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TROPHIC AND CYTOPROTECTIVE NUTRITION FOR INTESTINAL ADAPTATION, MUCOSAL REPAIR, AND BARRIER FUNCTION

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■ **Abstract** Intestinal epithelial cell turnover (proliferation, migration, differentiation, and apoptosis) and gut barrier functions are dynamic processes that are markedly affected by nutritional status, the route of feeding, and the adequacy of specific nutrients in the diet. Emerging studies are defining potential therapeutic roles for specific nutrients and diet-derived compounds (including arginine, glutamate, glutamine, glutathione, glycine, vitamin A, zinc, and specific lipids) in gut mucosal turnover, repair, adaptation after massive bowel resection, and barrier function. The role and regulation of endogenous bowel flora in generating short-chain fatty acids from diet-derived fiber and other diet-derived compounds and the effects of these agents on gut function are increasingly being elucidated. Results of these investigations should define new nutritional methods for trophic and cytoprotective effects on the intestine in conditions such as inflammatory bowel disease, malnutrition, and short bowel syndrome.

CONTENTS

The mammalian intestinal mucosa is one of the most rapidly replicating tissues in the body (91, 185). For example, kinetic studies in rodents demonstrate that the small intestinal epithelium is completely replaced every two to three days (91, 185). In small bowel, stem cells located in the crypt region differentiate into enterocytes, enteroendocrine cells, and mucus-secreting goblet cells. These specialized cells migrate upward along the intestinal villus and eventually undergo apoptosis or are extruded into the gut lumen (23, 91, 135). Paneth cells, whose function appears to involve barrier defense against luminal microorganisms, move downward into the crypt base region (23, 135). Small bowel and colonic cell turnover is a function of rates of gut mucosal stem cell proliferation, migration along the crypt-villus axis in small bowel and along the crypts in colon, and cell death via apoptosis (23, 135). Recent nutrition research has focused on regulation of anatomic and immunologic gut barrier functions that protect against invasion (translocation) of endogenous luminal microorganisms and/or their toxins (188, 202).

EFFECTS OF NUTRITIONAL STATUS AND ROUTE OF FEEDING ON GUT MUCOSAL GROWTH AND ADAPTATION

Generalized malnutrition, protein depletion, or deficiencies of specific nutrients, including essential fatty acids, folate, zinc, vitamin A, and vitamin B12 inhibit the growth and turnover of the intestinal mucosa (54, 89, 185, 201). During total starvation or severe protein-calorie malnutrition, the enteric mucosal and muscular layers atrophy to a disproportionate degree compared to the changes in body mass and weight of other tissues (26, 199). Malnutrition is also associated with altered or diminished intestinal cell digestive/absorptive capacity (54, 168). Generalized malnutrition induced by fasting for one to three days in rats causes a significant decrease in villus height and/or crypt depth in jejunum, ileum, and, to a lesser extent, colon (52, 199). In addition, fasting and other forms of protein-energy malnutrition are associated with gut mucosal cell impairment marked by decreased levels of reduced glutathione (GSH), the major intracellular thiol antioxidant, enhanced permeability to macromolecules, increased bacterial translocation from the lumen, and stimulation of epithelial cell apoptotis (89, 92, 202). Food deprivation also significantly reduces the specific activity and expression of certain digestive enzymes in the small bowel mucosa (91, 185). In rabbits, a 72-h fast significantly reduced transport capacity for glutamine (Gln) and arginine (Arg) in small bowel

brush border membrane vesicles, due to a decreased number of functional amino acid transporter proteins per mg mucosal protein (146). Refeeding via the enteral route results in rapid stimulation of small bowel, and, to a lesser extent, colonic mucosal growth, upregulates mucosal GSH redox state, increases expression of digestive enzymes and nutrient transporters, and normalizes intestinal barrier function (92, 185). In rodents, pigs, and other animals, increased intestinal cell proliferation (hypertrophy and hyperplasia) also occurs in remnant small bowel and colon after massive bowel resection, a process known as intestinal adaptation (200).

The route of feeding and the complexity of the diet influence intestinal cell proliferative and barrier functions as well as fecal flora composition (139, 185). Parenteral nutrition (PN) and provision of elemental or semi-elemental enteral diets (e.g., containing free amino acids and simple sugars) are associated with mucosal atrophy and increased translocation of luminal bacteria (133, 185). This occurs despite provision of adequate micro- and macronutrients, presumably because these modalities do not adequately stimulate factors important for intestinal cell renewal and/or provide inadequate amounts of specific nutrients. The atrophic effects of PN or elemental enteral diets are rapidly reversed when enteral diets containing whole protein, complex carbohydrates, and fiber are given (185, 201).

Both the quantity and quality of food intake are known to regulate gastrointestinal hormones that are important in gut growth and repair, including gastrin, epidermal growth factor (EGF), and insulin-like growth factor-I (IGF-I) (201) Milk is a nutrient source rich in a variety of gut-trophic growth factors including GH, IGF-I, insulin, prolactin, and EGF. These peptides interact with specific gut mucosal receptors to stimulate regeneration and function of enterocytes and may also be absorbed for systemic effects on the whole body (201). The gut is a target tissue for IGF-I (199, 200), a nutrient-stimulated growth factor available to mucosal cells via autocrine and paracrine routes, the circulation (endocrine) route, and the gut lumen (via milk, saliva, and pancreatic-biliary secretions). Food deprivation in rats markedly decreases plasma and small bowel expression of IGF-I, but IGF-I levels are rapidly upregulated with refeeding (199). Thus, nutrients in the lumen appear to be important for adequate synthesis of local growth factors that, in turn, may regulate mucosal cell turnover and renewal. Luminal nutrients also increase pancreatic-biliary secretions, gut neuronal activity, peristalsis, and splanchnic blood flow, among other effects (Table 1). Certain growth factors and specific nutrients may interact in a synergistic or additive manner to increase the growth, repair, and barrier function of the gut mucosa (201).

The vast majority of the information summarized above has been derived from animal models and relatively little information is available from human studies on the intestinal effects of nutritional status, depletion of essential nutrients, use of parenteral nutrition, and intestinal adaptation after bowel resection (29, 134, 204). Mild mucosal atrophy is observed after long-term PN, but this is reversed with the administration of complex enteral diets (29, 134). Limited data to date suggest that the dynamic intestinal growth response to massive small bowel resection observed in rodent models may not occur in humans (204). Despite knowledge of

TABLE 1 Potential mechanisms of intestinal growth related to luminal nutrition

- Increased splanchnic blood flow and oxygen, nutrient, and growth factor delivery to gut mucosal cells
- Increased gut neuronal activity and peristalsis
- Increased salivary, gastric, pancreatic-biliary, and gut epithelial cell secretions, with increased delivery of growth factors, glutathione, etc., to the gut lumen
- Direct delivery of nutrients to mucosal cells via the lumen
- Provision of antioxidant nutrients present in food
- Mucosal generation of growth factors for endocrine, paracrine, and/or autocrine action

the physiology of gut epithelial cell renewal and nutritional factors that affect it, underlying molecular mechanisms responsible for regulation of cell growth and repair in response to diet and specific nutrients remain unclear. Major gut-trophic nutrient substrates are outlined in Table 2 and are covered below.

GLUTAMINE

The amino acid Gln has become one of the most intensively studied nutrients in gastrointestinal research (48, 109). Gln is a substrate in many key metabolic processes, including inter-organ nitrogen transfer, protein synthesis, gluconeogenesis, acid-base homeostasis, and nucleic acid biosynthesis. Gln is also utilized as a major fuel/substrate by intestinal mucosal cells and by immune cells throughout the body, including those of the gut-associated immune system (109, 148, 187, 202). Gln also serves as a substitute for biosynthesis of glutamate (Glu), which is also used as an intestinal fuel.

Gln is a nonessential amino acid and is adequately synthesized to meet metabolic needs during health, but appears to be required in greater quantities under certain catabolic conditions owing, in part, to its increased utilization by the

TABLE 2 Some nutrients and dietary substrates with beneficial effects on the intestinal tract

- Arginine
- Dietary fiber
- Glutamine
- Glutathione
- Short-chain fatty acids
- Vitamin A
- Zinc
- Enteral feeding in general (versus parenteral feeding)

gastrointestinal tract (48, 201). During illness, skeletal muscle exports large amounts of Gln into the blood (>35% of all amino acid nitrogen). Concomitantly, Gln-utilizing tissues such as the gut and immune cells markedly increase Gln uptake and metabolism. When tissue Gln utilization exceeds endogenous production, plasma Gln levels decrease (as a function of illness severity) (109). Provision of conventional PN (in which Gln is typically absent) or enteral feedings (which typically contain low amounts of Gln) do not appear to adequately meet Gln requirements during severe illness.

It has been proposed that gut mucosal turnover and barrier function is compromised during stress states due, in part, to relative Gln deficiency (109, 202). In support of this hypothesis, numerous studies in animal models show that enteral or parenteral Gln supplementation enhances gut mucosal growth, repair, and function, decreases gut-origin sepsis and inflammation, and improves nitrogen balance in animal models of intestinal atrophy, injury, and adaptation (109, 200, 202). Gln also functions as a precursor to GSH, a potent antioxidant that detoxifies free radicals, toxins, and carcinogens (94).

Several investigations suggest that Gln or Gln dipeptide administration improves growth and/or function of gut mucosal cells in humans (202). Addition of either L-Gln or the dipeptide alanyl-glutamine increased cellular proliferation in cells isolated ex vivo from ileal and proximal and distal colonic mucosal biopsies of normal adults (148). PN-dependent patients given glycyl-Gln-supplementation of PN versus standard Gln-free PN demonstrated significantly increased duodenal villus height and decreased intestinal permeability (173).

Inflammatory Bowel Disease

An increasingly active area of in vivo Gln research involves models of gut mucosal inflammation (114). Earlier studies in rodents and pigs demonstrated beneficial effects of enteral or parenteral Gln as a method to diminish mucosal injury following experimental colitis, abdominal irradiation, chemotherapy, and sepsis (109, 195, 202). A recent study showed that a Gln-enriched diet significantly decreased enteritis and bacterial translocation after a single large dose of abdominal radiation in rats (51). In a porcine model of ischemic ileitis, luminal L-Gln infusion enhanced postinjury ileal recovery of enzymes critical for mucosal triacylglycerol biosynthesis, while combination treatment with Gln + transforming growth factor-α (TGF-α) improved ileal mucosal healing (2). In a rat indomethacin-ileitis model, oral Gln administration (given either before or after injury) significantly attenuated macroscopic ileal mucosal injury and microcirculatory disturbances (increased leukocyte adherance, leukocyte rolling, venular wall shear) (13). Trinitrobenzene sulfonic acid (TNBS)-induced colitis was significantly attenuated and colonic levels of malondialdehyde, an index of oxidative stress, were reduced when animals were given L-Gln enemas (2% solution given twice daily for seven days postinduction of colitis) (97). Dietary Gln supplementation decreased bacterial translocation, proinflammatory cytokine production, and colonic injury in the inflamed tissue of colitic rats (8). Oral Gln also reduced endotoxin levels and improved the mucosal

barrier defense in guinea pigs with experimental colitis (57). In contrast, another study showed that rats given different levels of enteral L-Gln (0, 12%, 24% of dietary nitrogen) for one, three, or five weeks after TNBS-induced colitis demonstrated worsened colonic injury with the highest Gln dose and no improvement with lower doses (153). Foitzik et al. found that oral L-Gln had no effect on colonic permeability or infection rates in TNBS colitis; however, Gln supplementation did significantly improve colonic blood flow in noninjured areas of colonic mucosa (56).

Supplemental Gln did not improve outcomes in two small clinical trials in inflammatory bowel disease (IBD). In one study, 21 g/day L-Gln or glycine (control) was given for four weeks to adult Crohn disease (CD) patients with demonstrated increased gut permeability (44). Gln treatment did not significantly alter plasma Gln levels, gut permeability, or disease activity compared to controls (44). A Gln-enriched diet (42% of dietary amino acids as Gln) also did not benefit a group of children with active CD compared to a standard low-Gln diet (4). However, these small studies must be interpreted with caution as these authors used a relatively high level of Gln. As a fuel for immune cells, Gln has the potential to increase gut mucosal inflammatory responses (202). Additional clinical research on the potential beneficial role of Gln in gut inflammatory states (enteral and parenteral) seems warranted in light of the animal data to date and benefits observed in other clinical disorders (202).

Short Bowel Syndrome

Results of Gln supplementation have been mixed in animal models of short bowel syndrome (SBS), with some studies showing stimulation of adaptive gut mucosal growth (68, 164, 200) and others showing no effect (119, 174). However, in some of these studies parenteral feeding with Gln enrichment was used (68, 164). The relative efficacy of enteral versus parenteral Gln on gut growth and function in SBS is unknown. In vitro studies show that Gln is essential for endogenous and growth factor-stimulated intestinal epithelial cell proliferation and this amino acid also inhibits gut epithelial cell apoptosis (99, 202). Furthermore, some studies in animal models of SBS suggest that the combination Gln and growth hormone (GH) or IGF-I has additive or synergistic effects on intestinal adaptative growth following small bowel resection (196, 200). Zhou et al. found that Gln + GH resulted in an additive increase in gut glucose and palmitate absorption in resected rats (196). Conversely, another study found that although GH improved anabolic indices in parenterally fed small bowel-resected rats, parenteral Gln + GH did not have an additive effect (72). We recently demonstrated that diets enriched in L-Gln upregulate mucosal GSH redox indices in residual small bowel of rats following massive small bowel resection (71). In a rat model of partial small bowel resection and orthotopic jejunal transplantation, Gln-supplemented organ preservation solution protected intestinal segments from cold ischemic injury and improved mucosal transport function (195). Gln-enriched enteral diets also decreased in vivo bacterial translocation (195).

Clinical trials of Gln administration, alone and in combination with GH, have been performed and others are currently underway in human SBS. In a recent

crossover study, Scolapio et al. (150) found that 30 g/day of supplemental oral L-Gln combined with a high-carbohydrate/low-fat diet had no effect on duodenal villus height and crypt depth, gastric emptying, or intestinal fluid, xylose, and fat absorption in eight patients with severe chronic SBS. A pilot unblinded study by Byrne et al. (31) in patients with PN-dependent SBS showed that a three-week regimen of GH administration, intravenous or oral Gln (30 g/day), and a high-carbohydrate/low-fat diet significantly improved intestinal sodium, fluid, nitrogen, and energy absorption and improved lean body mass. In a larger group of chronic SBS patients undergoing the same protocol of GH + Gln + diet modification for three weeks followed by maintenance on the modified diet and Gln supplementation alone, PN requirements were either eliminated or markedly decreased in a large proportion of the patients at follow-up one year later (32). A recent unblinded study also suggested that the combination of GH + Gln + diet modification improved gut nutrient absorption and decreased PN needs in patients studied in the acute phase after massive small bowel resection (197). However, two small double-blind randomized studies in chronic SBS patients (using different regimens of GH + Gln + diet and antidiarrheal drug strategies) have shown whole body anabolic effects with this treatment but no marked effects on gut nutrient absorption (149, 162), although one of these studies found a significant improvement in intestinal electrolyte absorption with this therapy (149). In light of the limited clinical data to date, and the suggestion of benefit from some studies, additional randomized, controlled trials of Gln alone and GH + Gln in the context of appropriate dietary modification seem warranted. These are needed to define optimal patient selection criteria (e.g., nature of residual bowel, age, underlying illnesses), timing and duration of therapy, and specific dietary regimens. In addition, other growth factors, such as glucagonlike peptide-2, hold promise and could be combined with Gln or other dietary manipulations to study gut adaptive processes (88).

Underlying nutritional status, adherence to SBS dietary guidelines (small frequent feedings, avoidance of simple sugars, decreased intake of fat and specific food items that worsen diarrhea, use of oral rehydration solutions), and appropriate use of antidiarrheal medication regimens likely have a major impact on the intestinal responses to Gln (and growth factor) treatment (32, 172). Thus, to define the true efficacy of Gln therapy, future clinical studies in SBS will need to carefully control for these variables. Larger, controlled clinical trials and more uniform patient selection and treatments are necessary to define the efficacy of combination Gln and growth factor treatment in SBS.

Radiation/Chemotherapy/Critical Illness

Numerous studies in animals and an increasing number in humans demonstrate benefits of supplemental Gln on the small bowel in catabolic stress models (e.g., infection, trauma, chemotherapy/irradiation) (48, 93, 202). In a rat splanchnic ischemia/reperfusion model, luminal L-Gln decreased small bowel mucosal injury, improved ionic transport function, and upregulated mucosal ATP levels (105). Enteral Gln supplementation is effective in preventing radiation-induced

enteropathy in rats (37, 39, 51, 82). Clinical studies in this area have not been conducted, thus the role of Gln supplementation in patients receiving radiation therapy alone remains unknown. Several clinical trials have been published on the effects of parenteral and enteral Gln supplementation as a strategy to decrease oral mucositis after high-dose chemotherapy and irradiation (203). No effect on mucositis has been observed with administration of intravenous Gln. However, some, but not all, of several controlled studies demonstrated decreased incidence or severity of mucositis with Gln given as a swish-and-swallow regimen (203).

An increasing number of clinical investigations demonstrate that Gln-supplemented enteral and parenteral nutrition support decreases hospital-acquired infections and improves other clinical outcomes (hospital length of stay, posthospital survival) in critically ill patients (48, 66, 69, 80, 93, 110, 128, 131, 186, 189, 198) (Table 3). Although gut mucosal histology or specific functions were not evaluated in these trials, the decrease in infections from organisms that colonize the GI tract suggests that Gln-enriched nutrition may improve gut barrier function. In one study, critically ill patients given PN enriched with alanyl-Gln dipeptide had significantly greater D-xylose absorption (194% increase) compared to matched patients receiving Gln-free PN (48).

In summary, numerous studies in animal models and an increasing number of clinical trials indicate that Gln-supplemented nutrition has beneficial effects in

TABLE 3 Clinical, intestinal, and metabolic effects of enteral or parenteral glutamine supplementation observed in recent clinical trials*

- Improved nitrogen retention (IV Gln in postoperative, BMT, and trauma patients)
- Maintained skeletal muscle glutamine concentrations (IV Gln in postoperative patients)
- Increased protein synthesis (IV Gln in postoperative patients)
- Increased systemic lymphocyte cell number (IV and enteral Gln in postoperative, BMT, trauma patients)
- Maintained jejunal villus height and intestinal permeability during PN (IV Gln in stable PN-dependent patients)
- Improved D-xylose absorption (IV Gln in critically ill ICU patients)
- Improved intestinal nutrient absorption when combined with a modified diet and growth hormone (IV and enteral Gln in SBS patients)
- Reduced microbial colonization and clinical infection rates and shortened hospital length of stay after bone marrow transplantation (IV Gln in BMT patients)
- Decreased rates of bacteremia (enteral Gln in premature infants, IV Gln in burn patients)
- Decreased rates of pneumonia, bacteremia, and systemic sepsis (enteral Gln in trauma patients)
- Improved six-month survival after ICU discharge (IV Gln in critically ill ICU patients)

*Abbreviations: BMT, bone marrow transplantation; Gln, glutamine; ICU, intensive care unit; IV, intravenous; SBS, short bowel syndrome

certain clinical situations. Although much work on Gln mechanisms of action in the gut remains to be done, the existing literature suggests a number of potential mechanisms by which Gln exerts beneficial effects on intestinal cells (Table 4) (109, 186, 188, 202).

GLUTAMATE

Glutamate (Glu) is an important constituent of dietary protein and can be formed, with ammonia, from Gln via glutaminase. A body of recent work by Reeds, Burrin, and colleagues strongly suggests that Glu is a major substrate of the intestinal epithelial cells. Using isotopic tracer and arteriovenous difference methods in infant pigs, these authors found that labeled enteral Glu was almost completely (95%) metabolized by the gut during absorption (139a). In a subsequent study in fed piglets, enterally administered Glu was demonstrated to be a preferential substrate for small bowel mucosal GSH synthesis (139b). Additional studies in growing pigs showed that approximately 50% of enterally presented Glu was metabolized to CO_2 and that this level of metabolism toward energy was much higher than either glucose or Gln in this model. Reeds and colleagues also showed that enteral Glu was a specific precursor for GSH, arginine, and proline by small bowel mucosa (139c). Taken together, these studies indicate that diet-derived Glu plays an important role in intestinal physiology and metabolism. However, surprisingly little investigation on the role of Glu supplementation in models of gut inflammation, injury, or adaptation has been performed. In one study, pigs fed a low-protein diet demonstrated suppressed oxidation of Glu (and leucine) compared to controls, while the percentage of glucose oxidized for energy increased under these conditions of undernutrition (176a). In a catabolic rat burn model, animals were fed a conventional control diet or a diet in which Glu was supplemented to 30%

TABLE 4 Some mechanisms of action of glutamine in intestinal growth, repair, and function

- Use as an energy substrate
- Stimulation of protein synthesis
- Stimulation of cell proliferation and inhibition of apoptosis
- Enhanced growth factor signaling (via mitogen activated protein kinase pathway)
- Stimulation of epithelial cell migration
- Upregulation of mucosal cell glutathione production (source of glutamate)
- Upregulation of heat-shock proteins
- Increased number and function of gut-associated immune cells
- Decreased bacterial translocation
- Decreased proinflammatory cytokine responses

of total dietary amino acid for 64 h after injury; the Glu-supplemented group had a significantly greater concentration of GSH in small bowel mucosa and significantly increased gut mucosal protein synthesis (77a). Additional studies on the efficacy of dietary (or intravenous) Glu as a trophic and cytoprotective nutrient are needed.

GLYCINE AND HISTIDINE

Recent in vivo studies suggest that dietary or luminal glycine and histidine may have protective effects on gastrointestinal tissues and supplementation studies in diarrheal illness are in progress. Dietary glycine supplementation decreases hepatic injury in models of endotoxemia, hemorrhagic shock, ischemia-reperfusion and liver transplantation (184). Glycine perfusion of isolated vascularly perfused intestine decreased small intestinal mucosal ischemia-reperfusion injury in a rat model (111). Prefeeding with supplemental glycine decreased lung and liver (but not ileal) injury and decreased proinflammatory cytokine elaboration in a two-hit model of sepsis in rats (70). In mouse, small intestinal loops challenged with *Salmonella typhimurium*, fluid accumulation, acute inflammation, and extensive structural damage to the small intestinal mucosa occurred (132). However, intraperitoneal and intestinal luminal injection of L-histidine reduced the amount of fluid accumulating in the intestinal lumen and protected the intestinal tissue from *S. typhimurium*-induced damage (132).

ARGININE

Several lines of evidence suggest that arginine (Arg) supplementation may have beneficial effects on the intestine (48, 49, 61, 155). Arg is an intermediary metabolite in the urea cycle, where it is hydrolyzed to urea and ornithine by the enzyme arginase and thus is indirectly linked to the citric acid cycle and the oxidation of fuel molecules for energy (49, 61). Arg plays an important role in nitrogen transport, storage, and excretion and the small intestine is an important site of Arg metabolism (48). Conversion to ornithine explains arginine's role in the production of polyamines, which are key molecules involved in cellular growth and differentiation. A large number of animal studies suggest that Arg-supplemented enteral feeding has beneficial effects on systemic immune cell number and/or function (48). In addition to these immunostimulatory effects, Arg-enriched diets attenuate thymic atrophy, improve animal survival to septic challenge, and enhance wound healing (190, 192).

L-Arg is the substrate for synthesis of nitric oxide (NO), formed through oxidation of guanidine groups of L-Arg by NO synthase (NOS) (107). Arg's role in NO production is critical to the body's homeostatic mechanisms, because NO is a major regulator of the vascular endothelium as a vasodilator and is involved in macrophage physiology and cellular inflammatory responses, among other

cellular functions. The constitutive NOS isoenzymes [endothelial (eNOS) and neuronal (nNos)] generate low concentrations of NO, but the inducible isoenzyme (iNOS) produces large amounts of NO in response to a variety of cytokines, growth factors, and inflammatory stimuli in gut and other tissues (190). The constitutively expressed NOS is critical for normal physiology, but the role of local NO production via iNOS in mediating intestinal inflammation remains controversial. NO has been identified as an inflammatory mediator in inflammatory bowel disease (IBD). Patients with active ulcerative colitis have increased iNOS and NO concentrations in inflamed colonic mucosa compared with noninflamed controls (192). In some studies, a positive correlation between colonic NO levels and disease activity was observed; treatment with corticosteroids and 5-aminosalicylates decrease NO production via inhibition of iNOS (74). In contrast, local NO also appears to inhibit intestinal inflammation because iNOS-deficient mice have increased gut mucosal injury in response to inflammatory agents (107). Inhibition of NO synthesis also increases intestinal damage in animal models of bowel injury induced by surgical stress, ischemia, toxins, and hypoxia (6, 107, 167, 192). NO production plays a crucial role in maintaining intestinal blood flow and causes local vasodilation in the face of inflammation or injury (6, 107). Depending on the experimental system, NO has been shown to variously stimulate or inhibit cell proliferation, apoptosis, and cellular differentiation during intestinal inflammation and injury (192). NO also stimulated epithelial cell migration, and reduction of paracellular transepithelial permeability also appears to be involved in the maintenance of gastrointestinal barrier function (192).

In mice, Arg supplementation of drinking water attenuated hypoxia/reoxygenation-induced necrotizing enterocolitis histologically and decreased reactive oxygen species (ROS)-induced mucosal lipid peroxidation (3). Arg-supplemented diets (2% by weight) improved survival in gut-derived sepsis and peritonitis by modulating bacterial clearance in mice; these effects were significantly attenuated by the nitric oxide inhibitor N-α-nitro-L-arginine (NNA) (65). Insufficient NO production by premature infants secondary to developmentally deficient gut NOS may be associated with the incidence of necrotizing enterocolitis (NEC), a severe clinical syndrome very similar to experimental ischemia-reperfusion injury (107). Plasma Arg concentrations are decreased in premature infants with NEC (18, 194). Intravenous infusion of L-Arg ameliorated intestinal injury in experimental models of NEC (46). In a recent double-blind controlled study, 152 premature infants received supplemental L-Arg (1.5 mmol/kg/day) or placebo with oral feeds and/or parenteral nutrition during the first days of life (9). NEC developed only in 5 infants in the Arg-supplemented group compared with 21 infants in the placebo group ($P < 0.001$). The authors did not observe any significant adverse effects including hypotension with Arg supplemention. Plasma Arg levels increased significantly at 14 and 28 days with supplementation, and were lower in those infants with the diagnosis of NEC (9).

Arg supplementation has been shown to improve wound healing and immune cell function in animal and human models of gastrointestinal ulceration and surgery

(28, 49, 190) and accelerates intestinal mucosal regeneration after radiotherapy (192). In iNOS-deficient mice, wound healing is delayed and positive effects of supplemental L-Arg do not occur, suggesting that the metabolism of arginine via iNOS is essential for wound healing (151). An additional effect of arginine on wound healing is mediated through its immunostimulatory effects. Dietary supplementation of Arg is accompanied by an increase in lymphocyte and monocyte function, activation of macrophage and natural killer cytotoxicity, increased phagocytosis, and increased cytokine production (157).

Administration of enteral liquid supplements or tube feeding formulas enriched in Arg and other immunomodulatory nutrients, including n-3 fatty acids, Gln, and nucleotides, reduce hospital infectious complications and overall length of stay after gastrointestinal or pancreatic surgery for cancer (17). These positive clinical outcomes are also associated with increased serum NO concentrations and improved immune function, nutritional status, and ileal blood flow (27, 141). A recent randomized controlled trial showed that preoperative or perioperative oral supplementation with a specialized formula enriched in Arg, n-3 fatty acids, and RNA significantly decreased infectious complications and length of hospital stay in patients undergoing elective surgery for gastrointestinal cancer (64). No clear adverse effects on blood pressure or hemodynamic stability attributable to enteral or parenteral Arg administration have been reported in humans at doses of 10–30 g/day (192). However, a recent review of data from a large number of completed clinical trials suggested that an increase in mortality with the use of Arg-enriched immmunomodulatory enteral diets may occur in critically ill, unstable patients with severe sepsis, possibly due to potential vasodilator effects of Arg-derived NO (78).

The role of Arg in tumorigenesis remains ambiguous (115). Arg supplementation may enhance or suppress tumor growth in animal models depending on the relative activities of NOS and arginase pathways (192) and the stage of carcinogenesis. Arg supplementation given to rats receiving a carcinogen decreased colorectal tumor production and crypt cell hyperproliferation during the initiation stage of carcinogenesis but stimulated colorectal tumor growth when given during the promotion stage (115). On the other hand, Arg enhanced antitumor immune function in cancer patients without any adverse effect on clinical outcome (27).

Glutathione and Other Dietary Antioxidants in Intestinal Disorders

GLUTATHIONE Glutathione (L-glutamyl-L-cysteinyl-glycine; GSH) is the major cellular thiol and plays a key role in detoxification of cellular free radicals, toxins, and carcinogens in gut and other tissues (94). GSH is synthesized in gut mucosal cells, can be derived from diet (as the intact tripeptide or via synthesis via dietary sulfur amino acids, Gln, glycine, and Glu) or may enter the lumen via bile or by direct secretion by mucosal cells (15, 30, 94). GSH is required for normal intestinal function, in part, by protecting epithelial cell membranes from damage by electrophiles and fatty acid hydroperoxides and by maintaining mucus

fluidity (16, 127). Recent in vitro and in vivo studies in gut epithelial cells show that compared to cells undergoing differentiation, GSH concentrations are higher and GSH redox potential more reducing when cells undergo proliferation (92, 130).

Malnutrition is known to diminish glutathione levels in body tissues, including the gut (92, 123). Depletion of cysteine markedly oxidizes intracellular GSH redox pool in human colonic epithelial cells in vitro (120). Chemical agents that alter glutathione levels markedly influence intestinal growth and function (118, 142). Buthionine sulfoximine (BSO) decreases GSH concentrations in blood and tissues by inhibition of the rate-limiting enzyme for GSH synthesis, γ-glutamyl cysteine ligase; BSO decreases jejunal GSH levels in association with villus atrophy, epithelial cell damage, and mitochondrial degeneration in mice (118). These effects are prevented by oral GSH or GSH monoethyl ester, each of which increases free intracellular GSH levels (118, 142).

GSH also appears to be important for gut barrier function because bacterial translocation from the gut and increased mortality occur when GSH is chemically depleted by diethyl maleate in rat models (142, 160). Of interest, dietary administration of either GSH itself or Gln increase GSH levels in plasma, gut mucosa, and other tissues in rodents (14, 79). We recently found that recombinant keratinocyte growth factor (KGF) in fasted/refed rats stimulated gut mucosal growth and prevented the decrease in small bowel and colonic GSH redox status (52, 92). Thus, administration of certain gut-trophic growth factors and specific dietary substrates for GSH synthesis is a potential strategy to improve gut mucosal GSH redox status.

INFLAMMATORY BOWEL DISEASE Intestinal inflammation, as occurs in Crohn disease (CD) and ulcerative colitis, is associated with increased gut mucosal production of ROS, peroxidation of polyunsaturated fatty acids (PUFAs), and depletion of GSH in affected gut mucosa (30, 43, 154). In addition, plasma levels of several antioxidants, including vitamins A, C, and E, β-carotene, selenium, zinc, and GSH are decreased and indices of oxidative stress are increased in patients with IBD (1, 24, 30, 62, 100, 113, 123, 154, 156, 183). Such deficiencies may contribute to gut mucosal injury and impair mucosal restitution. Therefore, treatment with various dietary antioxidants has been proposed in the therapy of IBD (60, 114).

Antioxidant vitamins inhibit gut mucosal damage and improve healing in experimental IBD. For example, enteral administration of water-soluble vitamin E inhibited colonic mucosal injury and reduced mucosal lipid peroxidation in rats with experimental colitis (193). In a similar model, dietary supplementation with n-3 fatty acids plus vitamin E reduced colonic lipid peroxidation and increased colonic mucosal blood flow (152). In colitis induced by oral dextran sulfate, iron supplementation increased colonic inflammation, but this deleterious effect was ameliorated by vitamin E supplementation (36). In a recent clinical study in patients with Crohn disease, Geerling et al. found that dietary supplementation with n-3 fatty acids plus a combination of antioxidants (but not antioxidants alone) significantly improved plasma antioxidant status and resulted in a less proinflammatory plasma and adipose tissue pattern of eicosanoids (e.g., the

proportion of arachidonic acid decreased and the proportion of eicosapentanoic acid and docosahexanoic acid increased) (59).

Dietary bioflavonoids have been evaluated in experimental IBD. In an animal model of colitis, Sato et al. found that dietary catechins plus vitamin E consumed after induction of colitis reduced colonic damage, inhibited neutrophil infiltration into the colonic mucosa, decreased lipid peroxidation, and prevented the development of colonic adhesions (147). Another study found that after alcohol removal, the remaining red wine extract reduced cytokine-induced inflammatory cell infiltration in the jejunum of rats fed a zinc-deficient diet (34). Morin, a flavonoid found in figs, prevented colonic mucosal damage, reduced oxidant production, and decreased proinflammatory eicosanoid production in colitic rats (147). Lycopene administration decreased total inflammatory area and lipid peroxidation in the colon of rats with chemically induced colitis (140). In patients with both short bowel syndrome and/or IBD, blood vitamin E levels are commonly decreased; administration of water-soluble forms of this vitamin are an effective supplementation strategy (170). Although it is unclear whether dietary factors are involved in the pathogenesis of IBD, the available data strongly suggest adequate nutrition contributes to mucosal repair (114).

CRITICAL ILLNESS AND RADIATION/CHEMOTHERAPY Mucosal damage from intestinal ischemia/reperfusion (I/R) has been attributed to production of free radicals and oxidants, both from xanthine oxidase-dependent production of superoxide and activation of circulating and mucosal neutrophils. Supplemental vitamin C decreased small intestinal injury and mucosal production of lipid peroxide and glutathione disulfide in a rat model of gut I/R (73). In other models of splanchnic I/R injury, water-soluble vitamin E and vitamin C administration significantly inhibited increased vascular permeability, local xanthine oxidase production, and lipid peroxidation and increased plasma GSH characteristic of I/R (73). Several studies in rats subjected to abdominal radiation indicate that pretreatment with vitamin E alone or vitamin E in combination with vitamin C or selenium decreased indexes of gut mucosal damage, enhanced fluid absorptive capacity and decreased oxidative injury markers (37, 50, 53, 125). These studies in animal models provide evidence that I/R-induced damage to small bowel and colon may be potentially prevented or reversed by administration of certain nutrient antioxidants. Whether these beneficial effects occur in clinical settings is presently unknown.

VITAMIN A

Vitamin A and its analogues are key nutritional regulators of growth and differentiation of intestinal epithelial cells. Vitamin A deficiency decreases small bowel villus height and disaccharidase activity and worsens intestinal injury in experimental IBD in rats (182). As noted above, below-normal vitamin A levels in blood are common in patients with IBD and short bowel syndrome. During chemotherapy, rats with diet-induced vitamin A deficiency demonstrate increased

intestinal damage that is prevented by vitamin A repletion (182). Vitamin A supplementation also prevents some of the early side effects of radiation on the small intestine (20). This protective effect may partially result from vitamin A's ability to induce crypt cell differentiation, making these cells less susceptible to genomic damage (144). In addition, vitamin A has antioxidant properties that may reduce cellular sensitivity to radiation.

Vitamin A appears to regulate the early stages of intestinal adaptation following small bowel resection in rats by increasing crypt cell proliferation in the adapting intestine (180). Swartz-Basile et al. found that preexisting vitamin A depletion significantly inhibited the adaptive response of the small intestine to massive small bowel resection, while vitamin A repletion rapidly improved the adaptive response versus depleted rats (161). Several studies in developing countries suggest that repletion of vitamin A in vitamin A-deficient individuals decreases the risk of diarrhea and gut barrier dysfunction, supporting an important role for this nutrient in gut mucosal repair and function (48).

FATTY ACIDS AND PROSTAGLANDINS

Inflammatory Bowel Disease

The role of dietary lipid composition in IBD treatment has been the subject of much recent discussion (10, 19, 35, 58, 114). To date, much of the research on dietary lipid content in IBD has been conflicting, particularly with regard to enteral feeding. These mixed results have been attributed to a number of factors including type of disease (ulcerative colitis versus CD), disease activity, experimental design, choice of placebo [e.g., monounsaturated fatty acids (MUFA) or n-6 polyunsaturated fatty acids (PUFA)], and the use of concurrent drug regimens (19).

A fish oil supplement providing 2.7 g/day n-3 fatty acids (eicosapentanoic acid and docosahexanoic acid) significantly increased one-year remission rates in patients with CD versus placebo-treated subjects (19). This effect possibly occurred through competition by n-3 fatty acids with n-6 fatty acids for incorporation into cell membranes, which experimentally decreases cellular production of proinflammatory fatty acid metabolites. To date, this beneficial response to dietary fish oil has not been reproduced in a larger randomized, controlled study in CD. Two small studies of dietary fish oil supplementation in patients with ulcerative colitis have produced conflicting results (7, 47).

In experimental animals, consumption of n-3 fatty acid supplements reduces blood levels of proinflammatory cytokines, such as TNF and IL-1B (129). In a recent study in experimental rat colitis, Campos et al. found that parenteral lipid emulsions with higher n-3:n-6 ratios reduced diarrhea, mucosal inflammatory changes, and inflammatory eicosanoid concentrations (33). Likewise, Nieto et al. found that fish-oil-enriched diets decreased necrotic areas within colonic mucosa, increased goblet cell number and mucin production, and improved histological repair in rats with experimental colitis (129).

In a controlled, randomized, double-blind study of the effect of high (30%) versus low (5%) long-chain triglyceride diets on patients with active CD, Leiper et al. (112) found no differences between the low- and high-long-chain triglyceride diets on the CD remission rate. However, these diets contained other PUFAs; thus, the effects of different fatty acids such as MUFAs and fish oils cannot be ruled out. Gassull et al. (58) investigated diets enriched in MUFAs and PUFAs versus steroid treatment on remission rate in CD patients. After four weeks of treatment, remission rates were 27% for the high-MUFA diet, 63% for the high-PUFA diet, and 79% for steroid treatment. Thus, diet seemed to have an effect on CD remission rate; however, the high-MUFA diet, despite its potential anti-inflammatory effects, was not more effective at inducing remission of CD and may even have been detrimental (58). Medium-chain triglycerides (MCTs) contain fatty acids with 8–12 carbons, do not require packaging into chylomicrons for absorption, and are rapidly hydrolyzed and used for energy. One prospective, randomized, controlled study of enteral MCT supplementation in active CD found that this approach did not alter clinical remission in active CD (145). Thus, recommendations for ingestions of specific dietary lipid products in IBD cannot be made at this time in light of the still relatively limited and inconsistent data in this area.

Short Bowel Syndrome

Optimal diet composition, coupled with adequate micronutrient (e.g., zinc, vitamin A) and protein-energy intake and appropriate antidiarrheal medications, plays a critical role in ameliorating diarrhea and impaired digestion and absorption in SBS patients. Major principles that decrease diarrhea in many patients with SBS include use of small frequent feedings, avoidance of simple sugars, high intake of dietary fat and hypertonic liquids, avoidance of lactose, increased intake of complex carbohydrates [in part, to stimulate production of short-chain fatty acids (SCFAs)], and appropriate use of oral rehydration solutions (especially in patients without remnant colon) (32, 150). Traditionally, SBS patients are encouraged to follow a low-fat diet because of a reduction in lipid absorption and resultant steatorrhea, increased fluid loss, and weight loss (67). However, not all studies have shown a potential benefit of low-fat diets, especially in patients without a colon and in young children during the early period following massive bowel resection (158, 191). Furthermore, because low-fat diets may be less palatable, advising SBS patients to consume low-fat diets may decrease food consumption as well as predispose patients to essential fatty acid deficiency, especially in those without a colon in situ (84, 85).

In an animal model of SBS, Hart et al. (77) found that essential fatty acid (EFA)-deficient small bowel-resected rats experienced a significant decrease in adaptive intestinal mucosal hyperplasia compared to essential fatty acid-sufficient resected rats. Short-term refeeding (two weeks) with an EFA-sufficient diet allowed significant intestinal mucosal adaptation compared to resected rats remaining on the EFA-deficient diet. Thus, adequate EFA nutritional status may be necessary for

optimal intestinal adaptation following resection (77). In addition, the route of EFA administration appears to be important. Jeppensen et al. found that in patients with SBS, enteral linoleic and linolenic acids maintained plasma levels more effectively than an equal amount supplied parenterally (83).

Recently, it has been suggested that SBS patients consume increased amounts of medium-chain triglycerides (MCTs) (87, 159, 172). It is also known that MCTs are absorbed in the colon similar to the manner of SCFA absorption (143). Thus, substitution of MCT for LCFA may reduce fecal fat excretion and increase total caloric absorption; however, the efficacy of MCT substitution is dependent on the existence of a functioning colon (85, 86). Of note, in 75% of small bowel-resected rats, residual bowel adaptation and function were decreased with a high-MCT diet (175). Conversely, dietary supplementation with LCFAs in small bowel-resected rats improved residual bowel adaptation in a dose-dependent manner, particularly with increased n-3 fatty acids (101). Vanderhoof et al. also found that resected rats consuming fish oil had increased small bowel mucosal weight, DNA, and protein content compared to rats fed other fat sources (175). Increased dietary LCFAs, including fish oils and other n-3 fatty acids, may be important during the acute phase of SBS to allow optimal residual bowel adaptation, whereas during the maintenance phase increased consumption of MCTs may help to increase lipid absorption and caloric usage. New research in human SBS is needed to clarify the role of specific dietary lipid components for optimal gut adaptation and nutrient absorption.

Critical Illness/Radiation/Chemotherapy

In mice receiving chemotherapy, consumption of 3% or 6% fish oil diets ameliorated intestinal adverse effects compared to mice consuming 7% corn oil (75). Moreover, it was recently determined that dietary n-3 PUFAs in mice treated with chemotherapy decreased apoptotic crypt cells in the duodenum, which suggests that n-3 fatty acids may prevent the genomic DNA damage that causes apoptosis and loss of intestinal cells (76). In a study of endotoxin-induced intestinal ischemia in rats, Pscheidl et al. found that fish oil–supplemented parenteral diets improved killing of translocated bacteria and prevented a decrease in intestinal blood flow (136). Chavali et al. found a decrease in death rates and an increase in levels of IL-10 (an anti-inflammatory cytokine) in mice subjected to cecal ligation and puncture that were fed sesame oil as opposed to mixed oils in the diet (38).

DIETARY FIBER, SHORT-CHAIN FATTY ACIDS, AND PREBIOTICS

Dietary fiber is comprised principally of a variable mixture of nonstarch polysaccharides (NSPs), which are resistant to digestion in small bowel and reach the colon undigested. Dietary fiber has been classified into soluble and insoluble fiber, based on its solubility in aqueous solutions (48, 169). Most foods contain both

soluble and insoluble components in varying ratios. Once in the colon, NSPs are hydrolyzed and fermented by colonic bacteria, producing the SCFAs butyrate, propionate, and acetate, together with carbon dioxide, methane, and hydrogen gases, thus yielding energy for microbial growth (48, 55, 169). The amount of SCFAs produced depends on the rate and extent of degradation of polysaccharides by bacteria and thus is a function of the type and amount of flora in the bowel lumen. In addition, the proportion of each SCFA produced varies among individuals and also depends on gender, age, and the type of polysaccharide ingested (169).

Resistant starch refers to all products from starch that escape small intestinal digestion due to chemical structure, cooking method, and mastication. An example is high-amylose maize starch, an amylase-resistant starch that has been used successfully to decrease cholera-induced diarrhea (137). Resistant starch appears to provide a significant contribution to the final SCFA production, especially in Western countries, but the resistant starch content of most foods has not been determined and precise values of intake in mixed meals are unknown. A significant number of persons cannot ferment resistant starch and the rates of SCFA production may be characteristic of the individual and not influenced by diet (169). Another source of SCFAs in the colon are oligosaccharides, such as fructo-oligosaccharides and inulin, which are prepared commercially or found in foods such as garlic, onion, artichoke, and asparagus. Oligosaccharides that resist digestion in the small bowel are completely fermented by colonic bacteria (166).

Intestinal and metabolic effects of dietary fiber, resistant starch, and frucotooligosaccharides from both preclinical and clinical studies are summarized in Table 5. SCFAs are taken up by colonocytes in a concentration-dependent manner, coupled to Na+ or K+ and H+ exchange, and absorption leads to increased sodium

TABLE 5 Intestinal and metabolic effects of dietary fiber, resistant starch, and/or frucoto-oligosaccharides observed in preclinical and clinical studies

- Delay in gastric emptying
- Slowed absorption of sugars, amino acids, bile acids, and drugs
- Reduced postprandrial hyperglycemia
- Reduced cholesterol levels in hyperlipidemia
- Altered calcium, iron, and magnesium absorption
- Stool bulking and laxative effect
- Stimulation of intestinal mucosal cell growth and differentiation
- Protection against oxidative stress
- Maintenance of intestinal barrier function
- Antidiarrheal effect
- Energy provision via short-chain fatty acid generation by colon in short bowel syndrome
- Decrease in inflammatory or chemotherapy-induced colitis

and water transport (25). This effect is partially responsible for the antidiarrheal effect of soluble fibers and oligosaccharides (126, 171, 179). In addition, SCFAs may facilitate colonic absorption of calcium and magnesium (122, 163). Energy is also derived from the carbohydrate moiety of SCFAs; thus, undigested fiber or starch provides an important source of energy in patients with short bowel syndrome (84, 86, 88, 143).

SCFAs, especially butyrate, are preferred metabolic fuels for colonic epithelial cells and directly stimulate colonocyte proliferation and differentiation both in vitro and in vivo (81, 106). SCFAs also enhance mesenteric blood flow (108), decrease intestinal permeability (116), and stimulate intestinal mucosal expression of the enteroglucagon gene. Glucagon-like peptide-2, a product of the enteroglucagon gene, is a trophic peptide for gut epithelial cells (165). The systemic actions of SCFAs may underlie the stimulation of jejunal and ileal mucosal growth with intravenous administration of these fatty acids (81, 103, 165). Enteral administration of SCFAs, fiber, or oligosaccharide prevents gut barrier failure associated with parenteral nutrition in rodents (124). In rats treated with 5-fluorouracil, bacterial translocation was lower in rats fed with enteral nutrition plus fiber or chow than in rats fed with standard tube feeding formula (45). A pectin-supplemented elemental diet given via gastrostomy enhanced adaptive small intestinal growth following massive small bowel resection in rats (102).

In contrast to the trophic effect on normal gut mucosal epithelial cells, addition of butyrate to tumor cell lines causes cell proliferation arrest, differentiation, and apoptosis (117). The mechanism is caspase-dependent and involves signal transduction via the Fas-ligand death receptor (90). As cells become differentiated, they become more refractory to these effects of butyrate, perhaps secondary to the rapid use of butyrate for energy production. Butyrate and acetate also inhibit DNA oxidative damage in isolated rat colonic cells. Animal studies have shown that resistant starch and fructo-oligosaccharides may reduce the incidence of aberrant colonic crypt foci and increase the apoptoptic index (166). However, epidemiological and clinical evidence of a protective effect against colon cancer with high dietary fiber intake is still unclear. A low-fat, high-fiber diet or administration of wheat bran or oat bran supplementation did not reduce the recurrence of polyps or adenomas compared to maintaining a Western diet (5).

SCFAs have been shown to have anti-inflammatory roles on intestinal mucosa and have a potential role in the management of IBD (178). Butyrate administration and dietary supplementation with germinated barley foodstuffs, which are high in resistant starch, attenuated mucosal damage in chemically induced colitis and in rat models of spontaneous ulcerative colitis (11, 96). Several mechanisms are implicated in the anti-inflammatory roles of SCFA, including inhibition of DNA-binding activity of nuclear factor kB (95, 96). Additionally, butyrate may modify levels of interleukins involved in intestinal inflammation, including IL-8 (96) and IL-6 (121). Clinical trials of SCFA enemas or fiber supplementation in patients with IBD have overall shown little benefit, especially when compared to standard treatment (42). Vernia et al. observed a trend toward improvement in clinical,

endoscopic, and gut mucosal histological scores of patients with ulcerative colitis with administration of an oral butyrate preparation plus mesalazine compared to placebo plus mesalazine (177).

Administration of oligosaccharides such as inulin and oligofructose, resistant starch such as germinated barley, and other nondigestible food ingredients selectively stimulate growth and activity of certain species of bacteria in the colon. These agents are termed "prebiotics" (48). The mechanism of bacterial selection involves lowering of colonic pH and the production of metabolites that both inhibit growth of certain bacteria and simultaneously stimulate the growth of "protective" bacteria such as bifidobacteria and lactobacilli (48). The alteration in gut flora appears to improve the antidiarrheal effects of oligosaccharides (163). Limited data suggest that other potentially beneficial effects may be mediated by oligosaccharides in IBD, including maintenance of intestinal barrier function and decreased mucosal inflammation. The major disadvantage of consumption of resistant starch and nonstarch polysaccharides in the clinical setting are symptoms such as abdominal pain, eructation, flatulence, and bloating due to luminal gas production (42). A number of clinical studies are now evaluating the clinical efficacy of these agents and their effect on bowel microflora. Studies on the effects of specific foods, dietary patterns, and intravenous feeding on gut flora are limited and more information in this area is needed (98).

ZINC

The trace element zinc is necessary for a variety of physiological and biochemical functions, including maintenance of intestinal barrier and gut-associated immune function, reduction of oxidative stress, and inhibition of apoptosis (22). The gastrointestinal tract is the major site for regulation of zinc homeostasis. When zinc intake decreases, an increase in the rate of zinc transport across the mucosal membrane occurs, mediated by a specific zinc carrier, which increases the efficiency of zinc absorption (40). With extremely low or with prolonged marginal zinc intake, secondary homeostatic events occur, including reduced urinary zinc excretion, increased plasma zinc turnover, and increased release from tissues such as bone (98).

There is increasing evidence that subclinical zinc deficiency is widespread, based on plasma zinc values and the prevalence of inadequate zinc intakes. When accounting for the decreased bioavailability of zinc by the presence of diet-derived inhibitors of absorption such as phytate, nearly half of the world's population is at risk of low zinc intakes (138). In the United States, suboptimal intake of dietary zinc has been observed in young children, adolescent females, and elderly persons. Deficiencies in zinc also accompany many Western diseases and conditions, such as gastrointestinal disorders, renal disease, sickle cell anemia, alcoholism, some types of cancers, AIDS, and burns (138).

Dietary zinc deficiency is associated with the development and maintenance of diarrhea through different mechanisms. Dietary zinc deficiency is usually

associated with protein-calorie malnutrition, which alters the capacity to absorb zinc in small intestinal mucosa in animals (181) and causes generalized malabsorption due to mucosal atrophy. Prolonged zinc deficiency induces morphological atrophy of intestinal mucosa (176) and decreases the absorption of other nutrients such as water and electrolytes independently of food intake (63, 181). Finally, diarrhea induces further gastrointestinal losses of zinc, which, in turn, inhibits mucosal turnover, leading to further malabsorption of zinc and other nutrients (181). Multiple zinc supplementation trials in developing countries demonstrate that zinc supplementation reduces the duration and severity of diarrheal episodes (21, 205).

Zinc deficiency results in immunodepression that impairs defense against bacterial and parasitic infections (21, 138). Rodent models show that parasites develop more rapidly into adult worms and survive better in zinc-deficient hosts than in well-nourished hosts, with a graded response depending on the magnitude of the dietary zinc restriction (104). Zinc deficiency appears to be involved in impaired antigen presentation and function of T-cells in gut-associated lymphoid tissue and spleen (104).

Enhanced uroguanylin production by zinc deficiency has also been proposed as a possible mediator of diarrhea associated with low zinc status. Administration of a zinc-deficient diet to rats for 18 days resulted in upregulation of prepro uroguanylin (22). Uroguanylin and guanylin are members of a family of natriuretic peptide hormones, produced as prepropeptides secreted into the gut lumen or bloodstream. Both activate a guanylate cyclase-C receptor initiating a cGMP cascade that results in stimulation of the cystic fibrosis transmembrane conductance regulator, which increases the transport of chloride and water into the intestinal lumen (22). Upregulation of uroguanylin during zinc deficiency could increase chloride and water secretion in the intestine, resulting in secretory diarrhea. Other possible effects of zinc in the protection of gastrointestinal mucosa include its role as a free radical scavenger, either as an intrinsic constituent of superoxide dismutase or via prevention of disulfide formation that triggers formation of free radicals (41, 181).

SUMMARY

The gut mucosa turns over more rapidly than most other tissues in the body and plays a key role in barrier defense in addition to nutrient digestion, absorption, and metabolism. The dynamic processes of intestinal epithelial cell proliferation, migration, and apoptosis are highly affected by general nutritional status, route of feeding, and adequacy of specific nutrients in the diet. This research has defined potential therapeutic roles for specific nutrients and diet-derived compounds for gut adaptation, barrier function, and mucosal repair, including arginine, glutamine, glutathione, vitamin A, zinc, and specific lipids such as fish oil. Emerging studies are defining the role of specific nutrients as trophic and cytoprotective agents and their interaction with endogenous and exogenous growth factors in the intestine. The role and regulation of the endogenous bowel flora in generation of

short-chain fatty acids from diet-derived fiber and other compounds and the effects of these products on gut function are increasingly being elucidated. Results of these investigations should enable development of new nutritional methods to support the intestine in conditions such as short bowel syndrome, malnutrition, and inflammatory bowel disease.

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