

Leaky Gut Syndromes: Breaking the Vicious Cycle

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From the perspective of function, the contents of the gut lumen lie outside the body and contain a toxic/antigenic load from which the body needs to be protected. Protection is supplied by complex mechanisms which support one another: intestinal secretions (primarily mucus and secretory IgA), the mucosal epithelium, and intramural lymphocytes [1]. This primary, intestinal barrier is supported by the liver, through which all enterically-derived substances must pass before entering the arterial circulation for transport to other tissues and organs. Kupffer cells in the hepatic sinusoids remove absorbed macromolecules by phagocytosis. Hepatic microsomal enzymes alter gut-derived chemical substrates by oxidation and by conjugation to glycine and glutathione (GSH) for excretion into bile and for circulation to the kidneys. The cost of detoxification is high; reactive intermediates and free radicals are generated and anti-oxidants like GSH are consumed [2, 3]. Any compromise of intestinal barrier function increases the production of oxygen radicals and carcinogens by the liver's cytochrome P-450 mixed-function oxidase system. The excretion of oxidation by-products into bile and the reflux of this "toxic" bile into the pancreatic ducts may be the major cause of chronic pancreatic disease.[4, 5]

Compromised intestinal barrier function can also cause disease directly, by immunological mechanisms. [6-9] Increased permeability stimulates classic hypersensitivity responses to foods and to components of the normal gut flora; bacterial endotoxins, cell wall polymers and dietary gluten may cause "non-specific" activation of inflammatory pathways mediated by complement and cytokines. [10] In experimental animals, chronic low-grade endotoxemia causes the appearance of auto-immune disorders.[11-13]

Leaky Gut Syndromes are clinical disorders associated with increased intestinal permeability. They include inflammatory and infectious bowel diseases [14-19], chronic inflammatory arthritides [9, 20-24], cryptogenic skin conditions like acne, psoriasis and dermatitis herpetiformis [25-28], many diseases triggered by food allergy or specific food intolerance, including eczema, urticaria, and irritable bowel syndrome [29-37], AIDS [38-40], chronic fatigue syndromes [Rigden, Cheney, Lapp, Galland, unpublished results], chronic hepatitis [41], chronic pancreatitis [4, 5], cystic fibrosis [42] and pancreatic carcinoma. Hyperpermeability may play a primary etiologic role in the evolution of each disease, or may be a secondary consequence of it which causes immune activation, hepatic dysfunction, and pancreatic insufficiency, creating a vicious cycle. Unless specifically investigated, the role of altered intestinal permeability in patients with Leaky Gut Syndromes often goes unrecognized. The availability of safe, non-invasive, and inexpensive methods for measuring small intestinal permeability make it possible for clinicians to look for the presence of altered intestinal permeability in their patients and to objectively assess the efficacy of treatments. Monitoring the intestinal permeability of chronically ill patients with Leaky Gut Syndromes can help improve clinical outcomes.

Triggers and Mediators of the Leaky Gut

Leaky Gut Syndromes are usually provoked by exposure to substances which damage the integrity of the intestinal mucosa, disrupting the desmosomes which bind epithelial cells and increasing passive, para-cellular absorption. The commonest causes of damage are infectious agents (viral, bacterial and protozoan) [43-46], ethanol [47, 48], and non-steroidal anti-inflammatory drugs [20, 49, 50]. Hypoxia of the bowel (occurring as a consequence of open-heart surgery or of shock) [51, 52], elevated levels of reactive oxygen metabolites (biliary, food-borne or produced by inflammatory cells) [53], and cytotoxic drugs [54-56] also increase para-cellular permeability.

The Four Vicious Cycles

Cycle One: Allergy

The relationship between food sensitivities and the leaky gut is complex and circular. Children and adults with eczema, urticaria or asthma triggered by atopic food allergy have baseline permeability measurements that are higher than control levels [57-59]. Following exposure to allergenic foods, permeability sharply increases. Most of this increase can be averted by pre-treatment with sodium cromoglycate [32, 34, 57-59], indicating that release from mast cells of atopic mediators like histamine and serotonin is responsible for the increase in permeability. It appears that an increase in intestinal permeability is important in the pathogenesis of food allergy and is also a result of food allergy.

Claude Andre, the leading French research worker in this area, has proposed that measurement of gut permeability is a sensitive and practical screening test for the presence of food allergy and for following response to treatment [57]. In Andre's protocol, patients with suspected food allergy ingest 5 grams each of the innocuous sugars lactulose and mannitol. These sugars are not metabolized by humans and the amount absorbed is fully excreted in the urine within six hours. Mannitol, a monosaccharide, is passively transported through intestinal epithelial cells; mean absorption is 14% of the administered dose (range 5-25%). In contrast, the intestinal tract is impermeable to lactulose, a disaccharide; less than 1% of the administered dose is normally absorbed. The differential excretion of lactulose and mannitol in urine is then measured. The normal ratio of lactulose/mannitol recovered in urine is less than 0.03. A higher ratio signifies excessive lactulose absorption caused by disruption of the desmosomes which seal the intercellular tight junctions. The lactulose/mannitol challenge test is performed fasting and again after ingestion of a test meal. At the Hospital St. Vincent de Paul in Paris, permeability testing has been effectively used with allergic infants to determine which dietary modifications their mothers needed to make while breast feeding and which of the "hypoallergenic" infant formulas they needed to avoid in order to relieve their symptoms [60].

Cycle Two: Malnutrition

Disruption of desmosomes increases absorption of macromolecules. If the epithelial cells themselves are damaged, a decrease in trans-cellular absorption may accompany the increased para-cellular absorption. Because nutrients are ordinarily absorbed by the trans-cellular route, malnutrition may occur, aggravating structural and functional disturbances [61]. Under normal conditions, intestinal epithelium has the fastest rate of mitosis of any tissue in the body; old cells slough and a new epithelium is generated every three to six days [62, 63]. The metabolic demands of this normally rapid cell turnover must be met if healing of damaged epithelium is to occur. When they are not met, hyperpermeability exacerbates [64, 65].

Correction of nutritional deficiency with a nutrient-dense diet and appropriate supplementation is essential for the proper care of patients with Leaky Gut Syndromes. Specific recommendations are made in the last section of this review. Because of the association between hyperpermeability and pancreatic dysfunction, pancreatic enzymes may also be required.

Cycle Three: Bacterial Dysbiosis

Dysbiosis is a state in which disease or dysfunction is induced by organisms of low intrinsic virulence that alter the metabolic or immunologic responses of their host. This condition has been the subject of a recent review article [66]. Immune sensitization to the normal gut flora is an important form of dysbiosis that has been implicated in the pathogenesis of Crohn's disease and ankylosing spondylitis [67-81]. Recent research findings suggest that bacterial sensitization is an early complication of altered permeability and exacerbates hyperpermeability by inducing an

inflammatory enteropathy [82, 83]. This has been most studied in the response to NSAIDs. Single doses of aspirin or of indomethacin increase para-cellular permeability, in part by inhibiting the synthesis of protective prostaglandins [20, 49, 50, 84, 85]. Hyperpermeability is partially prevented by pre-treatment with the prostaglandin-E analogue, misoprostol. Chronic exposure to NSAIDs produces a chronic state of hyper-permeability associated with inflammation, which can not be reversed by misoprostol but which is both prevented and reversed by the administration of the antibiotic, metronidazole [83, 86]. The effectiveness of metronidazole in preventing NSAID-induced hyperpermeability probably reflects the importance of bacterial toxins in maintaining this vicious cycle. A single dose of bacterial endotoxin, administered by injection, increases the gut permeability of healthy humans [87]. Chronic arthritis can be induced in rats by injection of cell wall fragments isolated from normal enteric anaerobes [88]. Patients with rheumatoid arthritis receiving NSAIDs have increased antibody levels to *Clostridium perfringens* and to its alpha toxin, apparently as a secondary response to NSAID therapy [89].

There is ample documentation for a therapeutic role of metronidazole and other antibiotics in Crohn's disease and rheumatoid arthritis [90-98]. The mechanism underlying the response has been in dispute. In the case of tetracyclines, one group has asserted that mycoplasma in the joints cause rheumatoid arthritis; others have countered this argument by demonstrating that minocycline is directly immunosuppressive in vitro [99]. Because all patients with arthritis have used NSAIDs, and because NSAID enteropathy is associated with bacterial sensitization, it is possible that the antibiotic-responsiveness of some patients with inflammatory diseases is a secondary effect of NSAID-induced bacterial sensitization which then exacerbates the Leaky Gut Syndrome. Altering gut flora through the use of antibiotics, synthetic and natural, probiotics, and diet is a third strategy for breaking the vicious cycle in Leaky Gut Syndromes. With regard to diet, patients whose disease responds to vegetarian diets are those in whom the diet alters gut ecology; if a vegetarian diet does not alter gut ecology, the arthritis is not improved [100].

Cycle Four: Hepatic Stress

The liver of Leaky Gut patients works overtime to remove macromolecules and oxidize enteric toxins. Cytochrome P-450 mixed-function oxidase activity is induced and hepatic synthesis of free radicals increases. The results include damage to hepatocytes and the excretion of reactive by-products into bile, producing toxic bile capable of damaging bile ducts and refluxing into the pancreas [4, 5]. In attempting to eliminate toxic oxidation products, the liver depletes its reserves of sulfur-containing amino acids [101]. These mechanisms have been most clearly demonstrated in ethanol-induced hepatic disease [47]. Sudduth [102] proposes that the initial insult is the ethanol-induced increase in gut permeability which creates hepatic endotoxemia. Endotoxemia can further increase permeability, alter hepatic metabolism, and stimulate hepatic synthesis of reactive species which are excreted in bile. This toxic bile, rich in free radicals, further damages the small-bowel mucosa, exacerbating hyperpermeability.

A Practical Approach

Suspect a pathological increase in gut permeability when evaluating any patient with the diseases listed in Table 1 or the symptoms listed in Table 2. Measure permeability directly using the lactulose/mannitol challenge test. Indirect measures of gut permeability include titers of IgG antibody directed against antigens found in common foods and normal gut bacteria. These tests may be useful but cannot substitute for the direct permeability assay, especially when one is following the response to treatment.

IF ALL COMPONENTS OF THE LACTULOSE/MANNITOL TEST ARE NORMAL, repeat the challenge after a test meal of the patient's common foods. If the test meal produces an increase in lactulose excretion (signifying hyperpermeability) or a decrease in mannitol excretion (signifying malabsorption), specific food intolerances are likely and further testing for food allergy is warranted. Once the patient has been maintained on a stable elimination diet for four weeks, repeat the lactulose/mannitol challenge after a test meal of foods permitted on the elimination diet. A normal result assures you that all major allergens have been identified. An abnormal result indicates that more detective work is needed.

IF THE INITIAL FASTING MANNITOL ABSORPTION IS LOW, suspect malabsorption. This result has the same significance as an abnormal D-xylose absorption test. Look for evidence of celiac disease, intestinal parasites, ileitis, small bowel bacterial overgrowth and other disorders classically associated with intestinal malabsorption and treat appropriately. After eight weeks of therapy, repeat the lactulose/mannitol challenge. An improvement in mannitol excretion indicates a desirable increase in intestinal absorptive capacity. The lactulose/mannitol assay has been proposed as a sensitive screen for celiac disease and a sensitive test for dietary compliance [46, 103-106]. For gluten-sensitive patients, abnormal test results demonstrate exposure to gluten, even when no intestinal symptoms are present. Monitoring dietary compliance to gluten avoidance by testing small bowel permeability is especially helpful in following those patients for whom gluten enteropathy does not produce diarrhea but instead causes failure to thrive, schizophrenia or inflammatory arthritis [107-115].

In the case of relatively mild celiac disease or inflammatory bowel disease, mannitol absorption may not be affected but lactulose absorption will be elevated. A recent study published in the Lancet found that the lactulose-mannitol ratio was an accurate predictor of relapse when measured in patients with Crohn's disease who were clinically in remission [116].

IF THE INITIAL FASTING LACTULOSE IS ELEVATED, OR IF THE INITIAL FASTING LACTULOSE/MANNITOL RATIO IS ELEVATED, consider the possibility of mild inflammatory bowel disease or gluten enteropathy. There are four other primary considerations:

(A) Exposures. Does the patient drink ethanol; take NSAIDs or any potentially cytotoxic drugs? If so, discontinue them and have the lactulose/mannitol challenge repeated three weeks later. If it has become normal, drug exposures were the likely cause of leaky gut. If it has not, bacterial sensitization may have occurred. This may be treated with a regimen of antimicrobials and probiotics. My preference is a combination of citrus seed extract, berberine and artemisinin (the active alkaloid in *Artemisia annua*), which exerts a broad spectrum of activity against Enterobacteriaceae, Bacteroides, protozoa and yeasts [117-120].

If the patient has no enterotoxic drug exposures, inquire into dietary habits. Recent fasting or crash dieting may increase permeability. Counsel the patient in consuming a nutritionally sound diet for three weeks and repeat the test.

Patients with chronic arthritis may have difficulty stopping NSAIDs. Alternative anti-inflammatory therapy should be instituted, including essential fatty acids, anti-oxidants or mucopolysaccharides [121-125]. Changing the NSAID used may also be helpful. NSAIDs like indomethacin, which undergo enterohepatic recirculation, are more likely to damage the small intestine than NSAIDs that are not excreted in bile, like ibuprofen [126]. Nabumetone (relafen) is a pro-NSAID that is activated into a potent NSAID by colonic bacteria; the active metabolite is not excreted in bile. Nabumetone is the only presently available NSAID that does not increase small intestinal permeability.

(B) Infection. The possibilities include recent acute viral or bacterial enteritis, intestinal parasitism, HIV infection and candidosis. Stool testing is useful in identifying these. Repeat the permeability test six weeks after initiating appropriate therapy.

(C) Food allergy. Approach this probability as described in the section above on food allergy in patients with normal fasting test results. The difference lies in degree of damage; food intolerant patients with abnormal fasting permeability have more mucosal damage than patients with normal fasting permeability and will take longer to heal.

(D) Bacterial overgrowth resulting from hypochlorhydria, maldigestion, or stasis [41, 127, 128]. This is confirmed by an abnormal hydrogen breath test. Most of the damage resulting from bacterial overgrowth is caused by bacterial enzyme activity. Bacterial mucinase destroys the protective mucus coat; proteinases degrade pancreatic and brush border enzymes and attack structural proteins. Bacteria produce vitamin B12 analogues and uncouple the B12-intrinsic factor complex, reducing circulating B12 levels, even among individuals who are otherwise asymptomatic [129, 130]. In the absence of intestinal surgery, strictures or fistulae, bacterial overgrowth is most likely a sign of hypochlorhydria resulting from chronic gastritis due to *Helicobacter pylori* infection. Triple therapy with bismuth and antibiotics may be needed, but it is not presently known whether such treatment can reverse atrophic gastritis or whether natural, plant-derived antimicrobials can achieve the same results as metronidazole and ampicillin, the antibiotics of choice.

Bacterial overgrowth due to hypochlorhydria tends to be a chronic problem that recurs within days or weeks after antimicrobials are discontinued. Keith Eaton, a British allergist who has worked extensively with the gut fermentation syndrome, finds that administration of L-histidine, 500 mg bid, improves gastric acid production in allergic patients with hypochlorhydria, probably by increasing gastric histamine levels [personal communication]. Dietary supplementation with betaine hydrochloride is usually helpful but intermittent short courses of bismuth, citrus seed extract, artemisinin, colloidal silver and other natural antimicrobials are often needed. The first round of such treatment, while the patient is symptomatic, should last for at least twelve weeks, to allow complete healing to occur. Repeat the lactulose/mannitol assay at the end of twelve weeks, while the patient is taking the antimicrobials, to see if complete healing has been achieved. The most sensitive test for recurrence of bacterial overgrowth is not the lactulose/mannitol assay but the breath hydrogen analysis.

Atrophic Therapies

Many naturally occurring substances help repair the intestinal mucosal surface or support the liver when stressed by enteric toxins. Basic vitamin and mineral supplementation should include all the B vitamins, retinol, ascorbate, tocopherol, zinc, selenium, molybdenum, manganese, and magnesium. More specialized nutritional, glandular and herbal therapies are considered below. These should not be used as primary therapies. Avoidance of enterotoxic drugs, treatment of intestinal infection or dysbiosis, and an allergy elimination diet of high nutrient density that is appropriate for the individual patient are the primary treatment strategies for the Leaky Gut Syndromes. The recommendations that follow are to be used as adjuncts:

(1) Epidermal Growth Factor (EGF) is a polypeptide that stimulates growth and repair of epithelial tissue. It is widely distributed in the body, with high concentrations detectable in salivary and prostate glands and in the duodenum. Saliva can be a rich source of EGF, especially the saliva of certain non-poisonous snakes. The use of serpents in healing rituals may reflect the value of

ophidian saliva in promoting the healing of wounds. Thorough mastication of food may nourish the gut by providing it with salivary EGF. Purified EGF has been shown to heal ulceration of the small intestine [131].

(2) *Saccharomyces boulardii* is a non-pathogenic yeast originally isolated from the surface of lichee nuts. It has been widely used in Europe to treat diarrhea. In France it is popularly called "Yeast against yeast" and is thought to help clear the skin in addition to the gut. Clinical trials have demonstrated the effectiveness for *S. boulardii* in the treatment or prevention of *C. difficile* diarrhea, antibiotic diarrhea and traveler's diarrhea [132, 133]. Experimental data suggest that the yeast owes its effect to stimulation of SIgA secretion [134]. SIgA is a key immunological component of gut barrier function.

Passive elevation of gut immunoglobulin levels can be produced by feeding whey protein concentrates that are rich in IgA and IgG. These have been shown to be effective in preventing infantile necrotizing enterocolitis [135].

(3) *Lactobacillus casei* var GG is a strain of lactobacillus isolated and purified in Finland. Like *S. boulardii*, *Lactobacillus GG* has been shown effective in the prevention of traveler's diarrhea and of antibiotic diarrhea and in the treatment of colitis caused by *C. difficile*. *Lactobacillus GG* limits diarrhea caused by rotavirus infection in children and in so doing improves the hyperpermeability associated with rotavirus infection. [136-139] The mechanism of action is unclear. The ability of other *Lactobacillus* preparations to improve altered permeability has not been directly tested, but is suggested by the ability of live cultures of *L. acidophilus* to diminish radiation-induced diarrhea, a condition directly produced by the loss of mucosal integrity.

(4) Glutamine is an important substrate for the maintenance of intestinal metabolism, structure and function. Patients and experimental animals that are fasted or fed only by a parenteral route develop intestinal villous atrophy, depletion of SIgA, and translocation of bacteria from the gut lumen to the systemic circulation. Feeding glutamine reverses all these abnormalities. Patients with intestinal mucosal injury secondary to chemotherapy or radiation benefit from glutamine supplementation with less villous atrophy, increased mucosal healing and decreased passage of endotoxin through the gut wall [140-143].

(5) Glutathione (GSH) is an important component of the anti-oxidant defense against free radical-induced tissue damage. Dietary glutathione is not well absorbed, so that considerable quantities may be found throughout the gut lumen following supplementation [144]. Hepatic GSH is a key substrate for reducing toxic oxygen metabolites and oxidized xenobiotics in the liver. Depletion of hepatic glutathione is a common occurrence in Leaky Gut Syndromes contributing to liver dysfunction and liver necrosis among alcoholics and immune impairment in patients with AIDS. The most effective way to raise hepatic glutathione is to administer its dietary precursors, cysteine or methionine. Anti-oxidant supplementation for Leaky Gut Syndromes should therefore include both GSH and N-acetyl cysteine. Because protozoa are more sensitive to oxidant stress than are humans and because most anti-parasitic drugs and herbs work by oxidative mechanisms, high dose anti-oxidant supplementation should be withheld during the treatment of protozoan infection, especially during treatment with Artemisia.

(6) Flavonoids are potent, phenolic anti-oxidants and enzyme inhibitors with varied effects depending on the tissues in which they act. Quercetin and related flavonoids inhibit the release of histamine and inflammatory mediators. Taken before eating, they may block allergic reactions which increase permeability. Catechins have been used in Europe to treat gastric ulcerations. The flavonoids in milk thistle (silymarin) and in dandelion root (*taraxacum*) protect the liver against reactive oxygen species [145].

(7) Essential fatty acids (EFAs) are the substrates for prostaglandin synthesis. Differential feeding of EFAs can profoundly affect prostanoid synthesis and the systemic response to endotoxin. In experimental animals, fish oil feeding ameliorates the intestinal mucosal injury produced by methotrexate and, additionally, blunts the systemic circulatory response to endotoxin [146]. The feeding of gamma-linolenic acid (GLA), promotes the synthesis of E-series prostaglandins, which decrease permeability. EFAs should be consumed in the most concentrated and physiologically active form to avoid exposure to large quantities of polyunsaturated fatty acids from dietary oils. Consumption of vegetable oils tends to increase the free radical content of bile and to exacerbate the effects of endotoxin [147].

(8) Fiber supplements have complex effects on gut permeability and bacterial composition. Low fiber diets increase permeability. Dietary supplementation with insoluble fiber, such as pure cellulose, decreases permeability. Dietary supplementation with highly soluble fiber sources, such as fruit pectin or guar gum, has a biphasic effect. At low levels they reverse the hyperpermeability of low residue diets, probably by a mechanical bulking effect which stimulates synthesis of mucosal growth factors. At high levels of supplementation, they produce hyperpermeability, probably by inducing synthesis of bacterial enzymes which degrade intestinal mucins [148-151]. For maximum benefit with regard to intestinal permeability, dietary fiber supplementation should therefore contain a predominance of hypoallergenic insoluble fiber.

(9) Gamma oryzanol, a complex mixture of ferulic acid esters of phytosterols and other triterpene alcohols derived from rice bran, has been extensively researched in Japan for its healing effects in the treatment of gastric and duodenal ulceration, thought to be secondary to its potent anti-oxidant activity [152, 153].

Summary

Altered intestinal permeability is a key element in the pathogenesis of many different diseases. Hyperpermeability initiates a vicious cycle in which allergic sensitization, endotoxic immune activation, hepatic dysfunction, pancreatic insufficiency and malnutrition occur; each of these increases the leakiness of the small bowel. Effective treatment of the Leaky Gut Syndromes requires several components: avoidance of enterotoxic drugs and allergic foods, elimination of infection or bacterial overgrowth with antimicrobials and probiotics, and dietary supplementation with trophic nutrients. Direct measurement of intestinal permeability allows the clinician to plan appropriate strategies and to gauge the effectiveness of treatment, using objective parameters.

Table 1

Diseases Associated with Increased Intestinal Permeability

Inflammatory bowel disease
Infectious enterocolitis
Spondyloarthropathies
Acne
Eczema
Psoriasis
Urticaria
HIV infection

Cystic fibrosis
Pancreatic insufficiency
AIDS, HIV infection
Hepatic dysfunction
Irritable bowel syndrome with food intolerance
CFIDS
Chronic arthritis/pain treated with NSAIDs
Alcoholism
Neoplasia treated with cytotoxic drugs
Celiac disease
Dermatitis herpetiformis
Autism
Childhood hyperactivity
Environmental illness
Multiple food and chemical sensitivities

Table 2

Symptoms Associated with Increased Intestinal Permeability

Fatigue and malaise
Arthralgias
Myalgias
Fevers of unknown origin
Food intolerances
Abdominal pain
Abdominal distension
Diarrhea
Skin rashes
Toxic feelings
Cognitive and memory deficits
Shortness of breath
Poor exercise tolerance

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