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REVIEW ARTICLE

Small Bowel Review
Diseases of the Small Intestine

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In the past year there have been many advances in the area of small bowel physiology and pathology and therapy. In preparation for this review, over 1500 papers were assessed. The focus is on presenting clinically useful information for the practicing gastroenterologist. Selected important clinical learning points include the following: (1) glutamine may restore the AIDs-associated increased intestinal permeability to normal; (2) substance P is a major mediator of diarrhea caused by *Costridium difficile* toxin A, acting by binding to a G-protein-coupled receptor, and represents a possible 2therapeutic target; (3) the serological diagnosis of celiac disease has been greatly enhanced with the use of anti-endomysial antibody testing, and the recent antitransglutaminase; (4) a quarter of patients with celiac disease may have secondary pancreatic insufficiency and require enzyme replacement therapy; (5) in the patient with unexplained elevation in the serum transaminase concentration, consider celiac disease as an obscure possibility; (6) bosentan and endothelin receptor agonist may prove to be useful in reducing gut ischemia in patients with septic shock; and (7) the administration of recombinant human fibroblast growth factor-2 may prove to be useful to prevent radiation damage to the gastrointestinal tract.

KEY WORDS: small bowel; small intestine; intestinal permeability; diarrhea; celiac disease; diarrhea; septic shock; radiation damage.

MICROBIOLOGY

Cellular microbiology represents the interface between cell biology and microbiology. The topic of how enteric pathogens socialize with their intestinal host has been reviewed (1). The topic of the modification of the gut flora by dietary means also has been reviewed (2).

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Escherichia coli

Enterohemorrhagic *Escherichia coli* (EHEC) is a common cause of both acute nonbloody diarrhea as well as hemorrhagic colitis. EHEC includes the serogroup 0157:H7 (3), a cause of "hamburger colitis." *E. coli* 0157:H7 also may be associated with pseudomembrane formation (4).

Most outbreaks of *E. coli* 0157:H7 infection have been associated with contaminated cattle products, such as undercooked beef or raw milk. A recent outbreak has been traced to the consumption of unpasteurized juices (5). The most serious complication of *E. coli* 0157 infection is the hemolytic uremic syndrome, which causes acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. The degree of hemolytic uremic syndrome is closely related to levels of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) *E. coli* 0157 adheres to the membrane, and

develops "attaching and effacing" lesions, but in Caco-2 cells the *E. coli* 0157 does not penetrate the monolayer (6).

Enteropathogenic *E. coli* (EPEC) causes acute and chronic diarrhea in young children in both developing and developed countries and causes sporadic cases of diarrhea in adults. A new surface organelle has been identified that is involved in protein translocation into epithelial cells, which forms a physical bridge between the bacterium and the infected cell surface (7). *E. coli* strains isolated from the ileal mucosa of patients with Crohn's disease adhere to differentiated intestinal cells, and may disrupt the intestinal barrier by synthesizing an α-hemolysin (8).

Diarrhea associated with enterotoxigenic *E. coli* (ETEC) infection results in an increased morbidity and mortality in adults and infants. ETEC induces diarrhea by stimulating the secretion of fluid and electrolytes, and the severity of ETEC-induced diarrhea is reduced by psyllium (9).

Aids and HIV Diseases

The topic of AIDS and the gastrointestinal tract has been reviewed (10). Diarrhea occurs in 30–60% of North American and European AIDS patients and in nearly 90% of AIDS patients in developing countries. This is a leading cause of morbidity and mortality in HIV-infected children. In about one patient in four with HIV-associated severe diarrhea, no detectable intestinal pathogen is identified. HIV-infection induces a pronounced polyclonal B-cell activation, and there are normal mucosal B-cell responses following oral vaccination (11). There are multifactorial mechanisms including opportunistic infection, malabsorption, reduced food intake, metabolic alterations, and tissue damage inflicted by HIV itself. HIV may stimulate crypt cell proliferation and a fall in the villous surface area (12). There may be underproduction of a trophic factor required for appropriate lamina propria T-cell function in patients with HIV disease. Glutamine is a primary fuel for enterocytes and lymphocytes. Intestinal permeability may increase in patients with AIDS, and this is diminished by the administration of 4 or 8 g/day of glutamine (13).

Clinical Learning Point: Glutamine may restore the AIDs-associated increased intestinal permeability to normal.

Cryptosporidium parvum is an important cause of diarrhea in both immunocompetent and immunosuppressed hosts, and infection with this organism is responsible for 1–2% of deaths in patients with acquired immunodeficiency syndrome (AIDS). *C. parvum* activates both prostaglandin (PG) H synthase 2 expression and PGE_2 and $PGF_{2\alpha}$ production in human intestinal epithelial cells (14). The incidence of intestinal tuberculosis (TB) is increasing in patients with AIDS, and in only 20% of these TB patients is there associated pulmonary disease. The most commonly affected intestinal areas are the jejunum, ileum, and cecum (15).

Clostridium difficile

Clostridium difficile is a common pathogen causing symptomatic diarrhea. The bacterium produces toxin A and toxin B. In patients with *C. difficile* toxin-positive disease, 18.5% are positive for toxin A, 48.2% are positive for toxin B, and 33.3% are positive for both toxins. This suggests that testing for either toxin A or toxin B alone will result in more frequent misdiagnosis than testing for both toxins (16). Toxin A is thought to be the primary pathogenic toxin of *C. difficile* disease. The intestinal secretory response elicited by toxin A involves the participation of immune and inflammatory cells within the lamina propria. The release of neuropeptides and substance P-containing containing sensory neurons may be involved in the response to toxin A. Mast cells also participate in the pathogenesis of toxin A-associated diarrhea and enteritis. *C. difficile* toxin A elicits intestinal fluid secretion and neutrophil infiltration by both mast cell-dependent and -independent pathways; substance P participates in both pathways (17). Substance P is an 11-amino acid peptide member of the tachykinin family and substance is a major mediator in inflammatory diarrhea caused by *C. difficile* toxin A. Substance P mediates its effects by binding to its specific neurokinin-1R, a member of the family of G protein-coupled receptors. Neurokinin-1R expression is increased in the intestinal epithelium shortly after exposure to toxin A and may be important in toxin A-induced inflammation (18).

Clinical Learning Point: Substance P is a major mediator of diarrhea caused by *C. difficile* toxin A, acting by binding to a G-protein-coupled receptor, and represents a possible therapeutic target.

T. Whippelii

T. whippelii causes Whipple's disease, a rare chronic systemic illness characterized by abdominal pain and diarrhea, arthralgias and infiltration of tissues with PAS-positive macrophages. The polymerase chain reaction (PCR) assay may be used to detect a portion of the 16S ribosomal RNA gene sequence

corresponding to the Whipple bacillus, *T. whippelii*. Following antibiotic therapy, histological improvement in tissues lags behind the clinical and molecular evidence of improvement (19).

Rotavirus

Rotaviruses are nonenveloped double-stranded RNA viruses that are a major cause of diarrhea in infants and young children, and in developing countries rotaviruses cause many deaths each year. Rotavirus infection induces the expression of a subset of chemokines, a novel class of small cytokines that are able to recruit and activate leukocytes. These chemokines may play a role in the initiation and modulation of the immune response to rotavirus infection (20).

CELIAC DISEASE

The topic of the pathogenesis of celiac disease (gluten-sensitive enteropathy) has been reviewed (21). Celiac disease is a human, genetically linked disorder characterized morphologically by villous atrophy and enhanced crypt proliferation. Celiac disease is a T-cell-mediated immunological disease, and the identification gliadin-derived epitope of T cells is a key step towards the development of strategies to interfere in the mechanisms involved in the pathogenesis of celiac disease (22, 23). In addition, in celiac disease there is increased epithelial expression of human leukocyte antigen (HLA) class II molecules and a transmembrane secretory component, the polymeric immunoglobulin receptor. In celiac disease there is a marked increased density of intraepithelial lymphocytes, and $CD4^+$ T cells employing the α/β T-cell receptor are central to the immunopathology of celiac disease. Programmed cell death (apoptosis) refers to the genetically determined processes by which cells die in response to physiologic extracellular and intracellular signals. Normal intestinal mucosa shows an occasional intraepithelial lymphocyte with serine esterase granules, but there is a marked increase in intraepithelial lymphocyte among the surface enterocytes of untreated celiac mucosa (24). Increased production of interferon-γ and TNF-α may be cytotoxic to the epithelial cells, and mucosal gluten exposure in patients with Celiac disease elicits high levels of IFN-γ expression and lower levels of IL-2, IL-4, IL-6, and TNF-α (25). T-cell activation requires recognition of the antigen that is specific for each single T clone, and a second complimentary nonclonal signal and the (CTLA)-4 immunoglobulin (CTLA-41g) down-regulate the expression of CD25, intercellular adhesion molecule-1 (ICAM-1), IL-2, and IFN-γ (26).

Susceptibility to celiac disease is strongly associated with particular HLA class II alleles, but non-HLA loci may also be determinants of the inheritance of celiac disease. The CTLA-4 (T-lymphocyte-associated cytotoxic) gene located on chromosome 2q33 in humans encodes a cell-surface molecule providing a negative signal for T-cell activation. CTLA-4 may be a non-HLA determinant that predisposes to celiac disease (27). Interestingly, the celiac-associated HLA phenotype shows a geographical north–south gradient, with DR3 being more common in northern Europe and DR7 more common in the south. However, there is no evidence that clinical features of celiac disease are associated with different HLA genotypes (28).

The topic of the diagnosis of celiac disease has been reviewed (29). Celiac patients have increased prevalence of serum anti-single-stranded DNA (14%), anti-double-stranded DNA (23%), anti-cardiolipin (14%), and anti-endomysial autoantibodies (63%) (30). Serum antibodies to gluten, reticulum, and endomysium (the lining of smooth muscle bundles) are currently used in screening for celiac disease. Anti-gliadin antibodies of patients with celiac disease react with structures on gliadin and potential autoantigens on enterocytes (31). IgA-EMA (endomysial antibody) has a sensitivity of 68–100% for the diagnosis of untreated celiac disease in adults and 85–100% in children. The specificity of IgA-EMA may be as high as 100%.

Transglutaminase has several species including those involved in blood coagulating factor VIII, as well as the soluble and insoluble tissue transglutaminase. Transglutaminase is a new class of glutamyl-transpeptidase-binding protein and may influence polyamine function in the intestine (32). Transglutaminase is associated with cell proliferation, cell differentiation, receptor-mediated endocytosis, cell senescence, programmed cell death, intracellular matrix, and aging. Transglutaminase is the antigen recognized by EMA. Transglutaminase is present both intracellularly and extracellularly. An active site cysteine residue of transglutaminase binds to the peptide-bound glutamine substrate, forming a thioester bond. Tissue transglutaminase is present in the subepithelial region of the mucosa of control subjects and those with untreated celiac disease. In patients with untreated celiac disease, the subepithelial region staining positive for transglutaminase is heavily infiltrated with T cells carrying the CD3 antigen and large cells expressing DQ molecules. The activity of trans-

glutaminase is increased in patients with celiac disease, and transglutaminase is the main target for celiac disease-associated anti-endomysium autoantibodies (33). Transglutaminase is also able to accept gliadin as one of its few substrates (34). Gliadin-specific T cells isolated from intestinal celiac lesions recognized deamidated gliadins. Transglutaminase forms a physical linkage to glutamine residues in gliadin and catalyses the formation of the peptide bond between glutamic acid residues formed by removing ammonia from glutamine, with lysine residues in the T-cell DQ2 binding pocket. Deamidated gliadin active peptide binds to DQ2 peptide binding sites and induces T-cell activity.

EMA may be used as serological tests of celiac disease, and the endomysial antigen is tissue transglutaminase. Gliadin, a subfraction of gluten, has high substrate affinity for transglutaminase, and the presence of EMA is specifically associated with continuing exposure to gluten and only indirectly with the intestinal inflammatory process. Thus, patients may have only very subtle evidence of a pathological lesion, such as raised intraepithelial lymphocytes, and yet the EMA is positive. Following a gluten-free diet, the EMA disappears despite the presence of continuing inflammation. Measuring EMA may represent a useful means to assess the patient's compliance with their gluten-free diet.

The IgA anti-transglutamine assay is quantitative (35), and the new autoantibody ELISA test correlates well with the endomysial antibody test (36). Measurement of IgA antibodies to transglutamine (IgA-transglutamine) gives sensitivities of 95–98% and specificities of 94–95%. The titers of IgA-transglutamine fluctuate with dietary gluten exposure, consistent with previous observations of monitoring IgA-EMA to determine the patient's compliance with a gluten-free diet.

Clinical Learning Point: The serological diagnosis of celiac disease has been greatly enhanced with the use of anti-endomysial antibody testing, and the recent discovery of tissue transglutaminase.

Suction biopsies may be superior to endoscopically obtained pinch biopsies for the diagnosis of celiac disease in children. If endoscopy is used to obtain biopsies, it is suggested that the patient should be over 2 years of age, and a minimum of four biopsies should be obtained with forceps of greater than 2 mm diameter (37).

Tests of small bowel permeability may be used to increase the suspicion for the diagnosis of celiac disease and to select persons for a small bowel biopsy. The presence of the disaccharide sucrose in the serum after an oral load shows promise as a noninvasive test for celiac disease (38). The excretion of peptides in the urine is also increased in patients with celiac disease (39). In celiac disease there is a decreased number of tight junction horizontal strands and reduced meshwork depth, which parallel the decrease in epithelial resistance and the increase in permeability. This suggests that the epithelial barrier function is disturbed by these structural modifications of the tight junction in patients with untreated celiac disease (40) and explains why the permeability tests may be useful diagnostically.

Gluten-dependent inflammatory changes have been demonstrated in the rectal mucosa in persons with celiac disease. Gliadin is able to activate cell-mediated immunity in the rectal mucosa in celiac patients and in a subset of their first-degree relatives (41). The intraepithelial lymphocyte number in the rectal mucosa patients with active celiac disease regresses on a gluten-free diet (42). It is unknown whether this observation may be used clinically.

Activation of the compliment system initiates a number of defense mechanisms intended to protect the body from invading microorganisms and other insults. However, uncontrolled compliment activation may lead to tissue damage. In celiac disease there is expression of cell membrane compliment regulatory glycoproteins (43).

In order for food to be considered to be "gluten-free," it must have less than 10 mg of gliadin per 100 g of food. In the past testing of foods for gliadin was performed by HPLC, polymerase chain reaction, and by mass spectroscopy. A highly sensitive capture ELISA assay has been reported for the detection of gliadin in food (44). This will be useful to better help designate foods that are tolerable to celiac disease patients.

Feeding mice, rats, and piglets gliadin reduces the activities of selected brush border membrane enzymes in an animal model of celiac disease (45). The Irish setter dag is also a model of gluten enteropathy (46).

Exocrine pancreatic insufficiency is present is some patient with celiac disease. This may arise in part from a defective meal-stimulated pancreatic lipase output because of gut damage affecting the intestinal release of secretin and cholecystokinin. The mixed-triglyceride breath test may be used to assess fat digestion and to monitor the need for enzyme replacement therapy in the approximately one celiac

disease patient in four with pancreatic insufficiency (47).

Clinical Learning Point: A quarter of patients with celiac disease may have secondary pancreatic insufficiency and require enzyme replacement therapy.

Adult patients with steatorrhea due to celiac disease have a higher prevalence of esophageal symptoms and a lower esophageal sphincter pressure, compared to those with celiac disease without steatorrhea or control subjects. This esophageal dysfunction reverts to normal when the patient is on a gluten-free diet (48). Reactive lymphoid follicles have been described in the stomach of *Helicobacter pylori*-negative celiac patients, and this mucosa-associated lymphoid tissue (MALT) regresses on a gluten-free diet (49).

Refractory or unclassified sprue is a rare diagnosis made after exclusion of any other disorder mimicking celiac disease and after failure of a strict gluten-free diet to restore intestinal architecture to normal. In active celiac disease immunohistochemical studies have shown an expansion of intraepithelial lymphocytes bearing T-lymphocytes expressing either T-cell receptor $\gamma\delta$ or T-cell receptor $\alpha\beta$ and CD103. In patients with refractory sprue, the villous atrophy is associated with an increased number of intraepithelial lymphocytes. In a description of six patients with refractory sprue, the intestinal epithelium was massively infiltrated by small lymphocytes that lacked CD8, CD4, and T-cell receptor, but contained CD3 ε and restricted rearrangements of the T-cell receptor γ chain (50).

Dermatitis herpetiformis is a cutaneous manifestation of celiac disease, characterized by a symmetrical pruritic rash and pathognomonic IgA deposits in the skin. About 80% of patients with *Dermatitis herpetiformis* have villous atrophy, and the remaining 20% show subtle inflammatory changes in the small bowel mucosa. Some patients with celiac disease may be able to tolerate oats, and patients with *Dermatitis herpetiformis* have also been shown to lack oat toxicity (51).

Clinical Learning Point: In the patient with unexplained elevation in the serum transaminase concentration, consider celiac disease as an obscure possibility.

Celiac disease may be seen in association with a variety of autoimmune disorders including insulin-dependent diabetes mellitus, primary myxedema, thyrotoxicosis, Addison's disease, pernicious anemia, alopecia, and in 3% of patients with autoimmune hepatitis (52). Of importance, 9% of patients with cryptogenic hypertransaminasemia have serological evidence of gluten sensitive enteropathy. After six months on a strict gluten-free diet, all patient's transaminase levels and serum antibody levels returned to normal with intestinal villus regrowth (53).

ETHANOL

Pretreatment of Caco-2 cells with low concentrations of ethanol (a mild irritant) attenuates the subsequent injury induced by higher damaging concentrations (54). This "adaptive cytoprotection" of low concentrations of ethanol is abrogated when cells are pretreated with an endogenous prostaglandin inhibitor or when the mild irritant is administered in a calcium-free medium.

Chronic alcohol consumption increases intestinal permeability, and this may enhance the local invasion by gut luminal antigens including bacterial flora. This then stimulates IgA production by gut mucosal lymphocytes, resulting in an increased circulating IgA of predominantly intestinal origin. Serum IgA antibodies to the 140-kDa colonic luminal protein are found in 76% of patients with alcoholic liver disease, and 24% of these persons had serum IgA antibodies to a 40-kDa colonic luminal protein (55).

The trefoil factor family peptides are highly concentrated in the mucus layer of the gastrointestinal tract. Trefoil factor family-3 is produced predominantly by goblet cells of the small and large intestine. The three human trefoil factor family genes are clustered within 50 kb in the genome, and their expression is coordinated. In hypertonic medium, trefoil factor family-1 and trefoil factor family-3 are downregulated in a colonic carcinoma cell line, but raising the osmolarity with ethanol results in an upregulation of trefoil factor family-3 (56).

DIABETES

In a small proportion of diabetic patients the orally administered antihyperglycemic agent metformin causes gastrointestinal symptoms such as diarrhea. Metformin does not alter the oral–cecal transit time in persons given this sulfhonylurea but does increase bile salt excretion and stool bile acid content. These changes may contribute to the liquidity of the stool (57). Intestinal ornithine transcarbamylase, which catalyzes the conversion of ornithine to citrulline in the small intestine, is decreased in streptozotocin diabetic rats. This reduction is restored by the administration of insulin or the limitation of food intake (58).

A number of gastrointestinal disorders occur in diabetic patients, including esophageal dysmotility,

gastroparesis, diarrhea, constipation, fecal incontinence, and impaired gallbladder contraction. The prevalence of these disorders in an unselected population of diabetic outpatients may reach as high as three persons in four. The gastrointestinal dysfunction in diabetic patients is often attributed to be due to the autonomic neuropathy that occurs in diabetes. However, the frequency of these gastrointestinal disorders is higher than the reported rates of autonomic dysfunction. The reason for this disconnect is unclear. In nonobese diabetic mice, a number of gastric inhibitor polypeptide (GIP)-, cholecystokinin/gastrin-, and serotonin-immunoreactive cells fall in the prediabetic state. This indicates that some of the changes of the duodenal endocrine cells could be attributed to the diabetic state, but others take place before the onset of hyperglycemia (59, 60).

Diet is an important factor in the development of diabetes in the Biobreeding (BB) rat, and changes in gut development and absorption of nutrients occurs in the diabetes-prone rat (Bbdp). Normal nondiabetic animals have higher levels of sodium dependent glucose transporter in brush border membrane (SGLT-1) and sodium-dependent fructose transporter in brush border membrane (GLUT5) mRNA than do Bbdp, and in nondiabetic rats these mRNA levels can be reduced by feeding casein or soy, as compared with chow (61).

AGING

Aging affects both the structural and functional properties of the small bowel. An altered adaptive response of the small intestine to nutritional stress has an adverse impact upon the nutritional status of elderly humans or senescent rats. Apoptotic cell death is a protective mechanism to remove cells with DNA damage or diseased cells that might interfere with normal intestinal functioning. Epithelial cell production rates are increased throughout the gastrointestinal tract in aging rats. Calorie restriction delays this abnormally high rate of cell production to a later time. Calorie restriction in the rat enhances apoptosis and may thereby protect the gastrointestinal tract from the accumulation of DNA-altered cells during the aging process (62). Oral pancreatic extract supplementation exerts a trophic effect on the ileal mucosal of aged rats in response to nutritional stress (63).

ISCHEMIA

Autoregulation of blood flow is present in the adult intestine, so that the vascular resistance increases as perfusion pressure rises. This is a response designed to maintain steady-state hemodynamic conditions. At birth the abrupt loss of the umbilical circulation is associated with a high flow rate in the vascular bed. In 3-day-old swine, vascular resistance increases immediately after the reduction in pressure and flow, possibly because of low nitric oxide production and/or local production of angiotensin (64). Blockade of nitric oxide synthesis with L-arginine analoges causes a greater rise in gut vascular resistance in 3- than in 35-day-old swine.

Substance P is a potent dilator whose effect is primarily mediated via nitric oxide production. Substance P relaxes the mesenteric artery in young swine, an effect that is eliminated by the mechanical removal of the endothelium or blockade with an L-arginine analog (65). The peptide exerts its vascular effect via the neurokinin-1 receptor, which is linked to endothelial cell nitric oxide synthase.

The neuropeptide Y has six receptors. The Y_1 receptor on isolated blood vessels potentiates vasoconstrictor substances, whereas the prejunctional Y_2 receptor reduces neurotransmitter release from extrinsic sympathetic as well as from intrinsic submucosal vasodilator nerves (66).

Ischemia–reperfusion injury underlies the gut dysfunction that occurs in early shock, sepsis, and trauma, and this injury appears to be mediated by reactive oxygen metabolites at an early stage and later by the priming and activation of polymorphonuclear neutrophils (67). The intestinal mucosa has a high blood flow, and oxygen consumption at rest accounts for about 20% of the body's total resting oxygen consumption. During food processing and absorption, the oxygen requirement may increase by up to 100%. This absorptive hyperemia is regulated, and most of the microvascular regulation occurs outside the mucosal tissues (68).

Ischemia–reperfusion induces mucosal barrier failure, with translocation of enteric bacteria through the intestinal barrier to extraintestinal sites and into the systemic circulation. This leads to the release of inflammatory mediators, leukocyte adhesion and trapping, pancreatic enzyme activation, endothelial dysfunction, epithelial disruption, and impaired intestinal motility. The response of the intestine to ischemia may relate to mucosal mast cells and their release of proteases. Apoptotic epithelial cells are increased

following ischemia. The severity of reperfusion injury is correlated with the period of ischemia (the pathway of cell damage and death) and with proteinase–antiproteinase imbalance (69). Following ischemia–reperfusion there is desquamation of epithelial cells, a transient increase of crypt cell production, and migration and differentiation of the replenished villus for functional recovery. The activity of each brush border membrane enzyme recovers in parallel with the encoding mRNA, although the time of recovery differs between enzymes. This suggests that the regulation occurs either by increased transcription and/or by mRNA stabilization (70). Despite the alterations of mucosal architecture with ischemia–reperfusion, nutrient transport is preserved (71).

The reperfusion of the intestine following a period of ischemia results in the release of proinflammatory mediators, which then activate the endothelium to express P-selectin. The rolling leukocytes adhere to the endothelium because of an interaction between integrins on the leukocyte with adhesion molecules of the immunoglobulin family, such as ICAM-1 on the endothelium. Recombinant ICAM-1 does not affect leukocyte rolling in an ischemia–reperfusion model in mice, but dose-dependently reduces adhesion of leukocytes to the endothelium (72).

Mast cells are important modulators of blood flow within the small intestine and are found in the submucosa and lamina propria. Nerves within the intestine may activate mast cells and lead to their release of histamine, serotonin, or arachidonic acid metabolites. Mast cell- and capsaicin-sensitive nerve-evoked laser dilator mechanisms act independently (73).

Mast cells may contribute to reperfusion injury. As compared with wild-type mice, those with mast cell deficiency exposed to ischemia-reperfusion do not develop the increase in mucosal permeability, leukocyte infiltration, and vascular permeability which is seen in animals with mast cells (74). Because reactive-oxygen-derived species have been implicated in mediating the intestinal ischemia-reperfusion damage, inhibitors of xanthine oxidase or low-molecular-weight antioxidants such as vitamin E have been used, but with disappointing results. Stable nitroxide radicals may be protective against intestinal damage with ethanol or NSAIDs, and these radicals may attenuate the ischemia–reperfusion injury in the rat intestine (75). This ischemia–reperfusion injury includes necrosis as well as apoptosis (76).

At a cellular level ischemia leads to depletion of adenosine triphosphate (ATP) and the loss of cytoskeletal integrity. With reperfusion, restitution and proliferation reduce the continued destruction of the villous structure. Transforming growth factor-α, IL-1β, IFN-γ, and epidermal growth factor (EGF) enhance restitution, possibly through the increased production of TGF-β. Heparin-binding EGF (HB-EGF) is a member of the EGF family that is a mitogenic growth factor, and it may protect the intestinal epithelium against hypoxia. This protection is achieved possibly by maintaining F-actin structure and ATP levels, as well as by increasing proliferation (77).

The loss of gut mucosal integrity has been implicated in the pathogenesis and perpetuation of multiple organ dysfunction syndrome. Intestinal nitric oxide metabolites decrease following resuscitated hemorrhage in rats, possibly due to increased endothelial cell production of nitric oxide (78).

Multiple organ dysfunction syndrome is characterized by the progressive deterioration and subsequent failure of the body's basic physiological systems. Multiple organ dysfunction syndrome may be caused by an hyperinflammatory response and by a loss of autoregulation of the normal inflammatory response. Patients who develop multiple organ dysfunction syndrome have greater intestinal permeability than those who do not develop this premorbid condition.

The multiple organ dysfunction syndrome that occurs with splanchnic ischemia may be due in part to the translocation of gut-derived bacteria and endotoxin, activation of neutrophils, mucosal acidosis, and vasoconstriction resulting from endothelin-1. The elevated plasma levels of endothelin-1 released during ischemia are produced in the splanchnic organs. Endothelin$_A$ receptors are on the vascular smooth muscle, and endothelin$_B$ receptors are on endothelial cells and smooth muscle cells. Circulating endothelin-1 impairs perfusion of the intestinal mucosa and may contribute to tissue injury (79). Pretreatment with an endothelin$_A$-receptor antagonist prevents endothelin-lung induced capillary perfusion failure and mucosal damage. Bosentan, a nonpeptide mixed endothelin-receptor antagonist, abolishes the reduction in oxygen delivery to the porcine intestine and reverses intestinal mucosal acidosis in a porcine endotoxin shock model (80).

Clinical Learning Point: Bosentan, an endothelin-receptor agonist, may prove to be useful in reducing gut ischemia in patients with septic shock.

There is a variety of sources of oxygen-derived free radicals during ischemia–reperfusion, including the endothelial cell with the hypoxanthine–xanthine oxidase system and activated neutrophils. The body's antioxidant system includes small antioxidative mole-

cules and antioxidative enzymes. These include uric acid, ascorbic acid, α-tocopherol, β-carotene, and protein SH groups. The increase in total antioxidant capacity in the serum that is induced by the oxidative stress of ischemia–reperfusion is sufficient to prevent lipoperoxidation in the serum and in the intestine (81). The epithelium-derived high output of nitric oxide synthesis by inducible nitric oxide synthase may account for a reduced viability of the epithelium, increased permeability, and increased bacterial translocation.

Activation of the nuclear enzyme poly(ADP-ribose) synthetase plays a role in mediating the endothelial and epithelial dysfunction as well as the hyperpermeability that occurs during endotoxic shock (82). The nitric oxide production that is accelerated by ischemia-reperfusion may participate in the breakdown in the intestinal mucosa (83). Small arteries and large arterioles rather than the terminal microvasculature are the major contributors to intestinal vascular regulation. Dilation of small arteries and large arterioles may occur in response to increased nitric oxide production. Nitric oxide concentrations increase during intestinal absorption of glucose (84). The generation of nitric oxide in the intestine is marginally enhanced by bacterial lipopolysaccharide and by inflammatory cytokines. After human intestinal microvascular endothelial cell activation, inducible nitric oxide synthase-derived nitric oxide is an endogenous antioxidant, down-regulating leukocyte binding (85).

The migration, accumulation, and activation of polymorphonuclear cells is a key event in ischemia–reperfusion. CD44 is a transmembrane glycoprotein expressed by neutrophils and lymphocytes that is involved in cell–cell and cell–matrix binding. Ischemia–reperfusion decreases the expression of CD44 within the jejunal mucosa, and may contribute to the failure of the gut barrier (86).

Endothelial cells that line the microvasculature exert a gatekeeper function in acute and chronic inflammation through their ability to recruit and translocate circulating leukocytes. In response to inflammatory stimuli, activated endothelial cells up-regulate cell adhesion molecules and the expression of chemokines, and ultimately bind and promote transmigration of immune cells into the interstitial space. The chemokine receptor CXCR4 is essential for vascularization of the gastrointestinal tract (87). Human intestinal microvascular endothelial cells in culture from chronically inflamed tissue of patients with inflammatory bowel disease show enhanced leukocyte binding, whereas such enhanced binding is not found in the uninvolved intestinal segments from the same individual (88). This suggests that leukocyte binding is an acquired effector and that vascularization of organs generally occurs by remodelling of the preexisting vascular system during their differentiation and growth. This enables them to perform their specific functions during development.

TUMORS

A patient with hereditary nonpolyposis colorectal cancer (or Lynch Syndrome) has been described with a moderately differentiated adenocarcinoma obstructing the small intestine at the ligament of Treitz (89).

RADIATION

Exposure to ionizing radiation remains a mainstay of treatment for abdominal pelvic malignancies. Radiotherapy is associated primarily with gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Alterations in mucosal function occur even before the morphological changes arise from the effects of radiation on the actively dividing cells in the crypt region. An acute inflammatory response occurs early after exposure to ionizing radiation. This acute response is reflected by an influx of neutrophils, as well as an increase in the concentration of inflammatory eicosanoids such as PGE_2, leukotriene (LT) B_4 and thromboxane (Tx) B_2 in the rectal dialysates. The severity of the acute response to radiation correlates with the incidence of chronic radiation enteritis, which occurs in the months or years following radiation exposure.

Alterations in intestinal fluid and electrolyte transport are common following abdominal radiation and may precede the denudation of the intestinal mucosa and motility changes. Exposing rats to ionizing radiation causes increases in the maximal carbachol-induced changes in short-circuit current as well as transepithelial conductance. This temporary stimulation of cholinergic regulation of mucosal intestinal function may result in radiation-induced diarrhea (90).

Prostaglandins, peptide growth factors including members of the fibroblast growth factor (FGF) family, and other regulatory peptides can affect cell survival, proliferation, differentiation, and migration of intestinal epithelial cells *in vitro*. In the small intestine of irradiated mice, the expression of FGF-2 protein and mRNA increase 12 h after γ-irradiation, and peak 48–120 h afterwards (91). FGF-2 is predomi-

nantly found in the mesenchyme surrounding regenerating crypts. The administration of exogenous recombinant human FGF-2 enhances crypt cell survival when given before irradiation. Insulin-like growth factor I (IGF-I) induces growth of the distal small intestine after intestinal damage by methotrexate, but IGF-I is not beneficial when administered coincidence with methotrexate (92).

Clinical Learning Point: The administration of recombinant human FGF-2 may prove to be useful to prevent radiation damage to the gastrointestinal tract.

Shortly after ionizing radiation, p53 protein levels are up-regulated in response to DNA damage, and p53 transcriptionally regulates many genes. After irradiation, there is a time- and dose-dependent increase in the expression of the p53-dependent peak in the intestinal crypts, and this expression is not affected in mice that are homozygously null for p53 (93).

Nitric oxide is produced along with L-citrulline through an enzyme-catalyzed reaction between L-arginine and molecular oxygen. There are three isoforms of the nitric oxide synthase enzyme. Neuronal nitric oxide synthase and endothelial nitric oxide synthase are constitutively expressed and are regulated through changes in the concentration of intracellular calcium. The inducible form of nitric oxide synthase is induced by inflammatory cytokines, such as IL-1 and TNF-α. There is a dexamethasone-sensitive expression of inducible nitric oxide synthase mRNA in both the ileum and colon within 2 hr of irradiation, and the elevated ileal nitric oxide synthase activity is reduced by treatment with an inducible nitric oxide synthase inhibitor (94).

The mouse *Cdx1* gene encodes a homeobox-containing transcription factor and the Cdx1 protein is localized in the proliferating immature epithelium during intestinal development (95). After radiation-induced intestinal damage *Cdx1* expression is diminished during the initial phase of cellular regression, and the normal pattern is restored one week after damage.

Following irradiation, there is an apparent relationship between mitotic and apoptotic levels, suggesting that these processes may be linked (96). After high doses of irradiation, the surviving crypts in old mice are both smaller and fewer in number than in young mice. This indicates the important age-related alterations in the capacity to regenerate the crypts after radiation damage (97). The normal apoptosis that occurs in the small intestine takes place predominantly in the crypts, associated with the stem cells. This spontaneous process is much less common in the large than in the small intestine. This absence of cell death in the stem cell location in the crypts in the large bowel is believed to be associated with the active expression of Bcl-2. Nitric oxide may exhibit its antibacterial action in anaerobic intestinal lumen without inducing apoptosis of Bcl-2-enriched mucosal cells (98). The levels of apoptosis in the crypts can be increased by exposure to a variety of cytotoxic agents, chemical mutagens, and ionizing radiation.

NEW TECHNIQUES

The traditional way to investigate the small intestine is the barium follow-through examination. Unfortunately, its sensitivity and specificity are low. The sonde and the push enteroscopes are commercially available. The sonde enteroscope, whose progression is facilitated by a balloon inflated after the pylorus, reaches the distal ileum in 70% of cases. However, this instrument has no tip angulation or biopsy channel, and only about 50–70% of the bowel surface reached by the endoscope can be properly visualized. The push enteroscope has tip angulation and will disclose a cause of chronic unexplained anemia in about 30% of patients in whom the small bowel x-ray has failed to provide a diagnosis (99).

Virtual endoscopy is being developed for visualization of the gastrointestinal tract (100). Magnification endoscopy with or without chromoscopy provides excellent images of fine mucosal patterns. Optical coherence tomography of the gastrointestinal wall has sufficient resolution to delineate the microscopic structure of the mucosa and submucosa (101).

The gold standard for the diagnosis of small intestinal bacterial overgrowth is the culture of the small bowel aspirate. This technique is technically difficult, and is hampered by a high rate of false-negative cultures. The diagnosis of small intestinal bacterial overgrowth may be undertaken by culturing a duodenal biopsy specimen (102). About a third of patients with cirrhosis have bacterial overgrowth, as measured by the glucose hydrogen or methane breath test (103).

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