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REVIEW ARTICLE

Small Bowel Review
Normal Physiology Part 2

A.B.R. THOMSON, MD, PhD,* M. KEELAN, PhD,* A. THIESEN, MD,* M.T. CLANDININ, PhD,* M. ROPELESKI, MD,† and G.E. WILD, MD, PhD†

In the past year there have been many advances in the area of small bowel physiology and pathology and therapy. In preparation for this review, over 1500 papers were assessed. The focus is on presenting clinically useful information for the practising gastroenterologist. Selected important clinical learning points include the following: (1) numerous peptides are being identified which stimulate the proliferation and functional response of the small intestine to disease or resection, and may in time find a clinical use; (2) under usual *in vivo* conditions, absorption of nutrients has little effect on the paracellular movement of water; (3) the permeability of the intestine is modified by the function of the tight junctions, and measuring intestinal permeability may be useful to reflect the presence of disease; (4) the release of serotonin is influenced by cholinergic, adrenergic, and nonadrenergic, noncholinergic mechanisms, and serotonin agonists and antagonists may play an important future role in the treatment of motility disorders; (5) the use of endothelin receptor antagonists may be useful for the treatment of intestinal anaphylaxis; (6) the alterations in intestinal pH and motility in patients with Crohn's disease may influence the action of pH- or time-dependent release medications; and (7) patients with irritable bowel syndrome may also have abnormalities in gastric and small intestinal motility.

KEY WORDS: small bowel; functional response; absorption; permeability; motility.

ADAPTATION

After resection of a portion of the small intestine, the remaining intestine undergoes an adaptive response resulting in an increased rate of crypt cell production and enhanced villus length and crypt depth. This ultimately leads to augmented absorptive capacity in the remnant adaptive gut. Luminal factors, hormones, growth factors, and neural and vascular substances may be involved in initiating the adaptive responses. There is a specific enterocytic component to the adaptive response, with the increased expression of several enterocytic genes in the remnant intestine. The method of subtractive hybridization has been used to isolate a cDNA that is differentially expressed in the remnant rat ileum after massive small bowel resection. This cDNA encodes a putative protein of 254 amino acids that is highly homologous to triosephosphate isomerase (1). Triosephosphate isomerase expression is also detected by reverse transcription–polymerase chain reaction (RT-PCR) in the normal ileum and pancreas, and its presence one week after massive small bowel resection raises the possibility that it may be important in the maintenance of the intestinal adaptive response.

The topics of neural injury, repair, and adaptation of the gastrointestinal tract have been reviewed (2–4). Depending on the animal species studied, the larger and more proximal the intestinal resection is, the greater the adaptive changes. Following initial resec-

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From the *Cell and Molecular Biology Collaborative Network in Gastrointestinal Physiology, Nutrition and Metabolism Research Group, Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; and †Division of Gastroenterology and Department of Anatomy and Cell Biology, McGill University, Montreal, Quebec, Canada.

Address for reprint requests: Dr. Alan B.R. Thomson, 519 Newton Research Building, University of Alberta, Edmonton, Alberta, Canada.

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tion in rats, the crypt cell proliferation index is unchanged. Brush border membrane disaccharidases in the remaining small intestine show decreased specific activities, possibly due to an expansion of an immature enterocyte population. This functional defect is largely compensated for by an increased mucosal mass. The morphologic adaptation in dogs and rabbits appears to be similar to that seen in rats. In pigs following a 75% proximal resection, there is macroscopic enlargement, increased height and depth of the villi and crypts in the remaining small bowel and unchanged crypt cell proliferation, with decreased specific but not total activities of maltase and sucrase–isomaltase (5). In the porcine ileum after a 75% proximal resection there is a decreased number and intensity of vasoactive intestinal peptide (VIP)-immunoreactive fibers in the mucosa and circular muscle, decreased galanin immunoreactivity in the circular muscle, and inhibition of the age-associated increase in enkephalin-immunoreactive nerve fibers (6). Following intestinal resection there is increased activity of the sodium dependent glucose transporter in the brush border membrane (SGLT1), associated with increased SGLT1 mRNA identified using RT-PCR (7).

Octreotide is a long-acting synthetic octapeptide of the naturally occurring hormone somatostatin. Although octreotide inhibits the secretion of potentially trophic hormones such as insulin-like growth factor-1 (IGF-1), it does not inhibit intestinal adaptation after massive small bowel resection (8).

The enteric nervous system is derived from the vagal, rostral–truncal, and sacral levels of the neural crest. The enteric neurons are supported by glia, which resemble astrocytes. The crest-derived population that colonizes the bowel contains multipotent cells, and terminal differentiation is presumed to occur in the intestine (9). After a massive small bowel resection, there are changes in the neuropeptide-containing innervation of the remaining small intestine. The number and intensity of VIP-immunoreactive fibers in the mucosa and circular muscle layer fall markedly after resection, gliadin immunoreactivity follows the circular muscle layer, and the number of enkephalin-immunoreactive fibers also fall (6). The authors suggest that these findings are compatible with altered motor activity and mucosal function in the remaining intestine.

Enteric nutrient availability is a major regulator of intestinal growth. Enteral nutrition directly delivers nutrients to mucosal cells and increases pancreatic–biliary secretions, gut neuronal activity, peristalsis, and splenic blood flow. Enteric nutrition also increases the production of several endogenous gut-trophic growth hormones such as growth hormone, insulin, IGF-1, epidermal growth factor (EGF), glucagon-like peptide-2 (GLP-2), and keratinocyte growth factor. Keratinocyte growth factor prevents the atrophy of duodenal and ileal mucosa during hypocaloric refeeding (10). EGF up-regulates the expression of mRNA and protein for its own intestinal receptor in mice *in vivo*, but the beneficial effect of EGF during adaptation is likely caused by other factors in addition to increased EGF receptor expression (11).

Seven days after intestinal resection there is increased intestinal IGF-I mRNA in the jejunum and ileum, up-regulation of IGF binding protein-4 (IGFBP-4) mRNA, and increased IGFBP-3 mRNA (12). Administration of recombinant IGF-I modestly increases ileal but not jejunal growth.

The immediate early gene, PC4/TIS7, mRNA levels are markedly increased at 16 and 48 hr but not one week after a 70% small intestinal resection in the rat (13). PC4/TIS7 is associated with the villus and may play a role in regulating cytodifferentiation. PC4/TIS7 mRNA and protein levels are increased during the early differentiation phase, and PC4/TIS7 is translocated from the cytoplasm to the nucleus. It may initiate cellular differentiation after the withdrawal of proliferating cells from the cell cycle.

Clinical Learning Point: Numerous peptides are being identified that stimulate the proliferation and functional response of the small intestine to disease or resection, and may in time find a clinical use.

The number of organisms in the jejunum is normally approximately 10^5 organisms/ml of aspirate, and they consist primarily of gram-positive aerobes. In the distal small intestine there are 10^7–10^8 organisms/ml, both aerobes and anaerobes. The intestinal microflora in dogs changes after a 50% proximal or distal resection, and the presence of an intact ileocecal junction protects against the proliferation of a flora which is characteristic of the distal intestine (14).

Hepatic failure develops in 3–19% of children with short bowel syndrome acquired in the neonatal period; in addition, cholestasis occurs in 30–60% of them. Exposure to intravenous nutrition is not a sufficient explanation for the development of the cholestasis and subsequent liver failure. A retrospective chart review of 42 patients at a single institution with neonatal small intestinal resection requiring parenteral nutrition for at least three months demonstrated that the duration of dependence on parenteral nutrition was longer in noncholestatic than in cholestatic patients progressing to liver failure. Bacterial infec-

tion early in life characterized the cholestatic patients (15).

Total parenteral nutrition is a safe and effective method to deliver nutrients to patients with the short bowel syndrome. For patients with short bowel syndrome on home parenteral nutrition, a quarter of the patients die within five years, a quarter are able to terminate home parenteral nutrition, and the others survive with home parenteral nutrition (16). However, total parenteral nutrition dependence causes significant impairment in the quality of life, whereas small intestinal transplantation restores the quality of life among recipients with functioning grafts (17). The absorptive function of the intestine is relatively well preserved following small intestinal transplantation (18). Total parenteral nutrition is associated with a loss of epithelial integrity and bacterial translocation. Pretreatment of epithelial cells with transforming growth factor-β_1 (TGF-β_1) prevents the increase of intestinal permeability seen with interferon-γ (IFN-γ). Intraepithelial lymphocyte may be responsible for the mediation of these cytokine responses (19). Transplantation of intestinal crypt cells and the epithelial–mesenchymal unit on biodegradable scaffolds survive, proliferate, and regenerate small cystic structures lined with intestinal mucosa (20). It is premature to determine if this technique may be adapted to patients with a short bowel syndrome.

Other new therapeutic possibilities for treating patients with short bowel syndrome include optimizing nutritional support and the use of growth-stimulating factors. The effects of growth hormone are mediated mainly by insulin-like growth factors I and II (IGF-I and IGF-II). Glutamine may enhance cell survival under stressful conditions by enhancing the stress response. Glutamine supplementation reduces heat-shock-induced cell death in rat intestinal epithelial cells (21). A glutamine-enriched diet and IGF-I independently stimulate adaptive hyperplasia in small bowel-resected rats.

The increase in peptide tyrosine–tyrosine and enteroglucagon in the portal blood after intestinal resection supports their hormonal role in the postresectional adaptive process. The increase in IGF-II in the ileal mucosa, without changes in the plasma, implies autocrine or paracrine growth stimulation after resection (22). Cholylsarcosine, a synthetic conjugated bile acid, improves fat absorption in patients with short bowel syndrome and increases the body weight gain (23).

Following a distal intestinal resection, the presence of an intact ileocecal junction protects against the proliferation of a bacterial flora characteristic of the distal intestine (24). In small bowel resected patients, the colon serves as a digestive organ for medium-chain fatty acids (24). Medium-chain fatty acids may be used to supplement the diet of patients with short bowel syndrome, but only those with a colon will benefit (24).

PERMEABILITY

The topic of the G protein diseases has been reviewed (25), as has the topic of epithelial cell adhesion in gastrointestinal homeostasis (26). Permeability refers to the ability of small molecules to penetrate the gastrointestinal mucosa. Under normal physiological circumstances Na^+–nutrient cotransport does not enhance paracellular permeability in unrestrained, unanesthetized, chronically catheterized rats (27). This is in contrast to the observations made using *in vitro* preparations.

Clinical Learning Point: Under usual *in vivo* conditions, absorption of nutrients has little effect on the paracellular movement of water.

The tight junctions are an important part of the intestinal barrier. The tight junctions are dynamic structures, and their barrier function may be modulated by nutrients such as glucose and amino acids, as well as by bacterial toxins and chemotaxins. Sodium caprate, a constituent of milk fat, increases tight junction permeability in rats (28). This raises the possibility that there may be numerous physiological constituents that modify intestinal permeability. Adenosine triphosphate (ATP) depletion induced by glycolytic inhibition or cellular hypoxia increases the permeability of intestinal epithelial monolayers by an intracellular ionized Ca^{2+}-dependent mechanism in which Ca^{2+} comes from the extracellular milieu via a mechanism unrelated to voltage-dependent Ca^{2+} channel (29). The barrier function is influenced by immune-derived factors such as IFN-γ and tumor necrosis factor-α (TNF-γ) and inhibition of TNF-α using neutralizing antibody or thalidomide reverse hypoxia-evoked changes in permeability in monolayer (30).

Clinical Learning Point: The permeability of the intestine is modified by the function of the tight junctions, and measuring intestinal permeability may be useful in determining the presence of disease.

Fibrosing colonopathy occurs in young children with cystic fibrosis treated with high doses of pancreatic enzymes. In rats with increased intestinal permeability in response to oleic acid or to reserpine, there is a potentiation of the intestinal damage caused by pancreatic enzymes (31).

Loss of the intestinal barrier function is associated with translocation of enteric bacteria in rodents, but in humans bacterial translocation is not associated with increased intestinal permeability or villous atrophy (32). Failure of the barrier from intestinal or biliary obstruction, immunosuppression, hemorrhagic shock, multiple trauma, or burn injury may contribute to the pathogenesis of systemic infections and may lead to the systemic inflammatory response syndrome. Endotoxin, a lipopolysaccharide found in the outer cell wall of gram-negative bacteria, may trigger the events that culminate in systemic inflammatory response syndrome. However, pure lipopolysaccharide does not pass across the intestinal mucosa in rats *in vitro*. The passage of lipopolysaccharide across the mucosa *in vivo* may be due to the release of bacterial cell wall fragments from killed bacteria (33).

Some drugs also alter intestinal permeability. Immunosuppression with tacrolimus uncouples mitochondrial oxidative phosphorylation and increases intestinal permeability. In humans, tacrolimus inhibits cellular energy production sufficiently to cause endotoxemia and impaired intestinal absorptive capacity (34). The topic of nonsteroidal antiinflammatory drug (NSAID) -induced gastrointestinal permeability has been reviewed (35). NSAIDs increase intestinal permeability in animals and in humans. In patients taking different NSAIDs for over six months, there is malabsorption of actively and passively absorbed sugars, and intestinal permeability is increased (35). An early event after the ingestion of NSAIDs is increased intestinal permeability, which can be reversed by administration of exogenous prostaglandins. Prostaglandins (PG) I_2 and E_2 have a synergistic role in restoring electrical transepithelial resistance in ischemia-injured porcine ileum via the second messengers Ca^{2+} and cAMP. The prostaglandin-associated recovery of transepithelial resistance occurs via the induction of Cl^- secretion and inhibition of Na^+ absorption, possibly by establishing a transmucosal osmotic gradient (36). TNF-α is increased following the ingestion of indomethacin. The TNF-α production is associated with the onset of macroscopic ulcerations of the small intestine and precedes nitrite production and tissue activity of myeloperoxidase (37). The administration of an inhibitor of TNF-α synthesis reduces ulcerations in the small intestine, as well as TNF-α and nitrite production.

The amino acid glutamine is the principal fuel used by the intestinal mucosa, where it accounts for approximately one third of the total metabolic requirements of the enterocytes. A lack of glutamine promotes mucosal atrophy and increases intestinal permeability. Indomethacin-induced ileitis, ulceration, and microcirculatory disturbances are reduced by the oral administration of glutamine (38). Glutamine deprivation induces apoptosis in rat intestinal epithelial cells (39). Total parenteral nutrition decreases luminal mucous gel and increases small intestinal permeability, but the addition of alanyl glutamine in total parenteral nutrition prevents these changes (40). Curiously, the use of an oral glutamine supplement does not restore the enteric permeability of the intestine seen in patients with Crohn's disease (41).

Apoptosis (programmed cell death) is characterized by cellular shrinkage, loss of normal cell-to-cell contacts, dense chromatin condensation, budding, phagocytosis, and small double-stranded fragments of DNA. The antitumor drug doxorubicin increases apoptosis of the intestine in rats, and this is associated with increased permeability of the intestinal barrier (42).

The normally greater intestinal permeability in young infants is enhanced further in the presence of necrotizing enterocolitis. Early feeding is associated with the reduction of permeability, feeding human milk versus formula decreases permeability, and antinatal steroid administration also decreases permeability in preterm infants (43). The polyamine, spermine, in higher concentrations enhances intestinal permeability, whereas lower concentrations of spermine result in a decrease in permeability (44). Ethanol has no effect on intestinal permeability, whereas acetaldehyde reversibly increases paracellular permeability of Caco-2 cell monolayers (45). While intestinal permeability is often measured with two sugars such as lactulose and mannitol, polyethyleneglycol may also be of use to assess passive diffusion across the membrane (31).

The assessment of intestinal permeability using the differential excretion of lactulose and mannitol, or comparable dual sugar markers, is useful clinically to evaluate the presence of intestinal damage. Urine is routinely collected for 5–6 hr after the ingestion of the two test sugars, but it is possible that the urine collection time may be shortened to 1–2 hr (46). Gastroduodenal permeability is increased in patients with Crohn's disease, and this may be predictive of histological damage in the upper gastrointestinal tract (47). Permeability is also increased during the induction treatment and the cytopenic period of the treatment of patients with acute myeloid leukemia (48). Intestinal permeability is increased in patients who are malnourished (49). In patients undergoing resection of upper gastrointestinal malignancy, intestinal

permeability is increased in the first postoperative day (50). There is an incremental decrease in urinary D-xylose recoveries in HIV-infected asymptomatic subjects, symptomatic subjects without body weight loss and/or diarrhea, and those with AIDS, but an increase in intestinal permeability is only found in the latter group (51).

BRUSH BORDER MEMBRANE

Spermine administered orally to neonatal rats induces the secretion of corticosterone and adrenocorticotrophic hormones. Spermine given to neonatal rats increases IL-1β, IL-6 and TNF-α plasma concentrations, and IL-1 given intraperitoneally increases the specific activity of sucrase-isomaltase in the small intestine. The intraperitoneal injection of IL-1β and IL-6 increase the spermine and spermidine content, and these cytokines also increase corticosterone secretion. This suggests that spermine may induce postnatal intestinal development and corticone secretion through a cytokine-dependent mechanism (52).

Homeobox genes, a new class of protooncogene, encode nuclear transcription factors involved in patterning and cell differentiation. Homeobox genes themselves are regulated by other homeobox genes, and the *Cdx2* homeobox gene is important in extracellular matrix-mediated intestinal cell differentiation (53). The level of the *Cdx1* and *Cdx2* homeobox gene expression is influenced by epithelial-mesenchymal cell interactions in the intestinal mucosa (54).

Polyamines are essential for early mucosal restitution *in vivo* and cell migration *in vitro* by a process that involves actin and myosins (55). The transcription factor activator protein 1 (AP-1) integrates various mitogenic signals; the activated AP-1 dimer binds to DNA at a consensus AP-1 site in the responsive regions of the gene promoter and regulates the transcriptional activity of AP-1 dependent genes. Jun protein is required for the functioning of the AP-1 transcription factors. Polyamines may influence cell growth by altering the balance of the positive and negative protooncogene Jun/AP-1 activities in epithelial cells (56).

Differentiating cells may produce molecules that act by a negative feedback loop on cell growth (chalones, inhibitors of cell division that are produced by differentiated cells but act on proliferating cells). A protein named intestinal antiproliferative factor has been isolated from human small intestine (57). This 120-kDa protein displays no homology with other known proteins, and the growth inhibitory effect of intestinal antiproliferative factor is maximal between mid-G_1 and early S phases.

There are eight different mucin genes and MUC2, MUC4, and MUC5AC are differently expressed in fetal intestine compared with expression in normal adults (58). MUC2 is the first secretory mucin gene to be cloned and sequenced. The primary function of the MUC2 gene product is to provide a protective barrier between the epithelial surfaces and the gut lumen (59).

MORPHOGENESIS, GROWTH, AND DEVELOPMENT

The topic of the biology of inherited disorders of the gastrointestinal tract has been reviewed by Martin (60); the topic of growth factors in the gastrointestinal tract has been reviewed by Murphy (61); and topic of the dietary regulation of genes expressed in the developing intestinal epithelium has been reviewed by Sanderson (62). The topics of the biology of regeneration and repair and growth control mechanisms in normal and transformed intestinal cells has been reviewed (63), as-well-as growth factors and gut function (64); and epithelial integrity, cell death, and cell loss in mammalian small intestine also have been reviewed (65).

Epidermal growth factor (EGF) and TGF-α enhance the proliferation and/or differentiation of epithelial cells. Both EGF and TGF-α have high affinity for the epidermal growth factor receptor, a transmembrane glycoprotein with tyrosine-specific protein kinase activity. Transforming growth factor-α mRNA levels are 10-fold higher than EGF mRNA in the small intestine of suckling rats (66). Steady-state mRNA levels result from a balance between the rates of mRNA transcription and mRNA degradation. The high levels of TGF-α mRNA accompanied by high degradation of the same RNA suggest a rapid turnover of intestinal TGF-α mRNA.

Five isoforms of TGF-β have been identified in this multifunctional polypeptide growth factor. TGF-β_2 but not TGF-β_1 is detected in the postnatal milk of rats. Their level declines in the first weeks of life, whereas the cell number and intensity of staining of TGF-β1 peptide in the small intestine increases markedly towards day 19 (67). The regulation of extracellular signal-regulated kinase (ERK) activation may be an important switch responsible for terminal differentiation of the components of the crypt–villus unit. The catalytic activity of most known protein kinases is regulated posttranscriptionally by a

protein–protein interaction and/or by phosphorylation. A new human serine–threonine protein kinase gene, h-sgk (the human homolog of the previously described rat serum- and glucocorticoid-regulated protein kinase) is modified during isotonic and isotonic alterations in cell volume. In the normal ileum, h-sgk mRNA is localized to the apical villus enterocytes. The crypts express h-sgk mRNA, and this immediate early gene is expressed in spacial correlation to TGF-β_1 protein (68). Protein kinase C-α but not other isoforms of protein kinase C may modulate the proliferation and differentiation of Caco-2 cells by a process which may involve p21wafl, a cyclin-dependent kinase inhibitor (69).

Mucosal T cells promote intestinal epithelial proliferation, and the level of soluble IL-2 receptor peaks during early infancy (70). TGF-α is a ligand for the EGF receptor. Overproduction of TGF-α in the mouse duodenal epithelium results in a pronounced increase in crypt epithelial cell proliferation, and an increase in the dimension of the crypt/villous unit (71). Anchored stem cells are located in the crypts of Lieberkühn and give rise to proliferating daughter cells that differentiate into four major intestinal epithelial cell types. These include enterocytes, enteroendocrine and goblet cells, as well as Paneth cells. Cellular differentiation occurs coincident with migration from the stem cell/proliferative region onto the villus or to the base of the crypts. Direct cell–cell contact between mesenchyme and endoderm is required for epithelial morphogenesis and cellular differentiation.

Insulin is also thought to be a growth regulatory factor for intestinal epithelial cells, and specific insulin receptors are expressed on the epithelial cell surface. The regulation of the proliferation of intestinal epithelial cells is an early step in the differentiation of these cells and may be caused by the sequential effects of IGF-I, insulin, and TGF-β1 (72). Among the regulatory peptides are TGF-β, IL-1, IL-6, IL-8, TNF, and IFN-γ.

Intestinal epithelial cell proliferation *in vitro* and *in vivo* are also stimulated by IGF-I and IGF-II, hepatocyte growth factor, and by members of the fibroblast growth factor family including keratinocyte growth factor. The growth-promoting effect of hepatocyte growth factor in fibroblasts and fibroblast-conditioned media is blocked with the use of anti-human hepatocyte growth factor neutralizing antibodies (73). Hepatocyte growth factor is important in the formation of the intestinal lumen, and the *forkhead* family of transcription factors are important mesenchymal genes. Epimorphin is another candidate mesenchymal morphogenetic factor. This is a membrane-associated protein that may play a role in the morphogenesis of the crypt–villus axis (74).

During the third week of postnatal life in the rat, important ontogenic changes occur in the small intestine, including alterations in the activity of glucosidases and aminopeptidases. Between postnatal life and adulthood there is a shift from sialylation to fucosylation in the brush border membrane and basolateral plasma membranes of the epithelial cells, and in brush border membrane glycoproteins and mucins. Glucocorticoids, thyroid hormones, and/or insulin play a role in intestinal maturation, and circulating insulin levels increase at weaning in parallell with α-1,2-fucosyltransferase activity. This suggests that the changes in insulin levels at weaning may be responsible for the regulation of the glycoprotein fucosylation process, essentially by increasing fucosyltransferase activity (75).

IGF-I is an important anabolic protein. During infection hepatic IGF-I output falls but intestinal IGF-I uptake is completely suppressed, so that because of these reciprocal changes the splanchnic production of IGF-I is unchanged (76). Six human IGFBPs have been identified, sequenced and cloned. This family of proteins, which has no sequence homology with the IGF-I receptor, functions as modulators of IGF-I actions. The expression and time-dependent production of some of these IGFBPs, and their regulation by endogenous TGF-β_1, represent mechanisms by which human intestinal muscle cells regulate autocrine IGF-I-mediated growth (77).

Keratinocyte growth factor is a member of the fibroblast growth factor family. Keratinocyte growth factor mRNA and peptide are produced by mesenchymal tissue, and the keratinocyte growth factor receptor is expressed by epithelial cells. Keratinocyte growth factor increases the intestinal weight in conjunction with plasma concentrations of gastrin, peptide YY, enteroglucagon, and GLP-1. Following proximal resection in the dog, the proximal intestinal motor response is decreased, whereas after distal resection there are transient increases in neurotensin and peptide YY (78). These differences may contribute to the inferior nutritional and absorptive outcome associated with resection of the distal as compared with the proximal intestine. Intestinal morphogenesis during differentiation is achieved by the cross-talk between the epithelium and the underlying mesenchyme during both fetal and adult growth life (79). The mesenchyme supports the growth and differenti-

ation of the adjacent epithelia that cannot undergo normal development in the absence of mesenchyme-derived cells. Mesenchyme–epithelial signaling plays a role in the establishment of regional specificity during intestinal development.

The rat homolog of epimorphin (syntaxin 2) belongs to a family of integral membrane proteins that function in the docking and fusion of vesicles. In fetal rat intestine epimorphin/syntaxin 2 mRNA levels are increased in the fetal gut during the formation of the lumen and morphogenesis of the villus. They are suppressed in the early stages of intestinal adaptation after small bowel resection (74), illustrating differences in the adaptive mechanisms included in ontogeny and following intestinal resection.

Mesenchymal cells and their adult derivatives, the pericryptal and subepithelial myofibroblasts, are separated from the epithelium by a specialized sheetlike extracellular matrix, the basement membrane. In humans and as well as in experimental animals, the intestinal basement membrane is composed of components produced from both the epithelium and the mesenchyme (80). TGF-α is a strong promotor, and TGF-β1 is a potent inhibitor of intestinal epithelial growth. TGF-β1 inhibits the synthesis of cyclin D_1 in gut epithelial cells, and this causes the TGF-β_1-mediated arrest of intestinal epithelial cell proliferation (81). Tumor necrosis factor causes a decrease in IGF-1 and IGFBP-3 mRNA levels in malnourished rats (82).

Cell proliferation in the intestinal mucosa is dependent upon the supply of polyamines to the dividing cells. Intracellular polyamine levels are regulated, depending on the activation or inhibition of ornithine decarboxylase (ODC). ODC is the first rate-limiting step in polyamine biosynthesis. ODC catalyses the conversion of ornithine to putrescine, the diamine precursor of spermidine and spermine. An increase in ODC activity is parallelled by increases in newly synthesized polyamines, which occur in concert with increases in the expression of a number of early response genes. Exposure of intestinal epithelial-6 cells, a line of normal rat small intestinal crypt cells, to EGF, gastrin or asparagine increases ODC activity, ODC mRNA, and protein levels (1). EGF and gastrin stimulate transcription of the ODC gene, whereas asparagine affects the posttranscriptional process.

The diamine, putrescine, and the polyamines spermidine and spermine are low-molecular-weight cationic molecules that influence cell proliferation and differentiation. Intestinal epithelial cells are exposed to polyamines from the diet, are synthesized by the intestinal microflora, are secreted in bile, and are derived from dead cells. Both human and rat milk, but neither bovine milk nor infant formula, contain sufficient bioactive polyamines to sustain cell growth during inhibition of polyamine synthesis (83). The intestinal brush border membrane contains at least three sites for specific polyamine binding and exhibits different ligand selectivity (84). Spermine provided subcutaneously, interperitoneally, or intravenously does not induce the same changes that are observed in the intestine when the polyamine is provided orally, indicating the possible presence of a mechanism using brush border membrane receptors. Dietary spermine induces all the morphological and biochemical modifications characterizing the intestinal postnatal maturation in a suckling rat, suggesting a role of the polyamines in the naturally occurring processes (85).

AP-1, a transcription factor composed of Fos and Jun family proteins, plays an important role in cellular growth and differentiation. Fos/Jun protein heterodimers play important roles in maintaining the epithelial mesenchymal interactions (86). Glial-derived neurotrophic factor is important for the maintenance of the adult enteric nervous system (87). Monitor peptide (pancreatic secretory trypsin inhibitor, PSTI-61) has been identified in the rat small intestine, where it stimulates cholecystokinin secretion and may stimulate the growth of intestinal epithelial cells (88).

Apoptosis at the luminal surface may be influenced by cell-to-contact, cell-to-extracellular matrix attachment, extracellular matrix composition, integrin expression, short-chain fatty acids, and cytokines. Detachment-induced cell death is a form of apoptosis in intestinal epithelial cells. Caspases, a family of proteolytic enzymes, play a role in initiating, amplifying, and executing apoptosis (89). The cytokines IL-1β and IL-6 increase the rate of apoptosis in Caco-2 cells, and preinduction of a heat-shock response can protect against cytokine or lipopolysaccharide-induced apoptosis (90).

The repair of mucosal defects in the gastrointestinal tract involves rapid migration (restitution) to reestablish epithelial continuity, as well as proliferation to replace destroyed intestinal epithelial cells. Three distinct mitogen-activated protein kinases have been identified. Within 5 min after injury of monolayers of intestinal epithelial-6 cells, ERK1 (extracellular signal-regulated kinase) and c-Jun-N-terminal protein kinase are also activated. The activation of ERK1 and ERK2 is partially inhibited by neutralizing anti-TGF-α (91). Tyrosine phosphorylation influences dif-

ferentiation in Caco-2 cells. There are likely two or more independent enzymes or pathways regulating tyrosine phosphorylation in the differentiation of the intestinal epithelium (92). Sodium butyrate is a differentiating agent, and in intestinal epithelial-6 cells butyrate induces the liver-type but not the intestinal-type of alkaline phosphatase activity within the cytosol (93).

The topic of the folding of secretory and membrane proteins has been reviewed (94). The absorptive and secretory functions of the intestine demonstrate heterogeneity of their characteristics with regard to segmental, spatial, and cellular polarization, as well as their response to various agonists (95).

Glutamine and glucose are important fuels for the enterocytes, and the metabolic fate of the glutamine carbon is a function of the rate at which glutamine carbon enters the tricarboxylic acid cycle (96). Selenium-dependent glutathione peroxidase is an antioxidant enzyme. Extracellular glutathione peroxidase is present in the small and large intestine in humans as well as in mice, and presumably protects the intestinal tract from peroxidative damage and/or intercellular metabolism of peroxides (97).

MOTILITY

Intestinal motility is regulated by ascending excitatory and descending inhibitory refluxes that modulate the activity of intestinal circular muscle. These motility refluxes may include a role for acetylcholine, tachykinins, 5-hydroxamine, nitric oxide, and VIP.

Electrical control activity in the gastrointestinal smooth muscle layers provides coordination in time and space of contractions by providing a window of opportunity for contractions if conditions are appropriate. The rhythmic nature of the transmembrane voltage has been modeled as a population of coupled relaxation oscillators. The interface between the circular and longitudinal muscles is the myenteric plexus, which contains nerve cells and interstitial cells of Cajal (ICC). Electrical fields produced during depolarization as well as low resistance pathways through gap junctions are electrical coupling mechanisms that coordinate electrical control activity in the smooth muscle. Small gap junctional conductances are effective for the coupling of smooth muscle, and field coupling is most efficacious when the ellipsoidal cells are coupled side by side and when cylindrical cells are coupled end to end (98).

Intestinal pacemaker activity is manifested by electrical slow wave activity that is generated in most gastrointestinal smooth muscle layers. The ICC are involved in the pacemaker activity associated with Auerbach's plexus in the stomach and small intestine and with the submuscular plexus in the colon. ICC are involved in setting the frequency and propagation characteristics of contraction activity of the circular smooth muscle of the stomach, small intestine, and colon. ICC express c-Kit receptor and are the pacemakers of intestinal peristalsis. The gene product of c-Kit is a receptor tyrosine kinase. There are four types of ICC, which are heterogeneous in ultrastructure, c-Kit dependency, and functional role (99). Stem cell factor is a ligand for Kit. Neurons expressing stem cell factor have been identified in the small intestine and may be important for the development of Kit-expressing ICC (100). W/W^v mice possess a mutant Kit gene, and lack ICC associated with Auerbach's plexus. The normal slow-wave-controlled peristalsis in the proximal small intestine occurs upon gastric emptying, and this motor pattern is absent in the w/w^v mice (101).

The inhibitory control of the intestinal smooth muscle may be mediated indirectly via the ICC and inhibitory nerve fibers containing VIP and nitric oxide synthase. ICC have immunoreactivity for the neurokinin I receptor, and this relationship is likely functional (102). Only small amounts of inhibitory neurotransmitters such as VIP are present in these motor neurons. In contrast, in intestinal circular muscle, excitatory cholinergic/tachykinin neurons and inhibitory motorneurons express or coexpress VIP, pituitary adenylate cyclase-activating polypeptide, and nitric oxide synthase. Thus, relaxation of circular muscle is mediated by the inhibitory neurotransmitters VIP and pituitary adenylate cyclase-activating polypeptide, as well as by nitric oxide generated in both nerve terminals and smooth muscle cells.

VIP- and pituitary adenylate cyclase-activating polypeptide neurons as well as cholinergic neurons exert a stimulatory or tonic inhibitory effect on the release of serotonin into the intestinal lumen (103). Serotonin release is influenced by cholinergic, adrenergic, and nonadrenergic, noncholinergic mechanisms. Nitric oxide inhibits the release of serotonin from enterochromatin cells by the release of an enteric neurotransmitter other than acetylcholine or substance P (104). Nitric oxide is a major nonadrenergic, noncholinergic neurotransmitter, and the inhibition of serotonin outflow by nitric oxide is due to the activation of soluble guanylyl cyclase.

The mechanisms by which the inhibitory cellular effects are mediated include either direct effects of

nitric oxide on cellular structures such as the stimulation of ion channels or activation of protein kinase C, or effects mediated by a stimulation of soluble guanylyl cyclase. cGMP-dependent protein kinase-1 is present in circular and longitudinal muscle, muscularis mucosa, smooth muscle cells of the villi, and fibroblastlike cells of the small intestine (105). Nitric oxide and adrenergic, dopaminergic, and somatostatinergic mechanisms cooperate in inhibiting the migrating myoelectric complex (MMC) after nociceptive stimulation of the peritoneum (106).

Endogenous nitric oxide tonically activates soluble gyanylyl cyclase in myenteric neurons, which leads to the inhibition of the release of the excitatory transmitter acetylcholine and substance P (107). Nitric oxide is synthesized on demand from L-arginine when nerve stimulation leads to an increase in the intraneuronal calcium concentration to activate nitric oxide synthase. Nitrergic myenteric neurons are equipped with $GABA_A$ receptors, which mediate the inhibition of nitric oxide synthesis (108). Interdigestive pancreatic secretion cycles in close association with the phases of the migrating motor complex (MMC) and release of regulatory hormones. This is tightly coordinated with the release of pancreatic polypeptide and motilin, as well as with gastric antral motor activity (109).

The pacemakers are modulated by nitric oxide from nonadrenergic, noncholinergic nerves, and possibly from the ICC themselves. The ICC pacemakers of the myenteric plexus and of the deep muscular plexus utilize gap junction conductances for pacemaker function. Coupling between the myenteric plexus and the deep muscular plexus ICC networks may utilize the circular muscle syncytium (110). Nitric oxide is an important inhibitory nonadrenergic, noncholinergic neurotransmitter in the small intestine, and nitric oxide release causes relaxation of the smooth muscle.

Neuronal nitric oxide synthase expression in the myenteric plexus is independent of the vagus nerve and is negatively regulated by the splanchnic nerves in the rat small intestine (111). There are three forms of nitric oxide synthase, two of which are constitutively expressed in neurons (neuronal nitric oxide synthase or nitric oxide synthase-I) and in endothelial cells (nitric oxide synthase-III), as well as inducible nitric oxide synthase (nitric oxide synthase-II). There are two types of neuronal nitric oxide synthase in the rat small intestine. These two neuronal nitric oxide synthase enzymes exhibit different subcellular locations and possible functions (112). Descending interneurons with immunoreactivity with nitric oxide synthase provide 14% of inputs to somatostatin-immunoreactive descending interneurons in guinea pig small intestine (113). Smooth muscle nitric oxide synthase is inactivated by protein kinase C. Endothelial nitric oxide synthase is expressed in human intestinal smooth muscle cells (114). Mature smooth muscle myocytes retain the developmental potential to dedifferentiate into proliferative, migratory, and synthetic smooth muscle myoblasts.

Isoactin is a molecular marker of smooth muscle development. Primary cultures of intestinal smooth muscle cells (ISMCs) recapitulate a portion of their *in vivo* myogenic program *in vitro*. This provides the methodology to study molecular mechanisms controlling smooth muscle myogenesis (115). As well, mechanical or chemical stimulation of the mucosa will illicit the peristaltic reflex. The oral phase of the peristaltic reflex consists of the contraction of circular muscle and the reciprocal relaxation of longitudinal muscle. The caudad phase of the peristaltic reflex consists of relaxation of the circular muscle and contraction of the longitudinal muscle.

The tachykinins, substance P, neurokinin A, neuropeptide Y, and neuropeptide γ, are contained in enteric neurons that provide extensive networks of terminals around nerve cell bodies in the intrinsic ganglia, in the muscle, as well as in the mucosa of the intestine (116). Together, they mediate neuroneuronal and neuromuscular transmission, and the cellular actions are brought about by three receptors that are expressed by intestinal nerve and muscle. Substance P and neurokinin A are excitatory cotransmitters of cholinergic enteric neurons whose actions are mediated by neurokinin-1, -2, and -3 receptors. Only the neurokinin-1 and -2 receptors sustain intestinal peristalsis when cholinergic neuroneuronal and neuromuscular transmission via muscarinic receptors has been suppressed (117). The tachykinins acting via neurokinin-1 receptors mediate transmission to inhibitory motor neurons, whereas neurokinin-3 receptors play a role in the transmission from intrinsic sensory neurons and from ascending interneurons to excitatory motor neurons (118).

Neurokinin-A is present in the excitatory motor neurons of the enteric nervous system. Neurokinin-A increases duodenal mucosal bicarbonate secretion by a process that is independent of neurons, may be mediated by prostanoids, and may be suppressed by mucosal nerves utilizing VIP as one of the transmitters (119).

Tachykinins excite muscle, increase blood flow and

secretion, and excite nerve cells. There are three tachykinin receptors; neurokinin-1, -2, and -3. Neurokinin-1 receptor-immunoreactive nerve cells occur in the majority of nitric oxide synthase-immunoreactive inhibitory motor neurons, in choline acetyltransferase (ChAT)/tachykinin-immunoreactive excitatory neurons to the circular muscle, in all ChAT/neuropeptide Y/somatostatin-immunoreactive secretomotor neurons, in a small proportion of ChAT/calbindin myenteric neurons, and in about 50% of ChAT/tachykinin submucosal neurons (120). Enteric glia play an essential role in maintaining the integrity of the bowel and depletion of the astroglial cells in mice results in fulminating and fatal jejuno-ileitis (121).

The topic of neuroregulation of gastrointestinal smooth muscle and the importance of G-protein-coupled receptors has been reviewed (122). Relaxation of the gastrointestinal smooth muscle is mediated by nonadrenergic, noncholinergic inhibitory mechanisms in which possible mediators include ATP, VIP, and nitric oxide. Nitric oxide stimulates ion channels, activates protein kinase C, and stimulates soluble guanylyl cyclase. The selective cGMP-dependent protein kinase (cGK) colocalizes with neuronal nitric oxide synthase, and cGK-1 may be involved in nitric oxide-induced relaxation of gastrointestinal smooth muscle (112).

The peristaltic reflex induced by mucosal stimuli is mediated by intrinsic sensory calcitonin gene-related peptide (CGRP) neurons activated by serotonin released from enterochromatin cells. A selective serotonin 4 antagonist applied to the mucosa in low concentration is capable of stimulating the peristaltic reflex in humans (123). CGRP induces relaxation of circular and longitudinal intestinal smooth muscle cells, with cAMP being involved in cells of both layers while nitric oxide is involved in the relaxation of circular cells (124). This may have some role to play in the future treatment of motility disturbances.

Clinical Learning Point: The release of serotonin is influenced by cholinergic, adrenergic, and nonadrenergic, noncholinergic mechanisms, and serotonin agonists and antagonists may play an important future role in the treatment of motility disorders.

Most food antigen-induced allergic reactions in the gastrointestinal tract are mediated by a type 1 IgE and a mast cell-dependent hypersensitivity response. Food protein-induced anaphylaxis alters gastrointestinal motility by a process that involves mast cells, substance P, and capsaicin-sensitive afferent nerves. Mast cell granulation with anaphylaxis is associated with alterations in motility as well as diarrhea. The mast cell degranulation occurs only at the site of direct challenge, yet the motility is altered both locally and in intestinal segments distant from the challenge. This remote response requires intact extrinsic but not necessarily vagal neural pathways (125).

After anaphylactic challenge there is increased expression of inducible nitric oxide synthase in peritoneal macrophages, and this process involves increased expression in mRNA coding for the p50 subunit of NF-κB transcriptor factor. Delayed-type hypersensitivity reactions in the small intestine of the rat can be reduced by depleting or stabilizing mucosal mast cells. Mucosal mast cell activation involves sensory neurons (126). Degranulation of mast cells is associated with the release of mediators such as histamine, serotonin and eicosanoid, leading to altered intestinal permeability, transport and motility.

Mucosal mast cells are degranulated by endogenous cholecystokinin release through the stimulation of cholecystokinin-B receptors (127). Proglumide, a cholecystokinin receptor antagonist, prevents amphetamine-induced inhibition of gastric emptying and the decrease in gastrointestinal transit. Selected cholecystokinin-A and cholecystokinin-B antagonists reverse the inhibitory effect of amphetamine on gastrointestinal transit (128).

Endothelin is a potent endothelium-derived contracting factor of which there are three isopeptides and two receptors. In a rat model of intestinal anaphylaxis mucosal concentrations of endothelin-1 and endothelin-3, as well as the expression of their mRNAs, were increased. Treatment with an endothelin$_A$-receptor antagonist but not an endothelin$_B$-receptor antagonist attenuates the anaphylaxis-associated increase in intestinal water flux, histamine release, and serum concentration of rat mast cell protease II (129).

Clinical Learning Point: The use of endothelin receptor antagonists may be useful for the treatment of intestinal anaphylaxis.

IGFs are trophic in the small intestine, where they act on mesenchymal cells in the lamina propria. IGF-II is a potent autocrine mitogen for intestinal fibroblasts and interacts with other fibroblast-derived growth factors and the extracellular matrix to stimulate the proliferation of intestinal epithelial cells in a paracrine manner (130). IGF-I activates an IGF-I receptor as well as the phosphatidylinositol (PI) 3-kinase and mitogen-activated protein kinase pathways. IGF-I receptors are present in the mucosal and muscle layers of the gastrointestinal tract. In human in-

testinal smooth muscle cells IGF-I activates distinct PI 3-kinase and MAP kinase signaling pathways, which act in conjunction to mediate growth (131).

The main products of proglucagon are glicentin and oxyntomodulin, as well as GLP-1 and glucagon. GLP-1 inhibits gastric emptying and small intestinal transit through an indirect effect by central or enteric nerves (132). Octreotide induces a phase III-like activity front in the small intestine and reduces the postprandial antral motility index (133). Intestinal segments from patients with neonatal necrotizing enterocolitis show an absence of immunoreactive VIP and nitric oxide synthase in the submucosal plexus and within the circular muscle layer. This suggests that nonadrenergic, noncholinergic inhibitory innervation may contribute to the functional obstruction seen in these patients (134).

The nonadrenergic, noncholinergic inhibitory neurotransmission in the gut is constituted by nitrergic and purinergic pathways. Nitric oxide is thought to be the nitrergic neurotransmitter (135). Nitric oxide is generated from the amino acid L-arginine and may also act as a neuromodulator by the inhibition of the release of other neurotransmitters within the same nerve ending or as a neurotransmitter acting on enteric neurons or smooth muscle cells of the gastrointestinal tract. Nitric oxide may act as a second messenger within smooth muscle or ICC.

Immunohistochemical studies have revealed a β_3-adrenoreceptor in vascular and nonvascular smooth muscle of the human gastrointestinal tract (136). Stimulation of this receptor causes relaxation and may play a role in the control of blood flow and motility.

Unabsorbed fat or protein in the ileum delays the passage of material through the small intestine by a process that has been referred to as the "ileal brake," which may be influenced by neurotensin, peptide tyrosine–tyrosine, and GLP-1. The brake increases the transit time in the small intestine, and activation of the ileal brake by oleic acid slows the transit of tablets through the small intestine (137). Glucose and peptone are potent stimulants of neurotensin, peptide tyrosine–tyrosine, and GLP-1 release, whereas only neurotensin is released with oleic acid stimulation (138). After the ingestion of protein there is a slowing of intestinal transit, but acceleration of ileocolonic transit (139). There is a matching between gastric emptying and nutrient absorption in order to avoid an overload on the capacity for the absorption of nutrients. After meals, the stomach empties equal amounts of energy despite large variations in meal composition. There is a close relationship between the energy-dependent absorption of nutrients and the energy-dependent feedback inhibition of gastric emptying (140).

Opioids have been used to alleviate diarrheal disorders. The δ-opioid receptor-mediated neuromodulation underlies the antipropulsive and antisecretory effects of opioids in the intestinal tract (141). The effect of opiates is mediated in part by δ-opioid receptors that are localized in neurons within the myenteric and submucosa ganglia, longitudinal and circular smooth muscle, and villous lamina propria (141). There appears to be an inhibitory pathway mimicking somatostatin, opioid and GABA neurons that regulate VIP interneurons, which in turn regulate tachykinins and probably cholinergic motoreurons (142).

In the *Trichinella spiralis*-infected guinea pig model, there are disturbances in small intestinal motility. There may be excitation–transcription-coupled changes in enteric neural microcircuits (143). There are T-cell-dependent and -independent components of the muscle response to this nematode infection in the mouse (144).

Infection with the nematode parasite *T. spiralis* suppresses the release of acetylcholine from the myenteric plexus of the rat jejunum. Up-regulation of major steps in the synthetic pathway for acetylcholine is not matched by increased production, suggesting that there may be inflammation-related defects in acetylcholine packaging, storage, and granule exocytosis (145). The intrinsic primary afferent neurons are cholinergic (146). Histamine may act as a mediator in mast cell-to-afferent nerve communication in the small intestine (147). The myenteric plexus meshwork and density of ganglion cells in the myenteric plexus decreases with age during the first three to four years of life (148).

Clinical Learning Point: The alterations in intestinal pH and motility in patients with Crohn's disease may influence the action of pH- or time-dependent release medications.

In rats with nematode-induced inflammation there is increased brain expression of c-fos in the caudal nucleus of the solitary tract and lateral parabrachial nucleus on day 1 and in the medial part of the nucleus of the solitary tract, LPB and L ceruleus on day 7, indicating specific and different brain nuclei are activated at the onset of pulmonary and intestinal inflammation (149). Endotoxemia causes dose-dependent changes in jejunal transit and absorption in rats (150),

possibly as a result of increases in the inducible and constitutive forms of nitric oxide synthase.

In patients with Crohn's disease having previously undergone ileocecal resection, the small intestinal transit time is shorter and the pH in the cecum is 0.9 pH units higher than in controls (151). Motor disorders were observed in the small intestine of 26 of 35 patients with inactive Crohn's disease, with reduced phase II contractions and increased incidence of propagated single and clustered contraction (152).

In the fasting state the motility of the stomach and small intestine is characterized by a cyclic pattern of contractions, the MMC. The MMC has an important role as the "intestinal housekeeper-", and the MMC is divided into three phases: phase I—motor quiescence, phase II—irregular contractile activity, and phase III—contractions at their maximum frequency and amplitude. The duration of the MMC cycle and the duration of phases I, II, and III depend on their place of origin. For example, a phase III of "antral" origin is almost twice as long as a phase III originating from the duodenum (153).

Enteral nutrition is usually administered through nasogastric or nasoenteric feeding tubes. In patients with gastric retention who are at risk of regurgitation and pulmonary aspiration, feeding is given by way of a nasoenteric tube. However, this may result in abdominal cramps, distension, and diarrhea, possibly as the result of the more rapid contraction of the gallbladder and acceleration of the small bowel transit time (154).

The abdominal prevertebral ganglia behave as true integrative nervous centers interposed between the central nervous structures and the muscular effectors. Moreover, the preganglionic neurons give a tonic drive to the postganglionic neurons, which, in turn, exert a permanent control on gut functions. Nitric oxide is involved in neuroneuronal and neuromuscular neurotransmission in the enteric nervous system, as well as in the extrinsic level of nerve control over gastrointestinal motility. Nitric oxide is involved in the nervous control exerted by the superior mesenteric ganglion over the ileal contractile activity (155).

The methods used to measure gastrointestinal motility have been reviewed (156). Scintigraphy is used to evaluate gastric motor function. Manometry is used to identify patterns suggestive of myopathy, neuropathy, or obstruction. Electrogastrography may identify dysrythmias or failure of signal power to increase postprandially. There may be substantial variability among subjects in the measurement of antral–duodenal and small bowel manometry, but there are no differences between males and females or between the duodenum and jejunum (157). A novel portable perfused manometric system for recording small intestinal motility has been described (158).

In hypertrophic ileum there is increased expression of VIP, pituitary adenylate cyclase-activating peptide, and galanin, presumably as part of an adaptive response to the increased work load. Neonates with intestinal pseudoobstruction have been reported in which the intestine showed a lack of ICC (159). At a later time, when their ileostomies were closed to restore intestinal continuity, repeat biopsies of the intestine showed a normal pattern of distribution of ICC. This suggests that a delay in the development of ICC in the gastrointestinal tract may be a cause of intestinal pseudoobstruction in the newborn.

Small intestinal motility, and in particular the interdigestive MMC, has a regulatory mechanism to prevent small bacterial overgrowth. The MMC is characterized by a typical cycling complex of myoelectrical activity consisting of three phases: phase I, myoelectrical quiescence; phase II, irregular myoelectrical activity; and phase III, a regular, aboral migrating cluster of intense myoelectrical spiking activity. The disruption of the MMC with morphine promotes duodenal bacterial overgrowth and bacterial translocation (160).

Gastrointestinal motility disorders are common in patients with diabetes mellitus. Orocecal transit time is prolonged, the small intestinal motor activity is abnormal, and there may be resistance to the flow of the contents from the stomach. This gastrointestinal dysmotility may be due to the presence of diabetic autonomic neuropathy, hyperglycemia, or hyperinsulinemia (161).

In patients with systemic sclerosis the most common gastrointestinal symptoms are heartburn (77%), nausea and vomiting (58%), dysphagia (61%), diarrhea (53%), constipation (31%), and fecal incontinence (13%) (162). The majority of patients with chronic ideopathic intestinal pseudo-obstruction do not have evidence of a herpes viral infection (163), suggesting that other factors are responsible for disease production in most patients.

Late pregnancy inhibits small intestinal transit, whereas gastric emptying remains unchanged. These alterations in small intestinal transit are not due to alterations in the plasma progesterone concentration (164). Volume-induced effects on intestinal motility are mediated by extrinsic nerves, whereas nutrient-

induced effects may be mediated by hormonal factors such as plasma peptide tyrosine-tyrosine (165).

About a third of irritable bowel syndrome patients have delayed gastric emptying, and in these individuals there are no interdigestive small bowel abnormalities but there is a higher phase II burst frequency (166). This suggests that a neural process may contribute to the pathogenesis of irritable bowel syndrome in a subgroup of these individuals. Interestingly, a prolonged active coping stressor produces a decrease in small bowel transit time (167).

Clinical Learning Point: Patients with irritable bowel syndrome may also have abnormalities in gastric and small intestinal motility.

IMMUNOLOGY

The topic of immunonutrition has been reviewed (168), including specific aspects pertaining to the pediatric experience (169); the role of biosurfactants, fiber, and probiotic bacteria (170); glutamine (171, 172); carbohydrates (173); taurine (174); amino acids and polyamines (175); and the role of ω-3 fatty acids (176).

Intestinal intraepithelial lymphocytes consist of both $\alpha\beta$ and $\gamma\delta$ T-cell receptor-bearing cells, with phenotypic and functional features distinct from cells in the peripheral lymphoid tissues. The number of $\alpha\beta$ intraepithelial lymphocytes producing IFN-γ and IL-5 is reduced in the cells from most intestinal crypts, as compared to villous tips. Villous tip $\alpha\beta$ intraepithelial lymphocytes exhibit higher responses to stimulation signals provided by interleukin-2 and/or interleukin-7 than do their crypt counterparts (177). Interferon-γ inhibits intestinal epithelial-6 cell proliferation, and induces class II antigen expression (178). Intraepithelial lymphocytes may be involved in generating antiviral immune responses early in simian immunodeficiency virus infection (179).

Polymeric immunoglobulin receptor (pIgR) expression is up-regulated by IFN-γ and IL-4 in HT-29 cells grown in normal media, but this is dampened when using a vitamin A-depleted media (180). Compared with peripheral blood lymphocytes, substantial proportions of intestinal epithelial and lamina propria lymphocytes spontaneously secrete IFN-γ and/or IL-4 (181). Primary cultures of human mucosal mesenchymal cells dose-dependently proliferate in response to IL-1β, IL-6, and TNF-α. Each cytokine differentially induces mRNA expression, suggesting that mesenchymal cells should be considered as active regulators of intestinal immunity (182).

The topics of intraepithelial lymphocyte T lymphocytes and the role of NF-κB in immune and inflammatory responses have been reviewed (183–185). In patients with Crohn's disease and ulcerative colitis, *in situ* hybridization and immunohistochemical studies have revealed increased numbers of mononuclear cells mainly in the submucosa producing IL-10, whereas the expression of IL-1β mRNA is preferentially increased in the lamina propria (186). IL-10 down-regulates mucosal T-cell activation (187). Polymorphonuclear neutrophil granulocytes from patients with inflammatory bowel disease are primed to secrete enhanced amounts of proinflammatory cytokines, accompanied by the detection of corresponding increases in their mRNAs (188).

Lymphocytes interact with endothelial cells and cross the endothelial barrier in postcapillary venules of Peyer's patches. A variety of adhesion molecules such as L-selectin have been implicated as organ-specific homing receptors for lymphocytes. Nitric oxide is an important modulator of lymphocyte migration in Peyer's patches and in nonlymphoid regions of the intestine (189).

The expression of adhesion glycoproteins on the surface of leukocytes and/or vascular endothelium are important in the interaction between leukocytes and endothelial cells (190). Intestinal microvascular endothelium may contribute to the cytokine network of the intestinal mucosa and with its ability to produce inflammatory mediators (191). Intestinal injury can occur when the gut becomes a cytokine-liberating organ (192).

Graft-versus-host disease occurs when the large number of functional lymphocytes transplanted with either the bone marrow or the small intestine recognize the host as foreign, and attack it. The initial immune reaction to intestinal grafts occurs in the mucosa and submucosa, with infiltration of immunocompetent cells. In graft-versus-host disease, a T-cell-mediated intestinal disease, the extracellular matrix component tenascin may be relevant for the regeneration of the intestinal tissue architecture (193). Lymphocyte function-associated antigen-1 and other leukocyte adhesion molecules increase during graft-versus-host disease after small bowel transplantation. Cyclosporin A treatment is associated with decreased lymphocyte function-associated-1 expression, and lymphocyte function-associated-1 may play a pivotal role in the immune-mediated injury of the intestine (194).

Flexible fiberoptic endoscopy is clinically useful to make the early diagnosis of intestinal allograft rejection. There are discrepancies between the histologic and endoscopic diagnosis (195).

Immune surveillance depends on the circulation of leukocytes between the bloodstream and the extravascular space, where pathogens are encountered and where local immune reactions are initiated. The extravasation of leukocytes involves their rolling along the activated endothelium, leukocyte activation, attachment, and transendothelial migration. Different families of adhesion molecules are involved in this process. P-selectin and intracellular adhesion molecule (ICAM) -1 are involved in the shaping of lymphocyte populations in the gut, but have only a minor influence on the systemic and regional host defense against intracellular bacteria (196).

ICAM-1 is an active participant in mediating leukocyte adhesion to endothelial and to epithelial cells. ICAM is up-regulated by inflammatory cytokines such as TNF-α and IFN-γ. The TNF-α induction of ICAM-1 expression is mediated by the transcription factor NF-κb and can be inhibited by blocking IκBa degradation (197).

Intestinal epithelial cells control the host's local and systemic exposure to the toxic luminal environment by providing a physical barrier to the uptake of bacterial and dietary antigens. Intestinal epithelial cells also serve an immunoregulatory function, as shown by their ability to present antigens to immune cells, secrete cytokines, express cell adhesion molecules, release eicosanoids, and produce nitric oxide. Interleukin-1 is a proinflammatory cytokine that is produced by activated monocytes, macrophages, fibroblasts, smooth muscle cells, and endothelial cells. Expression of an endogenous IL-1-receptor antagonist is part of the complex regulation of IL-1. Three variants of the IL-1-receptor antagonist gene product have been described. Interleukin-1-receptor antagonist, a glycoprotein secreted by activated monocytes and macrophages, is up-regulated by inflammation, inflammatory stimuli, and cellular differentiation (198). Interleukin-15 is a T-cell growth factor that binds to the IL-2 receptor and induces T- and B-cell proliferation, production of IFN-γ, as well as cytotoxic activity. Interleukin-15 is the most potent of the known cytokines derived from intraepithelial lymphocytes, inducing the highest levels of proliferation, IFN-γ production, and cytotoxicity (199).

Necrotizing enterocolitis is a potentially lethal disease affecting immature infants. Risk factors for necrotizing enterocolitis include prematurity, formula feeding, bacterial colonization, hypoxia, and intestinal ischemia. Inflammatory mediators such as platelet-activating factor, leukotrienes, and tumor necrosis factor play an important role in the genesis of necrotizing enterocolitis. Feeding an n-3 fatty acid diet decreases active prostaglandin and leukotriene production after the incorporation of these n-3 fatty acids into cell membrane phospholipids. Feeding these fish oil fatty acids may reduce the otherwise increased intestinal platelet-activating factor and LT-B_4 seen in an hypoxia-induced model of necrotizing enterocolitis (200).

Most microorganisms cross the epithelial barrier of the intestine and interact with mucosa-associated lymphoid tissue (MALT). Peyer's patches are the major sites of sampling of antigen and microorganisms, leading to immune responses or tolerance. MALT is separated from the intestinal lumen by the lymphoid follicle-associated epithelium, which contains M cells that transport antigens and microorganisms. Lymphocytes from Peyer's patches induce the reorganization of Caco-2 cells into M cells that transport bacterial (201). The role of M cells in the transepithelial transport of antigens and pathogens to the mucosal immune system has been reviewed (202).

The increased protein synthesis in the intestinal mucosa that occurs during sepsis and endotoxemia is due to increased cell turnover and increased biosynthesis in the individual enterocyte. The enterocyte production of VIP and peptide tyrosine–tyrosine is increased during sepsis. Endotoxemia also stimulates the production of compliment C3 and serum amyloid A by a process that may be regulated at the transcriptional level and that probably reflects increased synthesis of the acute-phase proteins in both enterocytes and cells of the lamina propria (55).

Intestinal mast cells are important in the protection of tissue from inflammatory damage and in intestinal maturation, releasing cytokines such as TNF-α and IL-10 (203). Oral antigen exposure induces anaphylactic reactions in the intestine. This is mediated by mast cells and eosinophils in response to the IgE–antigen complex in the early phase and also by lymphocyte migration after chronic antigen exposure (204). Intraepithelial lymphocytes express a different set of surface receptors than do peripheral blood lymphocytes. In humans, about 90% of intestinal intraepithelial lymphocytes are T lymphocytes, whereas about 80% of peripheral blood lymphocytes are T cells. Intestinal intraepithelial lymphocytes bear an oligoclonal repertoire of T-cell-antigen receptors, whereas peripheral blood lymphocytes are monoclonal. Cultured human intraepithelial lymphocytes are capable of migrating into polarized epithelial cells *in vitro*, and intraepithelial lymphocyte migration may be influenced by chemokine receptor-mediated signaling (205).

The intestinal epithelial cells are capable of pro-

ducing a variety of cytokines such as IL-1, -6, and -8; TGF-β, and TNF-α. Interleukin-6 enhances B cell immunoglobulin secretion and acts as a costimulator for T-cell proliferation. Caco-2 cells secrete IL-6 on stimulation by IL-1β or TNF-α, and the regulation of IL-6 secretion by the cells is not affected by differentiation (206). Intestinal epithelial cells may also serve as a target for locally produced cytokines. Receptors for IL-1β, IL-6, and granulocyte-macrophage colonate stimulating factor are detected on human intestinal epithelial cells (207). Tumor necrosis factor-α increases the proliferation and migration of intraepithelial lymphocytes (208). Interleukin-10 suppresses the activation of macrophages *in vitro* and inhibits tumor TNF-α and IL-1β, -6, and -8 synthesis by macrophages and activated monocytes. Interleukin-10 also prevents mucosal damage in the gut (205).

Tacrolimus is a macrolide lactone with potent immunosuppressive properties that has clinical use in the prophylaxis against organ rejection after liver transplantation. Tacrolimus is metabolized in the liver by the cytochrome P-450 system, and the oral bioavailability is approximately 25%. The metabolism of tacrolimus in the intestine contributes to its extensive and variable first-pass metabolism following oral administration (209).

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