# The Pathogenesis, Clinical Implications, and Treatment of Intestinal Hyperpermeability

Alan L. Miller, N.D.

#### **Abstract**

Normally, the gastrointestinal epithelium provides a semi-permeable barrier which allows nutrients to be absorbed while preventing larger, potentially toxic, antigenic, or pathogenic molecules or organisms from crossing into the bloodstream. Pathogenically-increased intestinal permeability predisposes the individual to diffusion of antigenic food molecules and translocation of bacteria and/or yeast from the gut to extra-intestinal sites, including mesenteric lymph nodes, liver, spleen, and systemic circulation. This can be secondary to drugs, microbial overgrowth, radiation, stress, alcohol intake, enteral/parenteral nutrition, or injury. Increased intestinal permeability occurs commonly with diseases including inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, asthma, eczema, food allergies, alcoholism, trauma, and surgery. Glutamine, phosphatidylcholine, flavonoids, soluble fiber, and fish oil, as well as probiotic organisms, including Lactobacilli and *Saccharomyces boulardii* can assist in correcting this abnormal permeability.

(Alt Med Rev 1997:2(5):330-345)

#### Introduction

The gastrointestinal tract is unique in that, as an infolding of our outer skin, it is a continuous tube from the mouth to the anus which allows the passage of nutrients into and through the body. Because the gastrointestinal tract is in contact with food and antigens from the outside world, yet also intimately in contact with the interior of the body and the blood-stream, highly-developed protective and absorptive mechanisms are in place to facilitate the absorption of nutrients, while blocking entrance of potentially harmful antigens to the blood-stream via the epithelial barrier and immune mechanisms.

The intestinal epithelial barrier has three major functions: (1) Absorption- transporting fluids, electrolytes, and nutrients selectively across the intestinal wall; (2) Protection- separating larger, non-absorbable, potentially toxic, antigenic, or pathogenic molecules or organisms from the blood; (3) Immune function- secretion of immunoglobins, mainly secretory IgA, which bind to bacteria and other antigens, preventing their attachment to epithelial cells, and facilitating their disposal. Optimal functioning of all three of these components is vital to the health of the intestinal epithelium and the rest of the body, as a disruption of any of these factors can cause an increase in intestinal mucosal permeability.

Alan L. Miller, N.D.—Technical Advisor, Thorne Research, Inc.; Senior Editor, Alternative Medicine Review. Correspondence address: P.O. Box 3200, Sandpoint, ID 83864. alan@thorne.com

Nutrients are absorbed from the lumen via two pathways: through the epithelial cells (transcellular) and via the junctions between them (paracellular) (see Figure 1). Because of the distinctive structure and electrical resistance of these routes, over 85% of the passive transport of molecules is paracellular.<sup>1,2</sup>

The primary physical regulator of passive absorption of molecules is the "tight junctions" between intestinal epithelial cells. Located at the lumenal base of epithelial microvilli, tight junctions are fused areas which encircle the cells, and contain pores or channels through which molecules can pass (see Figure 1). The number and density of tight junctions regulate the diffusion of molecules, and can vary depending on the location in the gut and the major absorptive pattern of that area. However, tight junctions are not static. The pores or channels can open and close, allowing larger or smaller molecules to pass. The electrical charge can also change, altering diffusion of ions.<sup>2,3</sup>

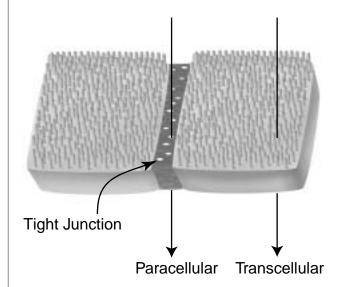
In some disease states tight junctions are obliterated by ulcerations or breaks between cells, thus increasing paracellular nutrient and antigen transport. In other diseases, such as Celiac sprue, tight junctions remain intact but still allow passage of large molecules transcellularly.<sup>2</sup> Another mechanism by which tight junctions can be altered is in inflammatory states, as cytokines attract polymorphonuclear cells (PMNs), which can mechanically alter tight junctions to allow their passage from the blood stream into the lumen of the intestines. During this inflammatory process tight junction activity can be severely impaired.<sup>2-6</sup>

Recent studies suggest that the selective permeability properties of the mucosal barrier are significantly altered in a number of health conditions or disease processes, including rheumatoid arthritis, 7,8 ankylosing spondylitis and other spondyloarthropathies, 8,9 food allergy, 10 asthma, 11,12 acute gastroenteritis, 13 trauma, 14,15 post-surgery, 16 alcoholism, 17 urticaria, 18 eczema, 19 pancreatic dysfunction, 20

celiac disease,<sup>21</sup> inflammatory bowel disease,<sup>22</sup> HIV disease,<sup>23,24</sup> burn injury,<sup>25</sup> endotoxemia,<sup>26</sup> and cystic fibrosis.<sup>27</sup> In some cases, as in food allergies, an altered epithelial barrier, and the resultant increase in the transport of larger molecules, is the proximate cause of the disease. In other cases the restrictive properties of the barrier deteriorate due to the disease process, as with alcoholism, or because of the treatment, as with non-steroidal anti-inflammatory drug use for rheumatoid arthritis.<sup>7</sup>

In addition to their absorptive and barrier functions, intestinal epithelial cells also function as an extension of the immune system. They secrete IgA, the most abundant immunoglobin in the gut and the main immune mechanism preventing bacterial adherence to the intestinal mucosa. Secretory IgA attaches to bacteria in the intestinal lumen, hindering its attachment to the gut wall. A decrease in secretory IgA causes increased bacterial ad-

**Figure 1.** Intestinal mucosal nutrient absorption pathways



herence, increased intestinal permeability, and bacterial translocation across the intestinal wall.

**Table 1.** Diseases/Conditions Associated With Altered Intestinal Permeability

acute gastroenteritis food allergy alcoholism HIV disease ankylosing spondylitis NSAID use

arthritis pancreatic dysfunction rheumatoid arthritis asthma burn injury schizophrenia celiac disease surgery

Crohn's disease trauma

ulcerative colitis cystic fibrosis

urticaria eczema

endotoxemia

Bacterial translocation is a phenomenon in which indigenous gut bacteria cross the intestinal wall and deposit in extra-intestinal tissue, including mesenteric lymph nodes, liver, spleen, kidney, and systemic circulation. In the extreme, bacterial translocation is believed to be a major contributing factor to multiple organ failure after trauma or surgery.<sup>28</sup>

The intestinal barrier is not fully developed at birth. The immunologic (secretory IgA, cell-mediated immunity) and non-immunologic (proteolytic activity, gastric acid, mucin production) portions of this barrier do not mature until after age two. Therefore, the intestinal epithelium is more permeable to potentially harmful contents of the intestinal lumen in infants and young children. Introducing solid foods before this barrier is adequately formed is thought to be a major cause, along with heredity, of food allergies in children. Exclusive breast feeding is recommended for at least the first six months, with subsequent avoidance of commonly allergenic foods (cow's milk, chicken, eggs, peanuts, soybeans, wheat, and fish), <sup>19,29</sup> especially in atopy-prone children. This approach provides the greatest protection if the child is at moderate risk for allergies, i.e., one parent is atopic, rather than at high risk, as when both parents are atopic.<sup>30</sup>

One possible mechanism of intestinal injury and increased permeability involves the inhibition of nitric oxide release. Nitric oxide (NO, also known as endothelium-derived relaxing factor) is involved in sphincter relaxation, gut motility, and gastrointestinal blood flow. Preliminary research also suggests NO release from damaged intestinal epithelial cells is a protective mechanism to attenuate further damage. This is indicated by the reduction in intestinal permeability after administration of L-arginine, an NO donor, to animals undergoing ischemia and reperfusion injury, 31,32 and the worsening of this injury in animals given NO inhibitors. 31 In rats, administration of mast cell stabilizing agents attenuated the increase in intestinal permeability caused by the NO synthesis inhibitor, N-nitro-L-arginine methyl ester, suggesting that mast cells are involved in the increased permeability following NO inhibition.<sup>33</sup> However, increased NO production by a form of nitric oxide synthase, which is induced by certain inflammatory stimuli, has been found in ulcerative colitis patients, but not in Crohn's disease patients or healthy controls.<sup>34</sup> This suggests that an excessive amount of NO is also potentially pathogenic.

## **Causes Of Increased Intestinal** Permeability (IP)

**Drugs**: A number of drugs, including NSAIDs, antibiotics, chemotherapeutic agents, gold compounds, estrogen, cocaine, and amphetamines can cause intestinal inflammation and increased permeability. This can be a direct effect (NSAIDs, chemotherapy, cocaine, methotrexate), or an indirect effect, as with colitis or bacterial overgrowth associated with antibiotic therapy.<sup>35</sup>

**Non-Steroidal Anti-inflammatory** Drugs (NSAIDs): It is well known that NSAIDs cause gastrointestinal mucosal inflammation and lesions. 36-38 This seems to be due to a negative effect on the secretion of protective prostaglandins, as well as by posbinding drug of the dipalmitoylphosphatidylcholine (DPPC), the

most-abundant protective phospholipid surfactant lining the gastrointestinal tract, making DPPC inactive and damaging the hydrophobic barrier. This allows potentially-corrosive GI contents such as gastric acid to come in contact with mucosal epithelial cells. One animal study prevented the negative effects of five NSAIDs on the GI tract by administration of the drugs after they were first complexed with a purified soy lecithin product (containing phosphatidylcholine).<sup>36</sup>

Decreased prostaglandin production secondary to NSAID use may actually precede the inflammation caused by NSAIDs. NSAIDs having the strongest inhibition cyclooxygenase have been shown to cause the greatest increase in intestinal permeability. This increased IP seems not to be a local, irritative response, but a systemically mediated one, as evidenced by increased permeability whether the drug is administered orally, rectally, or intravenously. It has been prevented in animals by prostaglandin administration, showing that adequate prostaglandin production and secretion is essential for the maintenance of normal intestinal mucosal barrier functioning. After the initial cyclooxygenase inhibition, bacterial adhesion and invasion of the GI mucosa causes an inflammatory response, leading to erythema, hemorrhage, and ulceration. This inflammatory response is absent in germ-free animals and in those treated with antibiotics, confirming a bacterial role in this process.37,38

Another potential cause of NSAID-related increased intestinal permeability is via an uncoupling of mitochondrial oxidative phosphorylation by NSAIDs, leading to decreased ATP production, degradation of enterocyte intercellular junctions, and subsequent cellular death.<sup>7</sup>

Antibiotics: Antibiotics alter the intestinal flora and cause an increased risk of overgrowth by opportunistic bacteria or fungi, and antibiotic-resistant bacterial strains, and

decrease the natural defense mechanisms of the gut; e.g., anaerobic bacteria which inhibit the growth of aerobic pathogens. Clinically, diarrhea is a common side-effect of antibiotic treatment, with the worst-case scenario being development of pseudomembranous colitis, a potentially fatal condition caused by a toxin produced by overgrowth of Clostridium difficile. Altered gut ecology and bacterial overgrowth have been shown to be conducive to bacterial and/or yeast translocation across the gut barrier into extra-intestinal lymphatics and organs, and into systemic circulation. The alteration of gut ecology by antibiotics is suggested as one cause of this translocation, which is correlated with increased IP.<sup>39,40</sup>

Animal studies suggest that overgrowth of certain organisms, such as *Pseudomonas aeruginosa* and *Candida albicans*, can cause suppression of systemic cell-mediated immunity. Administration of killed Pseudomonas and Candida to rats resulted in significant suppression of cell-mediated immunity, most likely caused by translocation of endotoxin from the cell wall of these killed cells.<sup>41</sup>

Administration of antibiotics to mice caused translocation of indigenous bacteria to the mesenteric lymph nodes (MLN), but not systemically. However, administration of a combination of prednisone and an antibiotic caused bacterial translocation to the liver, spleen, and general circulation.<sup>42</sup>

**Chemotherapy:** In rats, and in people, methotrexate is able to induce colitis. Its severity was reduced in rats after administration of *Lactobacillus plantarum* and *L. reuteri*. Oats were also given, and although they did not reduce bacterial translocation or reduce intestinal myeloperoxidase as Lactobacilli did, they did reduce enterotoxin levels.<sup>43</sup>

**Viral and Bacterial Gastroenteritis:** Acute viral gastroenteritis with diarrhea can also increase intestinal permeability, especially if the patient fasts while feeling ill. However,

the increased IP can be prevented by continuing regular feeding and hydration throughout the duration of the illness.<sup>13</sup>

Intestinal Yersinia infection causes a transient increase in gut permeability, which is probably a major factor in the etiology of the extra-intestinal complications often associated with Yersinia, including arthritis, Reiter's syndrome, and erythema nodosum.<sup>44</sup>

**Alcoholism:** Alcoholics have an increased IP due to the effects of ethanol on the gastrointestinal mucosa. In 36 alcoholics without cirrhosis, IP values were significantly higher in those who had recently imbibed (<4 days) compared with a control group (p <0.001). Intestinal permeability values decreased with time (p <0.002), normalizing at about day 15 of abstinence. This increased IP was traced to the intercellular tight junctions of the small intestine.<sup>45</sup>

**Radiation:** Abdominal radiation therapy can cause an increase in IP<sup>46-49</sup> which, if untreated, can become a chronic condition lasting years. <sup>49</sup> The proposed mechanism of injury is the formation of oxygen radicals which overwhelm the antioxidant status of the patient. <sup>50</sup>

**Trauma:** Researchers have noted that individuals experiencing severe trauma<sup>14,15</sup> or thermal injury <sup>25</sup> have increased IP, and although the mechanism has not been entirely elucidated, storage and utilization of the amino acid glutamine may be involved (see section on glutamine).

**Surgery:** In 50 patients undergoing cardiac surgery involving cardiopulmonary bypass (CPB), Riddington, et al, found an increase in intestinal permeability compared to controls. In 42% of the patients, endotoxin was present in the plasma following CPB, another indication of increased gut permeability.<sup>16</sup>

Enteral and Total Parenteral Nutrition (TPN): TPN, provided intravenously or orally, has been shown to cause cecal bacterial overgrowth, increased intestinal permeability, and bacterial translocation in animal

studies. Oral administration of cellulose fiber or kaolin decreased the incidence of bacterial translocation, but not the bacterial overgrowth or the loss of mucosal mass. 40,51,52

#### **Clinical Correlations**

Inflammatory Bowel Disease: With its chronic intestinal inflammation and with the mucosa's macroscopic appearance, an increase in IP in Crohn's disease is understandable, even predictable. Researchers have found a correlation between the presence of Crohn's disease and intestinal permeability, 22, 53-55 as well as a direct relationship between disease activity and degree of permeability found during a dual-sugar absorption test (see section on diagnostic testing), revealing decreased intracellular absorption (small molecules) and increased paracellular absorption (large molecules). In addition to the increased permeability in acute flares, abnormal permeability in Crohn's cases in remission appears to be a marker of risk of disease recurrence. In a yearlong study of Crohn's disease patients using the same dual-sugar test mentioned above, those with elevated permeability had a significantly greater probability of relapse during the year follow-up.53

The initial etiology of Crohn's disease is still undetermined, but it is hypothesized that an initial insult, possibly in genetically-predisposed individuals, might cause immunemediated tissue damage which increases gut permeability.<sup>56</sup> These areas of increased permeability could allow passage of antigenic material through the gut wall, possibly overwhelming the body's ability to handle the greatly increased antigenic load. Activation of immune cells in the mucosa by exogenous substances, as well as normal or abnormal microbial flora, could amplify the disease process, causing a worsening of the permeability and a cycle of inflammation, immune hyperactivation, and local and systemic toxic load.57

Studies of intestinal permeability in family members of Crohn's patients have yielded mixed results, with some researchers stating a primary intestinal permeability defect is present in a subset of first-degree relatives of Crohn's patients, 58-61 while other researchers say there is no increased incidence of elevated IP in relatives. 62-64 It is possible these equivocal results are due to the varying types of intestinal testing utilized in the studies. Ulcerative colitis patients also exhibit increased IP<sup>65</sup> and a genetic tendency toward the disease. 66

Celiac Disease: An increase in intestinal permeability of large molecules, coupled with malabsorption of small molecules, is common in celiac disease, or gluten-sensitive enteropathy. Significantly increased IP has also been found in relatives of people with this disease. One extra-intestinal complication of celiac disease is arthritis, which in one study was present in 26% of patients versus 7.5% of controls. Comparing individuals adhering to a strict no-gluten diet to those eating freely, arthritis occurrence was 21.6% in patients on a gluten-free diet and 41% in patients on a regular diet (P < 0.005).

**Food Allergy:** Increased intestinal permeability is the basis of the prevailing hypothesis of food allergy; i.e., large, antigenic protein or polypeptide molecules are absorbed across a leaky mucosal barrier, allowing those molecules to interact with the gut-associated immune system, creating antibodies, immune complexes, and a systemic immune response.

In a study of 60 individuals with food allergy, higher IP markers were noted after a dual-sugar IP test in a fasting sample compared to controls. After an antigenic challenge, IP increased significantly (p<0.002). This increase was attenuated by the administration of 300 mg sodium cromoglycate, a mast cell-stabilizing flavonoid analog. The authors indicate intestinal permeability testing can be a helpful diagnostic tool to evaluate food allergy and treatment efficacy.<sup>70</sup>

Intestinal permeability markers were found to be significantly higher in 36 children with food allergies than in controls (p<0.02), with a reverse relationship between intestinal permeability and age.<sup>10</sup>

**HIV/AIDS:** Enteropathy is a common feature of HIV infection, but its etiology is unknown. It is associated with villous atrophy, malabsorption, and intestinal permeability similar to celiac disease, especially in patients with diarrhea.<sup>23,24</sup>

Ankylosing Spondylitis: Ankylosing spondylitis (AS) is an inflammatory disease which mainly affects the axial skeleton, although it can affect large peripheral joints. The lumbar and sacral spine are most often involved. The prognosis varies, ranging from a mild flaring and remitting course to a progressive, unrelenting disease which creates an increasingly rigid spine, ultimately resulting in a crippling, inflammation-induced vertebral fusion.

Increased IP has been found in a large percentage of people with AS,8 as well as in a majority of their first-degree relatives. Martínez-González, et al, noted that 68% of AS patients studied had increased IP, while 60% of their healthy relatives also had increased IP, signifying a potential hereditary predisposition to the disease. Contributing to this conclusion is the fact that significantly more HLA-B27 antigen positivity was also found in patients and relatives as compared to controls. Half the patients were not taking antiinflammatory medications, and the researchers did not allow any individuals into the study who had taken NSAIDs within 10 days, to rule out any NSAID-induced increases in intestinal permeability. Because of the findings, the authors concluded the abnormal gut permeability found in AS precedes the development of the disease.

The most compelling studies to date of intestinal inflammation and its connection to AS and other arthropathies have been

ileocolonoscopic studies which revealed gut inflammation was present in 60% of cases of AS and 80% of juvenile arthritis cases. In those cases, a second follow-up ileocolonoscopy showed if intestinal inflammation resolved, so did the arthropathy, and conversely, in most cases, if the intestinal inflammation did not resolve the joint inflammation persisted.<sup>71-73</sup>

In AS as well as other inflammatory diseases, it is thought the immune system reacts to enteric bacteria by creating antibodies which then either cross-react with healthy tissue similar in amino acid sequence to the bacteria, or bind to the bacteria and then translocate across the gut wall, resulting in the deposition of bacteria and immune complexes in the gut mucosa and in extra-intestinal locations, such as joint structures. Ankylosing spondylitis patients have been found to have significantly increased serum IgA antibodies to Klebsiella pneumoniae<sup>74-76</sup> and also an increased incidence of positivity of specific HLA-B27 antigens. 77,78 It has been postulated that antibodies to Klebsiella bind to HLA-B27positive cells, creating complement activation and a systemic inflammatory response. High titers of IgA antibodies to Klebsiella may not be specific to AS, however, as patients with ulcerative colitis and Crohn's disease have also been shown to have significantly elevated IgA antibodies to this organism (all p < 0.001).<sup>79</sup>

Rheumatoid Arthritis (RA): It is difficult to accurately determine gut permeability in RA patients, as the near-ubiquitous use of NSAIDs in these individuals will itself cause increased IP.<sup>7,17,80</sup>

The gut has long been theorized as the underlying cause of RA, and it is well known that fasting an individual with RA decreases IP and RA symptomatology.<sup>81,82</sup> Even if increased IP is not involved in the etiology of RA, the subsequent altered IP during drug treatment induces food antigen absorption and possible systemic distribution of bacterial antigens or intestinally-derived inflammatory

mediators,<sup>57,80</sup> which may amplify or perpetuate the disease process.

Similar to AS, RA also has connections to enteric bacterial flora, specifically, increased antibodies to *Proteus mirabilis*. 83-87 In a study of RA patients with either active or inactive disease, antibody titers to *P. mirabilis* were significantly higher in patients with active disease compared to inactive disease and controls (p <0.001), suggesting a role for Proteus in the etiology of RA. 83 Interestingly, RA patients who fasted and were then placed on a vegetarian diet, which reduces RA symptomatology, showed decreased anti-Proteus antibody titers. 88

In a study comparing active RA versus AS, patients with active RA showed significant elevations in IgG antibody levels against *P. mirabilis* compared to AS and controls (p < 0.001).<sup>86</sup>

**Asthma:** In the only study to date investigating increased IP and asthma, Benard, et al studied 37 asthma patients (21 allergic and 16 non-allergic) vs. two control groups; 13 smoking chronic obstructive pulmonary disease (COPD) patients and 26 non-smoking, non-allergic controls. They found that regardless of symptom severity or whether the asthma patients had allergies, asthma patients had a significantly increased IP compared to COPD patients (p = 0.001) and controls (p =0.006). The authors theorized a primary mucosal defect might be present in numerous organs in asthmatics, which is symptomatically expressed in the lungs in response to allergic or environmental stimuli via a "common mucosal immune system" in which "activated T lymphocytes are able to migrate from one site to another."11 It is not known whether increased IP is part of the etiology or a consequence of the disease or its treatment.

**Atopic Dermatitis (Eczema):** Baseline IP measurements of children with eczema are higher than normal individuals and may improve with elimination diet therapy.<sup>89-91</sup> In

a study of 15 children with eczema, nine had at least a 75% improvement in their clinical score after a 14-day elimination diet. In the group which showed clinical improvement, the mean permeability was significantly lower than in non-responders (p<0.01).<sup>89</sup> Other studies have not confirmed this correlation in adults with eczema.<sup>92,93</sup>

**Urticaria:** Individuals with chronic urticaria, especially those with arthralgia, have increased IP and the resultant increase in IgG antibodies to food antigens.<sup>18</sup>

**Alcoholism:** Chronic ethanol ingestion has been shown to increase intestinal permeability. In a study of 36 alcoholics, Bjarnason, et al, found increased permeability in those who had drunk recently (within 48 hours), as well as those who had abstained for 5-13 days before the study, compared to controls, independent of the presence of gastric inflammation.<sup>17</sup>

## **Diagnostic Testing**

Measurement of intestinal permeability is based on the urinary assessment and quantification of orally-ingested molecules which have specific absorption characteristics but are not metabolized by the body. A number of substances have been utilized by researchers to determine intestinal permeability, including Cr-51 labeled EDTA, mannitol, lactulose, rhamnose, and varying molecular weights (and varying sizes) of polyethyleneglycol.

The most common clinically-used test of intestinal permeability is the lactulose/mannitol test. Lactulose and mannitol are water soluble molecules which are not metabolized by the body and are excreted intact in the urine. Lactulose (mol. wt. 342), a disaccharide consisting of galactose and fructose, is not well absorbed, and thus should not be present in large amounts in the urine. Mannitol (mol. wt. 182), a monosaccharide, is normally well absorbed and usually is present in greater

amounts in the urine. Mannitol is thought to be passively absorbed via the transcellular route, while lactulose, the larger molecule, is absorbed in small amounts by the paracellular (tight junction) route. Therefore, presence of mannitol in the urine measures through-thecell absorption, while urinary lactulose measures the selective barrier properties of the tight junctions.

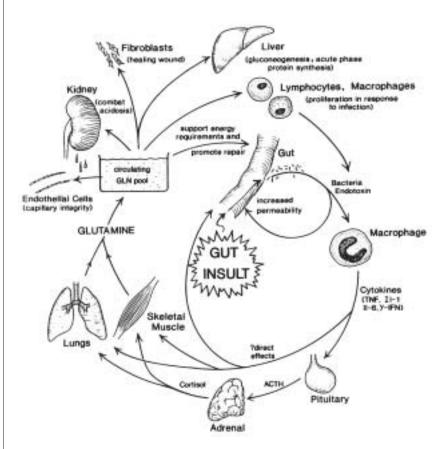
After an overnight fast, the patient provides a pre-test urine specimen, then drinks a solution containing lactulose and mannitol. Urine is collected for the following six hours. If mannitol levels are low, absorption of smaller molecules may be compromised. If lactulose levels are high it is indicative of increased intestinal permeability to large, potentially antigenic molecules.

#### **Treatment**

**Glutamine:** The amino acid glutamine is the principal fuel for small intestine enterocytes. It is the most abundant amino acid in the bloodstream and is considered to be a "conditionally essential" amino acid, as there may be times demand cannot be met by mobilization from other tissue stores. The lungs and skeletal muscle are the major producers of circulating glutamine, and the intestinal tract is the primary user. Intestinal uptake of glutamine in rats accounts for 40% of total glutamine uptake by the entire body. Glutamine is converted in the mitochondria of intestinal cells to glutamate, then alpha ketoglutarate, which then is utilized in the tricarboxylic acid cycle (TCA, Krebs) for ATP production. Colonocytes also use glutamine; however, short-chain fatty acids are the colon's principal metabolic fuel.

Circulating and tissue levels of glutamine drop drastically after infection, injury, or trauma. Figure 2 shows a typical scenario of interorgan glutamine flow and metabolism by the body during intestinal illness or injury.

**Figure 2.** Inter-organ glutamine flow following gut insult. From Souba WW.<sup>94</sup> Used with permission.



After a gut insult, increased permeability causes bacterial translocation. Leukocyte migration and cytokine release cause a further increased IP, which triggers the hypothalmic pituitary adrenal (HPA) axis to induce a release of glutamine from skeletal muscle and lungs into the circulating glutamine pool. It is subsequently taken up by the gut to be utilized for repair of the damaged intestinal barrier<sup>94</sup>

The tri-peptide glutathione (glutamic acid, glycine, and cysteine) is a potent intracellular antioxidant, is necessary for liver detox (phase II conjugation), and its formation is dependent on an adequate supply of glutamine. An animal study of the glutathioneeffects glutamine enhancing of supplementation revealed that acetaminophen toxicity caused a drastic decline in hepatic glutathione levels in rats on a standard total parenteral nutrition (TPN) solution which did not include glutamine. A glutamine-enriched TPN solution prevented this loss of hepatic glutathione.95 Glutathione depletion is

common in experimental models of shock and trauma, which may be at least in part due to inadequate gut glutamine.

Glutamine also serves as a precursor molecule for glucosamine synthesis. Glucosamine is essential for synthesis of mucin, the protective mucus layer in the gut. The first enzyme in glycoprotein biosynthesis, glucosamine synthase catalyzes the formation of Nacetylglucosamine and mucus. This enzyme is diminished in Crohn's disease and ulcerative colitis patients.<sup>96</sup>

Therapeutically, glutamine increases villous height and mucosal thickness, and increases sIgA secretion, which strengthens the intestinal barrier and decreases bacterial adherance and translocation. Glutamine supplementation has also been used in animal studies of radiation or chemotherapy injury to the gut, with significant improvement of mucosal healing and mortality in experimental animals. 97-99

Dietary Fiber: The short-chain fatty acids (SCFAs), butyrate, acetate, and proprionate, are the primary fuel of the colon, and are mostly derived from fermentation of soluble fiber by colonic bacteria. Of these three fatty acids, butyric acid is the main energy source of the colonic epithelium, and impaired absorption or oxidation of butyrate may be observed in patients with ulcerative colitis or Crohn's disease with colonic involvement. Therapeutically, SCFA concentrations increase significantly after supplementation with *Plantago ovata* (Psyllium) seeds<sup>100</sup> or oat bran, <sup>101</sup> and are unchanged after wheat bran. <sup>101</sup> Oats are rich in glutamine as well as β-glucans,

a highly fermentable cell wall polysaccharide. 102 Dietary or supplemental soluble fiber also decreases the pH of the intestines, encouraging the growth of beneficial organisms, and suppresses growth of pathogenic organisms such as *Clostridium difficile*. 103,104

**Phosphatidylcholine:** Preliminary animal studies suggest phosphatidylcholine supplementation has a protective effect against experimentally-induced colitis and bacterial translocation after surgery. These preliminary results warrant further investigation. <sup>105,106</sup>

Fish Oil: Omega-3 fatty acids derived from fish oil can be a beneficial addition to the treatment of intestinal inflammation and subsequent increased IP by decreasing the production of leukotriene B4, thromboxane A2, tumor necrosis factor, and pro-inflammatory 2-series prostaglandins, while promoting the formation of less inflammatory 3-series prostaglandins and thromboxanes. In a well-constructed recent study of fish oil supplementation (2.7 grams/day of an enteric-coated product) in Crohn's disease patients in remission, 59% of patients taking fish oil remained in remission after one year, compared with a 26% remission rate in the control group (p < 0.001). A significant reduction in lab indicators of inflammation was also found in the fish oil group.107

Quercetin, Ginkgo and Other Flavonoid Antioxidants: Mast cells are implicated as contributors to the pathogenesis of many intestinal disease processes, including food allergy and inflammatory bowel disease. Mast cell degranulation and release of histamine and other cytokines is thought to promote further inflammatory responses and mucosal injury. The flavonoid quercetin stabilizes mast cells and prevents their degranulation, 109 as does the synthetic flavonoid analog cromolyn sodium.

Ginkgo and other flavonoids exhibit antioxidant and anti-inflammatory activity. Ginkgo has been specifically studied in small

intestinal ischemic injury, and was found to have a protective effect against oxidative damage and subsequent intestinal permeability in an animal model.<sup>111</sup> In addition to antioxidant activity, green tea flavonoids also inhibit the growth of Clostridium organisms and promote the growth of beneficial Lactobacilli and Bifidobacteria species.<sup>112</sup>

Lactobacilli: Lactic acid-producing organisms have long been used to re-establish a beneficial gut flora after antibiotic use or on an ongoing basis in the form of supplements or fermented milk products. Lactobacilli reduce the pH of the gut, compete for nutrients and attachment sites with potentially pathogenic organisms, produce antimicrobial factors, and promote proper IgA secretion. 113,114 In a group of infants with atopic eczema and cow's milk allergy, Lactobacillus was shown to decrease tumor necrosis factor (a marker of inflammation), reduce IP, and promote secretory IgA.<sup>115</sup> Animal studies confirm reduction of IP with Lactobacillus therapy. 42,116,117 Lactobacillus casei GG supplementation significantly increased the gut antigen-specific IgA immune response in a study of 14 children with Crohn's disease or juvenile chronic arthritis. Intestinal permeability was not investigated in this study; however, the authors theorize that Lactobacillus use for ten days corrected a gut barrier defect.<sup>118</sup>

Saccharomyces boulardii: Saccharomyces boulardii is a beneficial yeast similar to baker's yeast (Saccharomyces cerevisiae), and has been used for a variety of intestinal complaints. Supplementation of Saccharomyces boulardii in mice previously inoculated with Candida albicans decreased the incidence of translocation of Candida from the gut to mesenteric lymph nodes. This might be explained by stimulation of host defense mechanisms, i.e., complement activation, macrophage activation, 113,120 and increased sIgA. 121

**Fructo-Oligosaccharides:** Fructo-oligosaccharides (FOS) are oligosaccharides composed of one molecule of sucrose and one

to three molecules of fructose, 122 and are found in varying amounts in many foods, including honey, beer, onion, Burdock (Arctium lappa), rye, asparagus, Jeruselum artichoke (Helianthus tuberosus), banana, and oats. FOS are virtually undigestible by human gastrointestinal enzymes, but are easily utilized by certain intestinal bacteria. 123 FOS supplementation increases the population of beneficial Bifidobacteria species in the stool, 124 increases fecal short-chain fatty acids, and decreases stool pH.125 FOS may also increase levels of some Lactobacilli, although not as consistently as Bifidobacteria. These changes, especially increases in Lactobacilli, can decrease an abnormal intestinal permeability. However, FOS can also encourage the growth of Klebsiella, 122 a potentially pathogenic organism associated with increased intestinal permeability and ankylosing spondylitis (see section on ankylosing spondylitis), which brings into question the safety of this supplement. A prudent protocol is to perform a stool microbiological assay before suggesting FOS supplementation, to reduce the possibility of feeding an established Klebsiella population. It is also important to know the growth-enhancing effects of FOS are quickly lost when FOS supplementation is discontinued. 124

#### **Discussion**

The intestinal epithelial barrier is a complex system of absorptive mechanisms, coupled with tight junctions and immune activity which prevent passage of antigenic, toxic, or pathogenic molecules or organisms. Abnormal functioning of these components, whether due to disease processes, such as inflammatory bowel disease, or from toxic substances like alcohol or NSAIDs, promotes a pathogenically increased intestinal permeability. This increased permeability predisposes the individual to absorb antigens and organisms through the "leaky gut," which can cause further damage to the intestinal

epithelial barrier, auto-immune crossreactivity of antibodies to food or microbial antigens with normal tissue, and deposition of immune complexes in tissue distant from the gastrointestinal tract. In its worst form it can be fatal, as in multiple organ failure after surgery or trauma.

To adequately treat abnormal intestinal permeability and the conditions it is associated with, it is necessary to focus on three areas:

#### 1) Preventing further damage

If possible, alcohol, NSAIDs, or other irritating or toxic substances should be minimized or discontinued. Flavonoids such as quercetin and Ginkgo or synthetic analogs like cromolyn sodium can inhibit mast cell degranulation and further damage.

#### 2) Correcting dysbiosis

Re-establishing the normal microbial flora, with the assistance of substances such as Lactobacilli, *Saccharomyces boulardii*, FOS (with caution after culture), and/or antimicrobials, is vitally important to re-establishing normal IP.

#### 3) Healing an inflamed intestinal mucosa

Healing the gut can be facilitated by, in some cases, fasting or fiber-containing enteral nutrition. Glutamine supplementation (some practitioners use up to 15 grams per day), fiber supplementation or dietary oats, phosphatidylcholine, and fish oil to reduce proinflammatory eicosinoid production, can also be utilized in this multi-faceted approach.

Eliminating toxic or irritating substances is of the utmost importance in restoring normal intestinal permeability. The body's efforts to heal and correct an abnormal intestinal permeability can be assisted by providing nutrients to the intestines, promoting proper immune function by restoring IgA secretion, re-establishing a normal, beneficial

bacterial flora, supplying essential fatty acids which promote anti-inflammatory metabolites, and stabilizing mast cells to reduce histamine and cytokine release.

### References

- Crissinger KD, Kvietys PR, Granger DN. Pathophysiology of gastrointestinal mucosal permeability. *J Int Med* 1990;228:S145-S154.
- 2. Madara J. Pathobiology of the intestinal epithelial barrier. *Am J Pathol* 1990;137:1273-1281.
- 3. Madara JL, Nash S, Moore R, Atisook K. Structure and function of the intestinal epithelial barrier in health and disease. *Monogr Pathol* 1990;31:306-324.
- 4. Nash S, Stafford J, Madara JL. Effects of polymorphonuclear leukocyte transmigration on the barrier function of cultured intestinal epithelial monolayers. *J Clin Invest* 1987;80:1104-1113.
- 5. Nash S, Stafford J, Madara JL. The selective and superoxide-independent disruption of intestinal epithelial TJs during leukocyte transmigration. *Lab Invest* 1988;59:531-537.
- 6. Cramer EB, Milks LC, Ojakain GK. Transepithelial migration of human neutrophils: An *in vitro* model system. *Proc Natl Acad Sci* 1980;77:4069-4073.
- 7. Bjarnason I, Peters TJ. Influence of antirheumatic drugs on gut permeability and on the gut associated lymphoid tissue. *Baillieres Clin Rheumatol* 1996;10:165-176.
- 8. Smith MD, Gibson RA, Brooks PM. Abnormal bowel permeability in ankylosing spondylitis and rheumatoid arthritis. *J Rheumatol* 1985;12:299-305.
- 9. Martínez-González O, Cantero-Hinjosa J, Paule-Sastre P, et al. Intestinal permeability in patients with ankylosing spondylitis and their healthy relatives. *Br J Rheumatol* 1994;33:644-647.
- 10. Tatsuno K. Intestinal permeability in children with food allergy. *Arerugi* 1989;38:1311-1318.
- Benard A, Desreumeaux P, Huglo D, et al. Increased intestinal permeability in bronchial asthma. *J Allergy Clin Immunol* 1996;97:1173-1178.
- 12. Moneret-Vautrin DA, Kanny G, Thevenin F. Asthma caused by food allergy. *Rev Med Interne* 1996;17:551-557.

- 13. Ioslauri E, Juntunen M, Wiren S, et al. Intestinal permeability changes in acute gastroenteritis: Effects of clinical factors and nutritional management. *J Pediatr Gastroenterol Nutr* 1989;8:466-473.
- 14. Langkamp-Henken B, Donovan TB, Pate LM, et al. Increased intestinal permeability following blunt and penetrating trauma. *Crit Care Med* 1995;23:660-664.
- 15. Pape HC, Dwenger A, Regel G, et al. Increased gut permeability after multiple trauma. *Br J Surg* 1994;81:850-852.
- Riddington DW, Venkatesh B, Boivin CM, et al. Intestinal permeability, gastric intramucosal pH, and systemic endotoxemia in patients undergoing cardiopulmonary bypass. *JAMA* 1996;275:1007-1012.
- 17. Bjarnason I, Ward K, Peters TJ. The leaky gut of alcoholism: possible route of entry for toxic compounds. *Lancet* 1984;8370:179-182.
- 18. Paganelli R, Fagiolo U, Cancian M, Scala E. Intestinal permeability in patients with chronic urticaria-angioedema with and without arthralgia. *Ann Allergy* 1991;66:181-184.
- 19. Przybilla B, Ring J. Food allergy and atopic eczema. *Semin Dermatol* 1990;9:220-225.
- 20. Mack DR, Flick JA, Durie PR, et al. Correlation of intestinal lactulose permeability with exocrine pancreatic dysfunction. *J Pediatr* 1992;120:696-701.
- 21. Cobden I, Rothwell J, Axon ATR. Intestinal permeability and screening tests for celiac disease. *Gut* 1980;21:512-518.
- Olaison G, Sjodahl R, Tagesson C. Abnormal intestinal permeability in Crohn's disease.
  Scan J Gastroenterol 1990;25:321-328.
- 23. Tepper RE, Simon D, Brandt LJ, et al. Intestinal permeability in patients infected with the human immunodeficiency virus. *Am J Gastroenterol* 1994;89:878-882.
- 24. Lim SG, Menzies IS, Lee CA, et al. Intestinal permeability and function in patients infected with human immunodeficiency virus. A comparison with coeliac disease. *Scand J Gastroenterol* 1993;28:573-580.
- 25. Ryan CM, Yarmush ML, Burke JF, Tompkins RG. Increased gut permeability early after burns correlates with the extent of burn injury. *Crit Care Med* 1992;20:1508-1512.
- 26. Van Deventer SJ, Knepper A, Landsman J, et al. Endotoxins in portal blood. Hepatogastroenterology 1988;35:223-225.

- Van Elburg RM, Uil JJ, van Aalderen WM, et al. Intestinal permeability in exocrine pancreatic insufficiency due to cystic fibrosis or chronic pancreatitis. *Pediatr Res* 1996;39:985-991.
- 28. Stechmiller JK, Treloar D, Allen N. Gut dysfunction in critically ill patients: a review of the literature. *Am J Crit Care* 1997;6:204-209.
- Butkus S, Mahan LK. Food allergies: Immunological reactions to food. *J Am Dietetic Assn* 1986;86:601-608.
- Zeiger RS, Heller S, Mellon M, et al. Effectiveness of dietary manipulation in the prevention of food allergy in infants. *J Allergy Clin Immunol* 1986;78:224-238.
- 31. Payne D, Kubes P. Nitric oxide donors reduce the rise in reperfusion-induced intestinal mucosal permeability. *Am J Physiol* 1993;265:G189-G195.
- 32. Schleiffer R, Raul F. Prophylactic administration of L-arginine improves the intestinal barrier function after mesenteric ischaemia. *Gut* 1996;39:194-198.
- 33. Kanwar S, Wallace JL, Befus D, Kubes P. Nitric oxide inhibition increases epithelial permeability via mast cells. *Am J Physiol* 1994;266:G222-G229.
- 34. Boughton-Smith NK, Evans SM, Hawkey CJ, et al. Nitric oxide synthase activity in ulcerative colitis and Crohn's disease. *Lancet* 1993;342:338-340.
- 35. Cappell MS, Simon T. Colonic toxicity of administered medications and chemicals. *Am J Gastroenterol* 1993; 88:1684-1699.
- Lichtenberger LM, Wang Z, Romero JJ, et al. Non-steroidal anti-inflammatory drugs (NSAIDs) associate with zwitterionic phospholipids: Insight into the mechanism and reversal of NSAID-induced gastrointestinal injury. *Nat Med* 1995;1:154-158.
- 37. Bjarnason I, Williams P, Smethurst P, et al. Effect of non-steroidal anti-inflammatory drugs and prostaglandins on the permeability of the human small intestine. *Gut* 1986;27:1292-1297.
- 38. Bjarnason I, Zanelli G, Smith T, et al. The pathogenesis and consequences of non-steroidal anti-inflammatory drug induced small intestinal inflammation in man. *Scan J Rheumatology* 1987;64:S55-S62.
- 39. Saadia R, Lipman J. Antibiotics and the gut. *Eur J Surg* 1996;576:S39-S41.

- 40. Berg RD. Bacterial translocation from the gastrointestinal tract. *J Med* 1992;23:217-244.
- 41. Marshall JC, Christou NV, Meakins JL. Immunomodulation by altered gastrointestinal tract flora. *Arch Surg* 1988;123:1465-1469.
- 42. Berg RD, Wommack E, Deitch EA. Immunosuppression and intestinal bacterial overgrowth synergistically promote bacterial translocation. *Arch Surg* 1988;123:1359-1364.
- 43. Mao Y, Nobaek S, Kasravi B, et al. The effects of Lactobacillus strains and oat fiber on methotrexate-induced enterocolitis in rats. *Gastroenterology* 1996;111:334-344.
- 44. Serrander R, Magnusson K, Kihlström E, Sundqvist T. Acute Yersinia infections in man increase intestinal permeability for low-molecular weight polyethylene glycols (PEG 400). Scand J Infect Dis 1986;18:409-413.
- 45. Bjarnason I, Williams P, So A, et al. Intestinal permeability and inflammation in rheumatoid arthritis: effects of non-steroidal anti-inflammatory drugs. *Lancet* 1984;2(8413):1171-1174.
- Thomson AB, Keelan M, Cheesman CI, Walker K. Fractionated low doses of abdominal irradiation alters jejunal uptake of nutrients. *Int J Radiat Oncol Biol Phy* 1986;12:917-925.
- 47. Coltart RS, Howard GC, Wraight EP, Bleehen NM. The effect of hyperthermia and radiation on small bowel permeability using 51 Cr EDTA and 14C mannitol in man. *Int J Hyperthemia* 1988;4:467-477.
- 48. Ruppin H, Hotze A, Dauring A, et al. Reversible functional disorders of the intestinal tract caused by abdominal radiotherapy. *Z Gastroenterol* 1987;25:261-269.
- 49. Yeoh E, Horowitz M, Russo A, et al. A retrospective study of the effects of pelvic irradiation for carcinoma of the cervix on gastrointestinal function. *Int J Radiat Oncol Biol Phys* 1993;26:229-237.
- 50. Parks DA, Bulkley GB, Granger DN. Role of oxygen-derived free radicals in digestive tract diseases. *Surgery* 1983;94:415-422.
- Spaeth G, Berg RD, Specian RD, Deitch EA. Food without fiber promotes bacterial translocation from the gut. Surgery 1990;108:240-246
- 52. Spaeth G, Specian RD, Berg RD, Deitch EA. Bulk prevents bacterial translocation induced by the oral administration of total parenteral nutrition solution. *JPEN J Parenter Enteral Nutr* 1990;14:442-447.

- 53. Wyatt J, Vogelsang H, Hübl W, et al. Intestinal permeability and the prediction of relapse in Crohn's disease. *Lancet* 1993;341:1437-1439.
- 54. Murphy MS, Eastham EJ, Nelson R, et al. Intestinal permeability in Crohn's disease. *Arch Dis Child* 1989;64:321-325.
- 55. Bjarnason I. Intestinal permeability. *Gut* 1994;35:S18-S22.
- 56. Shanahan F. Current concepts of the pathogenesis of inflammatory bowel disease. *Ir J Med Sci* 1994;163:544-549.
- 57. Sartor RB. Current concepts of the etiology and pathogenesis of ulcerative colitis and Crohn's disease. *Gastroenterol Clin North Am* 1995;24:475-507.
- 58. Peeters M, Geypens B, Claus D, et al. Clustering of increased small intestinal permeability in families with Crohn's disease. *Gastroenterology* 1997;113:802-807.
- 59. Hilsden RJ, Meddings JB, Sutherland LR. Intestinal permeability changes in response to acetylsalicylic acid in relatives of patients with Crohn's disease. *Gastroenterology* 1996;110:1395-1403.
- Katz KD, Hollander D, Vadheim CM, et al. Intestinal permeability in patients with Crohn's disease and their healthy relatives. *Gastroenterology* 1989;97:927-931.
- 61. May GR, Sutherland LR, Meddings JB. Is small intestinal permeability really increased in relatives of patients with Crohn's disease? *Gastroenterology* 1993;104:1627-1632.
- Teahon K, Smethurst P, Levi AJ, et al. Intestinal permeability in patients with Crohn's disease and their first degree relatives. *Gut* 1992;33:320-323.
- 63. Howden CW, Gillanders I, Morris AJ, et al. Intestinal permeability in patients with Crohn's disease and their first-degree relatives. *Am J Gastroenterol* 1994;89:1175-1176.
- 64. Munkholm P, Langholz E, Hollander D, et al. Intestinal permeability in patients with Crohn's disease and ulcerative colitis and their first degree relatives. *Gut* 1994;35:68-72.
- Issenman RM, Jenkins RT, Radoja C. Intestinal permeability compared in pediatric and adult patients with inflammatory bowel disease. *Clin Invest Med* 1993;16:187-196.
- 66. Binder V, Orholm M. Familial occurrence and inheritance studies in inflammatory bowel disease. *Neth J Med* 1996;48:53-56.
- 67. Kuitunen M, Savilahti E. Gut permeability to human alpha-lactalbumin, beta-lactalbumin, mannitol, and lactulose in celiac disease. *J Ped Gastroenterol Nutr* 1996;22:197-204.

- 68. Van Elburg RM, Uil JJ, Mulder CJ, Heymans HS. Intestinal permeability in patients with coeliac disease and relatives of patients with coeliac disease. *Gut* 1993;34:354-357.
- 69. Lubrano E, Ciacci C, Ames PR, et al. The arthritis of coeliac disease: prevalence and pattern in 200 adult patients. *Br J Rheumatol* 1996;35:1314-1318.
- Andre C, Andre F, Colin L, Cavagna S.
   Measurement of intestinal permeability to
   mannitol and lactulose as a means of diagnosing food allergy and evaluating therapeutic
   effectiveness of disodium cromoglycate. *Ann Allergy* 1987;59:127-130.
- 71. Mielants H, DeVos M, Cuvelier C, Veys EM. The role of gut inflammation in the pathogenesis of spondyloarthropathies. *Acta Clin Belg* 1996;51:340:349.
- 72. Mielants H, Veys EM, Cuvelier C, DeVos M. Course of gut inflammation in spondyloarthropathies and therapeutic consequences. *Baillieres Clin Rheumatol* 1996;10:147-164.
- 73. Mielants H, Veys EM, Cuvelier C, DeVos M. The evolution of spondyloarthropathies in relation to gut histology III. Relation between gut and joint. *J Rheumatol* 1995;22: 2279-2284.
- 74. Yuan GH, Shi GY, Ding YZ. Antibodies to *Klebsiella pneumoniae* in ankylosing spondylitis. *Chang Hua Nei Ko Tsa Chih* 1993;32:467-469.
- 75. O'Maloney S, Anderson N, Nuki G, Ferguson A. Systemic and mucosal antibodies to Klebsiella in patients with ankylosing spondylitis and Crohn's disease. *Ann Rheum Dis* 1992;51:1296-1300.
- 76. Sahly H, Podschun R, Sass R, et al. Serum antibodies to Klebsiella capsular polysaccharides in ankylosing spondylitis. *Arthritis Rheum* 1994;37:754-759.
- 77. Brown M, Wordsworth P. Predisposing factors to spondyloarthropathies. *Curr Opin Rheumatol* 1997;9:308-314.
- 78. Nasution AR, Mardjuadi A, Kunmartini S, et al. HLA-B27 subtypes positively and negatively associated with spondyloarthropathy. *J Rheumatol* 1997;24:1111-1114.
- 79. Tiwana H, Wilson C, Walmsley RS, et al. Antibody responses to gut bacteria in ankylosing spondylitis, rheumatoid arthritis, Crohn's disease and ulcerative colitis. *Rheumatol Int* 1997;17:11-16.

- 80. Fagiolo U, Paganelli R, Ossi E, et al. Intestinal permeability and antigen absorption in rheumatoid arthritis. Effects of acetylsalicylic acid and sodium cromoglycate. *Int Arch Allergy Appl Immunol* 1989;89:98-102.
- 81. Sundqvist T, Lindstrom F, Magnusson KE, et al. Influence of fasting on intestinal permeability and disease activity in patients with rheumatoid arthritis. *Scand J Rheumatol* 1982;11:33-38.
- 82. Skoldstam L, Magnusson KE. Fasting, intestinal permeability, and rheumatoid arthritis. *Rheum Dis Clin North Am* 1991;17:363-371.
- 83. Wanchu A, Deodhar SD, Sharma M, et al. Elevated levels of anti-proteus antibodies in patients with active rheumatoid arthritis. *Indian J Med Res* 1997;105:39-42.
- 84. Wilson C, Thakore A, Isenberg D, Ebringer A. Correlation between anti-Proteus antibodies and isolation rates of *P. mirabilis* in rheumatoid arthritis. *Rheumatol Int* 1997;16:187-189.
- 85. Fielder M, Tiwana H, Youinou P, Le Goff P. The specificity of the anti-Proteus antibody response in tissue-typed rheumatoid arthritis (RA) patients from Brest. *Rheumatol Int* 1995;15:79-82.
- 86. Tani Y, Tiwana H, Hukuda S, et al. Antibodies to Klebsiella, Proteus, and HLA-B27 peptides in Japanese patients with ankylosing spondylitis and rheumatoid arthritis. *J Rheumatol* 1997;24:109-114.
- 87. Tiwana H, Wilson C, Cunningham P, et al. Antibodies to four gram-negative bacteria in rheumatoid arthritis which share sequences with the rheumatoid arthritis susceptibility motif. *Br J Rheumatol* 1996;35:592-594.
- 88. Kjeldsen-Kragh J, Rashid T, Dybwad A, et al. Decrease in anti-*Proteus mirabilis* but not anti-*Escherichia coli* antibody levels in rheumatoid arthritis patients treated with fasting and a one year vegetarian diet. *Ann Rheum Dis* 1995;54:221-224.
- 89. Caffarelli C, Cavagni G, Menzies IS, et al. Elimination diet and intestinal permeability in atopic eczema: a preliminary study. *Clin Exp Allergy* 1993;23:28-31.
- Pike MG, Heddle RJ, Boulton P, et al. Increased intestinal permeability in atopic eczema. *J Invest Dermatol* 1986;86:101-104.
- 91. Dupont C, Barau E, Molkou P, et al. Food-induced alterations of intestinal permeability in children with cow's milk enteropathy and atopic dermatitis. *J Pediatr Gastroenterol Nutr* 1989;8:459-465.

- 92. Barba A, Schena D, Andreaus MC, et al. Intestinal permeability in patients with atopic eczema. *Br J Dermatol* 1989;120:71-75.
- 93. Hamilton I, Fairris GM, Rothwell J, et al. Small intestinal permeability in dermatological disease. *Q J Med* 1985;56:559-567.
- 94. Souba WW. Glutamine:physiology, biochemistry, and nutrition in critical illness. Austin, TX: RG Landes Co.;1992.
- Hong RW, Rounds JD, Helton WS, et al. Glutamine preserves liver glutathione after lethal hepatic injury. *Ann Surg* 1992;215:114-119.
- Goodman MJ, Kent PW, Truelove SC. Glucosamine synthetase activity of the colonic mucosa in ulcerative colitis and Crohn's disease. *Gut* 1977;18:219-228.
- 97. Fox AD, Kripke SA, DePaula J, et al. Effect of a glutamine supplemented enteral diet on methotrexate-induced enterocolitis. *JPEN* 1988;12:325-331.
- 98. Klimberg VS, Salloum RM, Kasper M, et al. Oral glutamine accelerates healing of the small intestine and improves outcome following whole abdominal radiation. *Arch Surg* 1990;125:1040-1045.
- 99. Souba WW, Klimberg VS, Hautamaki RD, et al. Oral glutamine reduces bacterial translocation following abdominal radiation. *J Surg Res* 1990;48:1-5.
- 100. Nordgaard I, Hove H, Clausen MR, Mortensen PB. Colonic production of butyrate in patients with previous colonic cancer during long-term treatment with dietary fibre (*Plantago ovata* seeds). *Scand J Gastroenterol* 1996;31:1011-1020.
- Bridges SR, Anderson JW, Deakins DA, et al. Oat bran increases serum acetate of hypercholesterolemic men. Am J Clin Nutr 1992;56:455-459.
- Elsen RJ, Bistrian BR. Recent developments in short-chain fatty acid metabolism. *Nutrition* 1991;7:7-9.
- Ward PB, Young GP. Dynamics of Clostridium difficile infection. Control using diet. Adv Exp Med Biol 1997;412:63-75.
- 104. May T, Mackie RI, Fahey GC Jr, et al. Effect of fiber source on short-chain fatty acid production and on the growth and toxin production by *Clostridium difficile*. *Scand J Gastroenterol* 1994;29:916-922.

- 105. Fabia R, Ar'Rajab A, Willen R, et al. Effects of phosphatidylcholine and phosphatidylinositol on acetic-acid-induced colitis in the rat. *Digestion* 1992;53:35-44.
- 106. Wang XD, Andersson R, Soltesz V, et al. Phospholipids prevent enteric bacterial translocation in the early stage of experimental acute liver failure in the rat. Scand J Gastroenterol 1994;29:1117-1121.
- Belluzzi A, Brignola C, Campieri M, et al. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. N Engl J Med 1996;334:1557-1560.
- 108. Crowe SE, Perdue MH. Functional abnormalities in the intestine associated with mucosal mast cell activation. *Reg Immunol* 1992;4:113-117.
- 109. Pearce FL, Befus AD, Bienenstock J. Mucosal mast cells. III. Effect of quercetin and other flavonoids on antigen-induced histamine secretion from rat intestinal mast cells. *J Allergy Clin Immunol* 1984;73:819-823.
- Miller AL. Antioxidant flavonoids: structure, function, and clinical usage. Alt Med Rev 1996;1(2):126-127.
- Otamiri T, Tagesson C. Ginkgo biloba extract prevents mucosal damage associated with small-intestinal ischemia. Scand J Gastroenterol 1989;24:666-670.
- 112. Yamamoto T, Juneja LR, Chu D, Kim M. Chemistry and applications of green tea. Boca Raton, FL:CRC Press;1997.
- Catanzarro JA, Green L. Microbial ecology and probiotics in human medicine (Part II). Alt Med Rev 1997;2:296-305.
- Hangee-Bauer C. Lactobacilli and human health. In: A Textbook of Natural Medicine. Seattle, WA. Bastyr University Publications; 1985:V:Lactob-1-5.
- 115. Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. *Allergy Clin Immunol* 1997;99:179-185.
- 116. Isolauri E, Kaila M, Arvola T, et al. Diet during rotavirus enteritis affects jejunal permeability to macromolecules in suckling rats. *Pediatr Res* 1993;33:548-553.
- 117. Isolauri E, Majamaa H, Arvola T, et al. *Lactobacillus casei* strain GG reverses increased intestinal permeability induced by cow milk in suckling rats. *Gastroenterology* 1993;105:1643-1650.

- 118. Malin M, Suomalainen H, Saxelin M, Isolauri E. Promotion of IgA immune response in patients with Crohn's disease by oral bacteriotherapy with *Lactobacillus* GG. *Ann Nutr Metab* 1996;40:137-145.
- 119. Berg R, Bernasconi P, Fowler D, Gautreaux M. Inhibition of *Candida albicans* translocation from the gastrointestinal tract of mice by oral administration of *Saccharomyces boulardii*. *J Infect Dis* 1993;168:1314-1318.
- 120. Caetano JAM, Paramés MT, Babo MJ, et al. Immunopharmacological effects of *Saccharomyces boulardii* in healthy human volunteers. *Int J Immunopharmac* 1986;8:245-259.
- 121. Buts JP, Bernasconi P, Vaerman JP, Dive C. Stimulation of secretory IgA and secretory component of immunoglobins in small intestine of rats treated with *Saccharomyces boulardii*. *Dig Dis Sci* 1990;35:251-256.
- Mitsuoka T, Hidaka H, Eida T. Effect of fructo-oligosaccharides on intestinal microflora. *Nahrung* 1987;31:427-436.
- Molis C, Flourie B, Ouarne F, et al. Digestion, excretion, and energy value of fructooligosaccharides in healthy humans. *Am J Clin Nutr* 1996;64:324-328.
- 124. Buddington RK, Williams CH, Chen S-C, Witherly SA. Dietary supplement of neosugar alters the fecal flora and decreases activities of some reductive enzymes in human subjects. *Am J Clin Nutr* 1996;63:709-716.
- 125. Campbell JM, Fahey GC Jr, Wolf BW. Selected indigestible oligosaccharides affect large bowel mass, cecal and fecal short-chain fatty acids, pH and microflora in rats. *J Nutr* 1997;127:130-136.