Small bowel review: Part II

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ABR Thomson, M Keelan, A Thiesen, MT Clandinin, MJ Ropeleski, G Wild. Small bowel review: Part II. Can J Gastroenterol 2001;15(7):446-466. In the past year, there have been many advances in the area of small bowel physiology and pathology. In preparation for this review, over 1500 papers were assessed. Some have been selected and reviewed, with a particular focus on presenting clinically useful information for the practising gastroenterologist. Relevant review articles have been highlighted, and important clinical learning points have been stressed. The topics are varied in scope and wherever possible show a logical progression from basic physiology to pathophysiology to clinical disorders and management.

Key Words: *Diabetes mellitus; Ethanol; Gluten-sensitive enteropathy; Intestinal ischemia; Short bowel syndrome; Small bowel*

Revue de la documentation scientifique sur l'intestin grêle : 2e partie

De nombreux progrès ont été réalisés au cours de la dernière année en ce qui concerne la physiologie et la pathologie de l'intestin grêle. Plus de 1 500 articles ont été évalués dans le cadre de la présente revue. On a d'abord sélectionné et examiné un certain nombre d'entre eux, notamment ceux qui contenaient de l'information utile sur le plan clinique pour les gastro-entérologues praticiens, puis on a retenu les articles les plus intéressants et fait ressortir des points cliniques importants pour l'apprentissage. Les sujets traités sont très diversifiés et ils témoignent, dans la mesure du possible, d'une suite logique depuis la physiologie jusqu'à la physiopathologie, les troubles cliniques et le traitement.

BLOOD FLOW AND INTESTINAL ISCHEMIA

The gastrointestinal tract is important in the pathophysiology of multiple organ failure. In multiple organ failure, reduced mucosal blood flow leads to disruption of the intestinal barrier, which promotes the translocation of endogenous endotoxin into the portal circulation. This translocation of endotoxin leads to the systemic release of various cytokines, which culminates in the clinical picture of sepsis. In a rat model of hemorrhagic and endotoxic shock, mesenteric levels of tumour necrosis factor (TNF)-alpha and interleukin (IL)-6 are increased by hemorrhage (1).

The leukocyte-endothelial cell adhesion (rolling) observed with ischemia/reperfusion (I/R) injury involves P selectin. P selectin expression is mediated by a 5-lipoxygenase-dependent nitric oxide-inhibitable mechanism (2). In rats exposed to intestinal I/R, there is a progressive increase in plasma IL-6 concentration with reperfusion. The administration of monoclonal antibody against TNF before the onset of I/R blunts the subsequent release of IL-6 (3).

The proinflammatory secretory phospholipase A_2 is a stress-induced protein, as well as a priming agent in the development of I/R injury (4). The selectins are implicated in the recruitment of leukocytes into tissues exposed to I/R.

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These adhesion glycoproteins on endothelial cells such as P selectin are regulated by a transcription-dependent mechanism that functions in parallel with, but independent of, the rapidly induced translocation of P selectin from storage granules. L and P selectin mediate the initial capture of leukocytes from the blood stream, while the coordinated action of L and E or P selectin is required for optimal and stable leukocyte rolling.

Intracellular adhesion molecule-1 resides on endothelial cells, and is important for cell adherence and transmigration. Platelet-activating factor plays an important role in endotoxic shock and I/R, and in other inflammatory responses in the intestine. In mice, selectins (especially P selectin) play an important role in mediating the systemic and local inflammatory responses to platelet-activating factor-induced injury (5).

Clinical learning point: The selectins are adhesion glycoproteins on endothelial cells that may be targets to reduce the intestinal damage seen with I/R.

Inhibition of nitric oxide synthase (NOS) increases arteriolar responses to sympathetic nerve stimulation and attenuates sympathetic neurogenic constriction in the intestinal arteriolar network. The alpha$_2$-adrenoceptor-dependent pathway does not influence resting tone or sympathetic constriction of proximal arterioles in the intestinal submucosa (6). This suggests that alpha$_2$ receptor activation does not serve as a stimulus for arteriolar nitric oxide release during periods of increased sympathetic nerve activity. Hypoxic vasoconstriction is mediated by a hypoxia-induced loss of constitutive nitric oxide production. The magnitude of hypoxic vasoconstriction mediated by hypoxia-induced suppression of nitric oxide production is greater in young than in older swine (7). This may partially explain why young animals are more susceptible to ischemic damage to the intestine.

During lipopolysaccharide-induced sepsis in rats, mucosal blood flow to the ileum decreases, yet perfusion to the remaining intestine is preserved (8). The use of a NOS inhibitor decreases mucosal blood flow through the small intestine, and perfusion of the small intestine may be dependent on physiological nitric oxide production. Tissue hypoxia results from acute events such as vascular insult or thrombosis, or from chronic events such as fibrosis or vessel narrowing. Hypoxia may act as a 'priming' to cells to respond differentially to inflammatory mediators found within the tissue microenvironment.

The endothelins (ETs) are a family of 21 amino acid peptides produced by vascular endothelial cells. The plasma levels of ET-1 are enhanced during ischemia, hypoxia, sepsis and bacteremia. ET-1 induces local leukocyte accumulation and polymorphonuclear leukocyte aggregation. ET-1 also induces leukocyte rolling and adherence by a receptor-mediated mechanism in the submucosal venules of the intestinal microcirculation (9).

Clinical learning point: ETs are peptides produced by vascular endothelial cells and may be involved in the pathophysiology of gastrointestinal I/R injuries, alpha$_1$-acid glycoprotein (AGP) and transforming growth factor (TGF)-α, and glutamine supplementation may also prove in the future to be useful to treat ischemic damage to the intestine.

Intestinal ischemia is a complement-mediated process and involves neutrophil sequestration arising from neutrophil-endothelium rolling. α_1-AGP is an acute-phase protein. Rats treated with a form of AGP have a reduction in the anticipated increased permeability that occurs with I/R (10). Intestinal I/R causes the formation of reactive oxygen intermediates as well as glutathione, a scavenger of reactive oxygen intermediates. Glutamine supplementation may be protective when given to rats with I/R, possibly as the result of the lowering of these oxygen-reactive metabolites (11).

Nonocclusive intestinal ischemia (NOII) may result from decreased splanchnic circulation secondary to hypovolemia, decreased cardiac output, cardiac arrhythmias, hypotension and some drugs, such as digitalis, affecting mesenteric blood flow. It is estimated that 25% of cases of acute mesenteric ischemia and 85% of acute colonic ischemia have a nonocclusive etiology. For unknown reasons NOII has a female to male ratio of 4.5 to 1. Coronary artery disease and atrial fibrillation are common comorbidites of NOII, and the overall mortality rate is high (67%) (12).

Clinical learning point: NOII associated with decreased splanchnic circulation is a common and deadly condition in elderly women.

Small bowel infarction may be caused by venous or arterial thrombosis, and may be associated with hypercoagulable conditions. These include antithrombin III, protein C and protein S deficiency, and myeloproliferative syndromes, as well as a new homeostasis-related genetic abnormality detected by abnormal protein C resistance associated with a mutation factor V gene (13). The prevalence of these hypercoagulable states in persons with intestinal ischemia is unknown.

The small intestinal ulcers that occur in patients with Crohn's disease tend to arise along the mesenteric margin where the blood vessels pass through the muscularis propria. In the rat, there may be vascularly compromised sites along the mesenteric margin, and it is at this point that the intestine is particularly susceptible to indomethacin-induced injury (14).

The intrinsic microsomal enzymes monoacylglycerol acyltransferase and diacylglycerol acyltransferase catalyze the major pathway for triacylglycerol biosynthesis.

Intestinal ischemia is associated with a marked decrease in both monoacylglycerol acyltransferase and diacylglycerol acyltransferase activities in the intestine. The recovery of the activity of these enzymes is enhanced by the luminal administration of solutions containing L-glutamine plus TGF-α (15). I/R injury in transgenic mice overexpressing copper-zinc superoxide dismutase (SOD) have lower levels of intestinal malondialdehyde than do nontransgenic mice (16). This raises the possibility that enhancing the expression of SOD may be useful to protect tissues from neutrophil infiltration and lipid peroxidation during intestinal I/R damage. An additional novel therapeutic approach to the treatment of I/R injury is the administration of an α_1-AGP given intravenously to rats (10).

Clinical learning point: The overexpression of SOD protects tissues from the neutrophil infiltration and lipid peroxidation that occurs during intestinal I/R. The therapeutic implications of these observations remain to be defined.

The intestinal mucosa is a rich source of interferon (INF)-gamma, and INF-γ receptors are restricted to the basolateral membrane of epithelial cells. Activation of this receptor decreases epithelial barrier function, decreases epithelial ion transport, induces proinflammatory surface markers and regulates polymorphonuclear leukocyte trafficking across the intestinal epithelium. During hypoxia, there is release of TNF-α, which potentiates the effect of INF-γ on the epithelial barrier function (17). Thus, during hypoxia, epithelium-derived mediators such as TNF-α have the potential to regulate permeability through autocrine pathways.

In contrast to necrosis, apoptosis is an active process of gene-directed cellular self destruction. Apoptosis is characterized by morphological changes such as cell shrinkage, condensation of chromatin and nuclear fragmentation. Apoptosis occurs during intestinal ischemia by a process that is independent of ornithine decarboxylase (ODC) activity (18). Disruption of the epithelial cell-matrix interaction plays a part in the induction of apoptosis in detached ischemic cells (19). Modulation of a genetic regulatory and biochemical effector machinery of apoptosis might be an important therapeutic target to treat or to prevent I/R injury (20). Another approach to accelerate the repair of the mucosa during reperfusion after ischemic injury is to administer oral solutions containing a polyamine precursor such as ornithine alpha-ketoglutarate (21).

Clinical learning point: Novel approaches to the treatment of intestinal ischemia include the use of TNF-α-modifying gene-directed cellular self-destruction (apoptosis), or the use of polyamines or polyamine precursors.

GLUTEN-SENSITIVE ENTEROPATHY

Celiac disease (CD) is an abnormal immune response in genetically susceptible individuals that is triggered by the ingestion of gliadin and related peptides of cereals such as wheat, rye, barley and possibly oats. Gliadins are the ethanol-soluble fraction of gluten – a protein contained in these grains. The prolonged consumption of small amounts of gliadin present in products containing wheat starch also may cause symptoms in some patients with CD and may give rise to a relapse of skin lesions in patients with coexisting dermatitis herpetiformis (DH) (22). There is a T cell-mediated immune response to gliadin, and the majority of gliadin-specific T cell clones from the small intestinal mucosa of patients with CD produce INF-γ and IL-4 (23). The cytokines may play an important role in the mucosal lesions in celiac sprue. It is unknown whether the cytokines may contribute directly to symptoms or malabsorption in persons with CD.

Clinical learning point: Cytokines may play a role in the pathogenesis of the intestinal lesion that occurs in patients with CD.

Gluten sensitivity is histologically expressed by a wide variety of T cell-mediated pathological features. While the major site of gut involvement in CD is the jejunal mucosa, changes have also been observed in the stomach and in the rectal mucosa. Rectal gluten challenge is a simple, sensitive and specific test of mucosal gluten sensitivity, and the intraepithelial lymphocyte (IEL) response after gluten installation into the rectum is higher in CD patients as well as in some of their relatives (24).

Clinical learning point: Gluten enteropathy extends to the stomach and rectum, as well as to the small intestine, where these tissues demonstrate T cell-mediated pathological changes. The sensitivity and specificity of rectal lesions in diagnosing CD are not known.

Gluten-sensitive patients develop immunoglobulin (Ig) G and IgA antibodies to gliadin, and to an unknown component of the gut endomysium (the connective tissue surrounding the smooth muscle fibres in the gut). The autoantigen-eliciting antiendomysial antibody in CD appears to be the intracellular enzyme transglutaminase (25-27). T cell activation appears to occur in patients with CD, with the DQW2-restricted T lymphocyte releasing proinflammatory cytokines such as INF-γ in response to gluten peptides. Tissue transglutaminase evokes IgA antibodies to gut endomysium, and gliadin appears to be the preferred substrate of transglutaminase.

Clinical learning point: The autoantigen-eliciting antiendomysial antibody in patients with CD is an intracellular transglutaminase. Measuring antiendomysial antibody may be useful to identify persons who need to be further investigated with a small bowel biopsy for suspected gluten enteropathy. CD should not be diagnosed on the basis of serological tests alone, but must be confirmed by the presence of villous atrophy and crypt hyperplasia on small bowel biopsy.

Increased proximal small intestinal luminal concentrations of total IgA and lgM, as well as IgA and IgM antigliadin antibodies occur in patients with CD and DH, and may persist after the resolution of villous atrophy. Increased small intestinal luminal concentrations of total IgA and IgA antigliadin antibodies are detected in about one-third of patients with small intestinal bacterial overgrowth, which should not be confused with the presence of 'latent' CD (28). Thus, positive luminal antigliadin antibodies in small intestinal bacterial overgrowth probably occur as epiphenomena.

Subtotal villous atrophy has been described in four adults who were unresponsive to a gluten-free diet. These patients were human leukocyte antigen (HLA)-DQ2 positive, but interestingly IgA antigliadin and antiendomysial antibodies were not found in these patients. They were considered to have an autoimmune enteropathy (29).

The topic of the ontogeny and function of gamma-delta T cells in the intestine has been reviewed (30), as has the topic of the interaction among cytokines, growth factors, adhesion molecules and the process of apoptosis (31). In healthy individuals, most IELs are T cells – three-quarters of which express T cell receptor (TCR)-alpha-beta and have the CD8 rather than the CD4 coreceptor. The second subset of IEL expresses the TCRγδ. In patients with active CD, immunohistochemical studies have shown an expansion of IELs bearing T lymphocytes expressing either TCRγδ or TCRαβ and CD103. The increased density of TCRγδ-positive IELs is the only characteristic in the jejunum of patients with CD and DH that is not normalized by a gluten-free diet. The density of gamma-delta-positive cells in these individuals is positively correlated with their age (32). In patients with refractory sprue, but not in normal control subjects or patients with active CD, the intestinal epithelium is infiltrated by small lymphocytes that lack CD8, CD4 and TCR, but instead contain an abnormal subset of IELs containing CD3ε (33).

Clinical learning point: Over time, histological abnormalities in the small intestine of persons with CD revert to normal, except for the increased density of TCRγδ in the IELs. This may prove to be useful in confirming the diagnosis of gluten sensitivity in a patient with a questionable diagnosis of sprue and who is on a gluten-free diet.

Selective IgA deficiency (SigAD) is associated with CD (2.6%), representing a 10-to 16-fold increased prevalence over that in the population in general (34). Patients with SigAD have a higher incidence of silent CD, recurrent infections and atopic diseases. The association of autoimmune and malignant diseases is similar in CD patients with and without SigAD. Of importance, in all patients with SigAD, antibodies for gliadin and endomysium are absent. Persons being screened for possible CD who have absent IgA antigliadin antibodies and antiendomysial antibodies should have their serum IgA levels measured.

Clinical learning point: If the patient with CD also has SigAD, antibodies for gliadin and endomysium may be absent. The false-negative nature of the serological testing in this setting means that the patient must be referred directly for a small bowel biopsy rather than a stepwise approach using initial serological testing.

CD may be associated with T cell lymphoma, and a case has been reported of isolated central nervous system disease mimicking primary central nervous system lymphoma (35). The term 'immunoproliferative small intestinal disease' has replaced the older terms 'Mediterranean lymphoma' and 'alpha chain disease'. Immunoproliferative small intestinal disease is a disorder characterized by profound malabsorption and lymphoplasmacytic infiltration of the small intestinal mucosa, together with the presence of the alpha heavy chain in the serum or duodenal juice; in the nonsecretory form, the alpha heavy chain is confined to the cytoplasm of the infiltrating plasma cells (36).

The prevalence of primary biliary cirrhosis (PBC) is 3% in patients with CD, and the prevalence of CD is 6% in persons with PBC (37). It is now refuted that CD and PBC are co-associated by more than chance alone (38).

Persons with CD may develop microscopic colitis. In four patients with collagenous colitis and five with lymphocytic colitis, all of whom had a normal small bowel biopsy, the IEL counts were normal, the intestinal antigliadin antibodies were elevated in two of six patients and intestinal permeability measured with the lactulose to mannitol differential sugar permeability test was abnormal in two of eight cases and borderline in one (39). This suggests that subclinical small intestinal CD is common in these forms of microscopic colitis.

Clinical learning point: CD and microscopic colitis may coexist, but CD is probably not co-associated with PBC.

Mouth to cecum transit time is prolonged in patients with CD compared with control subjects, and returns toward normal after a gluten-free diet (40). It is unknown whether this contributes to intestinal symptoms or malabsorption.

Bone mineral density is often reduced in patients with CD, independent of its severity. The spine bone mineral density values in late-diagnosed CD patients are lower than in early-diagnosed patients or in CD patients who have been on a gluten-free diet for less than 12 months (41). Bone mineral density is increased by dietary treatment in most but not all adult CD patients (42). Longitudinal studies suggest that the degree of bone improvement varies from person to person. A high rate of osteosynthetic activity before treatment is predictive of the satisfactory recovery of bone mass after institution of a gluten-free diet (43).

The decreased bone mineral density observed commonly in both treated and untreated patients with CD may be due to many factors, including the high levels of proinflammatory cytokines such as IL-1β and IL-6 (44).

Clinical learning point: Decreased bone mineral density is common in patients with CD. All persons with CD should be screened appropriately for decreased bone mineral density, which is usually managed satisfactorily with dietary treatment.

Using antiendomysial antibody testing, five of eight adult patients with insulin-dependent diabetes of a sample of 101 were found to have histological evidence of CD (45).This confirms earlier studies that showed that the prevalence of CD is increased in patients with diabetes mellitus.

Clinical learning point: It is important to diagnose CD. With proper treatment, the risk of malignancy, osteoporosis, infertility and neurological disorders may be lessened.

SHORT BOWEL SYNDROME, INTESTINAL ADAPTATION, CELL GROWTH AND DIFFERENTIATION

The topic of the short bowel syndrome (SBS) in children and adults has been reviewed (46,47). There is a quantitative relationship between the load and the capacity in adoptively regulated physiological systems. Humans can tolerate an approximately 50% resection of the small intestine without developing clinically impaired digestive function, but more extensive resection leads to the condition of impaired function known as the SBS. The most frequently used animal model for studying SBS, the rat, can tolerate approximately 80% resection. When the compensatory regrowth of the small intestine is exceeded, such as occurs with a 70% resection in mice, the animal does not survive (48).

The small bowel adaptation that occurs after intestinal resection is due to luminal nutrients, hormones and pancreaticobiliary secretions. The trophic effect on the intestinal mucosa of peptides such as growth hormones (GH), neurotensin (NT), gastrin-releasing peptide (also known as bombesin) and epidermal growth factor (EGF) has been demonstrated. In the suckling rat, NT enhances the intestinal proliferative phenomenon but does not improve the course of medium term postresection growth (49). NT also increases the adaptive intestinal process after colon resection and reduces plasma enteroglucagon-like immunoreactivity in rats (50).

In a randomized, six-week, double-blind, placebo controlled crossover study, eight patients with SBS were administered GH, oral glutamine and a high carbohydrate/low fat diet. Active treatment transiently increased body weight, increased the absorption of sodium and potassium, and decreased gastric emptying; unfortunately, the assimilation of macronutrients, stool volumes and morphometry of the small bowel mucosa were unchanged compared with those of patients who received placebo (51). The initial enthusiasm for the treatment of patients with SBS with recombinant human GH, intravenous or oral glutamine, and a high carbohydrate/low fat diet has been challenged in another randomized, controlled study (51).

In a rat model of SBS (70% jejunal-ileal resection), no evidence was found that the combination of glutamine and GH enhanced mucosal mass, protein, DNA levels or sucrase activity (52). GH has a nonspecific effect on small intestinal growth. GH is released by arginine; in a rat model of small bowel resection, the administration of L-arginine had no effect on food intake, body weight or plasma insulin-like growth factor (IGF)-1 levels (53). The administration of EGF or IGF-1 after massive small bowel resection in rats does not modify villous length, crypt length or the villous to crypt ratio (54).

Clinical learning point: It is premature to treat patients with the SBS using GH, glutamine and a high carbohydrate diet.

During early adaptation in the remnant small intestine in rats, the genes involved in nutrient trafficking, protein processing and cell cycle regulation are transcriptionally regulated in the residual small intestine. This regulation occurs in distinct temporal and regional patterns consistent with a complex multifaceted response to intestinal resection (55). Following small bowel resection, a number of genes are induced in the adapting remnant. These include the genes for cellular retinal binding protein II and apolipoprotein A_1. Provision of a liquid diet, using a small number of sutures for the anastomosis, and resection of no more than 50% of the proximal small intestine are important for the survival of the mouse following small bowel resection (56).

Clinical learning point: Luminal nutrients and pancreaticobiliary secretions are necessary for the normal function of the intestine. When these are removed during fasting or with the use of total parenteral nutrition (TPN), intestinal atrophy and malabsorption may develop.

Luminal nutrients (such as glutamine, soluble fibres and short-chain fatty acids), intestinal hormones (such as GH, EGF, enteroglucagon and IGF-1) and pancreaticobiliary secretions are important for the process of intestinal adaptation. Segmental reversal of the small bowel may reduce parenteral nutrition dependency in patients with SBS (57).

Clinical learning point: A variety of peptides enhance the intestinal adaptive process and eventually may be found to be useful in patients with SBS.

Polyamines are required for the normal repair of duodenal damage. The inhibition of ODC, the rate-limiting enzyme of polyamine biosynthesis, adversely affects the normal healing process. Polyamines are important for cell attachment and expression of the integrin $alpha_2beta_1$, a putative receptor for collagen and laminin (58). The impairment of protein cross-linking, and the inhibition of the expression of cell surface receptors that bind extracellular matrix proteins, may be part of the mechanism by which polyamine deficiency retards cell migration in the small intestine.

The amino acid glutamine stimulates mucosal growth and promotes intestinal health. When glutamine is coupled with growth factors such as GH, IGF-1, glucagon-like peptide-2 (GLP-2) and IL-11, a high level of bowel protection can be obtained (59). Glutamine stimulates the induction of ODC, and glutamine activates extracellular signal-regulated kinases (ERKs) and Jun nuclear kinases, resulting in increased activating protein 1-dependent gene transcription (60).

The topic of the molecular aspects of mucosal repair has been reviewed (61), as has the topic of epithelial cell growth and differentiation (62). The superfamily of G protein-coupled receptors includes receptors for peptide and nonpeptide hormones and neurotransmitters. A common functional feature of cellular responses to G protein-coupled receptor agonists is that they are rapidly attenuated. This downregulation is characterized by the depletion of the cellular receptor content due to alterations in the rate of receptor degradation and synthesis (63).

It is unknown why different genes are expressed in the proximal versus the distal intestine. This may arise from specific variations in the transcription factors that interact with the promotor and the enhancer regions of these genes. Homeodomain transcription factors (known as homeobox genes) are involved in establishing gradients of differentiation during development and in maintaining these patterns of expression through continued expression in adult tissues. The homeobox gene product Cdx-2 interacts with the promoters for several genes expressed in the intestine, such as brush border membrane (BBM) sucrase-isomaltase. Many homeobox genes are expressed in adult human small intestinal mucosa, and some are found predominately in one region (64).

Protein kinase C (PKC) is a family of serine/threonine kinases that play a central role in signal transduction. PKC has been implicated in the control of cell growth differentiation and transformation. PKC activation initiates a signalling cascade, leading to alterations in gene expression and modulation of a variety of cellular functions. PKC also may be involved in the inhibition of cell growth and differentiation. PKCα is implicated in the negative regulation of intestinal epithelial cell growth both in vitro and in situ via pathways that involve modulation of the Cip/Kip family cyclin-dependent kinase inhibitors (65).

Clinical learning point: PKC is a family of serine/threonine kinases that are important in signal transduction, growth and differentiation of the intestine.

Members of the src family of the nonreceptor protein tyrosine kinases play a role in the proliferation and differentiation of cells. The catalytic domain of the src-related protein tyrosine kinase has been cloned. Complete nucleotide sequencing of the gastrointestinal-associated tyrosine kinase has been demonstrated. In the rat intestine, gastrointestinal-associated tyrosine kinase plays a specialized role in the growth and differentiation of gut columnar epithelial cells (66).

The immediate-early response genes are a group of genes that are rapidly increased after various mitogenic and other pathological stimuli. The protein products of some of these genes act at the transcriptional level to initiate downstream events that are believed to culminate in cellular proliferation. *Nup* 475 and c-*jun* are two immediate-early genes that are found in the nucleus. mRNA levels of both *Nup* 475 and c-*jun* are markedly increased following small bowel resection in rats (67).

GH induces IGF-1 synthesis, and IGF-1 may play an important role in the regulation of intestinal growth and maturation. IGF-1, or GH plus IGF-1, increases intestinal growth parameters in rats fed by TPN, whereas GH alone has no effect (68). Human intestinal muscle cells produce IGF-1, and both TGF-α and TGF-β1 in a time-dependent reciprocal fashion that parallels their effects on growth (69).

There is a bidirectional network among the neural, endocrine and immune systems. IL-1β, IL-6 and TNF-α are polypeptides that are predominantly produced by monocytes and macrophages. They also stimulate the corticotropin-releasing factor-containing cells, and thereby activate the pituitary-adrenal axis. These cytokines are present in the intestinal mucosa and may be modulators of intestinal function. The polyamine spermine given by mouth to neonatal rats increases plasma concentrations of IL-Iβ, IL-6 and TNF-α (70). This polyamine induces postnatal intestinal development and corticosterone secretion through a cytokine-dependent mechanism. The administration of spermine to neonatal mice increases the intestinal length, decreases lactase activity and increases sucrase activity, mimicking the normal ontogenic development. These findings are the same when glucocorticosteroids are administered. Spermine treatment also increases the percentage of IELs expressing TCRαβ, CD4, CD5 and CD54.

This indicates that oral spermine treatment to neonatal mice also results in precocious maturation of the murine intestinal immune system (71). This suggests that there is a role for polyamines, cytokines and glucocorticosteroids in the adaptive intestinal response that occurs after intestinal resection.

Clinical learning point: The polyamine spermine induces precocious development of intestinal digestive and transport functions, as well as the intestinal immune system. The interaction among glucocorticosteroids, polyamines and cytokines needs to be explored to define a therapeutic potential.

INTESTINAL IMMUNOLOGY AND SMALL BOWEL TRANSPLANTATION

The topic of intestinal inflammation has been reviewed (31), as have the topics of the anatomical basis of intestinal immunity (72) and mucosal immunity (73). The effector arm of the mucosal immune system is comprised of the lamina propria (LP), the epithelium-associated cells and the IEL. The lymphocytes of the LP are CD4 and CD8 T cells, B cells and plasma cells secreting primarily IgA. IEL are mainly $CD3^+$ T cells, and the majority of these are $CD4^-CD8^+$. Many IEL cells express TCR$\gamma\delta$. A novel method has been reported that allows for the characterization of IEL isolated from different portions of the crypt-villus axis (74). It is unknown whether there is regional specialization of IEL, although this is not dependent on microbial colonization (75).

Acute inflammation of the intestine is associated with transepithelial migration of polymorphonuclear leukocytes. There are sequential early and late mechanisms by which epithelial discontinuities are repaired (76). In the intestinal mucosa, IEL are scattered among epithelial cells, adjoining their basolateral surfaces and overlying the basement membrane. These IEL are mainly $CD8^-$ T cells and proliferate poorly in response to T cell mitogens or to stimuli of the CD3 pathway. Optimal IEL growth depends on their contact with mesenchymal cells, an interaction that is initiated by very late activation (VLA)-4 and major histocompatibility class (MHC) I mechanisms, which in turn are likely served by basement membrane myofibroblasts (77).

The topic of antigen presentation in the intestine has been reviewed (78). Intestinal epithelial cells constitutively express a low level of HLA class II molecules, with elevated levels seen in the setting of mucosal inflammation. There may be two distinct pathways of HLA class II antigen processing in enterocytes, with differential immunomodulatory properties in the presence or absence of mucosal inflammation (79). Rat IEL include a significant population of class II MHC^+ T cells, predominately in the $CD8^+$ $CD4^-$ $\alpha\beta TCR^+$ subset of lymphocytes (80). Epithelial cells of the intestine act as antigen-presenting cells to the surrounding lymphoid tissue and may play a pivotal role in the maintenance of the pool of peripheral T lymphocytes (81). Microvascular endothelial cells express MHC class II molecules in the normal human intestine. The expression of the MHC class II molecules on the BBM is due to the ability of these cells to present antigen to T lymphocytes (81). MHC expression is regulated, and IFN-γ is the principle inducer of MHC class II molecules; TNF-α enhances this expression in a synergistic fashion. Diversion of bile from the gastrointestinal tract reduces MHC class II expression (82). Enhanced MHC expression is found in chronic inflammation. MHC class II expression is diminished with bile drainage, presumably because of the removal of bile TNF and INF-γ present in bile (82).

IEL are functionally cytolytic T cells that express granzyme A in situ, whereas in vitro, activated IEL express granzyme B, Fas ligand (FasL), TNF-α and INF-γ (83). Cell death can be attributed to necrosis and to apoptosis (programmed cell death). Apoptosis comprises an active biochemical response to changes in the local environment and is triggered by a nuclear endonuclease and by a transglutaminase. Small intestinal allograft rejection-associated apoptosis, in addition to necrosis, plays an important role in the cause of organ failure (84). Apoptosis may be mediated by Fas through the natural ligand FasL, a member of the TNF family. Binding of FasL to Fas induces interactions between signalling molecules that initiate a cascade of proteases that eventually lead to cell death. Fas is a 45 kD type I cell surface receptor, and a member of the nerve growth factor/TNF receptor superfamily. In contrast, FasL is a type II cell surface protein and a member of the TNF family. Fas/FasL-mediated cytotoxicity by host-derived IELs may be partly responsible for the enteropathy that occurs during acute graft versus host disease (GVHD) in mice (85).

GVHD commonly occurs in patients after bone marrow transplantation, and also has been reported to occur after small bowel and liver transplantation. The principle organs affected are the skin, and organs of the immune system and the gastrointestinal tract. Gastrointestinal manifestations include anorexia, pain and bloody diarrhea. GVHD occurs when the large number of functional lymphocytes transplanted from either the bone marrow or the small intestine recognize the host as being foreign and attack it. Lymphocyte function-associated antigen-1 and other leukocyte adhesion molecules play pivotal roles in other forms of immune-mediated inflammation in GVHD as well as in the intestine (86). The movement of lymphocytes and macrophages from the LP across the basement membrane into the epithelial monolayer occurs through discreet 'tunnels' through which the immigrating T cells, macrophages and eosinophils migrate (87).

Increased severity of GVHD is mediated by systemic increases in TNF-α (88). In GVHD, donor cells recognize and eliminate host cells. In the intestine of patients with GVHD, the total number of IEL are increased, and apoptosis of the intestinal epithelial cells occurs. GVHD is mediated by the activity of cytotoxic T cell function, one of which is dependent on perforin and one of which is dependent on Fas. Both the perforin and the Fas-mediated

pathways are involved in the systemic signs of GVHD, but target organ epithelial injury to the liver and skin appear to be especially restricted to Fas-mediated injury. FasL-mediated death of intestinal epithelial cells by IEL is a major cause of apoptosis in GVHD (89,90).

The intestinal mucosa secretes IL-7 (91), IL-8 (92) and IL-10 (93,94). The topic of IL-10 and the intestine has been reviewed (95). IL-8 is a pro-inflammatory cytokine, and a chemoattractant for neutrophils, basophils, peripheral blood T lymphocytes, natural killer cells and jejunal epithelial lymphocytes. IL-8 is produced by intestinal epithelial cells after stimulation with cytokines such as IL-1 and TNF-α. Human IEL are predominantly T cells of the $CD8^+CD45RO^+$ phenotype and have a chemotactic response to IL-8. The IL-8 responsiveness of IEL is desensitized by chemokines of the alpha and beta families – likely occurring by the binding of the chemokines to common receptors (96). IFN-γ is produced by the activated T and natural killer cells, and inhibits IgE production. The expression of exogenous genes and coding secretory proteins in the polarized intestinal epithelium is one approach to somatic gene transfer. In Caco-2 cells the delivery of IFN-β has been accomplished both to the luminal and to the blood sides (97).

M cells are specialized antigen sampling cells that are interspersed between epithelial cells of the follicle-associated epithelia of the gastrointestinal tract. They differ morphologically from the adjacent enterocytes; the M cells show preferential affinity for certain microorganisms and take up and transport antigens by a process of transcytosis. M cells are believed to act as an antigen sampling system. Human M cells do not differ from adjacent enterocytes in the composition of their intermediate filament cytoskeleton. This supports the hypothesis that there is an epithelial origin of human intestinal M cells and suggests that M cells may derive from differentiated enterocytes (98).

However, M cells are heterogenous with regard to the glycosylation pattern of their membrane glycoconjugates. The presence of M cells in the crypts surrounding the domes suggests that these cells are derived from undifferentiated crypt cells and do not develop from differentiated enterocytes (99).

Obtaining an endoscopic biopsy may be useful for diagnosing episodes of rejection, Epstein-Barr or cytomegalovirus infections (100). It is suggested that frequent surveillance ileoscopies with biopsies be performed after small bowel transplantation. If the patient deteriorates clinically with fever, diarrhea, bacteremia or gastrointestinal bleeding, and if the cause is not elucidated by ileoscopy, an upper endoscopy with biopsies is recommended.

Clinical learning point: Modulation of the immunosuppression following small bowel transplantation is necessary to minimize both rejection and opportunistic infections.

Chronic rejection is the major cause of late intestinal allograft dysfunction. Chronic rejection in the rat damages the muscularis and the enteric nervous system before mucosal changes become evident (101). Following intestinal transplantation, there is increased hypersensitivity in ileal circular smooth muscle. This is due to hypersensitivity to noradrenaline related to extrinsic denervation, possibly mediated through an increase in the number of receptors on smooth muscle cells but not on enteric nerves (102). This may explain in part the motility disorder that follows intestinal transplantation.

The topic of small intestinal transplantation for irreversible intestinal failure in children has been reviewed (103). Intestinal transplantation is associated with a high incidence of rejection. This is associated with altered mucosal integrity, bacterial translocation and systemic sepsis. Steps to prevent rejection with the use of excessive amounts of immunosuppressants may result in further infectious complications or in post-transplantation lymphoproliferative disorders. Rejection of allografts is predominantly a cellular phenomenon, but antibody and complement deposition in vascular allograft rejection also occurs. The administration of cobra venom factor may be useful to control the hyperacute rejection (104). The mechanism of this effect needs to be established.

The immune response to small bowel transplantation involves a unique profile of cytokine expression within the graft parenchyma. Early after transplantation, there is infiltration of recipient-derived cells into the mesenteric lymph nodes and Peyer's patches of the small bowel grafts. This early immune response occurring in lymphoid tissue may not be controlled by immunosuppression, which is administered only at the time of transplantation. This may explain the difficulty in achieving adequate immunosuppression in small bowel transplantation (105).

Because of the denervation of the intestinal transplanted segment, this has been a useful model with which to study the role of extrinsic and intrinsic cholinergic nerves and their role in the release of gastrointestinal peptides such as cholecystokinin (106). The immunosuppressant cyclosporin A, which is used in patients with small bowel transplantation, causes intestinal hemodynamic and functional impairments. The elevated vascular resistance and decreased blood flow in a rat small intestinal transplantation model treated with cyclosporin A is prevented with the concomitant use of a calcium channel blocker nifedipine (107). It is unknown how a calcium channel blocker can prevent the reduction in intestinal blood flow observed with the use of cyclosporin A, nor is it known whether this experimental observation can be applied to a clinical situation.

Malnutrition is a common cause of immunodeficiency and is associated with impairment of cell-mediated immunity and phagocyte function, impairment of the complement system, reduced secretory IgA antibody concentrations and diminished cytokine production (108). All of these factors explain the high prevalence of infection in persons with malnutrition. In an animal burn model, feed-

ing a diet supplemented with arginine and glutamine, and treatment with a natural endogenous steroid (dehydroepiandrosterone) reverse the susceptibility to infections caused by prednisone (109). Patients with bone marrow transplantation may develop mucositis of the oral cavity and the gastrointestinal tract. As a result, they may develop diarrhea, abdominal pain and bacterial translocation. The gastrointestinal clinical toxicity requiring therapy can be predicted from the increased intestinal permeability measured with ^{51}Cr-EDTA (110).

The cytostatic drug Ara-C (cytarabine) causes histological damage to the small intestine of mice, and the extent of the inflammation and necrosis is reduced by the oral administration of physiological concentrations of short chain fatty acids (111).

ETHANOL

In chronic ethanol-fed rats, hydrophilic homologs of ciprofloxacin are absorbed at a faster rate than in control animals, whereas lipophilic homologs do not change their absorptive rate relative to control animals (112). The administration of 4% ethanol-containing solutions to healthy volunteers modifies postprandial duodenal and jejunal motility by inducing propagative motor patterns (113). Ethanol damages the lining of the stomach and intestine, and prostaglandins have a protective effect. This protective effect of prostaglandins is possibly a result of their beneficial influence on the organization and stabilization of microtubules (114).

The tumour-promoting effect of ethanol on cancers of the upper respiratory/digestive tract may be related to the first product of ethanol metabolism – acetaldehyde (115).

Clinical learning point: Ethanol results in a host of damaging effects on the structure and function of the stomach and small intestine, alters upper intestinal motility and may have a promoting effect on some cancers.

AGING

Postnatal intestinal growth is associated with structural and functional changes that occur early after birth. Feeding colostrum induces a rapid decline of glucose transport in the proximal small intestine. Within the first two days of suckling, there is a dramatic increase in glucose utilization capacity in enterocytes. The overall glucose utilization rate is doubled in suckling versus fasting two-day-old pigs. Stimulation of both the hexokinase activity and the basolateral glucose transporter (GLUT2) in the proximal jejunum accounts for this site-specific effect of suckling (116). Early intestinal development is influenced by epithelial-mesenchymal cell interactions, and retinoic acid may modify these cell interactions during intestinal development (117).

Epithelial cells of the gastrointestinal tract undergo biochemical, ultrastructural and morphological changes during the suckling period, leading to the development of a mature BBM. With aging, there is increased BBM phospholipid, cholesterol and glycosphingo-lipid content along the crypt-villus axis associated with a reduction in BBM fluidity and decreased permeability to macromolecules. Protein energy malnutrition in lactating pigs is associated with reduced BBM cholesterol, phospholipid and triglyceride. There is a sharp decline in the relative percentages of n-3 and n-6 long-chain polyunsaturated fatty acids in plasma, and these alterations in BBM lipids affect the activity of BBM hydrolytic enzymes (118).

The topic of the effect of aging on the gastrointestinal tract has been reviewed (119). The calciotropic hormone 1,25-dihydroxy-vitamin D_3 [$1,25(OH)_2D_3$] effects are mediated through a specific vitamin D nuclear receptor (a member of the superfamily receptors) that modulates gene transcription, as well as by genomic-independent mechanisms that involve the activation of signal transduction pathways. $1,25(OH)_2D_3$ regulates PKC activity by a non-genomic mechanism that involves the rapid influx of extracellular calcium (Ca^{2+}) and the activation of PKC-mediating hormonal stimulation of intestinal Ca^{2+} uptake. This process is impaired with aging (120).

With aging, the ratios of BBM cholesterol to proteins and phospholipids to proteins fall, the ratio of cholesterol to phospholipids rises, there is a decrease in BBM fluidity (increased viscosity), and the uptake of amino acids and D-glucose falls by about 50% (121).

Clinical learning point: The intestinal absorption of several nutrients is impaired with aging, in part because of physicochemical changes in the enterocyte BBM.

SUGARS AND CARBOHYDRATES

Starches are a mixture of two structurally different polysaccharides – amylose and amylopectin. Alpha-amylase is the endoenzyme found in mature human salivary and pancreatic secretions, and produces linear maltose oligosaccharides by the hydrolysis of the alpha$_{1\text{-}4}$ linkages. Hydrolysis of the nonreducing ends of amylose is carried out by BBM sucrase-isomaltase and by maltase-glucoamylase (MGA). MGA may serve as an alternate pathway for starch digestion when luminal alpha-amylase activity is reduced. MGA has two catalytic sites that are identical to those of sucrase-isomaltase, but the proteins are only 59% homologous (122). This suggests that divergences in the carbohydrate-binding sequences determine the substrate specificities of the different enzyme activities that share a conserved catalytic site.

More than 70% of adults throughout the world experience lactose intolerance and maldigestion due to a genetically programmed loss of intestinal lactase-phlorizin hydrolase (LPH) activity. Failure of the development of LPH or its downregulation in later life may lead to lactose intolerance, which is present in approximately 15% of Western Europeans and Americans, and more than 60% of Asians. The bacteria in the bowel adapt to chronic lactose

maldigestion, but the apparent improved clinical tolerance to milk of some lactase-deficient subjects over time when they are consuming lactose may be a placebo effect (123).

In adults, lactose maldigestion may give rise to a variety of gastrointestinal symptoms such as abdominal pain, diarrhea and distention. The development of gastrointestinal symptoms after a lactose challenge is associated with the amount of hydrogen excreted, and the hydrogen breath test is superior to the measurement of the blood glucose increment as a diagnostic tool for lactose malabsorption (124). The term 'lactose malabsorption' is used when a significant rise in breath hydrogen (10 to 20 parts per million or higher) is generated after an oral lactose challenge. In patients with a low ethnic risk of lactase deficiency (such as many white Europeans), the prevalence of lactose malabsorption is increased in patients with Crohn's disease and decreased in those with ulcerative colitis compared with control subjects (125). The addition *of Lactobacillus bulgaricus* to 2% milk is superior to *Lactobacillus acidophilus* to reduce the abnormal breath hydrogen and symptoms in persons with lactose maldigestion (126).

LPH is synthesized as a high molecular mass precursor comprising four tandemly repeated domains. LPH enzyme synthesis is a complex process controlled by a series of transcriptional and post-transcriptional events that culminate in the insertion of the mature protein into the BBM. Multiple levels of intramolecular interactions occur within the LPH precursor to produce the mature enzyme (127). LPH examined in transgenic mouse lines has indicated that the region from –2038 to +15 of the rat LPH gene contains regulatory elements that direct the correct tissue, cell and vertical (ie, crypt-villus) expression of LPH but may not contain all of the elements necessary for appropriate horizontal expression (ie, duodenum to ileum) and temporal control (128). LPH enzyme activity is lower in parenterally fed animals than in enterally fed animals. Parenteral nutrition decreases protein synthesis in the small intestine, yet the absolute synthesis rate of LPH is maintained (129).

Transgenic mouse technology has also been useful to characterize the *cis*-acting elements that are involved in the regulation of intestinal gene transcription, including sucrase-isomaltase (SI). A short SI gene promotor containing cis-acting elements has been described and is responsible for developmental- and differentiation-dependent transcriptional regulation of SI expression (130). Glucocorticosteroids probably have an effect on these cis-acting elements in a way that is not yet well understood.

Fructose is transported in humans by facilitative transport across the BBM by GLUT5, as well as paracellularly via glucose-activated solvent drag (131). The ontogenic changes in levels of the BBM GLUT5 mRNA correlate with the known ontogenic changes in the rates of intestinal fructose transport. In contrast, levels of GLUT2 in the basolateral membrane and the sodium-dependent glucose transporter (SGLT-1) in the BBM mRNA are relatively more elevated throughout the suckling and weaning periods than in later life (132). In neonatal rats, precocious introduction of dietary fructose enhances fructose uptake by GLUT5. The signals that regulate GLUT5 expression in weaning pups occur in the intestinal lumen (133). The corticosterone surge during weaning is not necessary for the precocious enhancement of intestinal fructose transport and of GLUT5 mRNA expression by dietary fructose (134). However, administration of prednisone or budesonide in weaning rats increases the uptake of fructose.

The topics of the molecular events involved in glucose-induced SGLT1 expression (135) and regulation of SGLT1 expression have been reviewed (136). The potential role of protein kinase modulation of SGLT1 expression has been defined in oocytes expressing rabbit SGLT1. The activation of protein kinase A (PKA) increases the maximum rate of sodium/glucose cotransport by 30%, whereas activation of PKC decreases the maximum rate of transport by 60%. A chloride ion conductance resembling the cystic fibrosis transmembrane regulator is colocalized with SGLT1 in rat and human small intestine (137), which suggests that abnormalities in glucose absorption observed in patients with cystic fibrosis may be a secondary effect of defects in chloride channel function.

The sugar content of the diet influences the expression of SGLT1, and the amount of SGLT1 correlates well with measurements of SGLT1 activity (138). In lambs, the amount of SGLT1 protein correlates with measurements of SGLT1 activity, and modulation of the activity of SGLT1 in response to luminal sugars is due to corresponding changes in the absolute levels of SGLT1 protein (138). In humans, the activity and expression of SGLT1 are maintained by the presence of luminal nutrients (139). The activation of SGLT1 (at least within oocytes) is associated with the entry of water, raising the possibility that water movement occurs through the BBM as well as across the tight junctions (140). Atrial natriuretic peptide inhibits water, sodium and glucose absorption by blocking SGLT1 through mechanisms mediated by cGMP and/or nitric oxide (141).

Clinical learning point: Water is absorbed by passive movement across the tight junctions between enterocytes but may also pass across the BBM itself when glucose transport is stimulated.

The specificity of sugars for SGLT1 includes only D-glucose and D-galactose. The rate-limiting step of the transport of the sugars across the BBM may be the conformational change (ie, isomerization) of the cotransporter that translocates both the sugar and the sodium from outside to inside the enterocyte (142). Adrenaline increases the binding ability of the SGLT1 to glucose, and phosphorylation of SGLT1 with PKA increases the binding of phlorizin, reflecting enhanced glucose transport (143). Thus, the regulation of phosphorylation of SGLT1 may lead to alterations in its function.

SGLT1 may be upregulated by EGF, which also increases sodium uptake, and these altered transport changes are associated with an increase in the activity of sodium/potassium adenosine triphosphate (144). The EGF-associated transport changes are due to alterations in the maximal transport rate (Vmax) but not in the affinity constant (Km). This stimulatory effect of EGF is greater when it is applied to the basolateral membrane than when it is applied to the BBM.

The duodenojejunal segmental absorption rates of water and glucose produced by a rapid and sustained gastric emptying rate cannot be increased by delivering a greater load of glucose and water by intestinal perfusion (145). The use of an alpha-glycohydrolase inhibitor reduces glucose absorption by inhibiting disaccharide digestion, and this inhibition delays subsequent monosaccharide absorption. In addition, acarbose (an alpha-D-glucosidase inhibitor) decreases glucose absorption and accumulation within the enterocyte, possibly by actin directly on SGLT1 (146).

With chronic inflammation of rabbit ileum, coupled sodium chloride absorption is reduced because of an inhibition of chloride/bicarbonate, but not of sodium/hydrogen ion expression in the BBM. The reduced glucose uptake is also associated with diminished abundance of SGLT1 protein and mRNA levels (147). Experimental cirrhosis in rats is associated with reduced galactose transport in everted jejunal rings, and this malabsorption is corrected after the administration of IGF-1 (148).

The addition of enkephalins to the serosal side of the intestine stimulates D-glucose absorption by interacting with mu-receptors located in the myenteric plexus of rabbit ileum (149). Changing from a low to a high carbohydrate diet upregulates glucose transport by a process in which the effector compartment is in the intestinal crypt and in which vagal afferents are involved in the sensing and integrative process (150). The uptake of L-lactate by rat jejunal enterocytes is facilitated by both sodium and hydrogen gradients (151). Glucagon-37 (also named oxyntomodulin) increases intracellular cyclic AMP concentrations and enhances intestinal glucose absorption (152).

AMINO ACIDS, PROTEINS AND FOOD ALLERGIES

Taurine is one of the major intracellular beta-amino acids, and it plays an important role in osmoregulation, antioxidation and detoxification processes. The requirements for taurine in mammals are met by dietary sources and by biosynthesis. In newborns, the biosynthetic capacity for taurine is low. Some amino acid transporters are subject to adaptive regulation. In Caco-2 cells, the taurine transporter is regulated by PKC. The activity of taurine transport is downregulated in cultured cells containing taurine, and this is also associated with reduced mRNA levels of the transporter (153). The sodium-dependent carrier-mediated process decreases in activity with age (154). In Caco-2 cells, dexamethasone and lipopolysaccharide downregulate taurine uptake (155).

Reverse transcription-polymerase chain reaction (RT-PCR) and restriction enzyme analysis of the RT-PCR products indicate that the human intestine and the human kidney proximal tubular cell line express the neutral amino acid transporter B^0 (ATB^0) that is identical to the ATB^0 expressed in Caco-2 cells (156). Caco-2 cells have been used to characterize the efflux of L-lysine across the basolateral membrane. Different mechanisms operate in the basolateral efflux of L-lysine, depending on the extracellular availability by their amino acids (157). Using an in vivo perfusion method in isolated rat intestine, it has been shown that surgical bowel manipulation causes a decrease in the active transport of glucose, as well as of proline and leucine (158).

The BBM sodium-dependent transporter of branched-chain and aromatic amino acids has been characterized. The neutral amino acid transport in rabbit jejunum and in Caco-2 cells has been cloned (156). The absorption of L-leucine is inhibited by serotonin by a process that include 5-hydroxytryptamine $(5\text{-HT})_2$, 5-HT_3 and 5-HT_4 receptors (159). The uptake of glutathione by human small intestinal epithelial cells is by a sodium-independent transport system (160).

The biology and function of active dipeptide and tripeptide (oligopeptide) transporters in the human intestine have been reviewed (161). The peptide transporter in the BBM is proton-dependent and sodium-independent, and this carrier shows affinity toward a broad range of peptide-like drugs such as beta-lactam antibiotics and angiotensin-converting enzyme inhibitors (162). The affinity of the peptide transporter can be altered by chemical substitution such as esterification of the free carboxylic acid moiety, introduction of a second negative group and steric hindrance of the free carboxylic acid (163). The transport rate of the peptide transporter is influenced by BBM peptidases, and the intracellular pathway probably involves transcytosis (164). The dipeptide transport can be inhibited by a variety of drugs and chemicals, such as vitamin E (165).

Clinical learning point: Some drugs are absorbed by the BBM peptide transporter.

The intestinal hydrogen ion/peptide symporter (PepT1) is driven by a transmembrane proton gradient and mediates the symport of substrates with the hydrogen ion. The impairment of peptide absorption in patients with CD is less than for amino acid absorption. In rats exposed to 5-fluorouracil, there is a reduction in the activities of sucrase and SGLT1, but the amount of PepT1 protein remains largely unaffected (166). The presence of a peptide bond is not a requirement for rapid translocation by PepT1 (167). Only the trans conformation is transported by PepT1 (168). The uptake of phenylalanylglycine can be enhanced by the covalent attachment of butyric on caproic acid to the N-terminal of phenylalanylglycine (169).

The uptake of polyamines by the basolateral membrane of the enterocyte is by a saturable high-affinity transport

system (170). Alpha-lactalbumin increases cell replication in Caco-2 cells (171). In a mouse model of food-sensitive enteropathy, reducing the cell membrane levels of n-6 fatty acid by feeding less n-6 fatty acids or supplementing the diet with n-3 fatty acids reduces mucosal damage (172).

Oral delivery of peptide drugs is restricted by their susceptibility to enzymatic metabolism and by their physicochemical properties, which limit their membrane permeation. A positive net charge of hydrophilic peptides enhances their permeation across the intestinal mucosa via the paracellular pathway. However, the effect of the net charge becomes less important with molecules of larger molecular weight (173).

Intestinal cells have a poor capacity for the biosynthesis of nucleosides and rely on nucleoside transport proteins in the BBM for efficient salvage of luminal nucleosides from the diet and from catabolized nucleotides from sloughed epithelial cells. There are multiple transporters for nucleosides across cell membranes, and five subtypes of sodium-dependent nucleoside transporters have been identified. The N1 purine-specific and the N2 pyrimidine-specific transporters are present in the human jejunum (174). Sodium-dependent nucleoside transporters are present in the human jejunal BBM, and they have broad substrate selectivity for purines and pyrimidines (175). Sodium-independent nucleoside transporters are expressed on the basolateral membrane.

Antigen transport across the intestine occurs through specific and nonspecific mechanisms. Macromolecules are absorbed in immunologically significant amounts by two functional transcellular pathways – one degradative and the other involving direct transcytosis of intact macromolecules. Antigens and pathogens in the gut normally penetrate the mucosal barrier, albeit infrequently, only through gateway cells called M cells. These M cells are located over subepithelial lymphoid follicles called Peyer's patches. Peyer's patches have a specialized transport mechanism, and IFN-γ increases macromolecular transport before gut maturation across the Peyer's patches (176). The M cells transport soluble and particulate antigens across their cytoplasm. M cells subsequently trigger the induction of secretory immunity by the delivery of the luminal antigens to the antigen-processing and antigen-presenting cells in the lymphoid follicles. Enterocytes can be induced to switch to an M cell phenotype as a result of information provided by lymphocytes derived from Peyer's patches (177).

Clinical learning point: Immunologically important amounts of antigens and pathogens are transported across the intestine by M cells as well as by the antigen-presenting enterocytes. IFN-γ and other proinflammatory antigens may enhance this protein absorption and possibly contribute to food allergies.

In antigen-presenting cells, exogenous proteins are also taken up by endocytosis. The proteins are then processed by cathepsins into peptides of 13 to 17 amino acids that are able to bind to MHC class II molecules. The MHC II/peptide complex is translocated to the external membrane for direct presentation to lymphocytes. Proinflammatory cytokines such as IFN-γ are secreted by lymphocytes in the intestinal mucosa in pathological conditions. Under these circumstances, the enterocytes upregulate both MHC class II molecule expression and epithelial permeability to small molecules and macromolecules. IFN-γ stimulates the transport and processing of proteins such as horseradish peroxidase (HRP), thereby increasing the antigenic load to the intestinal mucosa (178).

The macromolecular probe HRP has been used to study enterocyte handling of macromolecules. In HT29 intestinal cells, HRP fluxes comprise 50% amino acids, 40% peptides and 10% intact HRP (178). Proinflammatory cytokines such as IFN-γ are secreted by lymphocytes in the intestinal mucosa in inflammatory bowel conditions, and in these situations, the enterocytes upregulate both MHC class II molecule expression and epithelial permeability to small molecules and macromolecules. IFN-γ stimulation increases HRP flux without modification of the relative proportions of amino acids, peptides or intact HRP. This raises the possibility that during inflammatory conditions where levels of proinflammatory cytokines are increased, the antigenic load in the intestinal mucosa may be enhanced.

Absorption of macromolecules can occur under certain circumstances and can contribute to diseases such as food hypersensitivity. Bromelain, a biologically active plant protein present in pineapple stem and fruit, has been used as a model protein to study the intestinal absorption of undegraded proteins in humans (179). Antigen absorbed into the intestine results in the release of a number of active mediators including histamine, serotonin and prostaglandins. These mediators stimulate net ion secretion from epithelial cells. Antigen added to the luminal side of isolated segments of jejunum evokes a rapid secretory response. Specific sensitization enhances the initial uptake and transcytosis of antigen across rat intestinal epithelium. Subsequent to activation of mast cells, antigen transport is enhanced further by its penetration through the paracellular pathway (180). Microspheres have also been used to assess permeation of large molecules. The composition of the diet is important in gastrointestinal transepithelial translocation of these microspheres (181). Bovine serum albumin can also pass from the serosa into the intestinal lumen by a process that is saturable, energy-dependent and involves microtubules, but that is not under neural regulation (182).

A small proportion of the population experiences food intolerance by a mechanism that involves an immunological reaction to foreign protein classified as a type 1 immediate, IgE-mediated hypersensitivity reaction. Activation of mast cells contributes to the clinical manifestations of gastrointestinal anaphylaxis. This process can be inhibited by a novel peptide, submandibular gland peptide-T (183). Mast cells mediate the alterations in ion transport that

occur with intestinal tissue obtained from patients with inflammatory bowel disease (184).

The diagnosis of food allergy is difficult because laboratory tests such as skin testing are of limited value in confirming or excluding the diagnosis. A new diagnostic approach for intestinal food allergy is the colonoscopic allergen provocation test, which may be a useful diagnostic measure in patients with suspected intestinal food allergy (185). This test needs to be studied further before it can be recommended for widespread use.

A sensitive dot blot chemiluminescence assay has been developed to study protein binding to small intestinal BBM vesicles (186). By using this assay, saturation of BBM binding of food proteins such as gliadin peptides, alpha-casein, beta-lactoglobulin and ovalbumin has been demonstrated.

Clinical learning point: A sensitive dot blot chemiluminescence assay may be used to demonstrate protein binding to the intestinal BBM. The use of this technique to study food allergies remains to be established. In the future, the colonoscopic allergen provocation test may prove to be useful to diagnose patients with suspected intestinal food allergy.

BBM MORPHOLOGY AND CELL TURNOVER

The topics of cell adhesion and migration (187), and epithelial cell growth and differentiation (188) have been reviewed. There are no specific intestinal stem cell markers, and the topic of the various experimental techniques used to infer stem cell properties has been reviewed (189). The digestion and absorption of nutrients by the small intestine depend on the coordinated expression of specialized genes in the enterocytes. Little is known about the basis for the differences in gene expression that occur along the length of the intestine. These differences may result from variations in transcription factors that interact with the promoter enhancer regions of these genes. Indeed, homeodomain transcription factors (the homeobox genes) are involved in establishing gradients of differentiation during intestinal development and in maintaining these patterns of expression through continued expression in adult tissues. Cdx-2 interacts with the promoters for several genes that are expressed in the intestine, including sucrase-isomaltase. The use of RT-PCR in human tissue has demonstrated numerous homologs of the homeobox transcription factors, and these vary between the proximal and distal intestine (64). The homeobox gene expression in mouse intestine is influenced by epithelial mesenchymal cell interactions (190).

The role of the homeobox genes in the intestine have been explored in Caco-2 cells; overexpression of Cdx2 stimulates sucrase-isomaltase and lactase expression in cells in which the endogenous expression of Cdx2 is reduced by antisense RNA attached poorly to the substratum (191). Cdx2 overexpression also modifies the expression of molecules such as E-cadherin involved in cell-cell and cell-substratum interactions. The role of E-cadherin-catenin in the maintenance of intestinal epithelial homeostasis has been reviewed (192).

The addition of fibre to an elemental diet is associated with increased intestinal mass as well as epithelial cell proliferation; fibre decreases the levels of enteroglucagon and peptide YY observed in germ-free animals. This suggests that the effects of fibre are both direct and indirect, with fermentation-derived products influencing plasma hormones (193). Supplementing the murine diet with pectin increases the intestinal crypt depth and villus height compared with those of mice fed cellulose (194). It is unknown whether pectin affects intestinal digestive and transport capabilities.

The asialoglycoprotein receptor is a model for receptor-mediated endocytosis and for intracellular protein trafficking to the basolateral membrane (195). Intravenous administration of the tachykinins neurokinin A, neurokinin B and substance P increases the production of malondialdehyde in the stomach, duodenum and jejunum. This reflects the influence of these tachykinins on the liberation of free radicals and lipid peroxidation (196).

Mucins lubricate and protect the epithelium because of their hydrophilic gel nature. The hydrophilic and viscoelastic properties are due to the content of glycoproteins that are collectively known as mucins. These are large, heterogeneous and highly glycosylated proteins in which the majority of the carbohydrate side chains are O-linked to threonine and serine residues of the polypeptide backbone. There is considerable mucin heterogeneity, and in humans, at least nine different mucin genes encode epithelial mucins. The mucosa of the intestine is covered by a mucous gel layer comprised of glycoproteins that are synthesized by the mucosal epithelium. The mucins (mucous glycoproteins) are either secretory or membrane bound, and contain many tandemly repeated amino acid sequences that are rich in serine and threonine residues. These tandem repeats are unique for each mucin, may vary in number among individuals and are densely O-glycosylated. Mucin expression is tissue- as well as cell-type specific, with MUC2 detected throughout the goblet cells of the small and large intestine and MUC3 detected in the enterocytes of the duodenum and jejunum (197). MUC3 contains two EGF motifs and a putative transmembrane domain (198). Expression of MUC3 is detected in the small intestine and colon from 13 weeks' gestation (199). The MUC3 gene is large and complex, and encodes for a large glycoprotein with a structure different from that of other mucins (200). The phospholipids in mucus play a role in the barrier function of the intestine and the total phospholipid content of mucus falls with age (201).

Cytochrome P-450 comprises a superfamily of proteins that catalyse the oxidation of numerous xenobiotics such as drugs and chemical carcinogins. Several forms of P-450 are present in the intestine (202). The new human cytochrome P-450 arachidonic acid epoxygenase (CYP2J2) is expressed

in the small intestine and colon. CYP2J2 products may be involved in the release of intestinal neuropeptides influencing motility and transport (203).

The topic of reactive oxygen species and antioxidants in spinal transduction and gene expression has been reviewed (204). The transmembrane BBM enzymes aminopeptidase N and sucrase-isomaltase reside in a glycolipid-rich environment. The protein galactin-4 also has an extracellular location, is secreted by a nonclassical pathway and is a member of a novel class of natural ligands (205).

Chlorinated hydrocarbon insecticides are used on a large scale in developing countries. Insecticides such as lindane (the g isomer of hexachlorocyclohexane) may be ingested with food. Lindane increases the intestinal uptake of glucose and reduces that of glycine and calcium in well nourished animals. In contrast, feeding lindane to malnourished animals increases the uptake of glucose, glycine and calcium, and depresses the BBM activity of sucrase, alkaline phosphatase and peptidases (206). Thus, the nutritional state of the animal alters the effect of insecticides on the intestinal uptake of nutrients.

Clinical learning point: The nutritional state may influence a person's susceptibility to insecticides and possibly other toxins.

The intestinal epithelium is characterized by rapid cell turnover, with pluripotent stem cells in the crypts of Lieberkühn providing a continuous supply of cells that are directed into a variety of maturation pathways. The development and maintenance of normal intestinal morphology require regulation of the daughter cells' proliferative status, lineage allocation, migration, differentiation and apoptosis. The topic of the physiology and pathophysiology of apoptosis in the intestine has been reviewed (207).

The topic of the growth factors that are important in the intestinal epithelial cell growth and differentiation has been reviewed (208). EGF is trophic to the intestine. When EGF levels are reduced by sialoadenectomy in mice, luminal EGF levels fall and intestinal permeability to EDTA is increased (209). A two-week subcutaneous infusion of EGF to Sprague-Dawley rats increases the intestinal absorption of galactose and glycine, as well as DNA and protein content (210). Thus, EGF plays a role in the maintenance of ileal mucosal integrity and alters intestinal transport function.

EGF receptor (EGFR) ligands and phosphatidylinositol phospholipase C are involved in the process of cell migration. The EGFR responsiveness to EGF is mediated by the surface expression of high affinity EGFR, which is associated with the cytoskeleton and related signalling proteins (211). EGF-stimulated intestinal cell migration requires intact EGFR tyrosine kinase, phospholipase and PKC activities (214). PKC consists of a family of serine- and threonine-specific protein kinases that play an important role in transmembrane signalling for a number of cellular processes, including growth and differentiation. There are at least 11 isoenzymes of PKC; in Caco-2 cells, PKC-α but not other isoforms of PKC modulate the proliferation and differentiation (213).

An EGFR raf-dependent mechanism is necessary for Ras but not for src transformation of intestinal epithelial cells (214). Polyamines (putrescine, spermidine and sperminine) are involved in DNA, RNA and protein synthesis and thus the polyamines are essential for cell proliferation and growth. Putrescine is taken up from the systemic circulation by the small bowel and is converted to succinate. Uptake and conversion increase with fasting, suggesting that putrescine may be an energy source for the small intestine (215). ODC is the rate-limiting enzyme of polyamine synthesis. ODC activity is higher and more putrescine is found in the nonproliferating epithelial cells of the villi than in the crypts. Prefeeding after a fast markedly increases the ODC activity in the intestine, with the greatest activity occurring in the villus tip cells and at the villus-crypt junctional area (216). Exogenous but not de novo-formed histamine competes with putrescine incorporation into enterocyte as catalyzed by transglutaminase activity (217).

IGF is a class of low molecular weight growth-promoting peptides. IGF-1 and IGF-2 are present in a variety of biological fluids, including mammalian milk. IGF is stable in the lumen of the intestine, and this stability increases with age (218). This raises the possibility that milk-borne IGF has biological activity in the intestine. The intestinal atrophy that occurs with TPN can be reduced by IGF-I but not by GH. IGF-I but not GH stimulates crypt cell proliferation. IGF-I and GH independently and synergistically stimulate one of the IGF binding protein mRNAs (219). GLP-2 plus either GH or IGF-I causes a greater increase in histological parameters of small intestinal growth in mice than does GLP-2 alone (208).

GLP-2 promotes intestinal epithelial proliferation by increasing the crypt cell proliferation rate, and by decreasing the enterocyte apoptotic rate (220). The administration of GLP-2 to mice for 10 days increases small intestinal weight RNA and protein content, and increases the activities of maltase, sucrase, lactate and other brush border enzymes (221).

Various growth factors and cytokines present in the epithelium or LP of the intestinal mucosa modulate epithelial cell migration and growth in vitro. Hepatocyte growth factor is present in high concentrations in amniotic fluid and stimulates intestinal epithelial cell migration during the development of the fetal small intestine (222). Gut-enriched Kruppel-like factor is a transcription factor that plays a role in gut development and tumorigenesis in mice (223).

The mitogen-activated protein kinase pathways are a major signalling system by which cells transduce extracellular signals. In the intestinal epithelial cell-6 model of wounded monolayers, tyrosine phosphorylation of several proteins (including ERK1) was rapidly increased; c-Jun-M-terminal protein kinase was also increased.

Activation of ERK1 and ERK2 is mediated in part by TGF-α (224). Epithelial cell kinase is a member of a large family of receptor tyrosine kinases that may also play a role in epithelial cell development, migration and barrier function (225).

Intestinal trefoil factor is a small peptide secreted by intestinal goblet cells that maintains mucosal integrity and promotes epithelial wound healing. A putative receptor for intestinal trefoil factor, a 50 kDa membrane glycoprotein, has been described in the rat small intestine using in situ binding and ligand blotting (226). Prostaglandins are also cytoprotective for the gastrointestinal epithelium.

Prostaglandin E_2 (PGE_2) and PGF_2 have a synergistic role in the restoration of intestinal barrier function, acting to increase intracellular cAMP and Ca^{2+}, which in turn signal cytoskeletal-mediated tight junction closure (227).

The pattern of fetal porcine small intestinal development is similar to that reported for fetal human small intestine. The fetal pig may be a good model to use for investigations of human small intestinal development (328).

DIABETES MELLITUS

Patients with long standing insulin-dependent diabetes mellitus develop absorption and motility abnormalities in the intestine. The abnormal postprandial duodenal chyme transport is characterized by disturbed chyme clearance (229). Duodenal bicarbonate secretion is reduced in diabetic rats due to vagal-dependent neuronal dysfunction, and to decreased sensitivity of the bicarbonate secreting cell (230). Acute hyperglycemia inhibits gastric and pancreatic secretion, gallbladder motility and gastric emptying. Acute hyperglycemia upregulates GLUT2 activity in the basolateral membrane of the enterocyte. In healthy volunteers, hyperglycemia prolongs the duodenal-cecal transit time, increases duodenal migrating motor complex cycle frequency and inhibits antral motility (231). Hyperinsulinemia reduces antral motor activity but has no effect on interdigestive duodenal motility or duodenal-cecal transit time, suggesting that factors other than insulin mediate the inhibitory effect of hyperglycemia on interdigestive intestinal motility and transit.

In streptozotocin-treated diabetic rats, there is increased intestinal glucose and fructose transport associated with increased BBM levels of SGLT-1 and GLUT5, enhanced basolateral membrane GLUT2 and increased GLUT1 in the basolateral membrane and BBM. Insulin treatment in diabetic rats increases GLUT1 levels in the BBM but does not affect the expression of the protein in the basolateral membrane (232). Diabetes hyperpolarizes the BBM, resulting in a greater driving force for sodium-dependent BBM sugar transport by SGLT1 (233).

The premature induction of BBM enzymes by exogenous insulin is mediated by the binding of the hormone to its intestinal receptor. Binding of insulin to the extramembranous domain of the intestinal receptor induces a conformational change allowing phosphorylation of the tyrosine kinase domain. This binding of insulin to its receptor is higher in the crypt than in villus cells, and is higher in the ileum than in the jejunum. The BBM activities of lactase and sucrase fall with age, by a process that likely involves a post-transcriptional process (234). The age-related decrease in insulin binding is the result of a decline in low and high affinity receptor classes, without any change in the affinity constants (235).

Insulin suppresses the development of diabetes in non-obese diabetic mice and alters the balance from a T helper (Th) 1 to a Th2 type cytokine pattern in inflamed pancreatic islets. When low doses of oral insulin are given in conjunction with an adjuvant, there is upregulation of IL-4 Th2 cells in infiltrated islets and sustained local IL-2 gene expression. The same shift to the Th2 type reactivity and downregulation of inducible NOS in the intestine is also observed with low doses of insulin (236).

BB rats spontaneously develop insulin-dependent diabetes mellitus around or after puberty. The nature of the insulinitis may vary between 'benign' and 'beta-cell destructive' damage. Th2-type cytokines such as IL-4 and IL-10 are associated with benign insulinitis. Th1-type cytokines such as IFN-γ and IL-2 dominate during destructive insulinitis and are associated with progression to diabetes. The nature of the dietary fat may influence the development of diabetes in BB rats; changing the type of fat in the diet does not affect the rise of IFN-γ gene expression or the influx of leukocytes into the islets, but all the fat-enriched diets lead to significantly higher IL-10 mRNA levels (237).

ABDOMINAL IRRADIATION AND CHEMOTHERAPY

Acute radiation enteritis is a common occurrence after abdominal radiotherapy. This enteritis is associated with anorexia, nausea, diarrhea and weight loss. Following radiotherapy, the rate of small intestinal transit is increased. Following irradiation in ferrets, there is an initial increase in the frequency of the ileal pressure waves (238), followed by a nonsignificant reduction in the frequency but not the amplitude of ileal pressure waves.

Clinical learning point: Abdominal radiation may accelerate small intestinal transit, which may contribute to symptoms such as diarrhea.

The radiosensitivity of proliferating intestinal crypt cells makes the intestine a major limiting factor in the use of radiotherapy for the treatment of abdominal cancers. The presence of a deficiency of the tumour suppressor p53 sensitizes clonogenic cells to irradiation in the large but not in the small intestine (239). Thus, the greater radioresistance of the crypts in the colon than in the small intestine may be partially attributable to the presence of p53. The signals initiated by cycling enterocytes may be transmitted to the crypt epithelium to induce p53 and to reduce their ionizing irradiation-induced apoptosis (240). While p53 may play a key role in determining the fate of cells that have received

potentially carcinogenic DNA damage, there is also a p53-independent mechanism that permits the engagement of apoptosis following gamma irradiation (241). The radioresistance of the villous enterocytes is not due simply to their cell cycle arrest.

Prostaglandins modulate gut epithelial cell proliferation and survival. Prostaglandins are synthesized from arachidonic acid by either of two cyclo-oxygenases (COX) – COX-1 or COX-2. COX-1 is constitutively expressed, and COX-2 is inducible by cytokines and by various other stimuli. Indomethacin, an inhibitor of COX-1 and COX-2, further reduces the number of surviving crypt cells in irradiated mice (242). Dimethyl PGE_2 reversed the indomethacin-induced decrease in crypt survival, whereas selected COX-2 inhibitors had no effect on crypt cell survival. This suggests that radiation injury results in increased COX-1 levels in the crypt stem cells and their progeny and that PGE_2 produced through COX-1 promotes crypt stem cell survival and proliferation.

Clinical learning point: Radiation may increase the constitutively expressed COX-1 in the intestine, and nonsteroidal anti-inflammatory drugs such as indomethacin may worsen this radiation-induced damage. The role of prostaglandins in protecting the intestine from the development of radiation enteritis remains to be determined.

Methotrexate (MTX) is used in the management of patients with osteosarcoma, rheumatoid arthritis and inflammatory bowel disease. Some patients treated with MTX experience nausea, vomiting, diarrhea, gastrointestinal ulceration, stomatitis and mucositis. The surface area of the intestine may be reduced by MTX treatment, and there may be associated diminution in the absorption of some drugs. Following MTX administration to mice, intestinal permeability to phenol red and fluoresceine isothiocyanate is increased (243). The side effects of MTX in humans can be reduced by the coadministration of folic acid (244).

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