Small bowel review: Part I

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ABR Thomson, M Keelan, A Thiesen, MT Clandinin, MJ Ropeleski, G Wild. Small bowel review: Part I. Can J Gastroenterol 2000;14(9):791-816. In the past year, there have been many advances in the area of small bowel physiology and pathology. More than 1500 papers were assessed in preparation for this review. Some were 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: *Absorption; Adaptation; Celiac disease; Motility; Secretion*

Revue de l'intestin grêle : 1re partie

RÉSUMÉ : 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 les points importants à retenir pour l'apprentissage clinique. Les sujets traités sont très diversifiés et les articles présentent, dans la mesure du possible, un lien logique entre la physiologie, la physiopathologie, les troubles cliniques et le traitement.

GASTROINTESTINAL HORMONES AND PEPTIDES

The topic of the biology of gut cholecystokinin (CCK) and gastrin receptors has been reviewed (1). Hyperinsulinemia increases plasma noradrenaline concentrations as well as muscle sympathetic nerve activity, even in the absence of hypoglycemia. In guinea pig-isolated ileal synaptosomes, insulin stimulates in a concentration-dependent manner the secretion of noradrenaline. This is mediated by signalling that involves insulin receptors through downstream activation of calcium influx (2). The luminal CCK-releasing factor is present throughout the gastrointestinal tract. Immunohistochemical analysis shows diffuse CCK immunoreactivity throughout the gastrointestinal tract and the pancreas (3).

Luminal nutrients and neuroendocrine peptides exert differential effects on somatostatin-28 release from the rat intestine compared with those of somatostatin-14 (4). The somatostatin analogue octreotide is effective in the treatment of the diarrhea and flushing that occur in patients with carcinoid syndrome. Octreotide retards colonic and small bowel transit. This action may be mediated by the associated reduction in circulating levels of peptide Y (PYY), neurotensin, vasoactive intestinal polypeptide (VIP) and substance P (SP); however, octreotide has no effect on plasma motilin concentrations (5). The topics of VIP and secretin receptors, and the G protein-coupled receptors have been reviewed (6).

The inactive proforms of gastrointestinal peptide hormones and neuropeptides (such as VIP, PYY and glucagon-like peptides) are processed in part by specific endoproteases through selective cleavage at the C-terminal side of paired basic amino acid sites. Prohormone convertase (PC)-6A mRNA is expressed throughout the entire gastrointestinal tract, with the highest levels in the small intestine (7). Ileal PC-6A mRNA expression increases with fasting and declines with refeeding, whereas dietary fat increases PC-6A mRNA levels in the ileum.

Neuropeptide Y (NPY) and PYY are structurally related peptides that mediate inhibitory activity in terms of gastro-

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Received for publication February 12, 1999. Accepted September 23, 1999

intestinal motility, secretion and blood flow. NPY receptors are present in the rabbit ileum and are subject to interaction by receptor antagonism (8). Several receptor subtypes of these peptides have been identified and cloned. Double immunofluorescence studies demonstrate that subpopulations of Y1 receptor-positive nerve cell bodies are immunopositive for NPY, VIP and nitric oxide synthase (NOS) (9). The Y receptor subtypes for PYY, NPY and pancreatic polypeptide bind to intestinal receptors and exert an antisecretory effect (10). Intestinal fluid secretion occurs in conjunction with some enteric infections and is mediated by prostaglandin (PG) H synthase (11).

After raising the intraluminal pressure, serotonin is released into the cytoplasmic matrix and then diffuses or is transported into the intestinal lumen (12).

INTESTINAL INFECTIONS AND INFLAMMATION

The bacterial, viral and parasitic infections of the intestine have been reviewed (13-15). Also reviewed are the topics of gastrointestinal infections in children (16) and their treatment (17). The Practice Parameters Committee of the American College of Gastroenterology has suggested guidelines for the care of adults with acute infectious diarrhea (18).

***Entamoeba histolytica*:** *E histolytica* is caused by two genetically distinct species, the invasive parasite *E histolytica* (which is the etiological agent of amoebic colitis and liver abscess) and the noninvasive *Entamoeba dispar*. A new approach to the detection of *E histolytica* and *E dispar* is based on antigen detection in the stool (19). In the severe combined immunodeficient mouse-human intestinal xenograft model of disease, infecting the human xenografts with *E histolytica* trophozoites increases the production of interleukin (IL)-1 and IL-8 (20). Humans are the only important host for *E histolytica*, and an effective vaccination program could potentially eradicate amebiasis. In gerbils, protective immunity against *E histolytica* after vaccination is correlated with the development of an antibody response to a region of 25 amino acid residues of the galactose- and *N*-acetylgalactosamine-inhibitable lectin (21). The use of such vaccines would be of great value in countries where the environmental conditions are not ideal.

***Giardia lamblia*:** *G lamblia* is a highly relevant gastrointestinal protozoal disease that usually manifests as a self-limited clinical course. Trophozoites are usually found in the mucosa of the duodenum (83%), ileum (12%), gastric antrum (9%) and jejunum mucosa (2%) (22). In less than 5% of giardia-infected subjects, the histological lesion resembles celiac sprue in the mild intestinal villus shortening, as well as inflammation in the lamina propria.

***Yersinia enterocolitica*:** The enterobacterium *Y enterocolitica* causes a broad range of gastrointestinal syndromes, ranging from acute enteritis and enterocolitis to mesenteric lymphadenitis. *Y enterocolitica* invades M cells located in the follicle-associated epithelium overlying Peyer's patches, and this infection results in the secretion of IL-8 (23). The clinical relevance of this cytokine production is unknown.

***Vibrio cholera*:** Both *V cholera* and enterotoxigenic *Escherichia coli* (ETEC) colonize the small intestine and produce diarrhea by elaborating enterotoxins. The secretory effect of cholera toxin (CT) and of the heat-labile ETEC declines in the aboral direction along the small intestine. In contrast, the effect of the heat-stable ETEC is greatest in the distal small intestine. Mucosal glucose and amino acids stimulate electroneutral and electrogenic sodium ion absorption to the same degree in the normal and cholera-treated small intestine. This is the physiological basis for placing glucose in oral electrolyte replacement solution. There is no segmental difference in stimulated electroneutral sodium chloride absorption, while electrogenic sodium ion absorption is highest in the mid and distal portions of the small intestine (24).

V cholera liberates its classic CT, a zonula occludens toxin. A membrane-damaging toxin, a hemolysin, also known as the *V cholera* cytolysin, is a second type of vibrio exotoxin. *V cholera* cytolysin produces pores in the enterocyte, resulting in ATP depletion and cell death (25). These toxins interact with specific high-affinity receptors on the intestinal brush border membrane (BBM). This activates adenylate cyclase within the enterocytes, thereby increasing the cellular concentration of the second-messenger 3':5'-cAMP. The CT then ribosylates alpha subunits of G protein (Gs), inhibiting GTPase activity, which results in maintenance of Gs in its activated state (simulating adenylate cyclase). This increase in cAMP results in secretory diarrhea.

***E coli*:** In the critically ill patient, translocation of enteric bacteria across the intestinal mucosa is thought to play a critical role in the pathogenesis of multiple organ failure. The interaction between enteric bacteria and their products with enterocytes, the influence of gut-associated lymphoid tissue and the secretion of cytokines by the enterocyte may alter intestinal function. Polarized monolayers of human enterocytes (Caco-2 cells) in culture increase the secretion of IL-6 and tumour necrosis factor (TNF) upon stimulation with *E coli*) (26). The cytokines may 'crosstalk' with mucosal mononuclear cells as well as with neutrophils, and may modulate intestinal epithelial barrier function. Also, the cytokines may increase enterocyte surface expression of molecules such as major histocompatibility complex antigens. Interferon (IFN)- and IFN- are upregulated by rotavirus infection, suggesting that cytokines also play a role in host defence against viral agents (27). While proinflammatory cytokines can be detected in biopsy specimens from the intestinal mucosa of individuals with inflammatory bowel disease (IBD), celiac disease or infectious colitis, their precise pathophysiological role in these diseases remains to be determined.

Clinical learning point: Cytokines modify intestinal function, and some may play a role in host defence against infections.

There is a growing body of evidence that suggests that enterocytes function as 'nonclassical' immune cells. Specifi-

cally, enterocytes play a major role as a source of proinflammatory cytokines and cytotoxins. A key proinflammatory mediator produced in the intestinal mucosa is the free radical nitric oxide, which is synthesized by inducible NOS (iNOS). Bacterial-induced expression of iNOS in Caco-2 cells induces the synthesis of nitric oxide, which can be blocked by inhibitors of nuclear factor kappa B such as glucocorticosteroid (GC) and of tyrosine kinase activation (28).

ETEC causes significant morbidity and mortality in children as well as in travellers. ETEC produces a heat-labile toxin and/or a heat-stable enterotoxin (either STa or STb). *E coli* 0157:H7 is increasingly recognized as a cause of bacterial diarrhea in the United States, and molecular subtyping methods are used to discriminate the various strains of the organism (29). In some geographic areas and in some age groups, isolation proportions from fecal specimens for *E coli* 0157:H7 surpass those of other common enteric pathogens (30). STa is an important causative agent of diarrheal disease. STa binds to specific receptors in the intestine, activates the guanylate cyclase C receptor, elevates cGMP levels and stimulates chloride secretion via cystic fibrosis (CF) transmembrane conductance regulator (CFTR). Knockout mice lacking guanylate cyclase C receptor are refractory to the secretory action of STa (31). Pharmacological inhibition of guanylate cyclase C and/or blocking of the guanylate cyclase C receptor could be targets for possible therapy in *E coli* infections.

With verotoxin (VT)-producing *E coli*, the diarrhea may be associated with hemorrhagic colitis and with the hemolytic uremic syndrome. Human intestinal epithelial cells (IECs) lack a receptor for VT, but VT-producing *E coli* bacterial strains lower the transmonolayer resistance of cells in culture. Immunoelectron microscopy confirms the transcellular transport of VT (32).

Enteropathogenic *E coli* (EPEC) are an important cause of gastroenteritis in infants under the age of one year. EPEC infections may lead to reductions in both villous height and the ratio of the villous height to crypt length (33). EPEC induce phosphorylation of the 20 kDa myosin light chain and thereby alter intestinal epithelial permeability (34).

Binding of *E coli* to the 32 to 33 kDa BBM proteins plays an important role in bacterial colonization (35). EPEC are not invasive and result in diarrhea as the result of a characteristic 'attaching and effacing' lesion in the BBM. After the initial attachment, signal transduction to the host cells leads to disruption of the BBM cytoskeleton and effacement of the microvilli. This is followed by further adhesion of bacteria to the BBM and accumulation of host cell cytoskeletal elements beneath the attached bacteria. Signal transduction to the host cells requires EPEC-secreted proteins. After initial adhesion, EPEC stimulate chloride secretion via CFTR, for which signal transduction to the host cells is a prerequisite (36). Infection with EPEC activates nuclear factor kappa B, which in turn initiates transcription of the anti-inflammatory cytokine and IL-10 (37). A pathogenic island of 35 kilobases, known as the 'locus of enterocyte effacement', achieves this effect by encoding an outer membrane adhesin called 'intimin', a type III secretion apparatus, as well as EspA, EspB and a new gene *esp*D (38). The EspD protein is secreted via the type III apparatus.

Enteroaggregative *E coli* are also an important cause of persistent diarrhea, especially in children in the developing world. These *E coli* release IL-8 from Caco-2 cells by way of a new heat-stable, high molecular weight protein (39). Enteroaggregative *E coli* may be a cause of outbreaks of gastrointestinal illness (40).

A proteolytic extract obtained from a chemical in pineapple, known as bromelain, prevents intestinal fluid secretion. This bromelain-inhibited secretion is mediated by secretagogues that act via 3':5'-cAMP, 3':5'-cGMP and calcium-dependent signalling cascades (41). Bromelain needs to be tested in humans to determine its antidiarrheal potency.

Antimicrobial proteins and peptides are components of phagocytes, one of which is known as defensin. Defensins are a group of microbicidal peptides expressed in Paneth cells. Human intestinal defensin may protect against invasion and parasitization by microbes (42,43). The clinical application of this observation is awaited.

Clinical learning point: The toxins produced by *V cholerae* and by ETEC bind to BBM receptors, increase intracellular second messengers and result in secretory diarrhea. The clinical usefulness of bromelain, an extract of pineapple, needs to be tested in persons with secretory diarrhea.

Human immunodeficiency virus: In human immunodeficiency virus (HIV)-infected persons, the incidence of diarrhea varies from 30% to 60% of patients from industrialized countries, to 97% of patients from developing countries. The topic of the therapy of gastrointestinal infections associated with acquired immune deficiency syndrome (AIDS) has been reviewed (44). When controlling for the level of lipid malabsorption, HIV-infected patients have lower energy intake than do HIV-negative patients with chronic malabsorption (45). The diarrhea is often associated with cytomegalovirus or *Mycobacterium avium* infection. HIV replication in the mucosa may lead to villus shortening, but there is no evidence that AIDS is associated with mucosal T-cell activation. In persons with HIV-associated diarrhea and malabsorption, wasting is greater in those with cryptosporidiosis than with microsporidiosis. While patients with HIV-related diarrhea have reduced villous height and increased crypt death compared with healthy controls, there is no difference between HIV-positive controls (46).

The entry of HIV into human intestinal cells involves both the gp120 receptor galactosylceramide and the CXCR4/fusin receptors (47). The intestinal permeability to lactulose/mannitol is greater in HIV-positive patients with or without diarrhea, as well as in those with diarrhea due to cryptosporidiosis, than in controls (48).The clinical presentation of cryptosporidiosis may mimic that of Crohn's disease (49). In addition, cryptosporidiosis may cause an acute exacerbation of symptoms in patients with IBD. The intra-

epithelial lymphocyte (IEL) may be important in the generation of immunity to cryptosporidium through a mechanism involving the production of IFN- (50). The depletion of CD4 T cells in the lamina propria is an early event in the course of HIV infection. This may lead to impaired secretory immunity because these cells play a critical role in mucosal B-cell differentiation and antibody production. Interestingly, immunoglobulin (Ig) A and IgM levels are normal in the supernatant of short term cultured biopsy samples from HIV-infected patients, whereas IgG levels are increased (51). HIV core protein p24 may be detected in higher concentrations in intestinal biopsies of HIV-infected patients than in serum. However, proviral loads may be similar in blood and intestinal biopsies, indicating that the intestinal mucosa is a major reservoir for HIV in these patients (52).

Computed tomography scanning of the abdomen may complement colonoscopy and biopsy for diagnostic purposes in patients with HIV-associated intestinal symptoms (53).

Microsporidiosis: Microsporidiosis has been reported in up to 39% of patients with AIDS and diarrhea, and is the most common organism detected among enteric pathogens present in this group of individuals. Two main species, *Enterocytozoon bieneusi*, the most commonly identified species, and *Encephalitozoon intestinalis*, may be responsible for disseminated disease. A recently described polymerase chain reaction (PCR) assay appears to be a rapid and reproducible method for the detection and identification of each intestinal species (54). Transmission and establishment of a persistent infection of *E bieneusi* from a human with AIDS to simian immunodeficiency virus-infected rhesus monkey have been described (55).

Albendazole may successfully eradicate *E intestinalis* from the intestinal tract of HIV-seropositive patients. Albendazole and metronidazole may reduce the volume of diarrhea, although neither clears the spores from the stool. Thus, clinical relapse is common. Thalidomide inhibits TNF- which is elevated in microsporidiosis, and has been shown to reduce stool frequency and improve weight in subjects with E *bieneusi* (56,57).

Clinical learning point: Microsporidiosis is a common cause of diarrhea in patients with AIDS. Treatment is with albendazole, metronidazole or possibly thalidomide.

HIV-infected patients display severe impairment of gastrointestinal function, characterized principally by diarrhea and malabsorption despite the absence of demonstrated opportunistic infections. HIV-1 proteins and nucleic acids have been detected in several cell types of the intestinal mucosa. HIV-1 infection impairs cellular differentiation, decreases transepithelial electrical resistance and inhibits BBM sodium/glucose cotransporter (sodium-dependent glucose transporter) 1, possibly by disrupting microtubules rather than necessarily directly infecting the IECs (58). Intestinal protein leakage may contribute to the hypoalbuminemia seen in some patients with AIDS (59).

***Salmonella typhi* and shigellosis:** Strains of *S typhi* that are resistant to chloramphenicol, ampicillin and trimethoprim have been responsible for numerous outbreaks in countries in the Indian subcontinent, Southeast Asia and Africa. Ciprofloxacin and azithromycin may be useful in the treatment of shigellosis (60). Unfortunately, resistance to ciprofloxacin has now emerged in multidrug-resistant strains of *S typhi* (61). Strains of *Shigella dysenteriae* type 1, the most virulent serotype of *Shigella* species, are caused by strains that are resistant to ampicillin and to trimethoprim-sulphamethoxazole. The shigella toxin induces fluid secretion by a process that involves protein kinase C (PKC), intracellular (but not extracellular) calcium stores and PGs (62). Growth retardation following diarrheal diseases in children has been documented in several studies, and a randomized clinical trial in Bangladesh demonstrated that feeding children an energy-dense, high-protein diet in addition to antibiotics during the acute phase of shigellosis is associated with greater weight for age and weight for height sustained at home one month after discharge (63).

Clinical learning point: Energy and protein supplementation in addition to antibiotics may be needed in the treatment of acute shigellosis in children.

***Tropheryma whippelii*:** Whipple's disease is a chronic disorder with both intestinal and extraintestinal symptoms. It is caused by a Gram-positive, rod-shaped bacterium named *T whippelii*. Involvement of the central nervous system (CNS) is a serious problem for some patients with Whipple's disease. CNS involvement is not always possible to diagnose using cerebral spinal fluid (CSF) examination for periodic acid-Schiff-positive particles. In some patients with Whipple's disease, a brain biopsy is necessary to diagnose CNS involvement. PCR testing of CSF may be useful to diagnose Whipple's disease of the CNS, both in persons with and persons without neurological symptoms (64).

Clinical learning point: PCR technology may be applied to the CSF of patients with Whipple's disease to diagnose CNS involvement with *T whippelii*, without the need to perform a brain biopsy.

In patients with Whipple's disease, there is altered cell-mediated immunity and delayed-type hypersensitivity, accompanied by persistent immunological alterations in the peripheral blood mononuclear cells. The peripheral blood mononuclear cells in patients with Whipple's disease have reduced monocyte IL-12 production, as well as decreased IFN- secretion (65). The pathophysiological significance of this finding is unknown.

***Clostridium difficile*:** *C difficile* toxin A mediates intestinal inflammatory responses by binding to a specific receptor on intestinal cells. This binding leads to activation of enteric nerves and immune cells in the lamina propria. Capsaicin, an

agent that ablates sensory neurons, inhibits fluid secretion and intestinal inflammation in response to C *difficile* toxin A. The inflammation and hypersecretion produced by toxin A from C *difficile* are abolished when rats are treated with antisecretory factor (AF). AF also markedly reduces the intestinal fluid response induced by this toxin (66). IL-11 is a novel cytokine that may have a protective effect against gastrointestinal injuries, altering the intestinal effects of C *difficile* toxin A activity. This may occur through the inhibition of the release of inflammatory mediators from mucosal mast cells and intestinal macrophages by IL-11 (67).

Guidelines have been published for the diagnosis and management of patients with C *difficile*-associated diarrhea and colitis (68). The C *difficile* toxin increases intestinal calcitonin gene-related peptide (CGRP) in the ileal mucosa and in the dorsal root ganglia. Pretreatment with a CGRP antagonist before installation of toxin A into ileal loops inhibits the toxin-mediated fluid secretion, as well as the altered mannitol permeability and histological damage (69).

Clinical learning point: An antagonist to CGRP inhibits the effect of C *difficile* on the intestine. AF and IL-11 may have a protective effect. The therapeutic potential of these observations needs to be explored.

Rotavirus: Rotaviruses are the major cause of infectious diarrhea in developing countries as well as in North America. These infections are characterized by viral replication within enterocytes, cell lysis and villus blunting. Rotaviruses contain two outer capsid viral proteins – the spike protein VP4 and the major capsid component VP7. Both of these capsid proteins are implicated in the entry of rotavirus into the cell. This rotavirus VP4-mediated cell entry may involve the 2 1 integrin, whereas VP7 appears to interact with x 2 and 4 1 integrins (70). BBM disaccharidase activities are reduced in rotavirus infection, and osmotically induced watery diarrhea and dehydration may ensue.

Protein-energy malnutrition prolongs diarrhea and delays small intestinal recovery in response to rotavirus infections (71). Natural rotavirus infection results in a specific circulating memory $CD4^+$ response that is limited to the gut-homing 4 7 subpopulation of lymphocytes. This may comprise cellular memory for intestinal antigens. The regulated expression of 4 7 may help to target and segregate intestinal versus systemic immune responses (72).

The rotavirus vaccines that have been evaluated to date are live, attenuated virus vaccines that are derived from bovine or simian strains. These vaccines are delivered orally to mimic natural infections. However, these vaccines have been shown to be only partially protective in humans. Importantly, T and/or B cells are necessary for clearing primary rotavirus infections. $CD8^+$ T cells mediate an in vivo antiviral effect, either by direct lysis of the virus-infected host cell or by the release of cytokines that induce an antiviral effect. This antirotaviral effect of $CD8^+$ T cells is not mediated by perforin nor by Fas and the release of IFN- (73).

Clinical learning point: Vaccination against rotavirus infection is not yet sufficiently developed for widespread use.

Enterocytes are active participants in the intercellular crosstalk with immune effector cells such as mononuclear cells and neutrophils. This interaction is mediated to a large extent by cytokines, and allows localized and specific modulation of epithelial and immune effector responses. In Caco-2 and HT-29 cells, IFN- and IFN- induce rotaviral resistance. This suggests that cytokines play a role in host defence against viral agents, possibly by changing the phenotype of IECs (27).

Astrovirus: Astroviral infections are a leading cause of acute, nonbacterial gastroenteritis in children. Helper T cells residing in the normal duodenal mucosa of adults recognize a common enteral pathogenic virus, and these $CD4^+$ T cells are presumed to be important in mucosal defense against recurrent astroviral infections (74). Protection against frequent reinfections with astrovirus may be maintained by cellular immune responses in the small intestinal mucosa.

***Blastocystis hominis*:** It is controversial whether *B hominis* is a cause of diarrhea because it is a common inhabitant of the human gastrointestinal tract. A case-control study among German tourists returning from tropical countries suggests that *B hominis* may be associated with the development of diarrhea in travellers to tropical destinations, but the diarrhea may also be associated with concurrent infections (75).

Infections and IBD: The cause of IBD remains elusive, and it is now disputed that a previous measles infection may be important in the cause of Crohn's disease (76). The immunosuppression used to treat some patients with IBD may increase their risk of developing a varicella infection. This is uncommon but must be promptly diagnosed and treated with acyclovir, and with the concomitant reduction in immunosuppressive therapy (ie, reduction in steroid dosage and discontinuation of azathioprine) (77).

DRUG ABSORPTION

Curiously, a glass of grapefruit juice (rich in fructose) increases the bioavailability of some drugs such as nifedipine, verapamil, midazolam and cyclosporin A. This may be the result of selective downregulation by constituents of the fruit juice of CYP3A4, a member of the cytochrome P-450 gene superfamily responsible for the metabolism of different drugs (78). There is considerable variability in the oral bioavailability of beta-lactam antibiotics. These are absorbed by the peptide transport system, as well as by a passive process. Some of the variability in the absorption of this class of drugs is due to the involvement of an energy-dependent efflux system that is distinct from the P-glycoprotein (Pgp)-mediated transporter (79). 5-Fluorouracil is widely used in the treatment of solid tumours, but their bioavailability varies widely due to the large and variable hepatic first-pass extraction (80).

Pgp is one of the important factors involved in the multidrug resistance of tumour cells. It is expressed in the intes-

tine and restricts the absorption of various compounds including methylprednisolone (81). In the presence of the calcium channel blocker verapamil, the retarded absorption of methylprednisolone is normalized. This suggests that Pgp is responsible for the unique features of methylprednisolone absorption. The multidrug resistance-reversing agent for verapamil inhibits secretion of Pgp substrates and, hence, increases apical to basolateral permeability (82). No association between Pgp and new nonsystemic steroids such as budesonide has been reported.

Clinical learning point: Certain food substances may influence the metabolism and, therefore, the bioavailability of some drugs.

New drug development has been accelerated by molecular diversity technology, with drug candidates derived by combinatorial synthesis and screening paradigms. Based on the chemical properties of a drug, its intestinal absorption characteristics can be predicted; however, direct testing of the absorption is still necessary. In situ perfusion preparations of rat intestine can be used to predict the in vivo absorption properties of drugs in humans (83). Caco-2 cells have been used to predict directly the in vivo human absorption of drugs (84). Mixtures of drugs can be tested in Caco-2 cells to obtain information on potential absorption properties (85). However, the experimental conditions need to be controlled carefully (86). The absorption of drugs by Caco-2 cells can be modified by absorption enhancers such as sodium caprate, sodium deoxycholate and dipotassium glycyrrhizinate (87).

Nonsteroidal anti-inflammatory drugs (NSAIDs) commonly cause damage to the gastrointestinal tract by a number of mechanisms. These include the inhibition of cyclo-oxygenase, alterations in intestinal permeability, changes in the margination of neutrophils and the uncoupling of oxidative phosphorylation by mitochondrial damage (88). The attachment of a nitric oxide group to an NSAID modifies the carboxylic group, which is essential for the effective inhibition of cyclo-oxygenase. These so-called 'NO-NSAIDs' may be associated with less macroscopic damage to the small intestine, but increases in intestinal permeability still occur (89). Early after intestinal exposure to NSAIDs, rats develop slowing of the blood flow to the mesenteric circulation, stasis, microvascular distortion, clumping and shortening of the epithelium (90). The importance of NSAIDs on the intestinal blood flow of humans is unknown.

Biodegradable microparticles have been developed as a drug carrier system for the gastrointestinal delivery of therapeutic agents and to enhance drug absorption. The orally administered microparticles also gain entry into the gut-associated lymphoid tissue. Using the Caco-2 cell system, it appears that microparticle uptake is dependent on the diameter and concentration of the microparticles, as well as on the incubation time and temperature used (91). Future development of this concept may allow improved bioavailability of drugs such as cyclosporine and hormones such as insulin.

GROWTH AND DIFFERENTIATION

The topic of IEC growth and differentiation has been reviewed (92-95). Undifferentiated cells in the intestinal crypts give rise to four differentiated cell types: absorptive enterocytes, mucus-producing goblet cells, enteroendocrine cells and Paneth cells. The enterocytes acquire differentiated functions, such as digestive enzymes and nutrient transporters. The development of these proteins is organized along the length of the villus and intestine, and at different time periods in the life of the animal. The horizontal (proximal-distal) and temporal (young-old) patterns of intestinal gene expression are established and maintained by regulation at the level of gene transcription. Studies in transgenic mice have indicated that cis-acting elements in the 5'-flanking regions of specific intestinal genes play a role in this regulation of membrane proteins.

Intestinal growth during weaning is dependent on and is promoted by the activation of T cells, and blockade of the IL-2 receptor reduces intestinal growth (96). Epidermal growth factor (EGF), transforming growth factor-beta and keratinocyte growth factor enhance the expression of fibroblast growth factor receptor 3. This demonstrates the integration between cytokines and the growth factor ligand-receptor systems in the IECs (97). The tyrosine kinases EGF receptor and fibroblast growth factor receptor, as well as a new family of receptor protein tyrosine kinases (RPTKs), the Eph/Eck family of RPTKs, may modify IEC migration and barrier function (98). This suggests that Eck interaction (a target of regulatory peptides) may play a role in IEC development, migration and barrier function.

Clinical learning point: Tyrosine kinases and RPTKs influence intestinal cell migration and barrier function. There is integration between cytokines and growth factor ligand-receptor systems in the IECs. This represents a possibility for the development of interesting new therapeutic targets.

Integrins are transmembrane alpha-beta heterodimers that are primary mediators of extracellular matrix-cell interactions and signalling. The integrin 7B 1 upregulates the onset of sucrase-isomaltase expression in Caco-2 cells. This suggests that integrin expression may be important in human enterocyte differentiation (99). The influence of steroids on sucrase-isomaltase expression may be mediated by their effect on integrin 7B 1 expression.

The trefoil peptides are a family of small peptides that are structurally unrelated to cytokines and other growth factors. The trefoil peptides contribute to the protection and healing of the epithelium, and are integrated into the mechanisms of mucosal defense. They repair through the enteric neuroendocrine system and are independent of constituents of the mucosal cytokine network (100).

Arginine is a precursor for a number of biologically important molecules such as proteins, nitric oxide and polyamines. Citrulline and arginine are synthesized from glutamine in the enterocytes. Proline is also an important substrate for the synthesis of citrulline and arginine (101). Glutamine and glucose are important sources of energy in rat intestinal mucosal cells (102). The oxidation of glutamine stimulates enterocyte sodium/hydrogen exchange, thereby enhancing electroneutral sodium chloride absorption. Glutamine has a trophic effect on the intestine when it is added to total parenteral nutrition (TPN) solutions. Glutamine-enriched TPN can attenuate bacterial translocation. The glutamine dipeptide alanyl-glutamine is capable of maintaining normal intestinal mucosal morphology and barrier function in TPN-fed rats that have been challenged with 5-fluorouracil (103).

Clinical learning point: The amino acid glutamine is a major metabolic fuel of the small intestine, and plays an important role in the growth of the intestine. The use of glutamine as a neutraceutical in humans remains to be established. Adding glutamine to TPN solutions may prevent the intestinal atrophy associated with this parenteral form of nutrition.

Glutamine induces ornithine decarboxylase activity and thereby enhances the synthesis of polyamines, which are implicated in intestinal proliferation. Glutamine is additive to the effect of EGF and insulin-like growth factor (IGF) -1 in stimulating DNA synthesis. Glutamine activates both extracellular signal-regulated kinases and Jun nuclear kinases (104). During sepsis, glutamine consumption is increased despite reduced glutaminase activity. This arises from the increased activity of other enzyme systems and/or increased utilization of this amino acid for DNA and protein synthesis (105). Glutamine balance may be important in preventing postsurgical complications, and disturbances in postoperative glutamine metabolism in bile duct-ligated rats can be prevented by the restriction of gut endotoxin (106).

PERMEABILITY AND PARACELLULAR TRANSPORT

The topics of intestinal tight junctions and permeability have been reviewed (107). The site of altered intestinal permeability (for example stomach, small intestine or colon) can be assessed by the use of different probes (108). The lactulose-mannitol ratio test has demonstrated that there is increased intestinal permeability in patients with cholestatic jaundice (109). The accompanied upregulation of human leukocyte antigen-DR expression on enterocytes and gut-associated lymphoid tissue suggests immune activation as a possible mechanism.

Tight junctions, and consequently paracellular permeability to ions and/or hydrophilic molecules, are modulated by a host of factors. These modulating factors include intracellular cAMP, luminal osmolality, insulin, IGF, palmitoyl-carnitine, activation of PKC, depletion of intracellular ATP stores, elevated intracellular ionized calcium concentration, cellular acidosis, reactive oxygen species, nitric oxide and various proinflammatory cytokines such as IFN and IL-4 (110,111). The cytokines probably alter tight junctions through the modulation of the cytoskeleton activity (111). Nitric oxide, a pluripotent signalling and effector molecule, is increased with mild acidosis and enhances intestinal permeability (112), possibly by promoting oxidant-mediated cytoskeletal damage and/or ATP depletion (113). The increased intestinal permeability observed in association with experimental colitis may be due to the release of proinflammatory cytokines (114). Patients with CF who are homogeneous or heterogeneous for DF508 have a higher lactulose to L-rhamnose ratio then do CF patients with unidentified genotypes (115).

IELs are effector cells that are capable of secreting cytokines, in response to stimulation, through the T-cell receptor. Cytokines such as IFN- and TNF- may act directly on intestinal epithelia to mediate changes in the epithelial permeability and in its capacity for electrogenic ion transport. Blocking protein synthesis prevents the effects of IEL supernatant on transepithelial electrical resistance. This suggests that mucosal T cells may influence intestinal barrier function by a process involving new protein synthesis (116) and that immunosuppressive drugs would affect intestinal permeability. This needs to be tested by direct study.

Clinical learning point: The tight junctions of the intestine are controlled by numerous signalling proteins, including cytokines. The permeability of the intestine may also be influenced by mucosal T cells. It remains to be established how the permeability of the intestine can be modified in a purposeful and beneficial manner.

Disruption of the gut mucosal barrier is the primary mechanism by which endotoxin promotes bacterial translocation. Endotoxin-induced mucosal injury and bacterial translocation are associated with enhanced calcium-iNOS activity and increased nitric oxide production (117). Lipopolysaccharide (LPS) (endotoxin) increases bacterial translocation in animals and in humans, and this may be mediated by the upregulation of iNOS mRNA expression (118). Nonlethal doses of endotoxin, administered intramuscularly or intraperitoneally, promote bacterial translocation. Gut translocation of bacteria is defined as the passage of gastrointestinal microflora across the lamina propria to local mesentery lymph nodes, and then to extranodal sites. Bacterial translocation may initiate a cytokine response that predisposes the host to the development of sepsis. In humans, bacterial translocation was identified in about 15% of surgical patients undergoing laparotomy; the most common organism was *E coli*. Postoperative septic complications developed in 23% of patients; enteric organisms were responsible for these complications in 74% (119). Failure of the gut barrier function may lead to this bacterial translocation.

Clinical learning point: Bacterial translocation is common in humans undergoing abdominal surgery and may predispose patients to the development of septic complications. It remains to be established how this can be prevented.

Bacterial LPS administered to the basolateral surface of IEC-6 disrupts barrier function and tight junctional proteins, whereas LPS does not have the same effect when administered from the apical surface (120). The oral administration of a proteoglycan is protective against the bacterial translocation that occurs in a TPN model (121), possibly acting to restore the impaired local immunity in the gastrointestinal tract to normal.

Cancer chemotherapy may produce mucosal ulceration (mucositis) and gastrointestinal symptoms. Intestinal permeability in humans increases following chemotherapy and peaks seven days after treatment (122). Intestinal permeability is also increased in patients with small intestinal bacterial overgrowth (123). Small intestinal bacterial overgrowth is not a major risk factor for the development of liver damage in humans, possibly by activating the immune system secondary to increases in endotoxins and bacteria (124). Nitric oxide donor compounds used concomitantly with NSAIDs may protect the gastrointestinal tract. As small bowel colonization increases in newborn rabbits, the intestinal permeability to dextran increases, and permeability to EDTA first increases and then decreases (125).

In patients with Crohn's disease, permeability of the small intestine and the stomach may be increased (126). The lactulose/mannitol ('sugar absorption test') is not recommended as a marker of disease activity in patients with IBD or as a predictor of NSAID-related upper gastrointestinal damage (115). The permeability of the intestine to lactulose/mannitol is increased in about a quarter of first-degree relatives of patients with Crohn's disease (127). There is no typical inherited family pattern for the altered intestinal permeability, and interestingly about a third of healthy spouses of patients with Crohn's disease also have increased permeability. This suggests the presence of a common nongenetic (environmental) factor.

EGF plays a role in the maintenance of intestinal integrity (128). In animals, enhanced proinflammatory cytokine production from intestinal macrophages is accompanied by increased intestinal permeability. This may contribute to the intestinal and systemic features of trinitrobenzene sulphonic acid-induced colitis (114). Transgenic human leukocyte antigen-B27/human beta2-microglobulin rats spontaneously develop inflammation before a change in mucosal barrier function is detected (129). Nitric oxide disrupts the tight junction zonula occludens that regulates the barrier function of the mucosa, and peroxynitrite (a reaction product of nitric oxide and superoxide anion) is a final common effector of cytotoxicity and tissue injury. Peroxynitrite but not nitric oxide increases transepithelial permeability in Caco-2 cells by inducing DNA strand breaks. This activates the poly(ADP-ribose) synthetase pathway and causes depletion of intracellular energy stores (130). Inhibition of poly(ADP-ribose) synthetase activity may be a novel strategy for ameliorating peroxynitrite-mediated epithelial injury during intestinal inflammation. A nitroxide stable free radical scavenger as well as the antibiotic metronidazole are protective against NSAID-induced increases in intestinal permeability in rats (131). It remains to be determined whether this approach is protective in humans. This is an important consideration because of the detrimental effect of NSAIDs on the small intestine.

Intracellular acidosis induced by the sodium/hydrogen exchanger (NHE) blocker, amiloride, favours the formation of peroxynitrous acid. This in turn augments the hyperpermeability of Caco-2 cells induced by a nitric oxide donor (132). Inhibitors of NOS degranulate mast cells and increase mucosal permeability to ^{51}chromium-EDTA by a process that is prevented by simultaneous treatment with either nitric oxide-donating agents or L-arginine. *N*(G)-nitro-L-arginine methylester is a NOS inhibitor and increases this fluid filtration rate from intestinal capillaries (133). Mast cell stabilizing agents such as doxantrazole and lodoxamide, as well as histamine H_1 antagonists, are also effective in blunting the increased mucosal permeability associated with NOS inhibition. Mast cells chronically inhibit iNOS activity in the gut. Inhibitors of iNOS elicit a larger increase in permeability when this tonic inhibitory influence is released by mast cell depletion (134).

Intestinal barrier function is also compromised in malnourished patients, with increased permeability measured from the lactulose/mannitol ratio. This increased permeability is associated with phenotypic and molecular evidence of activation of the lamina propria mononuclear cells and enterocytes, as well as with a heightened acute phase response (135). This alteration in intestinal permeability in malnourished patients explains the high prevalence of infection in these individuals.

The route of feeding (total enteral nutrition versus TPN) does not modify the clinical course after major upper gastrointestinal surgery (136). However, in animals, the composition of the diet may influence intestinal permeability; rats fed a solid pelleted diet have greater permeability than those fed a fluid diet (137). It is unknown whether these beneficial diet effects can be applied to alter intestinal permeability in humans.

DIAGNOSTIC TESTS

Steatorrhea: The detection of steatorrhea is clinically useful for identifying patients with pancreatic insufficiency or small bowel disease. However, this test is unpleasant for the patient and technician alike, even though it remains the gold standard for diagnostic purposes. The steatocrit (using a small amount of stool that is microcentrifuged and measuring the ratio of the fat layer to the solid layer) can be determined on a random stool sample, without specific dietary constraints or multiple day stool collections. The steatocrit correlates well with the 72 h stool quantitative fecal fat, with a sensitivity of

100%, a specificity of 95% and a positive predictive value of 90% for the detection of steatorrhea (138).

Clinical learning point: The steatocrit is both sensitive and specific for the detection of steatorrhea. This inexpensive test needs to be applied more widely for the diagnosis of maldigestion and malabsorption of lipids.

A number of tubeless methods have been used to detect steatorrhea or pancreatic insufficiency, including the p-aminobenzoic acid and flourescein dilaurate tests. Other tubeless tests include the determination of serum trypsin and fecal chymotrypsin concentrations. These lack sensitivity in patients with mild or moderate pancreatic insufficiency, as does the recently developed ELISA determination of elastase in feces. The ^{13}carbon-cholesteryloctanoate breath test also has low sensitivity and specificity (approximately 70%) for the detection of steatorrhea, and the curve of ^{13}carbon dioxide recovery in patients with mild to moderate pancreatic insufficiency is similar to that of healthy controls (139). This, therefore, limits the clinical usefulness of the cholesteryloctanoate breath test.

Bacterial overgrowth syndrome: Bacterial overgrowth syndrome is characterized by excessive numbers of bacteria (usually anaerobes) in the proximal intestine, with associated symptoms of diarrhea and malabsorption. The ^{13}carbon-xylose breath test with 50 mg of xylose demonstrates 100% sensitivity for the detection of bacterial overgrowth in children with the short bowel syndrome (140). The use of a transit marker increases the specificity of the [^{14}carbon]D-xylose breath test from 85% to 94% for the diagnosis of bacterial overgrowth (141). In patients with a total gastrectomy, the presence of bacterial overgrowth does not necessarily result in symptoms or abnormalities in nutrient absorption (142). It remains to be determined whether there are other clinical settings in which small bowel bacterial contamination is not necessarily pathological.

IBD: The role of the barium enema examination of the small intestine has been reviewed (143), as has the use of transabdominal and endoscopic ultrasonography (144). In patients with known Crohn's disease, small bowel follow-through is just as accurate as small bowel enteroclysis. Therefore, this is the diagnostic procedure of choice (145). When patients have symptoms suggestive of IBD, it is useful to obtain ileal biopsies at the time of colonoscopy, with multiple biopsy specimens showing definite pathology in about half of the patients examined in this manner (146). Enteroscopy is an important advance in the exploration of the small bowel. It is useful in detecting the cause of bleeding, chronic diarrhea or radiological abnormalities of the small intestine (147).

Histological changes were seen on examination of biopsies obtained during ileocolonoscopy in 51% of patients with reactive arthritis, 45% of those with psoriatic arthritis, 48% of those with ankylosing spondylitis, 38% of those with undifferentiated spondyloarthropathy and 15% of those with rheumatoid arthritis (148). Fifty per cent of patients with rheumatoid arthritis have abnormalities on electron microscopic examination of the intestinal tissue. The functional significance of these morphological changes is not known.

Clinical learning point: Gut inflammation may be common in patients with spondyloarthropathy. It is unknown whether this contributes to the pathogenesis of the arthritic process.

CF can be complicated by ileocecal and colonic stenoses, with submucosal proliferation sometimes requiring surgical intervention. Ultrasound studies may be used to measure the intestinal wall diameter in patients with CF. This diameter may be greater, particularly in patients who have been on doses of pancreatic enzyme preparations with 20,000 or more lipase units per capsule (149). The clinician caring for persons with CF being treated with pancreatic enzymes needs to be aware of the possibility of submucosal proliferation leading to obstructive symptoms.

Villous atrophy of the terminal ileum may be seen in patients with severe celiac disease or immunodeficiency syndromes such as HIV, or in association with microscopic colitis (150). Villous atrophy and the presence of surface epithelial abnormalities (called 'tufts') are seen in children with epithelial dysplasia associated with intractable diarrhea. This may be associated with alterations of the cell-cell and cell-matrix interactions (151).

MOTILITY

A 100-year perspective on gastrointestinal motility has been published (152). The role of the interstitial cells of Cajal (ICC) in the control of intestinal motility has also been reviewed (153). The ICC provide pacemaker activity to the muscle of the intestine by setting the frequency and propagation characteristics of contractile activity of the circular muscle layer of the small intestine. The importance of ICC in the generation of distention-induced peristalsis has been demonstrated in W/W^{v} mice that lack ICC associated with Auerbach's plexus (154). ICC have large gap junctions (155) and have been proposed as ideal targets for pharmacological intervention in patients with gastrointestinal motility disorders (156).

Clinical learning point: ICC may prove to be future targets for pharmacological intervention in patients with gastrointestinal motility disorders.

Fos, the protein encoded by the immediate early response gene c-*fos*, may be induced by intestinal distention, electrical stimulation, exposure to forskolin and peristalsis of the intestine (157). Contractile activity of the intestine is regulated by potassium and calcium currents, as well as by excitatory and inhibitory mediators. The large-conductance calcium-activated potassium channel is constitutively activated for modulations of spontaneous activation, as well as for muscle excitation. This occurs through the elevation of calcium ion levels, which stimulate these channels to suppress spontaneous activity (158).

The increase in intracellular calcium ions (Ca_i^{2+}) is part of a series of signal-transduction steps that result in the phosphorylation of contractile proteins. Calcium ion influx through the L-type calcium ion channels may be the primary source of calcium in stimulating in vivo phasic contraction in normal and inflamed ileum (159). The two primary sources of free Ca_i^{2+} are the entry of calcium from the extracellular space, and intracellular release from calcium stores in the endoplasmic reticulum (ER) and mitochondria. Release of calcium from these intracellular stores may be sufficient to raise Ca_i^{2+} to the level necessary to trigger muscle contraction. However, extracellular calcium is essential to replete intracellular stores and to sustain rhythmic contractions.

L-type calcium channel current in canine jejunal circular smooth muscle is regulated by the neural transmitter acetylcholine and by the gastrointestinal hormone motilin. Motilin, a 22-amino acid peptide produced by specialized M cells in the mucosa of the small intestine, is a potent agonist of gastrointestinal smooth muscle contraction. Motilin increases calcium entry through L-type calcium channels in both canine and human jejunum circular smooth muscle. Also, motilin regulates the initiation of phase III of the myoelectric motor complex (MMC). Motilin interacts with its receptors on gastrointestinal smooth muscle through a G protein-coupled mechanism (160). Motilin receptors are also present in the CNS, although the clinical significance of this finding is unknown (161).

CT-sensitive G proteins activate L-type calcium channels in isolated canine jejunal circular smooth muscle cells through protein phosphorylation (162). PKC plays an important role in the increase of calcium sensitivity in guinea pig ileal longitudinal muscle (163). The blockade of L-type calcium channels with verapamil suppresses giant migrating contractions and, therefore, diarrhea during small intestinal inflammation (164). The clinical use of this observation needs to be exploited.

The importance of tachykinins in the intestine has been reviewed (165,166). In the gastrointestinal tract, a family of neuropeptides called tachykinins (including SP and neurokinin [NK] A and NKB) are potent secretagogues because of their activation of NK receptors located on submucosal secretomotor neurons. These innervate the mucosal enterocytes through the release of both cholinergic and noncholinergic neurotransmitters. The tachykinins function as neurotransmitters in the enteric nervous system, and share a common carboxyl-terminal amino acid sequence. There are three tachykinin receptors: SP is most potent at NK1, NKA at NK2 and NKB at NK3 receptors. SP and NKA stimulate small intestinal motility in humans (167). NK1 receptors are found on submucosal neurons and arterioles of the guinea pig ileum (168).

Tachykinin-evoked secretion in the guinea pig ileum is mediated by NK1 and NK3 receptors on submucosal secretomotor neurons, and capsaicin-sensitive nerves release tachykinin(s) that activates the NK1 receptors (169). There are differences in isometric tonic and phasic contractile responses of guinea pig ileum longitudinal smooth muscle to tachykinins (170). NK3 receptors are expressed on both excitatory and inhibitory motor neurons (171). In the guinea pig ileum, 97% of NPY immunoreactive submucosal neurons colocalize NK1 receptor immunoreactivity, whereas VIP immunoreactive neurons are not NK1 immunoreactive (168). NKA increases duodenal mucosal permeability, bicarbonate secretion and fluid output by a process that requires NK2 receptor activation in the circular and longitudinal muscle layer of rat duodenum (172). SP inhibits intestinal peristalsis by the stimulation of tachykinin NK1 receptors through a process that can be prevented by the use of iNOS (173).

Stimulation of the $alpha_2$-adrenoceptors inhibits intestinal motility, and beta-adrenergic stimulation plays an important role in the regulation of the motility characteristics of the fasting pattern. In humans, beta-adrenoceptor stimulation reduces esophageal, antral and duodenal motility. Beta-adrenoceptor inhibition with propranolol has been found to enhance motility of the esophagus, promote gastric emptying, increase colonic intraluminal pressure and shorten the period of postoperative adynamic ileus after bowel surgery. Isoprenaline inhibits the activity fronts in the human proximal small intestine. Stimulation of beta-adrenoceptors may be of importance in the control of motor activity in the human small intestine, especially under stressful conditions where there is high adrenergic activity (174).

Clinical learning point: The intestinal adrenoreceptors influence intestinal motility, and may lead to understanding of the link between motility changes and stress.

In the mouse, IL-4 amplifies cholinergic excitation through a mast cell- and leukotriene D_4-dependent mechanism (175). Activation of primary afferents in the enteric nervous system releases sensory neuropeptides such as SP, CGRP and VIP. Sensory afferents may be important in the pathophysiology of inflammation. Also, acute and chronic inflammation of the small and large intestine are often associated with motility disturbances. During acute enteric inflammation in the rabbit, mucosal inflammatory mediators that influence the neural control of smooth muscle are released (176). In guinea pigs with trinitrobenzene sulphonic acid-induced ileitis, the contractility of circular and longitudinal muscle is altered due to stimulation of various receptors. These receptors are altered differentially, whereas nonreceptor-mediated contraction in response to potassium chloride depolarization is not modified (177).

Glutamine, the major excitatory neurotransmitter in the CNS, is also present in myenteric ganglia, and glutamate receptors are clustered on enteric neurons (178). Pituitary adenylate cyclase-activating peptide is a member of a structurally related regulatory peptide family that includes secretin, glucagon, gastric inhibitory peptide, VIP and growth hormone-releasing factor. In canine ileum, pituitary adenylate cyclase-activating peptide coexists with VIP in enteric nerves (179).

There are a variety of different subtypes of ileal muscarinic acetylcholine receptors (mAChR). Activation of different mAChR subtypes triggers various intracellular signals to influence intestinal tone and motility (180). Numerous neurons expressing the mu receptor-like proteins are found in the submucosal plexus, with comparatively few mu receptor-like proteins being present in the myenteric plexus. In contrast, a larger number of neurons expressing the kappa receptor-like immunoreactivity are visualized in the myenteric plexus, with only a small number in the submucous plexus (181).

IGF-1 action is modulated by six circulating IGF-binding proteins (IGFBP) (IGFBP-1 to IGFBP-6), which act as carriers that prolong the plasma half-life of IGF-1. IGF-1 is induced in chronic inflammation, and acts in an autocrine and paracrine manner on intestinal smooth muscle to increase collagen synthesis and to promote fibrogenesis. IGF-1 increases IGFBP-5 and collagen mRNAs in intestinal smooth muscle cells of the rat (182). IL-1 is a proinflammatory cytokine that induces collagenase expression and inhibits collagen expression in human intestinal smooth muscle (HISM) cells. Corticosteroids cause transrepression of certain genes including the collagenase gene. When HISM cells are exposed to IL-1 , the secretion of the collagenase mRNA and protein is increased, but this enhancement is completely abrogated by dexamethasone (183).

Enteric neuronal 5-hydroxytryptamine (5-HT) receptors are involved in the regulation of the MMC in animals and in humans. 5-HT_{1A}, 5-HT_{1P}, 5-HT_3 and 5-HT4 receptors are present on myenteric neurons. Administration of the 5-HT_{1P} receptor agonist, sumatriptan, prematurely induces intestinal phase 3 and reduces the plasma somatostatin concentration (184). Short chain fatty acids (SCFA) are produced by the fermentation of carbohydrate in the colon and may have an important direct effect on the colon. When the whole gut transit time is decreased by feeding senna, fecal SCFA concentrations increase, indicating that the bowel transit rate is a determinate of stool SCFA concentrations (185).

Clinical learning point: The nutrients in the diet influence motility, and the intestinal motility in turn may influence the concentration of chemicals in the lumen of the bowel (such as SCFA), which may modify intestinal function.

The topic of the brain-gut axis in health and disease has been reviewed (186). The tetradecapeptide bombesin (BBS) is present in the CNS, mainly in the hypothalamus. BBS is also present in endocrine cells, smooth muscle cells and myenteric neurons of the gastrointestinal tract. Intravenous infusion of BBS increases the frequency of the pacesetter potential, whereas the direct injection of BBS into the brain nuclei increases contractions in the small bowel. Intracerebral-ventricular injection of BBS increases the occurrence of MMC by an effect that does not involve motilin or adrenaline (187).

The potential for the CNS to affect gastrointestinal functions adversely has been widely recognized. Cold pain stress in humans induces gastrointestinal disturbances, possibly as the result of the release of mast cell mediators into the jejunum (188). In humans, meals disrupt the regular pattern of the interdigestive small bowel motor activity and convert it into the more irregular postprandial pattern. The nature and duration of postprandial motility in the small bowel depend both on the caloric load and on the chemical composition of the meal. The caloric value of a liquid meal regulates the duration of the postprandial interval in the human small bowel (189).

One type of constitutive NOS is known as neuronal NOS (nNOS). There is nNOS gene expression in gastrointestinal myenteric neurons and smooth muscle cells (190). Acute stress alters intestinal transport in a strain of rats that is susceptible to stress, and these changes are the result of the release of acetylcholine (191). With intestinal inflammation, intestinal motility is altered as the result of the effect of the inflammatory process on smooth muscle cells, as well as on the efferent and the afferent neurons of the enteric nervous system. Central sites receive projections from the sensory neurons, and in association with jejunal inflammation induced by *Nippostrongylus brasiliensis*, the cyclic intestinal motor pattern is replaced by an irregular activity. The expression of the early response gene c-*fos* in the brain is also increased, indicating a form of a gut-brain response to the intestinal inflammation (192). The Fas ligand is expressed by a large subset of enteric neurons, and may provide the basis for cytotoxic neuroimmune interactions in the intestines (193).

Clinical learning point: Intestinal inflammation may influence enteric as well as CNS activities, indicating a form of gut-brain response to this as well as possibly to other forms of stress. Intestinal infection may enhance the brain expression of selected signalling proteins, suggesting a further extension of the concept of the gut-brain axis.

PGs play an important role in mediating the intestinal immune response. PGE_2 acts as an excitatory neuromodulator of gastrointestinal motility through its direct action on neurons in the myenteric plexus (194). After exposure of macrophages to LPS, nitric oxide is produced by iNOS, resulting in large amounts of nitric oxide both locally and systemically. LPS reduces the MMC and increases spike bursts in rat intestine by a process that involves nitric oxide and arachidonic pathways, resulting in rapid transit through the gut (195). LPS changes intestinal motility through the nitric oxide and the arachidonic acid (AA) (PG) pathways, resulting in rapid transit along the length of the gut (195). In human intestinal epithelia, the regulation of iNOS gene expression occurs by posttranslational events (196).

Nitric oxide has an important role as a mediator of intestinal motility and is regarded as the nonadrenergic, noncholinergic (NANC) mediator responsible for the relaxation of the intestine. NANC inhibitory neuron-mediated descend-

ing inhibition in the intestinal tract is an important component of peristaltic reflux. ATP has been proposed as a NANC transmitter in the intestine and can be rapidly dephosphorylated to adenosine. Adenosine receptors are present in the rat ileum, and an adenosine receptor agonist relaxes intact ileum but contracts the muscularis mucosae (197).

Nitric oxide stimulates intestinal electrolyte secretion. The laxatives bisacodyl and colchicine decrease jejunal NOS activity. They also increase intestinal permeability by a process that is attenuated by pretreatment with mast cell stabilizers, and they prevent the decrease in NOS activity induced by these agents (198). Nitric oxide exerts an inhibitory effect on excitatory transmitters in guinea pig ileum, whereas purinergic mechanisms may modulate nitric oxide-dependent relaxation (199).

In healthy humans, duodenal and jejunal motor activity are different both in the digestive and interdigestive states in terms of the number of activity fronts and the organization of propagated clustered contractions, as well as subtle changes in the amplitude, duration and coordinated propagation of individual contractions. A high-frequency spiking activity, known as the electrical response activity, is associated with intestinal muscle contraction. An oscillating slow wave, known as the electrical control activity, or basic electrical rhythm, is present continuously in the intestine. The magnetic field produced by small intestinal electrical activity can be measured with superconducting quantum interference device magnetometers. These devices are capable of detecting the weak magnetic fields of biological origin. superconducting quantum interference device magnetometers can be used noninvasively to record intestinal basic electrical rhythm of the small bowel, which may be used to study clinical conditions (200). Indeed, prolonged ambulatory manometry in combination with computer-aided analysis has been described in healthy volunteers (201).

Clinical learning point: Noninvasive methods are available to study intestinal motility in health and disease. The clinical usefulness of such testing remains to be determined.

The glycosyl ureides may be a new useful marker of orocecal transit time (202).

In humans, the physical state of a meal affects the duration and the frequency of intestinal contraction, with greater changes seen after solid than after liquid meals (203). The effect of small intestinal lipid infusion on hunger is attenuated, and the stimulation of phasic pyloric pressure waves is increased in healthy older persons compared with healthy younger individuals (204). The caloric value of a meal regulates the duration of the fed activity in the human small bowel. The postprandial small bowel motor activity is similar during the daytime and nighttime (205). Ethanol enhances clustered contractions migrating aborally through the duodenum and jejunum (206). Intestinal transit is slowed when inhibitory sensors along the small intestine are exposed to nutrients, and this inhibition is nutrient load-dependent. Fibre-supplemented formula slows intestinal transit by intensifying the inhibitory feedback from the distal intestine (207). Guar, a viscous fibre, prolongs the duration of the postprandial motility pattern in humans (208). Medium-chain triglycerides, compared with long-chain triglycerides, shorten the MMC cycle length and accelerate the duodenocecal transit time (209).

Clinical learning point: The composition of a meal has a marked effect on the rate of transit along the length of the intestine. In the future, it may be possible to treat motility abnormalities by specific variations in the composition of the diet.

Chronic idiopathic intestinal pseudo-obstruction (CIIP) may be secondary to systemic diseases such as scleroderma, amyloidosis, small cell carcinoma of the lung and diabetes mellitus. As well, CIIP may be seen in association with Epstein-Barr virus infection, cytomegalovirus infection or fetal alcohol syndrome (210). In other individuals, CIIP is thought to be primary and is associated with either an enteric smooth muscle abnormality or a nervous system abnormality (visceral myopathy and visceral neuropathy, respectively). Some patients with a primary visceral myopathy have involvement of other visceral smooth muscle, such as the urinary tract and gallbladder. Visceral myopathy is more common than visceral neuropathy as the cause of CIIP, and the predominant symptoms are pain, vomiting, constipation and diarrhea (211).

Clinical learning point: A primary visceral myopathy may cause CIIP. CIIP may also be associated with diseases such as scleroderma, amyloidosis, small cell carcinoma of the lung and diabetes mellitus.

After nociceptive stimulation of the peritoneum, gastrointestinal motility is inhibited by a process that involves nitric oxide and adrenergic, dopaminergic and somatostatinergic mechanisms (212). Somatostatin immunoreactivity has been demonstrated in the enteric neurons of the myenteric and submucous plexuses, and somatostatin-immunoreactive neurons have distinct electrophysiological features (213). In patients with CIIP, fasting somatostatin levels are normal, whereas postprandial peptide responses are markedly impaired or absent (214). It is unknown whether the postprandial level of somatostatin predicts which patients will respond to somatostatin analogues such as octreotide. Octreotide may stimulate MMC-like activity in the small intestine of persons with CIIP, thereby reducing associated bacterial overgrowth and improving symptoms. Octreotide initiates activity fronts in the small bowel of healthy subjects and in those with intestinal motor disorders. Octreotide may be useful in patients with neuropathic abnormalities of the small bowel (215).

Clinical learning point: The somatostatin analogue octreotide has many clinical uses, including the stimulation of motility in persons with CIIP.

Small intestinal mechanosensitive pathways are disturbed in patients with functional dyspepsia, as well as in those with irritable bowel syndrome (IBS) (216). There may be beneficial effects of oral cisapride on small bowel motility in persons with IBS (217). Small bowel dysmotility also occurs in patients with postcholecystectomy sphincter of Oddi dysfunction (218). After cholecystectomy, disturbances of small bowel interdigestive motor activity are prevalent in patients with severe recurrent biliary-like pain who have no evidence of organic disease, particularly in those with objective evidence of sphincter of Oddi dysfunction (218).

Gastric emptying may be delayed in patients with IBS. Abnormal phase III-like activity is higher during the postprandial period in patients with diarrhea-predominant IBS (219), indicating that small bowel motor dysfunction occurs in some patients with IBS. Trimebutine is an agonist against peripheral mu, kappa and delta opioid receptors. Trimebutine releases several gastrointestinal peptides such as motilin; modulates the release of others such as VIP, gastrin and glucagon; accelerates gastric emptying; induces premature phase III of the MMC complex in the intestine; and modulates the contractile activity of the colon (220). Trimebutine may be effective in the treatment of both acute and chronic abdominal pain in persons with functional bowel disorders.

Clinical learning point: Trimebutine, an agonist of peripheral opioid receptors, may be effective in the treatment of both acute and chronic abdominal pain in persons with functional bowel disorders.

Abnormalities in small bowel motility occur in patients with liver cirrhosis. In two patients undergoing orthotopic liver transplantation, these motility changes normalized within six months after the transplantation (221).

Nutrients in the ileum inhibit postprandial and interdigestive motility of the upper gut, a phenomenon described as the 'ileal brake'. PYY, enteroglucagon, endogenous opioids and the neural pathways have all been proposed as candidate mediators of the ileal brake. An elevated concentration of plasma PYY is associated with inhibition of the duodenal MMCs in response to ileal nutrients. Increased volumes and unabsorbed nutrients in the proximal colon alter proximal small bowel motility. The volume-induced effects are mediated via extrinsic nerves, whereas the nutrient-induced effects may be mediated by humoral factors such as plasma PYY (222).

H_2 receptor antagonists inhibit gastric secretion, as well as gastrointestinal motility and secretion. This inhibition involves a process that is coupled to the adenylate cyclase pathway, as well as to activate the phosphoinositide signalling cascade through an independent G protein-dependent mechanism (223).

LIPIDS

AA and docosahexaenoic acid (DHA) are the predominant long chain polyunsaturated fatty acids that are derived by chain elongation and desaturation of the parent essential fatty acids (EFAs), linoleic acid and linolenic acid. AA and DHA may be conditionally essential for premature infants. Breast milk fat contains 98% triacylglycerols, 1% phospholipids, and 0.5% cholesterol and cholesterol esters. The fatty acid composition of these lipid classes is affected by diet. DHA and AA are absorbed as efficiently from triglyceride long chain polyunsaturated fatty acid-containing formula as from breast milk (224).

Conjugated bile acids solubilize the products of lipid digestion. The bile acids themselves are absorbed in small quantities by passive diffusion in the proximal intestine and by active transport in the distal ileum. The absorbed bile acids are extracted from the portal venous and hepatic arterial blood by the hepatocytes, where they exert negative feedback on their own synthesis. Biliary secretion completes the enterohepatic circulation of bile acids, and also induces the biliary secretion of cholesterol and phospholipids. During enterohepatic circulation, bile acids undergo bacterial modification that influences their solubilization, ileal absorption and hepatic extraction, as well as their ability to suppress bile synthesis or induce biliary secretion of lipids. Bile acid malabsorption upregulates hepatic low density lipoprotein receptors and cholesterol synthesis, and increases the proportion of cholesterol converted to primary bile acids by the activation of cholesterol 7alpha-hydroxylase. After the bile acids are internalized in the enterocyte, they bind to a specific cytosolic protein and exit the ileocyte by a poorly characterized anion exchange protein located in the basolateral membrane.

Lipid absorption requires an optimal concentration of bile acids in the intestinal lumen, and this concentration is maintained by the balance between ileal excretion and ileal active reabsorption of bile acids. The ileal sodium-dependent bile acid transporter (IBAT) has been cloned. IBAT is sodium-dependent, and shows substrate specificity for both conjugated and unconjugated bile acids (225). Expression of IBAT occurs in fetal intestine and is suppressed on day 7 of life, but then is reinduced by day 21 (226). GCs stimulate 7alpha-hydroxylase activity as well as bile acid synthesis in the liver. GCs also have a direct effect on the IBAT gene, acting through a GC-responsive element, leading to increased transcription and translation, increasing IBAT mRNA levels as well as protein and bile acid transport activity (227). Taurocholate transport by ileal BBM vesicles in rats is upregulated by the administration of pharmacological doses of GC, with the increase in the maximal transport rate of taurocholate corresponding to an increase in both IBAT mRNA and protein concentrations (227). IBAT mRNA and protein levels increase with bile acid feeding, and in biliary-diverted rats the abundance of the transporter protein falls (228). This suggests that the expression of IBAT is induced at a pretranslational level by free or taurine-conjugated cholic acid within the small intestine.

Clinical learning point: The IBAT has been cloned. Transporter activity, protein and mRNA abundance are influenced by luminal bile acid concentrations, by GCs and by the age of the animal.

The human ileal sodium/bile cotransporter cDNA has been isolated, and its gene localized to chromosome 13q33. Primary bile acid malabsorption (PBAM) is an uncommon idiopathic intestinal disorder associated with chronic diarrhea, steatorrhea and the interruption of the enterohepatic circulation of bile acids. Impaired ileal uptake of bile acids has been documented in several patients with PBAM, and the reduced bile acid uptake may be caused by inherited mutations in the cotransporter gene (229).

Photoaffinity labelling of the rabbit ileal sodium/bile-salt-cotransport system has been used to demonstrate the topology of this transport system. The transporter comprises a 93 kDa integral membrane protein and a peripheral 14 kDa bile acid-binding protein (230). Fluorescent bile acid derivatives have been used to establish the relationship between the chemical structure and the intestinal transport of bile acids in rats (231). Modifications at the 3 and 24 positions of the sterol nucleus allow the potential for small peptide conjugates to be transported by the IBAT. Some of these drugs have shown modest HIV-1 protease inhibitory activity (232). Blocking the ileal sodium-dependent bile acid transporter decreases serum cholesterol in hamsters (233).

Clinical learning point: PBAM should be suspected as a cause of chronic diarrhea and may be due to inherited mutations in the cotransporter gene. Inhibition of the bile acid transporter in the ileum may have future therapeutic advantages for the treatment of obesity and hyperlipidemia.

The bile acid ursodeoxycholate (UDCA) inhibits in a dose-dependent manner the production of IL-1 and IFN - stimulated nitrite/nitrate production in transformed human IECs (234). The NSAID indomethacin increases leukocyte adherence and migration in a rat model of ileitis, and the oral administration of urso-, cheno- or taurochenodeoxycholic acid reduces these effects in acute and chronic stages of indomethacin-induced inflammation (235). The cytoprotective and cytotoxic properties of bile acids correlate with their hydrophilicity and hydrophobicity, respectively. UDCA enhances indomethacin damage to the rat small intestine, whereas taurochenodeoxycholic acid normalizes the clinical inflammatory parameters (236). The production of nitric oxide by iNOS occurring from stimulation with IL-1 and IFN- is inhibited by UDCA, with reductions in iNOS mRNA, protein and activity (234).

A reduction in dietary lipids can be achieved by substituting dietary triglyceride for olestra, a nonabsorbable fat substitute consisting of fatty acids esterified to sucrose rather than to glycerol (237). Olestra impairs the absorption of fat-soluble but not water-soluble nutrients, and the concern about possible impairment of the absorption of fat soluble vitamins (A, D, E, K) has been addressed by selective vitamin supplementation of olestra. Another approach to the reduction in dietary lipid absorption is to administer orlistat (tetrahydrolipstatin), a highly specific potent lipase inhibitor. Orlistat given with a fatty meal reduces CCK release as well as the output of lipase, trypsin and bilirubin, and accelerates the rate of gastric emptying (238). This indicates that lipase is a possible regulator of upper gastrointestinal function.

Clinical learning point: The intake of unwanted lipids can be modified by the ingestion of olestra, a nonabsorbable fat substitute, or the use of orlistat, which prevents triglyceride hydrolysis.

Cholesterol esterase (also known as bile salt-stimulated lipase) and carboxyl ester lipase hydrolyze tri-, di- and monoglycerides and phospholipids, as well as cholesterol esters. Phospholipase A_2 may mediate cholesterol absorption by altering the physical-chemical state of cholesterol within the intestine (239).

Pancreatic enzyme replacement therapy does not fully normalize stool lipid losses in children with CF. The explanation for this incomplete correction of steatorrhea is unclear and does not appear to be due to a defect in the absorption of palmitic acid (240).

There is growing evidence that lipids are absorbed both by passive diffusion and by at least one protein-mediated component. The sterol transport protein in the BBM is an integral protein anchored in the lipid bilayer by at least one hydrophobic domain (241). Of note, this sterol transport protein may mediate the uptake of long chain triacylglycerols. The uptake of cholesterol of the BBM is inhibited by apolipoproteins (apo) (242). The method used to study lipid uptake may be important in identifying the possible presence of a protein-mediated step in lipid uptake. For example, when small intestinal segments are mounted in Ussing chambers, the diffusion of the bile salt micelles to the BBM appears to be rate limiting (243). In Caco-2 cells, the uptake of alpha-linolenic acid (18:3[n-3]), an EFA, occurs by a saturable process that follows Michaelis-Menten kinetics, arguing for the presence of carrier-mediated transport (244).

Lipids are presumably incorporated in the external lipid monolayer of the BBM; they subsequently diffuse through the BBM and are released from the inner lipid monolayer of the BBM into the cytosol of the enterocyte. Most cholesterol within the enterocyte is localized in the BBM, and there is targeted intracellular sorting of newly synthesized cholesterol and trafficking of plasma membrane cholesterol into the cell interior. Cholesterol is transported from the BBM to the ER in special transport vesicles that likely originate from the plasma membrane itself. The arrival of cholesterol at the plasma membrane is independent of new protein synthesis, a functional Golgi apparatus or microtubular function. Inhibitors of Pgp (which inhibit cholesterol transport from the plasma membrane to the ER) also reduce the amount of

newly synthesized cholesterol reaching the plasma membrane (245). The amount of cholesterol moving to the plasma membrane from the ER is constitutive, and is regulated at the level of cholesterol synthesis and not at the level of the transport process.

The uptake of lipids may also be influenced by cytosolic fatty acid-binding proteins (FABP). These 14 to 15 kDa proteins play a role in fatty acid trafficking and reversely bind with high affinity, especially to long chain fatty acids (LCFAs). Multiple FABP isoforms have been identified. The I-FABP isoform is confined to the small intestine, whereas L-FABP is also found in the liver and kidneys. High fat diets increase L-FABP in the jejunum, as well as L-FABP and I-FABP in the ileum. In the rat (but not in the mouse), LCFAs are strong inducers of L- and I-FABP gene expression (246). Feeding mice a lipid-enriched diet for seven days increases L-FABP mRNA and protein levels, but has no effect on I-FABP gene expression (246); this upregulation by dietary lipid is mediated by linoleic acid. I-FABP contains a single ligand binding site that displays a high affinity for both saturated and unsaturated LCFAs, an affinity that can be predicted on the basis of binding affinities, entropy and enthalpy (247). The tertiary structure of I-FABP has been studied (248). Caco-2 cells are useful in studying the intestinal expression of genes involved in lipid metabolism, including I-FABP (249). PYY is a member of a regulatory peptide family that includes NPY and pancreatic polypeptide. PYY is released by the presence of luminal free fatty acids. I-FABP transcripts are increased in response to PYY (250). Thus, PYY is a key part of the feedback system that determines the processing of cytosolic free fatty acids in the enterocyte. The FABP2 gene encodes I-FABP. A polymorphism of FABP2 has been identified in Pima Indians in Arizona, who exhibit a high prevalence of noninsulin-dependent diabetes mellitus. This polymorphism may be associated with insulin resistance and increased fat oxidation rates (251).

Clinical learning point: A component of lipid uptake may be protein-mediated, which opens the way for the development of new therapeutic targets for the treatment of hyperlipidemia and obesity, and to enhance the uptake of poorly absorbed drugs.

Cellular retinol-binding protein type II (CRBPII) is abundant in the small IECs. CRBPII plays an important role in intestinal absorption, cytoprotection, and metabolism of retinol and beta-carotene. Jejunal CRBPII mRNA and its protein levels increase when rats are fed a high fat diet. Unsaturated fatty acids such as oleic, linoleic and alpha-linolenic acids also enhance CRBPII mRNA levels. Medium-chain fatty acids and saturated fatty acids have little effect on CRBPII mRNA levels. CRBPII gene expression in rat jejunum is regulated predominantly by dietary fatty acids but not by dietary retinoids (252).

Inside the enterocyte, the lipolytic products are re-esterified and assembled into apo to yield chylomicra. These chylomicra are released at the basolateral membrane and reach the blood stream via the lymph, as well as via the portal circulation in smaller proportions. The important enzymes in the intracellular synthesis of lipids are monoacylglycerol acyltransferase (MGAT); 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (the key regulatory enzyme in the cholesterol pathway); and acyl CoA:cholesterol acyltransferase (ACAT) (responsible for cholesterol esterification). The monoglyceride pathway is used for the synthesis of chylomicron triglycerides. MGAT mediates the acylation of 2-monoacylglycerol and is important in the neutral lipid pathway. HMG-CoA reductase catalyzes the reduction of HMG-CoA to mevalonic acid and is the rate-limiting step in the cholesterol synthesis pathway. ACAT is involved in cholesterol esterification. The intestine responds to a requirement for enhanced triglyceride transport by producing chylomicrons of increased size, rather than by increasing their numbers. In the human fetal small intestine there is HMG-CoA reductase, ACAT and MGAT activity (253). There is a positive correlation between fetal age and the enzyme activities of HMG-CoA reductase and MGAT (253).

Triglyceride is resynthesized in the ER and is transported to the growing chylomicra by the microsomal triglyceride transport protein (MTP). The rate of transport of triglyceride from the ER to the Golgi is influenced by the intraduodenal infusion of lipids. This transport step may regulate the export of triglyceride from the enterocyte (254).

ApoB-100 and apoB-48 are essential for the assembly and secretion of triglyceride-rich lipoproteins in the liver and small intestine. These are derived from the same gene by a unique post-transcriptional mRNA editing mechanism. Oleic acid is the most effective of all fatty acids in stimulating triglyceride synthesis as well as the secretion of triglyceride, phospholipid and apoB. Oleic acid is the least effective of all fatty acids in stimulating apoA-1 secretion (255). ApoA-1 is the major structural protein of plasma high density lipoprotein. Intestinal apoA-1 gene transcription and protein synthesis are genetically determined, and are reduced in the presence of common mutations that induce binding of nuclear proteins (possibly a transcriptional repressor) (256). Stimulation of the synthesis and secretion of intestinal apoA-IV by intestinally infused lipid is mediated by capsaicin-sensitive afferent signals (257).

The surface components of the chylomicron include apoB-48, apoA-I, apoA-IV and apoC. The intracellular assembly of apoB-containing lipoproteins in enterocytes includes the association of apoB with lipid in a multistep process. This includes the cotranslational lipidation of apoB at the ER, mediated by MTP. MTP is present in the lumen of the ER and interacts with apoB during lipoprotein assembly. Using an MTP-inhibiting compound in Caco-2 cells results in a greater reduction in apoB-100 secretion than in apoB-48 secretion (258). In human jejunal explants in organ culture, hydrocortisone decreases the secretion of triglycerides, phospholipids and cholesteryl esters, as well as apoB-100 synthesis. On the other hand, hydrocortisone has a stimulatory

effect on apoB-48 and apoA-1 (259). In the postprandial state, the triglyceride fatty acid composition of chylomicrons resembles that of the lipid that was fed in the diet. The fatty acid composition of chylomicron phospholipids is also influenced by dietary fatty acids. Long term diets have been shown to alter the fatty acid composition of biliary phospholipids. In rats, long term feeding of a diet containing a supplementive sunflower oil or menhaden oil leads to greater total lymph fatty acid output than that of rats fed a standard low fat diet (260).

There are three related disorders of reduced apoB: a-betalipoproteinemia due to deficiencies of MTP; chylomicron retention disease, characterized by failure of chylomicron formation in enterocytes of unclear etiology; and familial hypobetalipoproteinemia, in which the expected phenotype of apoB truncation-producing mutation is not always observed (261).

Lipid malabsorption may lead to EFA malabsorption due to decreased phosphatidylcholine and bile secretion, as well as decreased chylomicron assembly and secretion (262).

Some patients with ileorectal anastomosis may develop bile acid malabsorption and steatorrhea. The impaired cholesterol absorption in these patients is correlated to changes in serum and biliary lipids (263). The intestinal absorption of dietary fat is normal after small bowel transplantation in the rat; fat absorption by the mesenteric duct is reduced but there is a compensatory increase in flow through retroperitoneal lymphatics (264).

SALT AND WATER ABSORPTION, AND DIARRHEA

The topic of the molecular biology of sodium absorption has been reviewed (265). Agents that stimulate epithelial salt and water secretion via increases in Ca_i^{2+} levels produce responses that are transient in nature compared with the more sustained cyclic nucleotide-driven secretion.

There are different isoforms of the NHE in many tissues. NHE2 is highly expressed in the sodium-absorptive epithelium of the jejunum, ileum and colon (266). In the jejunum, fluid secretion is driven by electrogenic chloride secretion. While the jejunal villus cells contain an apical chloride conductance, these cells are not thought to be secretory. Instead, their primary role is absorption of nutrients, fluid and electrolytes. The patch-clamp technique has been used to define ion channels in the cells located in the midregion of isolated jejunal crypts, and six different channels have been identified (267). There is a basolateral channel activated by cAMP-dependent secretagogues and a cAMP-dependent chloride conductance channel in the BBM. The presence of a chloride channel in the small intestinal villus enterocytes of guinea pig intestine has also been demonstrated (268).

In healthy individuals, there may be a self-limiting system that limits the extent of ion and fluid secretion in the gut. This braking system may involve paracrine agents released from the subepithelial environment, as well as neurotransmitters such as NPY released from enteric nerves. An inositol phosphate, D-*myo*-inositol 3,4,5,6-tetrabisphosphate, may be an intracellular messenger that limits the extent of carbachol-induced chloride secretion (269).

The proinflammatory cytokine IFN- disrupts epithelial barrier integrity and reduces secretagogue-induced chloride secretion. In T84 epithelial cell monolayers, IL-10 attenuates the IFN- -associated enhancement in electrical conductance, and prevents the IFN- -induced increase in mannitol fluxes (270). The paracellular pathway dominates the transepithelial permeability process, and the tight junctions have a larger conductance for cations than for anions. This cation selectivity can be decreased by cAMP-generating drugs, and the variation in transepithelial resistance in individual tissue preparations is inversely related to the cation selectivity of the tissue (271).

The topic of the use of transgenic mice to characterize the multipotent intestinal stem cell and to analyze the regulation of gene expression has been reviewed (272). Furthermore, the topic of gene therapy as it pertains to gastrointestinal diseases has been reviewed (273). The topic of the intestinal physiology and pathology in gene-targeted mouse models of CF has been reviewed (274). The most common mutation leading to CF is a phenylalanine deletion at the 508 position of the CFTR gene (F508), located on the long arm of chromosome 7. Basal and stimulated duodenal bicarbonate secretion may involve a CFTR-mediated transport pathway in mice, and CFTR either directly or indirectly may have a major function in mediating bicarbonate transport in the duodenum (275).

Clinical learning point: Gene therapy of gastrointestinal disorders is in its infancy.

Numerous mouse models are available to study the influence of the CFTR as an adenosine cAMP-regulated chloride channel (274). In these mouse models, cAMP regulation of electroneutral sodium chloride absorption is defective. In mice, a functional CFTR protein is required for cAMP-, cGMP- and calcium-dependent bicarbonate secretion (276). Mice without functional CFTR have a low basal short circuit current (Isc) in all areas of the intestinal tract. This results from a lack of spontaneous chloride secretion in response to agents that increase cAMP or intracellular calcium (277).

A major component of the alkaline secretion of the duodenum is regulated by intracellular cAMP, resulting in both passive and active transport of bicarbonate across the epithelium. The process of active bicarbonate secretion involves the concerted activities of an anion channel and a chloride/bicarbonate exchange in the BBM. Bicarbonate ions are secreted in response to a number of agonists that increase intracellular cAMP and calcium concentrations. These agonists include PGE_2, VIP, carbachol and enteric nerve activation. Most duodenal cAMP-stimulated bicarbonate secretion involves electrogenic secretion via a CFTR bicarbonate conductance, as well as electroneutral secretion via a CFTR-dependent chloride/bicarbonate exchange process that is closely associated with the carbonic anhydrase activ-

ity of the epithelium (278). Duodenal electrogenic bicarbonate secretion is proportionally greater than electroneutral bicarbonate secretion and is the secretory pathway activated by most secretagogues.

In the ileal absorptive cells, carbachol inhibits sodium chloride absorption and its component BBM NHE, acting via basolateral membrane receptors. The effects of carbachol on sodium chloride absorption are accompanied by an increase in BBM phospholipase C-gamma1 (phosphatidylinositol 4,5-bisphosphate-specific phospholipase C) associated with villin (a BBM actin-binding protein) and an increase in the tyrosine phosphorylation of villin (279). The f-actin stabilizing drug, jasplakinolide, prevents carbachol inhibition of ileal sodium chloride absorption. This suggests a role for villin in the signalling cascade that begins at the basolateral membrane, with carbachol binding to its receptor, and ends at the BBM with the inhibition of sodium chloride absorption.

Oral rehydration therapy has become widely accepted for the treatment of diarrheal status. Debate centres around the optimal electrolyte concentration in oral rehydration solutions (ORS), the presence of base or base precursors and the choice of ideal substrate osmolality. Studies in animal models and human volunteers have shown that the osmolarity of ORS may be a critical factor influencing the absorption of water and electrolytes from the small intestine. Hypotonic solutions with an osmolarity of 200 to 250 mmol/L perform better clinically than hypertonic or isotonic solutions. A sodium concentration of approximately 60 mmol/L and a glucose concentration between 50 and 100 mmol/L are optimal for the absorption of water from ORS. In a randomized, double-blind study involving children with acute diarrhea, stool output was less in patients receiving hypotonic ORS than in those receiving isotonic ORS (280).

The use of complex carbohydrate instead of glucose may reduce stool volume and result in a lower ORS intake. It has been hypothesized that the enhanced clinical efficacy of complex carbohydrate ORS is due to their hypotonicity (281). Glucose stimulates sodium absorption, as is the case with amino acids (282). Glucose polymers (starch) and amino acids (protein) in ORS enhance sodium and, therefore, water absorption. Using a rice-based ORS, there is improved water absorption in both normal and secreting rat intestine (283). The replacement of glucose by maltodextrins, and the addition of glutamine to the standard ORS (without changing its sodium content or osmolality), result in a reduction of sodium absorption in patients with short-bowel syndrome (284).

Nitric oxide may be a regulator of intestinal ion transport, and the main physiological precursor of nitric oxide is L-arginine, a nonessential amino acid. The addition of 1 mM L-arginine to ORS increases intestinal absorption of both sodium and water in humans, whereas higher concentrations of L-arginine lack this stimulatory effect (285).

Secretory diarrhea disturbs the normal densities and relative species abundance of microbiota. Adding fructo-oligosaccharide to ORS accelerates the recovery of bacteria that may be beneficial, while slowing the recovery of pathogenic forms (286).

Clinical learning point: ORS may be more effective when they are hypotonic, and contain starch and glutamine or arginine.

Uroguanylin is an intestinal peptide that is closely related to guanylin, another intestinal peptide. Uroguanylin and guanylin are secreted onto the intestinal epithelial surface, and regulate transepithelial salt and water transport through a receptor-mediated pathway. Guanylin binding to its receptor increases intracellular cGMP, resulting in activation of a protein kinase in the IEC. The subsequent intracellular events include stimulation of anion secretion via CFTR. Uroguanylin also stimulates intracellular cGMP production and transepithelial chloride secretion. In the mouse intestine, uroguanylin stimulates serosal-to-luminal bicarbonate secretion, together with a large increase in Isc (287). In CFTR knockout mice, the duodenal Isc response to uroguanylin is reduced. Uroguanylin is most effective in acidic regions of the small intestine, where it stimulates both bicarbonate and chloride secretion, primarily via a CFTR-dependent mechanism.

Guanylin and uroguanylin bind with high affinity to receptor guanylate cyclase signalling molecules found in the BBM of enterocytes. Activation of this cyclase in the intestinal mucosa culminates in the cGMP-mediated stimulation of chloride and bicarbonate secretion. Uroguanylin and guanylin mRNA are present in the small intestine, and may be targets for the regulation of transport by guanylin and uroguanylin via cGMP (288). The induction of the cDNA for the rat uroguanylin precursor in zinc-deficient rats may partially explain the beneficial effect of zinc supplementation in secretory diarrhea (289). These observations have been uncovered through differential display cloning techniques.

Clinical learning point: The stomach and intestine are potential targets for the regulation of intestinal secretion by guanylin and uroguanylin, acting through receptor guanylate cyclases and cGMP.

In mice, signal density for uroguanylin is greatest in the small intestine, whereas guanylin expression is greatest in the distal small intestine and colon (290). Uroguanylin mRNA is localized predominantly in the intestinal villi, whereas guanylin mRNA is localized in both the crypts and villi in the small intestine and in the superficial epithelial cells in the colon (291). Uroguanylin-expressing cells are also identified as a subpopulation of enterochromaffin cells (292). This raises the possibility that this uroguanylin is secreted both apically into the intestinal lumen and basolaterally into the circulation.

The role of the enteric nervous system in CT-induced

secretion has been reviewed (293). CT-induced intestinal secretion occurs as a result of activation of adenylate cyclase in the small IECs and the release of mediators such as 5-HT. 5-HT is present in enterochromaffin cells and acts through receptors in the enteric nervous system. 5-HT and 5-HT receptor agonists act on at least seven major types of receptors. 5-HT causes fluid secretion from the intestine of rats by a process that can be blocked by the intraluminal administration of a 5-HT_4 receptor antagonist (294). Alosetron, a 5-HT_3 receptor antagonist, increases basal fluid absorption in normal human small intestine but does not increase absorption in the presence of CT-induced secretion (295).

5-HT is located in the enterochromaffin cells as well as in the enteric nervous system of the intestine. 5-HT is involved in the control of the MMC. 5-HT reuptake inhibitors reduce orocecal transit time, and a 5-HT_3 receptor antagonist slows colonic transit. In patients with diarrhea-predominant IBS, the plasma 5-HT concentrations are higher than in normal volunteers, and the duration of the 5-HT peak is longer (296). This raises the possibility of treating these patients' diarrhea with a 5-HT receptor antagonist.

Clinical learning point: The 5-HT receptor antagonists may be useful to treat diarrhea, such as that occurring in some patients with IBS.

Several mechanisms involved in the nervous secretory refluxes of the enteric nervous system may be dependent on the flux of calcium across the plasma membrane. This calcium flux may be controlled by voltage-gated calcium channels. Nifedipine, a blocker of the L-type calcium channels, abolishes fluid secretion caused by a calcium ionophore in rats (297). Other calcium channel blockers may have a similar effect, and this does not appear to be on the efferent part of the secretory nervous reflux (298).

Cholinomimetic-induced electrogenic chloride secretion in rat intestine is mediated by M3 muscarinic receptors on enterocytes, as well as by M1 muscarinic receptors on submucosal neurons (299). Kinins are powerful stimulants of chloride secretion and act through a cascade of cAMP, PGs and CA_i^{2+} as second messengers. Kinin-associated chloride secretion depends on kinin beta$_2$ receptors and on CFTR chloride channels (300).

The endocrine and neural peptide PYY inhibits VIP-stimulated jejunal net water flux in vivo through a neural mechanism that implicates the participation of nicotinic synapses, alpha$_2$-adrenoceptors and sigma receptors (301). PYY also inhibits the secretion occurring in piglets with cryptosporidiosis (302). This antisecretory effect of PYY is likely mediated by the inhibition of PG induction of enteric nerve pathways. When the intestine is inflamed, for example in patients with Crohn's disease, there is increased intestinal permeability as well as increased tissue levels of mRNA and protein of TNF . TNF added to Caco-2 cells decreases the transepithelial resistance as well as Isc, and this is associated with increased paracellular permeability of the epithelium to sodium and chloride (303). The increase in transepithelial permeability across TNF-treated Caco-2 cell sheets arises from an alteration in the charge selectivity of the paracellular conductive pathway. It is unknown whether the increased intestinal permeability observed in some persons with Crohn's disease is caused by inflammation-associated increases in TNF. These data suggest that T helper 1-derived cytokines play a role in the pathophysiology of diarrhea in IBD.

NPY is localized in both the myenteric and submucous plexi of the intestine, and influences motility by causing relaxation of the longitudinal intestinal muscles. This occurs by stimulation of the release of noradrenaline from sympathetic neurons. The noradrenaline inhibits acetylcholine release from postganglionic neurons through interaction with alpha$_2$ receptors. NPY inhibits secretagogue-induced secretion and can stimulate fluid absorption. In HT-29 cells, NPY inhibits cAMP- and calcium-stimulated secretion via a reduction in the BBM chloride and basolateral potassium conductance (304).

Opioids inhibit intestinal fluid and electrolyte secretion by acting locally on central and peripheral opiate receptors, where they are degraded by neuropeptidases, a major one of which is enkephalinase. An orally active enkephalinase inhibitor reduces infectious and chemically induced diarrhea without affecting gastrointestinal motility and, therefore, may be useful therapeutic agents (305).

Clinical learning point: NPY-like analogues may be useful in developing proabsorptive agents to treat patients with diarrhea. Orally active inhibitors of apical degradation may also be developed for the treatment of diarrhea.

MINERALS AND VITAMINS

Iron: Iron homeostasis is maintained through the regulation of intestinal iron absorption. This is modulated by the nature of the iron in the diet, iron uptake across the BBM, intracellular processing and transport, and the release of iron across the basolateral membrane of the enterocyte into the plasma (306). The uptake of iron from the plasma across the basolateral membrane of crypt enterocytes is mediated by transferrin receptors (TfR), which are recycled back to the cell exterior and are influenced by the iron content of transferrin (307).

Expression of the TfR and ferritin genes is under transcriptional and posttranscriptional regulation; the posttranscriptional regulation is reciprocally controlled according to intracellular iron levels. Ferritin mRNA is most abundant in the epithelial cells of intestinal crypts and macrophages within the lamina propria, whereas the ferritin protein is most abundant in the apical two-thirds of the villus cells of normal and iron-loaded, but not iron-deficient, rats (308). This suggests that, in undifferentiated crypt cells, the ferritin genes are transcribed but the message is not translated. After differentiation of the cell, these genes may be controlled posttranscriptionally by intracellular iron stores. The iron regulatory proteins (IRPs) are cytosolic proteins that bind to structural elements, called iron responsive elements. The

IRPs are present in the untranslated region of mRNAs that encode ferritin, the TfR and aminolevulinate synthase.

In Caco-2 cells, the BBM iron uptake is responsive to the intracellular content of iron, and basolateral uptake of iron is transferrin-mediated. Low levels of intracellular iron cause IRP-1 to bind to, and subsequently stabilize, TfR mRNA, and to bind to ferritin mRNA, thereby diminishing its translation. In Caco-2 cells, transepithelial iron transport is inversely related to the intracellular iron concentration as well as to the IRP-1 activity, IRP-2 mass, TfR density and ferritin levels (309). Pretreatment of Caco-2 cells with IL-1 , IL-6 and TNF decreases BBM iron transport across the monolayer (310). This suggests that the proinflammatory cytokines are capable of inhibiting the iron transport activity of IECs.

Frequent doses of iron may reduce the absorption of subsequent doses, because of loading of the intestinal mucosal cells with iron (311). Chronic hypoxia enhances intestinal iron transport by increasing the value of the membrane potential difference, and increasing the expression of iron transport in duodenal BBM (312).

Biliary iron originates from nontransferrin-bound iron. The biliary iron is absorbed from the intestine and undergoes enterohepatic circulation if the transferrin is saturated. In iron-overloaded rats, biliary iron originating from plasma, nontransferrin-bound iron is not absorbed (313).

Improving the nutritional quality of stable foods is essential to developing a sustainable solution to the global micronutrient crisis ('hidden hunger'). The traditional methods for determining food iron availability are time consuming and expensive. A Caco-2 model has been developed to examine iron availability from infant formula. Approximately twice as much iron is in solution from digests of infant formula relative to that of human milk. However, smaller or equal amounts of iron are taken up from the infant formula relative to the human milk digest. Iron uptake promoters in the infant formula did not enhance Caco-2 cell iron uptake from infant formula digest (314).

Increased amounts of dietary calcium do not influence nonheme-iron absorption (315). Amino acids have a variable effect on iron absorption, and glutathione requires digestion to cysteine or cysteine-glycine to promote iron uptake (316).

Clinical learning point: Body iron homeostasis is controlled by the intestinal absorption of iron.

Calcium: Parathyroid hormone (PTH)-mediated responses to hypocalcemia include increased reabsorption of calcium from the kidney and reabsorption of calcium from bone. PTH stimulates calcium influx by a direct mechanism involving the activation of a dihydropyridine-sensitive calcium-influx pathway and the cAMP second messenger system (317). The regulation of extracellular ionized calcium (Ca^{2+}_0) is dependent upon a process of Ca^{2+}_0 sensitivity that is achieved by a calcium-sensitive receptor (CaR). CaR is a G protein-coupled heptahelical protein. The duodenum is the major site for the absorption of calcium; the jejunum and ileum both absorb and secrete calcium. Immunohistochemical studies have localized CaR in epithelial cells of the small intestinal villi and crypts. In situ hybridization and immunohistochemistry demonstrate CaR expression in Auerbach's myenteric plexus of the small and large intestine, and in the submucosa in the region of Meissner's plexus (318). CaR is also present at the base of epithelial cells as well as in the intestinal villi and crypts, and in a lesser amount in the apical surface of villus cells.

The duodenal absorption of calcium is a 1,25-dihydroxyvitamin D_3-dependent process, which increases the transcellular and mucosal-to-serosal flux of calcium. This active transport process is mediated by the vitamin D-dependent calcium-binding protein, calbindin. The enhancement of transepithelial conductance and calcium flux in Caco-2 cells is associated with upregulation of the expression of calbindin-9 kDa mRNA, with no significant contribution of the calcium-adenosine triphosphatase-mediated transcellular pathway (319). This suggests that the stimulation of calcium flux across the Caco-2 cells results from a genomic effect of vitamin D sterols on the assembly and permeability of tight junction complexes. Intestinal calcium absorption falls with age, and this is not explained by a decrease in the abundance of the intestinal vitamin D receptor. Thus, other factors must be responsible for this age-related change in calcium absorption (320).

High calcium diets reduce zinc absorption and may thereby increase the zinc requirement in adult humans (321).

Vitamin B_{12} and folate: Protein-bound vitamin B_{12} malabsorption is detected in less than 1% of elderly, hospitalized patients (322). Correction of vitamin B_{12} deficiency is usually achieved by intramuscular injection. However, the intranasal application of hydroxocobalamin in cobalamin-deficient patients results in fast nasal absorption and a sustained increase of baseline cobalamin concentrations (323).

Folate is one of the key vitamins involved in normal cellular functions, as well as in growth and development. In humans, the proximal jejunum is the major site of folate absorption. Folate may be absorbed by a pH-dependent, electroneutral, carrier-mediated mechanism (324). Two cDNA clones have been isolated and appear to be involved in folate transport. In mouse small intestine, the open reading frame of one of these clones is identical to that of the reduced folate carrier. There may be cell- or tissue-specific posttranslational modification(s) of the transporter. Also, there may be an axillary protein to account for the differences in the characteristics of the intestinal RFC when it is expressed in xenopus oocytes compared with when it is expressed in IECs (325).

Thiamine: The uptake of thiamine into the human small intestine occurs by a saturable process, with passive uptake at higher concentrations. At lower concentrations, the uptake of thiamine across the BBM is carrier-mediated, and the saturable component of the thiamine antiport has a stoichiometric thiamine to hydrogen ion ratio of one to one (326). In a thiamine-deficient patient, the duodenal saturable compo-

nent was increased, with higher values for the Michaelis constant and maximal transport rate (327).

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