal atrophy in starved patients remains to be established.

Mucosal EGF stimulates EGF-receptor phosphorylation in immature but not in mature rat intestine (79), and these differences are not explained by EGF-receptor abundance or localization. EGF receptors are on the basolateral membrane, and only basolateral membrane stimulation with EGF increases tyrosine kinase activity (80). This raises the possibility that the greater mucosal permeability of the immature gut may allow EGF to bind to the EGF receptor in the basolateral membrane and to mediate its effect in suckling but not in adult rat intestine. The EGF receptors are on the basolateral membrane, and only basolateral membrane stimulation with EGF increases tyrosine kinase activity (80). EGF concentrations in gastrointestinal tissues are higher in males than in females, and gonadectomy with sialoadenectomy leads to a decrease in EGF concentrations in the gastrointestinal tract of both genders (81). The current understanding of initiation of signals downstream of activation of the receptor tyrosine kinase of the EGF receptor involves the association of specific cellular proteins by *src* homology 2 domains that bind directly to phosphotyrosine-containing sequences. The *src* homologous collagen-like protein is an in vivo substrate of the intestinal EGF receptor (82).

Breast-fed infants from developing countries have less severe diarrhea and decreased mortality from diarrhea compared with infants fed formula. EGF and TGF-α are abundant in human milk. In a piglet model of rotavirus enteritis, TGF-α stimulated jejunal mucosal hypertrophy, improved barrier function and enhanced regrowth of villi, but did not facilitate restoration of functional activity or mucosal digestive enzymes (83). The role of oral TGF-α to facilitate intestinal epithelial recovery following a rotavirus infection remains to be established in humans.

TGF-β has an important regulatory role in cell proliferation, migration and differentiation. An oral delivery system targeting TGF-β1 has been developed, and when given to rats, induces stem cell quiescence in the intestinal mucosal (84). The biological activities of TGF-β are mediated through a set of cell surface glycoproteins. The regulation of mechanisms controlling expression of TGF-β receptor subtypes may underlie the loss of effective growth regulation by TGF-β in transformed intestinal epithelial cells and in IEC-18 cell clones expressing *H-ras*. Although *H-ras* expression of IEC-18 cells causes resistance to TGF-β-mediated growth inhibition, the cells remain responsive to TGF-β1 stimulation of fibronectin expression (85).

Smooth muscle cells secrete TGF-β during human fetal intestinal development. TGF-β stimulates or inhibits the expression of specific collagen chains, depending on gestational age (86). TGF-α induces the syntheses of both *c-fos* and *c-myc* (87).

Motilin: Motilin is a 22 amino acid polypeptide that plays an important role in the initiation of phase III activity of the interdigestive migrating motor complex in dogs and in humans. Motilin-containing cells have been identified by immunocytochemical methods in the gastrointestinal tract of rabbits (88).

PYY: Fat slows the movement of luminal contents, and intestinal transit through a jejunal segment is slowed during fat profusion of the distal small intestine. This effect has been called the 'ileal break', and possible mediators of this effect include PYY, enteroglucagon and neurotensin. In dogs, the fat-induced ileal brake depends upon PYY (89). PYY increases following the ingestion of fatty meals, and PPY is released from the ileum and colon in increased amounts following intraileal and intracolonic administration of fatty acid. The ileal release of PYY in rats, either into the lumen or into the vasculature, is triggered by postganglionic cholinergic neurons via muscarinic receptors (90). PYY receptors are present in the synaptosomes of the submucosal and myenteric plexus (91). The proximal colon also triggers the feed-

back inhibition of gut motility through PYY, a phenomenon known as the 'colonic break' (92).

Substance P: Substance P is an 11-amino acid peptide belonging to the tachykinin family. Substance P-like immunoreactivity is present in nerve fibres of the intestine in the myenteric and submucosal plexus. Substance P may influence intestinal ion transport, in part by promoting the release of mast cell-derived mediators (93).

Serotonin: Serotonin (5-hydroxytryptamine [5-HT]) is involved in the production of diarrhea in patients with carcinoid syndrome. 5-HT plays a role in numerous physiological and pathological conditions, including gastrointestinal motility and transmural transport of fluid and electrolytes. 5-HT is localized mainly in the interneurons of the myenteric and submucosal plexi and in enterochromaffin cells. 5-HT acts on 5-HT_{2A} and 5-HT_{2C} receptors located on postsynaptic cholinergic neurons in the canine jejunum. They thereby stimulate phasic contractions and phase III activity (94). A selective 5-HT_4 receptor agonist, 5-methoxytryptamine, induces a concentration-dependent increase of 5-HT in rat ileum (95). Numerous 5-HT receptors have been cloned and characterized pharmacologically and by radioligand binding. All but one (5-HT_3) belong to the family of receptors coupled to guanine nucleotide-binding proteins. In human intestinal muscle cells, 5-HT_{2A} receptors mediate contraction and 5-HT_4 receptors mediate relaxation. These receptors are coexpressed (96). Once released, 5-HT acts as a local hormone or as a neurotransmitter acting on a number of different 5-HT receptors. The 5-HT_4 receptor is characterized on the basis of both agonist and antagonist activities, but the effect of 5-HT_4 receptor agonists varies among intestinal sites and animal species (97). 5-HT_4 receptors are not localized to cell bodies of afterhyperpolorization neurons of guinea pig ileum and are not coupled to presynaptic facilitation of noncholinergic slow excitatory postsynaptic potentials in afterhyperpolorization neurons (98).

IGF-I: IGF-I regulates the growth of the small bowel mucosa. IGF-I acts on intestinal crypt epithelial cells in culture to stimulate DNA synthesis and cell proliferation. Systemic administration of exogenous IGF-I increases small bowel mucosal mass in rats after proximal small bowel resection. IGF is also expressed locally within the small bowel, so it may act in an endocrine manner as well as in a paracrine or autocrine manner. Fasting decreases the circulating concentrations of IGF-I. A reduced trophic effect of circulating IGF-I may contribute to fasting-induced decreases in the mass of the intestinal mucosa. During fasting and refeeding, alterations in jejunal mass correlate with changes in serum IGF-I and jejunal IGF-I mRNAs (99). Only small amounts of IGF-I or recombinant human IGF-I are absorbed from the jejunum of neonatal calves (100).

The action of IGFs are modulated by IGF-binding proteins (IGF-BPs), of which six have been described. The profile of IGF-BP secretion changes with differentiation, and IGF-I, EGF or TGF-α stimulate different types of IGF-BP (101). Giving IGF-I for three days stimulates small intestinal epithelial proliferation in rats (102). Circulating and luminal insulin, and IGF-I interact with functional intestinal insulin receptors (IRs) and IGF-IRs. Rat jejunal IRs and IGF-IRs are differentially regulated by nutrient availability. Upregulation of jejunal IGF-I and IGF-IR expression during refeeding suggests a role for the IGF action pathway in gut trophic responses to enteral nutrients (103). IGFs have been studied in cell culture using IEC-6 cells (104), HT29-D4 human colonic carcinoma cells (105) and Caco-2 cells (106, 107). IGF-I also may play a role in colonic adaptation after massive intestinal resection (108). IGF-I administration after small bowel transplantation improves mucosal structure and absorptive function, and reduces bacterial translocation to mesenteric lymph nodes (109).

EGF acts as a competence factor, priming cells for the subsequent actions of IGF-I, thereby allowing IGF to be a progression factor acting as a proliferative agent on the cycling epithelial cell population (110).

Enteroglucagon: Intestinal mucosal epithelial cells adapt rapidly to changes in the quantity or composition of the diet. Enteroglucagon is likely involved in this process. This is a collective term for a small family of peptides derived from proglucagon by post-translational processing in the L-cells of the distal small intestine and colon. High levels of enteroglucagon in the plasma occur during intestinal adaptation after small bowel resection or during lactation, and there is an association between enteroglucagon-secreting tumours and intestinal hyperplasia in humans. Certain types of soluble nonstarch polysaccharides (dietary fibre) stimulate the release of enteroglucagon in rats. Fermentable carbohydrates elevate plasma enteroglucagon concentrations, but high viscosity is also necessary to stimulate small bowel mucosal proliferation (111).

Preproglucagon contains glucagon and two glucagon-like sequences, glucagon-like peptide (GLP)-1 and GLP-2. Glucose absorption is necessary for the secretion of GLP-1 from the isolated perfused canine ileum – the absorption of glucose stimulates the secretion of GLP-1 and appears to be closely related to SGLT1 (112).

The enteroglucagons oxyntomodulin and glicentin are peptides that are secreted from the L-cells of the small and large intestine. Both enteroglucagons contain the sequence of pancreatic glucagon. Oxyntomodulin has an additional six amino acids at the carboxyl terminus, whereas glicentin has the same carboxyl-terminal extension in addition to a 32-amino acid extension at the amino terminus. The enteroglucagons are thought to be regulators of adaptive growth of small bowel mucosa. Plasma enteroglucagon levels increase in situations of adaptive growth of the bowel mucosa, including following proximal small bowel resection. The rise in ileal proglucagon mRNA after proximal small bowel resection is not inhibited by difluoromethylornithine, so that the proglucagon-derived peptides are possible modulators of adaptive bowel growth that do not stimulate growth when ODC activity is inhibited (44).

Neuromedin: Neuromedin U (NmU) is an abundant peptide found in the enteric nervous system, which stimulates contraction of the human ileum. The cDNA encoding NmU

precursor in humans has been identified, and similar levels of mRNA are found throughout the gastrointestinal tract (113).

CCK: CCK is a 33-amino acid peptide produced in various molecular forms resulting from differences in post-translational processing of a single gene product. CCK is secreted from the intestine in response to ingestion of food, and food increases the rate of transcription of the CCK gene and stimulates CCK release in rats. Somatostatin inhibits dietary-stimulated CCK secretion, and lowers intestinal mRNA levels through a process that involves phosphoinositide and adenylate cyclase cascades mediating stimulated CCK secretion (114).

Migrating myoelectric complexes (MMCs) are dependent on the release of gastrointestinal hormones such as CCK. Exogenous polyamines disrupt intestinal MMCs, and stimulate colonic motility through a release of CCK acting at CCK-A and CCK-B receptors (115). Enteric bacterial overgrowth plays an important role in the development of intestinal barrier failure and bacterial translocation, and these adverse processes can be prevented in rats with surgically induced acute liver failure by infusing CCK (116).

Calcitonin gene-related peptid: Calcitonin gene-related peptide (CGRP) is present in the myenteric neurons of the gastrointestinal tract, and CGRP relaxes smooth muscle by way of the second messenger cAMP. CGRP receptors are not found on the smooth muscle cells but on myenteric nerves. CGRP relaxes longitudinal muscle of guinea pig ileum through its specific receptors and involves the generation of cAMP but not the generation of cyclic guanosine monophosphate (117).

VIP: VIP is distributed in neurons of the submucosal and myenteric plexus of the gastrointestinal tract, especially in close relationship to vascular and nonvascular smooth muscle and secretory components. VIP is released locally as a neurotransmitter, and its involvement, in combination with nitric oxide, in the nonadrenergic, noncholinergic relaxation of the gastrointestinal tract has been demonstrated. VIP is generally considered to be an inhibitory neural transmitter in the enteric nervous system, and intravenous VIP injection in rats decreases alanine absorption and water absorption, and impairs gastric acid secretion (118).

Prolactin and GH: Two adenohypophysial peptide hormones, prolactin (PRL) and GH, are thought to have evolved from a common ancestral gene. Receptors for PRL and GH (PRLRs and GHRs, respectively) show high homology to each other and belong to the GH/PRL/cytokine receptor superfamily. In the gastrointestinal tract GH promotes water and electrolyte transport and calcium absorption, and produces proliferation. PRL acts on water and electrolyte transport as well as on calcium absorption. Human, rabbit, and fetal and adult rat PRLRs and GHRs have been identified in intestinal mucosa and gastric glands (119). These hormones may have a regulatory role in digestive and immune functions. In vivo GH induces a rapid increase in the absorption rates of water, sodium, chloride and potassium, but in vitro serosal but not mucosal addition of GH induces a rapid decrease of transepithelial potential difference and of short-circuit current (120).

HIV-INFECTED DISEASE

Biliary abnormalities such as sclerosing cholangitis and acalculous cholecystitis are often described in AIDS patients. In only approximately 60% of patients is an infection with cryptosporidia or cytomegalovirus identified. Analysis of duodenal/bile juice is a simple, rapid and effective method for detection of enteropathogens in HIV-related gastrointestinal and biliary dysfunction (121). Changes in T lymphocytes subset distribution in the peripheral blood of patients infected with HIV have been studied extensively. The HIV burden may be higher in the intestine or in other lymphoid tissue then in peripheral blood. There is an early and preferential loss of duodenal CD4 T cells in HIV infection, and immunological abnormalities in HIV infection are distinct among lymphoid compartments (122).

The topic of gastrointestinal infections in the immunocomprimised host has been reviewed (123). About 50% of AIDs patients suffer from gastrointestinal infection, which may be symptomatic or asymptomatic. At some time during the course of HIV infection, 50% to 90% of patients develop diarrhea, and the associated weight loss may be devastating. In North American patients, there is no correlation between diarrhea, weight loss and CD4 counts, so that factors other than chronic diarrhea and immunosuppresion appear to be responsible for the weight loss in HIV-infected patients (124). Malabsorption, which has nutritional implications, relates more to immune suppression than to jejunal morphological changes (125).

Villous engorgement and hypertrophy explain the granular endoscopic appearance of intestinal mycrobacterium avium complex (126).

Chronic diarrhea in an AIDS patient, which is associated with bile acid malabsorption, may respond to cholestyramine (127).

MISCELLANEOUS POINTS

- Cryptogenic multifocal ulcerous stenosing enteritis may be related to a particular form of polyarteritis nodosa, with mainly intestinal expression of an unclassified and independent vasculitis (128).
- An increase of intraepithelial lymphocytes is commonly found in lymphocytic colitis and collagenous colitis. The immune abnormalities are similar in each of these conditions and are probably different from those that are implicated in celiac disease (129).
- Corticosteroids plus colchicine may be useful in the management of patients with idiopathic sclerosing mesenteritis (also called retractile mesenteritis, multifocal subperitoneal sclerosis) (130).
- Brown bowel syndrome is a rare condition characterized by deposition of lipofuscin in the smooth muscle cells of the gastrointestinal tract and may be associated with vitamin E deficiency (131).

- Cholesterol crystal embolization to the alimentary tract occurs most commonly in the colon in patients who present with abdominal pain, diarrhea and gastrointestinal blood loss (132).
- Malignant melanoma shows an unusual predilection to metastasize to the small intestine. There are two subsets of primary melanoma: one that occurs among younger patients and is more aggressive with rapid metastasis and early death; and one that occurs among older patients, is more indolent and metastasizes less rapidly (133). Mesenteric vein thrombosis may be associated with intestinal stricture (134).
- Whipple's disease is a chronic bacterial infection with intestinal and extraintestinal manifestations. Polymerase chain reaction (PCR) methodology has demonstrated the Whipple's disease bacterium to be *Trotheryma whippelii*. This PCR assay is specific and sensitive for diagnosis (135).
- The hydrogen breath test with D-xylose is a useful test for diagnosis of intestinal malabsorption but requires a 5 h monitoring period to be reliable (136). A dose of D-xylose 15 g rather than 25 g may be ideal (137).
- Push-type enteroscopy may be useful for the diagnosis of obscure small bowel lesions (138), including the diagnosis of obscure causes of gastrointestinal bleeding. Laparotomy with on table enteroscopy may also be useful to elucidate causes of obscure gastrointestinal bleeding (139).

ACKNOWLEDGEMENTS: The authors express their sincere appreciation to Mrs Chandra Strasbourg for her word processing assistance.

REFERENCES

1. Gutierrez ED, Grapperhaus KJ, Rubin DC. Ontogenic regulation of spatial differentiation in the crypt-villus axis of normal and isografted small intestine. Am J Physiol 1995;269:G500-11.
2. Trahair JF, Harding R. Restitution of swallowing in the fetal sheep restores intestinal growth after midgestation esophageal obstruction. J Pediatr Gastroenterol Nutr 1995;20:156-61.
3. Lovat LB. Age related changes in gut physiology and nutritional status. Gut 1996;38:306-9.
4. Evers BM, Izukura M, Rajaraman S, et al. Effect of aging on neurotensin-stimulated growth of rat small intestine. Am J Physiol 1994;267:G180-6.
5. Nakamura T, Matsuzaki G, Takimoto H, Nomoto K. Age-associated changes in the proliferative response of rat intestinal intraepithelial leukocytes to bacterial antigens. Gastroenterology 1995;109:748-54.
6. Schmucker DL, Heyworth MF, Owen RL, Daniels CK. Impact of aging on gastrointestinal mucosal immunity. Dig Dis Sci 1996;41:1183-93.
7. Saltzman JR, Kowdley KV, Perrone G, Russell RM. Changes in small-intestine permeability with aging. J Am Geriatr Soc 1995;43:160-4.
8. Ikuma M, Hanai H, Kaneko E, Hayashi H, Hoshi T. Effects of aging on the microclimate pH of the rat jejunum. Biochim Biophys Acta 1996;1280:19-26.
9. Nowak TV, Chey WW, Chang TM, Weisbruch JP, Fouquet G. Effect of streptozotocin-induced diabetes mellitus on release of vasoactive intestinal polypeptide from rodent small intestine. Dig Dis Sci 1995;40:828-36.
10. Zoubi SA, Williams MD, Mayhew TM, Sparrow RA. Number and ultrastructure of epithelial cells in crypts and villi along the streptozotocin-diabetic small intestine: a quantitative study on the effects of insulin and aldose reductase inhibition. Virchows Arch 1995;427:187-93.
11. Minocha A, Katragadda R, Rahal PS, Ries A. Erythromycin shortens orocaecal transit time in diabetic male subjects: a double-blind placebo-controlled study. Aliment Pharmacol Ther 1995;9:529-33.
12. Goldin E, Casadevall M, Mourelle M, et al. Role of prostaglandins and nitric oxide in gastrointestinal hyperemia of diabetic rats. Am J Physiol 1996;270:G684-90.
13. Schedl HP, Christensen KK, Ronnenberg WC. Effects of diabetes on calcium uptake by rat brush border membrane vesicles. Clin Exp Pharmacol Physiol 1995;22:272-6.
14. Escobar O, Sandoval M, Vargas A, Hempe JM. Role of metallothionein and cysteine-rich intestinal protein in the regulation of zinc absorption by diabetic rats. Pediatr Res 1995;37:321-7.
15. Charles F, Phillips SF. Effects of ethanol, xylose, and glucose on canine jejunal motility. Am J Physiol 1995;269:G363-9.
16. Tabata T, Meyer AA. Ethanol ingestion potentiates PMN migration into small intestine after ischemia. J Surg Res 1995;58:378-85.
17. Montes JF, Estrada G, Lopez-Tejero MD, Garcia-Valero J. Changes in the enterocyte cytoskeleton in newborn rats exposed to ethanol in utero. Gut 1996;38:846-52.
18. Rodriguez-Castilla J, Lopez-Nuevo M, Delgado MJ, Murillo ML, Carreras O. Changes in the ileal disaccharidase activities in rats after long-term ehthanol feeding. Alcohol Alcohol 1996;31:69-74.
19. Giannarelli S, Nano JL, Fournel S, Rampal P. Effect of enprostil and cimetidine on ethanol-induced damage to intestinal epithelial cell lines IRD 98 and IEC 17. Digestion 1995;56:509-15.
20. Rubio CA, Jalnas M. Dose-time-dependent histological changes following irradiation of the small intestine of rats. Dig Dis Sci 1996;41:392-401.
21. MacNaughton WK, Prudhomme-Lalonde L. Exposure to ionizing radiation alters vasoreactivity in rat jejunum in vivo. Can J Physiol Pharmacol 1995;73:699-705.
22. Otterson MF, Koch TR, Zhang A, Leming SC, Moulder JE. Fractionated irradiation alters enteric neuroendocrine products. Dig Dis Sci 1995;40:1691-702.
23. Yeoh E, Horowitz M, Russo A, Muecke T, Robb T, Chatterton B. Alimentary tract and pancreas: The effects of abdominal irradiation for seminoma of the testis on gastrointestinal function. J Gastroenterol Hepatol 1995;10:125-30.
24. Herrara JL, Vigneulle RM, Gage T, MacVittie TJ, Nold JB, Dubois A. Effect of radiation and radioprotection on small intestinal function in canines. Dig Dis Sci 1995;40:211-8.
25. Kirby DF, Delegge MH, Fleming CR. American Gastroenterological Association technical review on tube feeding for enteral nutrition. Gastroenterology 1995;108:1282-301.
26. Kudsk KA. Gut mucosal nutritional support enteral nutrition as primary therapy after multiple system trauma. Gut 1994;1:S52-4.
27. Messing B, Lemann M, Landais P, et al. Prognosis of patients with nonmalignant chronic intestinal failure receiving long-term home parenteral nutrition. Gastroenterology 1995;108:1005-10.
28. Lennard-Jones JE. Review article: practical management of the short bowel. Aliment Pharmacol Ther 1994;8:563-77.
29. Briet F, Flourie B, Achour L, Maurel M, Rambaud JC, Messing B. Bacterial adaptation in patients with short bowel and colon in continuity. Gastroenterology 1995;109:1446-53.
30. Chin BC, Tan DTM, Scott RB. Massive intestinal resection depresses circular smooth muscle contractility in the rat. Can J Physiol Pharmacol 1995;73:1443-50.
31. Johnson CP, Sarna SK, Zhu Y, et al. Delayed gastroduodenal emptying is an important mechanism for control of intestinal transit in short-gut syndrome. Am J Surg 1996;171:90-6.
32. Heyland DK, Cook DJ, Guyatt GH. Does the formulation of enteral feeding products influence infectious morbidity and mortality rates in the critically ill patient? A critical review of the evidence. Crit Care Med 1994;22:1192-202.
33. Scheppach W. Effects of short chain fatty acids on gut morphology and function. Gut 1994;1:S35-8.
34. Marsman KE, McBurney MI. Dietary fiber increases oxidative metabolism in coloncytes but not in distal small intestinal enterocytes isolated from rats. J Nutr 1995;125:273-82.
35. Chance WT, Zhang X, Balasubramaniam A, Fischer JE. Preservation

of intestine protein by peptide yy during total parenteral nutrition. Life Sci 1996;58:1785-94.
36. Li J, Kudsk KA, Gocinski B, Dent D, Glezer J, Langkamp-Henken B. Effects of parenteral and enteral nutrition on gut-associated lymphoid tissue. J Trauma 1995;39:44-51.
37. Marchbank T, Goodlad RA, Lee CY, Playford RJ. Luminal epidermal growth factor is trophic to the small intestine of parenterally fed rats. Clin Sci 1995;89:117-20.
38. Hodin RA, Saldinger P, Meng S. Small bowel adaptation: Counterregulatory effects of epidermal growth factor and somatostatin on the program of early gene expression. Surgery 1995;118:206-11.
39. Sacks AI, Warwick GJ, Barnard JA. Early proliferative events following intestinal resection in the rat. J Pediatr Gastroenterol Nutr 1995;21:158-64.
40. Adrian TE, Thompson JS, Quigley EMM. Time course of adaptive regulatory peptide changes following massive small bowel resection in the dog. Dig Dis Sci 1996;41:1194-203.
41. Thompson JS, Quigley EM, Adrian TE. Effect of intestinal tapering and lengthening on intestinal structure and function. Am J Surg 1995;169:111-9.
42. Park JHY, Vanderhoof JA. Growth hormone did not enhance mucosal hyperplasia after small-bowel resection. Scand J Gastroenterol 1996;31:349-54.
43. De Segura IAG, Aguilera MJ, Codesal J, Codoceo R, De-Miguil E. Comparative effects of growth hormone in large and small bowel resection in the rat. J Surg Res 1996;62:5-10.
44. Ulshen MH, Hoyt EC, Fuller CR, Ghatei MA, Bloom SR, Lund PK. Increased ileal proglucagon expression after jejunectomy in not suppressed by inhibition of bowel growth. Dig Dis Sci 1996;41:677-83.
45. Rubin DC, Swietlicki EA, Wang JL, Dodson BD, Levin MS. Enterocytic gene expression in intestinal adaptation: evidence for a specific cellular response. Am J Physiol 1996;270:G143-52.
46. Cynober L. Can arginine and ornithine support gut functions? Gut 1994;1:S42-5.
47. Younoszai MK, Parekh VV, Steophen TC, Hoffman JL. Relation of ornithine decarboxylase and tyrosine kinase activity in the jejunal mucosa in vivo. Proc Soc Exp Biol Med 1996;211:339-45.
48. Wang JY, Viar MJ, Blanner PM, Johnson LR. Expression of the ornithine decarboxylase gene in response to asparagine in intestinal epithelial cells. Am J Physiol 1996;271:G164-71.
49. Maury J, Nicoletti C, Guzzo-Chambraud L, Maroux S. The filamentous brush border glycocalyx, a mucin-like marker of enterocyte hyper-polarization. Eur J Biochem 1995;228:323-31.
50. Basson MD, Hong F, Emenaker NJ. Specific modulation of intestinal epithelial brush border enzyme expression by a phorbol ester. J Surg Res 1995;59:121-6.
51. Hauer-Jensen M, Skjonsberg G, Moen E, Clausen OPF. Intestinal morphology and cytokinetics in pancreatic insufficiency. Dig Dis Sci 1995;40:2170-6.
52. Sansonetti A, Romeo H, Berthezene P, et al. Developmental, nutritional, and hormonal regulation of the pancreatitis-associated protein I and III gene expression in the rat small intestine. Scand J Gastroenterol 1995;30:664-9.
53. Chianale J, Vollrath V, Wielandt AM, et al. Differences between nuclear run-off and mRNA levels for multidrug resistance gene expression in the cephalocaudal axis of the mouse intestine. Biochim Biophys Acta 1995;1264:369-76.
54. Kandil HM, Argenzio RA, Chen AW, et al. L-glutamine and L-asparagine stimulate ODC activity and proliferation in a porcine jejunal enterocyte line. Am J Physiol 1995;269:G591-9.
55. Vajanaphanich M, Schultz C, Tsien RY, Traynor-Kaplan AE, Randol SJ, Barrett KE. Cross-talk between calcium and cAMP-dependent intracellular signalling pathways. J Clin Invest 1995;96:386-93.
56. Hodin RA, Meng S, Shei A. Differential cloning of novel intestine-specific genes whose expression is altered under conditions of villus atrophy. J Surg Res 1995;59:115-20.
57. Sands BE, Ogata H, Lynch-Devaney K, deBeaumont M, Ezzell RM, Podolsky DK. Molecular cloning of the rat intestinal trefoil factor gene. J Biol Chem 1995;270:9353-61.
58. Thim L, Woldike HF, Nielsen PF, Christensen M, Lynch-Devaney K, Podolsky DK. Characterization of human and rat intestinal trefoil factor produced in yeast. Biochemistry 1995;34:4757-64.
59. Chinery R, Cox HM. Immunoprecipitation and characterization of a binding protein specific for the peptide, intestinal trefoil factor. Peptides 1995;16:749-55.
60. Chinery R, Cox HM. Modulation of epidermal growth factor effects on epithelial ion transport by intestinal trefoil factor. Br J Pharmacol 1995;115:77-80.
61. Stern M, Knauss M, Stallmach A. Crypt-villus differentiation reflected by lectin and protein binding to rat small intestinal brush border membranes. Dig Dis Sci 1995;40:2439-45.
62. Davis TA, Burrin DG, Fiorotto ML, Nguyen HV. Protein synthesis in skeletal muscle and jejunum is more responsive to feeding in 7- than in 26-day-old pigs. Am J Physiol 1996;270:E802-9.
63. Clark MA, Jepson MA, Hirst BH. Lectin binding defines and differentiates M-cells in mouse small intestine and cecum. Histochem Cell Biol 1995;104:161-8.
64. Sharma R, Schumacher U. The influence of diets and gut microflora on lectin binding patterns of intestinal mucins in rats. Lab Invest 1995;73:558-64.
65. Sharma R, Schumacher U. Morphometric analysis of intestinal mucins under different dietary conditions and gut flora in rats. Dig Dis Sci 1995;40:2532-9.
66. Sharma R, Schumacher U, Ronaasen V, Coates M. Rat intestinal mucosal responses to a microbial flora and different diets. Gut 1995;36:209-14.
67. Zushi S, Shinomura Y, Kiyohara T, et al. Role of prostaglandins in intestinal epithelial restitution stimulated by growth factors. Am J Physiol 1996;270:G757-62.
68. Eberhart CE, Dubois RN. Eicosanoids and the gastrointestinal tract. Gastroenterology 1995;109:285-301.
69. Simmons JG, Hoyt EC, Westwick JK, Brenner DA, Pucilowska JB, Lund PK. Insulin-like growth factor-I and epidermal growth factor interact to regulate growth and gene expression in IEC-6 intestinal epithelial cells. Mol Endocrinol 1995;9:1157-65.
70. Potten CS, Owen G, Hewitt D, et al. Stimulation and inhibition of proliferation in the small intestinal crypts of the mouse after in vivo administration of growth factors. Gut 1995;36:864-73.
71. Savidge TC, Walker-Smith JA, Phillips AD. Novel insights into human intestinal epithelial cell proliferation in health and disease using confocal microscopy. Gut 1995;36:369-74.
72. Bardocz S, Grant G, Ewen SWB, et al. Reversible effect of phytohemagglutinin on the growth and metabolism of rat gastrointestinal tract. Gut 1995;37:353-60.
73. Wang J-Y, McCormack A, Viar MJ, Johnson LR. Inhibition of ornithine decarboxylase activity but not expression of the gene by cimetidine in intestinal mucosal cells. J Pharmacol Exper Ther 1995;274:521-9.
74. Dignass AU, Stow JL, Babyatsky MW. Acute epithelial injury in the rat small intestine in vivo is associated with expanded expression of transforming growth factor a and b. Gut 1996;38:687-93.
75. Playford RJ. Peptides and gastrointestinal mucosal integrity. Gut 1995;37:595-7.
76. Bishop WP, Lin J, Stein CA, Krieg AM. Interruption of a transforming growth factor a autocrine loop in Caco-2 cells by antisense oligodeoxynucleotides. Gastroenterology 1995;190:1882-9.
77. Purushotham KR, Offenmuller K, Bui AT, et al. Absorption of epidermal growth factor occurs through the gastrointestinal tract and oral cavity in adult rats. Am J Physiol 1995;269:G867-73.
78. Ulshen MH, Raasch RH. Luminal epidermal growth factor preserves mucosal mass of small bowel in fasting rats. Clin Sci 1996;90:427-31.
79. Thompson JF, Van Den Berg M, Stokkers PCF. Developmental regulation of epidermal growth factor receptor kinase in rat intestine. Gastroenterology 1994;107:1278-87.
80. Bishop WP, Wen JT. Regulation of Caco-2 cell proliferation by basolateral membrane epidermal growth factor receptors. Am J Physiol 1994;267:G892-900.
81. Sayegh M, Elder JB. Effect of gonadectomy on epidermal growth factor values in the gastrointestinal tract of male and female CD-1 mice. Gut 1995;36:558-63.
82. Polk DB. Shc is a substrate of the rat intestinal epidermal growth factor receptor tyrosine kinase. Gastroenterology 1995;109:1845-51.
83. Rhoads JM, Ulshen MH, Keku EO, et al. Oral transforming growth factor-α enhances jejunal mucosal recovery and electrical resistance in piglet rotavirus enteritis. Pediatr Res 1995;38:173-81.
84. Puolakkainen PA, Ranchalis JE, Gombotz WR, Hoffman AS, Mumper RJ, Twardzik DR. Novel delivery system for inducing quiescence in intestinal stem cells in rats by transforming growth factor β1. Gastroenterology 1994;107:1319-26.
85. Zhao J, Buick RN. Regulation of transforming growth factor β

receptors in H-ras oncogene-transformed rat intestinal epithelial cells. Cancer Res 1995;55:6181-8.
86. Perr H, Oh P, Johnson D. Developmental regulation of transforming growth factor β-mediated collagen synthesis in human intestinal muscle cells. Gastroenterology 1996;110:92-101.
87. Oliver BL, Sha'afi RI, Hajjar JJ. Transforming growth factor-α and epidermal growth factor activate mitogen-activated protein kinase and its substrates in intestinal epithelial cells. Proc Soc Exp Biol Med 1995;210:162.
88. Satoh M, Sakai T, Koyama H, Shiba Y, Itoh Z. Immunocytochemical localization of motilin-containing cells in the rabbit gastrointestinal tract. Peptides 1995;16:883-7.
89. Lin H, Zhao X-T, Wang L. Fat absorption is not complete by midgut but is dependent on load of fat. Am J Physiol 1996;271:G62-7.
90. Fujimiya M, Miyazaki M, Fujimura M, Kimura H. Effect of carbachol on the release of peptide YY from isolated vascularly and luminally perfused rat ileum. Peptides 1995;16:939-44.
91. Mao YK, Wang YF, Ward G, Cipris S, Daniel EE, McDonald TJ. Peptide YY receptor in submucosal and myenteric plexus synaptosomes of canine small intestine. Am J Physiol 1996;271:G36-41.
92. Wen J, Phillips SF, Sarr MG, Kost LJ, Holst JJ. PPY and GLP-1 contribute to feedback inhibition from the canine ileum and colon. Am J Physiol 1995;269:G945-52.
93. Wang L, Stanisz AM, Wershil BK, Galli SJ, Perdue MH. Substance P induces ion secretion in mouse small intestine through effects on enteric nerves and mast cells. Am J Physiol 1995;269:G85-92.
94. Graf S, Sarna SK. 5-HT-induced jejunal motor activity: enteric locus of action and receptor subtypes. Am J Physiol 1996;270:G992-1000.
95. Minami M, Tamakai H, Ogawa T, et al. Chemical modulation of 5-HT_3 and 5-HT_4 receptors affects the release of 5-hydroxytryptamine from the ferret and rat intestine. Res Commun Mol Pathol Pharmacol 1995;89:131-42.
96. Kuemmerle JF, Murthy KS, Grider JR, Martin DC, Makhlauf GM. Coexpression of 5-HT_{2A} and 5-HT_4 receptors coupled to distinct signaling pathways in human intestinal muscle cells. Gastroenterology 1995;109:1791-800.
97. McLean PG, Coupar IM, Molenaar P. A comparative study of functional 5-HT_4 receptors in human colon, rat oesophagus and rat ileum. Br J Pharmacol 1995;115:45-56.
98. Pan H, Galligan JJ. Effects of 5-HT_{1A} and 5-HT $_4$ receptor agonists on slow synaptic potentials in enteric neurons. Euro J Pharmacol 1995;278:67-74.
99. Winesett DE, Ulshen MH, Hoyt EC, Mohapatra NK, Fuller CR, Lund PK. Regulation and localization of the insulin-like growth factor system in small bowel during altered nutrient status. Am J Physiol 1995;268:G631-40.
100. Vacher P-Y, Bestetti G, Blum JW. Insulin-like growth factor I absorption in the jejunum of neonatal calves. Biol Neonate 1995;68:354-67.
101. Oguchi S, Walker WA, Sanderson IR. Profile of IGF-binding proteins secreted by intestinal epithelial cells changes with differentiation. Am J Physiol 1994;267:G843-50.
102. Steeb CB, Trahair JF, Read LC. Administration of insulin-like growth factor-I (IGF-I) peptides for three days stimulates proliferation of the small intestinal epithelium in rats. Gut 1995;37:630-8.
103. Ziegler TR, Almahfouz A, Pedrini MT, Smith RJ. A comparison of rat small intestinal insulin and insulin-like growth factor I receptors during fasting and refeeding. Endocrinology 1995;136:5148-54.
104. Corkins MR, Vanderhoof JA, Slentz DH, MacDonald RG, Park JHY. Growth stimulation by transfection of intestinal epithelial cells with an antisense insulin-like growth factor binding protein-2 construct. Biochem Biophys Res Commun 1995;211:707-13.
105. Remacle-Bonnet M, Garrouste F, El Atiq F, Marvaldi J, Pommier G. Cell polarity of the insulin-like growth factor system in human intestinal epithelial cells. J Clin Invest 1995;96:192-200.
106. Zhang Y, Wick DA, Seetharam B, Dahms NM. Expression of IGF-II and IGF binding proteins in differentiating human intestinal Caco-2 cells. Am J Physiol 1995;269:E804-13.
107. Oguchi S, Walker A, Sanderson IR. Differentiation and polarity alter the binding of IGF-I to human intestinal epithelial (Caco-2) cells. J Pediatr Gastroenterol Nutr 1995;20:48-55.
108. Mantell MP, Ziegler TR, Adamson WT, et al. Resection-induced colonic adaptation is augmented by IGF-I and associated with upregulation of colonic IGF-I mRNA. Am J Physiol 1995;269:G974-80.
109. Zhang W, Frankel WL, Adamson WT, et al. Insulin-like growth factor-I improves mucosal structure and function in transplanted rat small intestine. Transplantation 1995;59:755-61.
110. Duncan MD, Korman LY, Bass BL. Epidermal growth factor primes intestinal epithelial cells for proliferative effect of insulin-like growth factor I. Dig Dis Sci 1994;39:2197-201.
111. Gee JM, Finglas-Lee W, Wortley GW, Johnson IT. Fermentable carbohydrates elevate plasma enteroglucagon but high viscosity is also necessary to stimulate small bowel mucosal cell proliferation in rats. J Nutr 1996;126:373-9.
112. Manaka H, Sugiyama K, Fukase N, et al. GLP-1(7-36amide) Secretion from isolated perfused canine intestine is coupled with Na^+/glucose cotransporter. Biomed Res 1995;16:311-7.
113. Austin C, Lo G, Nandha KA, Meleagros L, Bloom SR. Cloning and characterization of the cDNA encoding the human neuromedin U (NmU) precursor: NmU expression in the human gastrointestinal tract. J Mol Endocrinol 1995;14:157-69.
114. Liddle RA. Regulation of cholescystokinin synthesis and secretion in rat intestine. J Nutr 1994;124:1308S-14S.
115. Fioramonti J, Fargeas M-J, Bertrand V, Pradayrol L, Bueno L. Induction of postprandial intestinal motility and release of cholecystokinin by polyamines in rats. Am J Physiol 1994;267:G960-G5.
116. Wang X, Soltesz V, Axelson J, Andersson R. Cholecystokinin increases small intestinal motility and reduces enteric bacterial overgrowth and translocation in rats with surgically induced acute liver failure. Digestion 1996;57:67-72.
117. Sun Y-D, Benishin CG. Effects of calcitonin gene-related peptide on cyclic AMP production and relaxation of longitudinal muscle of guinea pig ileum. Peptides 1995;16:293-7.
118. Nassar CF, Abdallah LE, Barada KA, Atweh SF, Saade NE. Effects of intravenous vasoactive intestinal peptide injection on jejunal alanine absorption and gastric acid secretion in rats. Regul Pept 1995:55:261-7.
119. Nagano M, Chastre E, Choquet A, Bara J, Gespach C, Kelly PA. Expression of prolactin and growth hormone receptor genes and their isoforms in the gastrointestinal tract. Am J Physiol 1995;268:G431-42.
120. Guarino A, Canani RB, Iafusco M, Casola A, Russo R, Rubino A. In vivo and in vitro effects of human growth hormone on rat intestinal ion transport. Pediatr Res 1995;37:576-80.
121. Franzen C, Salzberger B, Fatkenheuer G, et al. Stimulated duodenal/bile juice aspiration for diagnosis of enteric pathogens in HIV-infected patients. J Clin Gastroenterol 1995;21:33-7.
122. Shneider BL, Dawson PA, Christie DM, Hardikar W, Wong MH, Suchy FJ. Cloning and molecular characterization of the ontogeny of a rat ileal sodium-dependent bile acid transporter. J Clin Invest 1995;95:745-54.
123. Janoff EN, Smith PD. Gastrointestinal infections in the immunocompromised host. Curr Opin Gastroenterol 1996;12:95-101.
124. Mosavi AJ, Hussain MF, DuPont HL, Mathewson JJ, White AC Jr. Lack of correlation between diarrhea and weight loss in HIV-positive outpatients in Houston, Texas. J Clin Gastroenterol 1995;21:61-4.
125. Keating J, Bjarnason I, Somasundaram S, et al. Intestinal absorptive capacity, intestinal permeability and jejunal histology in HIV and their relation to diarrhea. Gut 1995;37:623-9.
126. Cappell MS, Philogene C. The endoscopic appearance of severe intestinal mycrobacterium avium complex infection as a coarsely granular mucosa due to massive infiltration and expansion of intestinal villi without mucosal exudation. J Clin Gastroenterol 1995;21:323-6.
127. Steuerwald M, Bucher HC, Muller-Brand J, Gotze M, Roser HW, Gyr K. HIV-enteropathy and bile acid malabsorption: response to cholestyramine. Am J Gastroenterol 1995;90:2051-3.
128. Perlemuter G, Chaussade S, Soubrane O, et al. Multifocal stenosing ulcerations of the small intestine revealing vasculitis associated with C_2 deficiency. Gastroenterology 1996;110:1628-32.
129. Mosnier J-F, Larvol L, Barge J, et al. Lymphocytic and collagenous colitis: an immunohistochemical study. Am J Gastroenterol 1996;91:709-13.
130. Genereau T, Bellin M-F, Wechsler B, et al. Demonstration of efficacy of combining corticosteroids and colchicine in two patients with idiopathic sclerosing mesenteritis. Dig Dis Sci 1996;41:684-8.
131. Drake WM, Winter TA, Price SK, O'Keefe SJD. Small bowel intussusception and brown bowel syndrome in association with severe malnutrition. Am J Gastroenterol 1996;91:1450-2.

132. Moolenaar W, Lamers CBHW. Cholesterol crystal embolisation to the alimentary tract. Gut 1996;38:196-200.
133. Elsayed AM, Albahra M, Nzeako UC, Sobin LH. Malignant melanomas in the small intestine: a study of 103 patients. Am J Gastroenterol 1996;91:1001-6.
134. Eugene C, Valla D, Wesenfelder L, et al. Small intestinal stricture complicating superior mesenteric vein thrombosis. A study of three cases. Gut 1995;37:292-5.
135. Herbay AV, Ditton HJ, Maiwald M. Diagnostic application of a polymerase chain reaction assay for the Whipple's disease bacterium to intestine biopsies. Gastroenterology 1996;110:1735-43.
136. Casellas F, Malagelada J-R. Clinical applicability of shortened D-xylose breath test for diagnosis of intestinal malabsorption. Dig Dis Sci 1994;39:2320-6.
137. Carlson S, Craig RM. D-xylose hydrogen breath tests compared to absorption kinetics in human patients with and without malabsorption. Dig Dis Sci 1995;40:2259-67.
138. Davies GR, Benson MJ, Gertner DJ, Van Someren RMN, Rampton DS, Swain CP. Diagnostic and therapeutic push type enteroscopy in clinical use. Gut 1995;37:346-52.
139. Lewis MPN, Khoo DE, Spencer J. Value of laparotomy in the diagnosis of obscure gastrointestinal hemorrhage. Gut 1995;37:187-90.