AN INTEGRATED APPROACH TO GASTROINTESTINAL DISORDERS

LEO GALLAND M.D.

The normal gastrointestinal tract contains the most toxic environment to which most people are ever exposed. From the mouth to the anus, every centimeter is colonized by bacteria, with the colon bearing the greatest load. The mucosal surface of the alimentary canal is in effect an external surface that has been internalized, but which remains continuous with the external environment. This surface represents a complex and dangerous frontier, through which pass all the nutrients required for growth and maintenance. The serosal side of the GI mucosa is a site of active surveillance. Two-thirds of the body's lymphocytes reside here, concentrated in Peyer's patches or scattered as intraepithelial lymphcoytes, making the small intestine the largest immulogic organ of the human body. Intestinal lymphocytes recognize soluble and insoluble antigens that cross the mucosal barrier by passive diffusion or endocytosis. This normal physiologic process, called "gut antigen sampling," may be greatly altered during states of inflammation. A complex neurologic network regulates intestinal motility and interacts with the intestinal immune system. It produces every neurotransmitter found in the central nervous system (CNS).

Although the gut nervous system interacts continuously with the CNS, it is complete enough to function in isolation and has been dubbed "the second brain." [REFERENCES ON THIS INTRODUCTION WILL FOLLOW]

This overview of the GI tract highlights features that are essential for an integrated understanding of gastrointestinal disorders. The GI tract is not only an organ of digestion, absorption and elimination, and GI disorders are not merely "digestive disorders." The GI tract serves the entire body as an organ of immune surveillance and response, detoxification and neuroendocrine regulation. Most gastrointestinal diseases result from dysfunction among the complex regulatory relationships just mentioned, and their effects are not limited to the gastrointestinal tract. Integrated therapies for GI disorders, as presented in this chapter, extend beyond the substitution of a "natural treatment" for a drug (*e.g.*, the use of peppermint oil instead of vagolytics for relieving intestinal cramps--REFERENCE TO FOLLOW). They derive from applying the principles of patient-centered diagnosis (described in Chapter.....) to the integrated physiology of the GI tract. Two concepts that are often neglected in conventional teaching play a central role in this application: *dysbiosis* and *permeability*.

DYSBIOSIS AND THE NORMAL GI FLORA

Symbiosis is Greek for "living together." We live together with about 100

trillion microbes, most of them residing in the colonic lumen, as many colony forming units (CFUs) as there are cells in the adult human body. Over 500 species of bacteria live in the healthy human alimentary canal; in the average adult they weigh about one kilogram. Predominant organisms at different sites are described in Table 1.[to follow]. In health, the relationship is either beneficial (*eu-symbiosis*, or mutualism) or neutral in its effects (commensalism). The normal colonic microflora ferment soluble fiber to yield short-chain fatty acids that supply 5-10% of human energy requirements (REF: McNeil, 1984). Endogenous flora synthesize at least seven essential nutrients, supplementing dietary intake: folic acid, biotin, pantothenic acid, riboflavin, pyridoxine, cobalamin and vitamin K (Mackowiak, 1982). They participate in the metabolism of drugs, hormones and carcinogens, including digoxin (Lindenbaum *et al.*, 1981), sulphasalazine, and estrogens (Gorbach, 1982). By demethylating methylmercury, gut flora protect mice from mercury toxicity (Rowland *et al.*, 1984). They prevent potential pathogens from establishing infection by numerous mechanisms, which include: production of short-chain fatty acids and bacteriocin (an endogenous antibiotic), induction of a low oxidation-reduction potential, competition for nutrients, deconjugation of bile acids (which renders them bacteriostatic), blockade of adherence receptors and degradation of bacterial toxins (Savage, 1980).

Germ-free animals have mild to moderate defects in immune function

when compared to control animals. These include lower levels of natural antibodies, hyporesponsive macrophages and neutrophiles, defective production of colony-stimulating factors, leukopenia, lymphoid hypoplasia, subnormal interferon levels and weak delayed hypersensitivity (DHS) responses. They are more susceptible to infection with intracellular parasites such as *Listeria, Mycobacterium* and *Nocardia*, but are not more susceptible to viral infection (Mackowiak, 1982). The immunologic effects of normal gut flora are in part due to antigenic stimulation and in part to the bacterial origin of specific immune activators, such as endotoxin lipopolysaccharicle (LPS) and muramyl dipeptides (Worrison and Ryan, 1979; Mackowiak, 1982; Stokes, 1984). The gut flora of healthy individuals is quite stable, largely because of interbacterial inhibition (Sprunt and Redman, 1968). Alteration in the level of normal flora by antibiotics has long been known to allow secondary infection by pathogenic bacteria and yeasts (Keefer, 1951; Seelig, 1966).

Dysbiosis, or *dys-symbiosis*, occurs when the relationship between gut flora and the human host becomes injurious to the host (parasitism). In dysbiosis, organisms of relatively low intrinsic virulence--organisms that generally exist in a state of mutualism or commensalism with their hosts--promote illness. At least five mechanisms of disease associated with dysbiosis have been described:

(1) Microbial enzymes may modify selected intra-luminal substrates, producing noxious substances. Microbial alteration of bile acids is thought to play a pathogenic role in cholelithiasis and colon cancer. The primary bile acids, cholate and chenodeoxycholate, are synthesized in the liver. Deoxycholate (DCA), a secondary bile acid, is produced from cholate by colonic bacteria. In the colon, DCA is a tumor promoter and fecal DCA concentrations are directly proportional to the rate of colon cancer in populations studied. DCA that is absorbed from the colon enters the portal circulation and reaches the liver, from which it is excreted in bile. DCA in bile increases its saturation with cholesterol. In patients with cholelithiasis, the degree of cile cholesterol supersaturation (the main reason for stone formation) correlates directly with DCA concentration.

2) Microbial antigens may cross-react with mammalian antigens, stimulating auto-immunity. Ankylosing spondylitis (AS), for example, occurs almost exclusively in HLA-B27 positive individuals. Immunologic cross-reactivity has been shown for HLA-B27 antigen expressed on the host cell membrane and antigens present in *K. pneumoniae, S. flexneri* and *Y. enterocolitica,* suggesting molecular mimicry in the pathogenesis of this disease (Yu, 1988). Workers in Australia have demonstrated bacteria with cross-reactive antigenic determinants in bowel flora of B27-positive AS patients; these bacteria are

almost never found in B27-positive controls without AS (McGuignan *et al.*, 1986).

(3) Components of the microbial cell wall may stimulate non-specific, dysfunctional immune responses that produce local or systemic inflammation. Intestinal lymphocytes from patients with Crohn's disease, but not controls, show a mitogenic response to Enterobacteria and Candida albicans, both normally present in the small intestine. [REF] Bacterial endotoxemia has been described in patients with psoriasis (Rosenberg and Belew, 1982a) and cystic acne (Juhlin and Michaelson, 1984). Activation of the alternative complement pathway (APC) by gut-derived endotoxin may play a role in the pathogenesis of these disorders.

(4) Bacterial enzymes may destroy components of the host's biological response system. In small bowel bacterial overgrowth (SBBO), for example, destruction of pancreatic and brush-border enzymes by bacterial proteases may cause maldigestion and malabsorption [REF]. Pseudomonas species colonizing the gut can inactivate gamma interferon [REF].

(5) The loss of beneficial microbes may cause disease by removal of protective effects of the normal gut flora. Antibiotic-induced diarrhea not only involves the overgrowth of toxin-producing bacterial species, like Clostridium difficile, but the loss of the neutralizing effect of the normal colonic flora on

Clostridial toxins.

In addition to its role in antibiotic-induced diarrhea and SBBO, intestinal dysbiosis may contribute to the pathogenesis of ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), gastric cancer and colon cancer [REFS]. Integrated therapies for patients with these disorders should include treatments that restore normal alimentary tract symbiosis.

The principal factors that regulate the composition and distribution of the GI flora are diet, motility, the nature of GI secretions, immune function and the ingestion of antibiotic or probiotic substances.

DIET: Carbohydrates, including fiber, serve as substrates for bacterial and fungal growth and fermentation. Products of bacterial fermentation and their effects are shown in Table 2. Simple carbohydrates tend to increase both growth and fermentation by microbes in the mouth, stomach and upper small intestine. Complex carbohydrates increase these activities in the ileum, and soluble fiber (found in fruit, legumes and some whole grains) normally exerts its effects in the cecum and colon. Feeding soluble fiber to rodents increases bacterial biomass and enzyme concentration in the cecum. Insoluble fiber, found in many vegetables and in wheat bran, by contrast, decreases cecal biomass and enzyme concentrations, mostly by dilution, perhaps also by

inhibition. In patients with gallstones whose bile is supersaturated with cholesterol, wheat bran added to the diet lowers cholesterol saturation and DCA concentration in bile, probably by interfering with colonic bacterial enzyme activity.

Products of gut micobial fermentation, especially short chain fatty acids (SCFAs) like butyrate, nourish colonic epithelial cells and lower stool pH. A slightly acidic stool is associated with protection against colon cancer. In the small bowel, fermentation proucts may as irritants. Lactic acid, for example, is a major factor in producing the symptoms of lactose intolerance.

Protein induces intestinal bacteria to synthesize enzymes involved in peptide, amino acid and amine catabolism, including peptidases, ureases, and tryptophanases. The putrefactive odor of stool is largely due to this enzyme activity, as is the production of ammonia. Tryptophanase not only contributes to putrefaction, but also yields carcinogenic indoles and skatoles, which may contribute to the epidemiologic association between high protein diets and colon cancer. The diamino acid, glutamine, in contrast, nourishes the small intestinal epithelium and the lymphocytes of the gut associated lymphoid tissue (GALT).

The effects of dietary fat on GI microflora are complex. Free fatty acids

are bacteriostatic; the presence of these in milk confers protection against intestinal infection with bacteria and protozoa. Increased bile flow, induced by fat ingestion, is also bacteriostatic. The protozoan, *Giardia lamblia*, however, thrives in the presence of bile. High rates of biliary secretion produce an increase in fecal bile acid concentration and at the same time increase fecal pH. Both these features are associated with an increase in the rate of colon cancer in humans and animals.

Among micronutrients, iron appears to have the greatest impact on gut flora, because all microbes, except *Lactobacilli* and *Bifidobacteria*, depend upon iron for growth and metabolism. Feeding iron to patients with bowel disease, especially when concentrated in pill form, can induce the overgrowth of pathogenic species. Lactoferrins are iron binding proteins found in colostrum and in leukocytes. Lactoferrins aid with intestinal iron absorption and inhibit bacterial, fungal and protozoan growth. Lactofeerrins in breast milk help to prevent diarrheal disease in infancy.

MOTILITY. Peristalsis moves the gut contents distally and helps to maintain the bacterial concentration gradient from stomach to anus. Altered motility may allow SBBO and may increase mucosal exposure to irritants. Motility in turn is influenced by diet, neuroendocrine factors, and consumption of drugs and herbs. High fiber diets tend to stimulate motility and decrease

intestinal transit time. Simple sugars have a bi-fold effect. They shorten small bowel transit but inhibit large bowel transit. This effect appears to be vagally-mediated and associated with the sweetness of the sugar. Herbs and spices have numerous pharmacologic effects. Ginger and capsicum, in particular, have been shown to increase motility.

Emotional distress may either stimulate or inhibit motility, contributing to diarrhea or constipation in the 30% of the US population with Irritable Bowel Syndrome (IBS). Changes in GI flora resulting from stress effects on motility are subtle, but may be significant. Russian Cosmonauts experienced a decrease in stool concentrations of *Lactobacilli* and *Bifidobacteria* before space missions; anger and hostility have been accompanied by an increase in the levels of tryptophanase-producing bacteria in stool. The activity of these might increase colonic putrefactive activity and the production of carcinogens from high protein foods. GI flora, in turn, may have considerable influence on gut motility; this will be discussed in the section on IBS.

SECRETIONS. Gastric HCl has the most significant influence of all GI secretions. HCl is not only the first line of biological defense against the acquisition of enteric infections, it helps to maintain relatively low concentrations of bacteria and fungi in the stomach, despite the high nutrient density that occurs post-prandially. Hypochlorhydria, whether resulting from

pathology or drugs, increases susceptibility to infection with enteric pathogens and also permits increased gastric colonization with bacteria and yeasts. Bacterial enzymes may convert dietary nitrates or nitrites to carcinogenic nitrosamines (one link between hypochlorhydria and gastric cancer). The gastric microbial overgrowth resulting from strong acid suppression or the hypochlorhydria of aging causes vitamin B12 malabsorption and gastric synthesis of ethanol following carbohydrate consumption.

The other secretory products with significant influence on GI flora are secretory IgA (SIgA) and mucins. Both impair bacterial attachment to mucosal epithelium, interfering with mechanisms of pathogenicity.

IMMUNITY. The immune regulatory network in the gut is composed of antigen-presenting cells (APCS), effector cells and the cytokines they produce, and antibodies, primarily SIgA. The most intense activity occurs in the jejunum and ileum. Intestinal columnar epithelium, which consists of normal enterocytes, functions as an APC, ingesting soluble antigen by endocytosis, transporting it to the serosal surface of the epithelium and presenting antigens to intra-epithelial lymphocytes (IEL). Most IEL have a CD-8 (cytotoxic/suppressor) phenotype and generate an immune response that is largely immune suppressive. Normal immune tolerance for dietary antigens appears to depend upon this enterocyte-mediated immune activity. IEL

activity, however, is not simply immune suppressive. The cytokines they produce stimulate macrphages to produce inflammatory ctyokines, which contribute to the pathogenesis of inflammatory bowel disease (IBD) [see discussion of Crohn's disease, below].

The small bowel epithelium is punctuated by squat, non-columnar epithelial cells called M-cells, that harbor a large indentation on the serosal side, in which macrophages reside. M-cells ingest and transport particulate or insoluble antigens and deliver them to their associated macrophages, which then travel to Peyer's patches and present the antigen to Peyer's patch lymphocytes (PPL). The predominant phenotype of PPL is CD-4 (helper); their activation leads to an increase in IgA specific to the antigen presented. Impaired small bowel immunity, whether acquired or congenital, permits colonization by pathogens and may also permit SBBO. Pathologically heightened immunity (sensitization) to components of the normal flora, occurs during the course of IBD.

ANTIBIOTICS, PROBIOTICS. Traditional cuisines from many cultures contain foods with natural antibiotic or probiotic activity. Many spices, including garlic, ginger, cinnamon, oregano, thyme and rosemary, have intrinsic antimicrobial components, most of which are heat-labile. They appear to have initially been added to food as preservatives, Human ingestion of these,

uncooked, may protect against enteric infection or microbial overgrowth in the upper bowel. Fermented foods, like sauerkraut or yogurt, contain lactic acid bacteria like *L. plantarum* or *L. bulgaricus*, respectively, that can successfully colonize the small and large intestine. Daily consumption of yogurt was shown to decrease the frequency of monilial vaginitis in a controlled study, but only if the yogurt contained viable organisms. Numerous probiotic supplements are commercially available in the U.S. The most intensively studied are *Lactobacillus GG* (a strain of *L.casei var. rhamnosus* originally cultured from a volunteer in Finland), *L. plantarum* (which naturally grows on plant surfaces and is found in cultured plant foods) and *Saccaromyces boulardii* (a yeast similar to baker's yeast that was originally cultured from lichee nuts in French Indochina during the 1920's). *Lactobacillus GG* and *S. boulardii* have been shown to protect against antibiotic-induced and traveller's diarrhea. *Lactobacillus GG* was successfully used to treat D-lactic acidosis. Administration of *L. plantarum* to patients undergoing major abdominal surgery decreased the incidence and severity of post-operative infection. Unlike the Lactobacilli, *S. boulardii* is not normal flora and only resides in the gut as long as it is ingested. It stimulates production of SIgA and can neutralize *Clostridium difficile* toxin A. *S. boulardii* has been shown to help prevent recurrent pseudomembranous colitis caused by *C. difficile*. New preparations of probitoics are being tested for therapeutic benefits in IBD and IBS (see below).

INTESTINAL PERMEABILITY AND GUT BARRIER FUNCTION

The intestinal epithelium is the site of vectorial transport of solvents, solute and macromolecules between the intestinal lumen and the circulation. The net effect is regulated by the tightness or leakiness of the barrier. Transport and barrier functions are physiologically regulated and may be significantly altered under conditions of disease. Two routes for transport are possible: transcellular or intercellular (paracellular). The regulation of each is spearate and specific. Transcellular transport may occur by passive or facilitated diffusion (e.g., water and magnesium), by active transport (e.g. glucose and most vitamins and minerals), or by endocytosis (particulate matter and macromolecules). (See Tables 4-6 and Figures 1-2). The transport of macromolecules, including intact dietary protein, across the small intestinal epithelium is a normal physiologic process that occurs after each meal. Intact enzymes like urokinase can be absorbed. Dietary macromolecules normally enter the systemic circulation post-prandially, in immunocompetent healthy volunteers. In fact, administration of a suspension containing *Candida albicans* to health male volunteers caused candiduria. and transient fever. The presumed mechanism was endocytosis of yeasts, their transport into the systemic circulation and their excretion intact through the renal glomeruli. The *Candida* ingestion

experiment does not recreate a physiologic state but does indicate that a healthy gut transports intact microbes into the systemic circulation. Excessive transport, with septicemia, usually results from impairment of mucosal immunity, induced by hypoxia or starvation. Cardiopulmonary bypass and hypovolemic shock induce splanchnic hypoxia and have been associated with bacteremia by this mechanism. [51, 52]. Total parenteral nutrition (TPN) starves the intestinal mucosa and may be complicated by septicemia, also by this mechanism. The bacteria causing sepsis in patients receiving TPN enter the circulation from the GI tract, not usually from the intravenous catheter.

The other conditions in which normal gut barrier function involving trans-cellular permeability is excessively increased are genetic. In hemochromatosis and in idiopathic hypercalciuria, excessive absorption of iron or calcium, respectively, results from enhancement of enzyme-driven active transport resulting from gene mutations.

The commonest increases in intestinal permeability follow the para-cellular route. Paracellular transport is always passive and is normally limited by cellular adhesion molecules (CAMs) that make up the tight junctions, adherens junctions and desmosomes that knit adjacent cells together (see Figure 3). Contraction of the epithelial cell cytoskeleton opens adherens junctions, transiently increasing paracellular permeability. This may be

stimulated by high intraluminal concentrations of glucose or by excessive cholinergic stimulation in the small intestine. Experiments with rodents that are genetically bred to produce a cholinergic response to stress (characterized by low frequency of avoidance behaviors), indicate that immersion stress and cold stress in these animals produces a measurable increase in para-cellular permeability that can be blocked by anti-cholinergic agents and that does not occur in animals bred differently. Similar effects appear to occur in humans, but definitive studies have not been performed. The healthy first degree relatives of patients with Crohn's disease represent a human population with a statistically significant increase in intestinal permeability, which is probably constitutional. Increased permeability may play an etiologic role in Crohn's disease, allowing abnormal entry of microbial antigens into the gut wall. Cholinergic neural pathways may play a contributory role.

Another physiologic influence on para-cellular permeability is an endogenous peptide called Zot (Zona occludens toxin), which transiently loosens tight junctions. Infectious agents like cholera produce Zot analogues that irreversibly open tight junctions, causing a leaky gut. The leaky gut of cholera is a separate phenomenon from the diarrhea caused by cholera, which is due to toxic stimulation of mucosal adenylate cyclase. Prostaglandin E, on the other hand, helps to maintain normal para-cellular permeability. Exposure to cyclooxygenase (COX) inhibitors, like aspirin and non-steroidal anti-

inflammatory drugs (NSAIDs) causes a transient increase in para-cellular permeability that may be blocked by administration of the Prostaglandin E analogue, misoprosterol. [20, 49, 50]. Exposure to high doses of NSAIDs for about two weeks renders this increase in permeability resistant to misoprosterol but reversible with the antibiotic, metronidazole. A sustained increase in small bowel permeability, as induced during the treatment of rheumatoid arthritis (RA) with NSAIDs, results in sensitization to gut microbial antigens and microscopic enteritis. Reducing mucosal antigen exposure and the gut inflammatory response with metronidazole is needed for reversal of hyper-permeability in these circumstances. This mechanism may explain the benefits of antibiotic therapy in the treatment of patients with IBD and RA. Antibiotics do not only alleviate symptoms in these patients but behave like disease-modifying agents.

Other factors that may produce a pathological increase in para-cellular permeability include infectious agents (viral, bacterial and protozoan) [43-46], ethanol [47, 48], exposure to cytotoxic drugs used in cancer chemotherapy, and ingestion of foods that provoke an allergic or inflammatory response[[54-56][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.

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 excessive para-ceullular permeability. 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].

Increased intestinal permeability may contribute to illness by permitting excessive exposure to luminal antigens derived from microbes or food.[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. 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 makes it possible for clinicians to look for the presence of altered intestinal permeability in their patients and to objectively assess the efficacy of treatments.

Treatment of hyperpermeability states has two phases:

(1) Remove the cause. This includes the treatment of an intestinal infection, avoidance of enterotoxic drugs (primarily NSAIDs and ethanol), and elimination of food allergens from the diet. Diagnostic methods for food allergy are controversial and a discussion of the merits and pitfalls of each method is beyond the scope of this chapter. Andre's method (described above) uses an increase in permeability to diagnose food allergy and is therefore specific to the role of food in creating hyperpermeability.

(2) Nourish the gut. 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]. To maintain its integrity, this epithelium requires protein, calories and essential fatty acids. Glutamine, among all the amino acids, appears to have a special role in restoring normal small bowel permeability and immune function

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]. Glutamine does not appear to play a trophic role in the colon, however. In the large bowel, this role is played by butyric acid, which is generated by the fermentation of soluble fiber. Supplementing the diet with glutamine at intakes of 5 to 30 gm/day has been shown to decrease hyperpermeability in severely ill individuals. Feeding butyrate by mouth is unlike to have any effect on the large bowel, because it is readily absorbed in the jejunum. Butyrate enemas, however, have been used to nourish colonic segments that are surgically isolated from the fecal stream.

Prostaglandins play a key role in the maintenance of normal para-cellular permeability, although the specific PG balance for optimal permeability is unknown. In experimental animals, fish oil feeding ameliorates the intestinal mucosal injury produced by methotrexate and, additionally, blunts the systemic circulatory response to endotoxin[146]. In tissue culture, both n-3 and n-6 EFA's stimulate wound healing of intestinal epithelial cells. Consumption of large amounts of vegetable oils, on the other hand, tends to increase the free radical content of bile and to exacerbate the effects of endotoxin[147].

Other trophic factors that may be helpful in improving enteric epithelial

hyperpermeability include:

Lactobacilli. The ability of *Lactobacillus acidophilus* 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. *Lactobacillus GG* limits diarrhea caused by rotavirus infection in children and has been shown to improve the hyperpermeability associated with rotavirus infection.[136-139]

Epidermal Growth Factor (EGF), 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].

Gamma oryzanol, a complex mixture of ferulic acid esters of phytosterosl 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].

Although epithelial integrity is the main factor maintaining normal permeability, it is not the only factor. Secretory IgA plays a supportive role. Levels may be boosted by adminisration of the non-prathogenic yeast, ***Saccharomyces boulardii***. 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]. Passive elevation of gut immunoglobulin levels can be produced by feeding colostrum, egg yolk antibodies from immunized hens, and whey protein concentrates that are rich in IgA and IgG. These have been shown to be effective in preventing infantile necrotizing enterocolitis[135], a disorder thought to be caused by the hyperpermeability of the infantile gut.

Severely ill patients are often treated with "bowel rest", clear liquid diets or TPN. Alternative practitioners sometimes use juice fasts for "cleansing". Whatever the therapeutic value of these methods, they carry with them the risk of inducing hyperpermeability of the small intestine. Patients and experimental animals that are fasted or fed only liquids 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. The only demonstrated exception to this has been patients with rheumatoid

arthritis. Fasting decreases intestinal permeability in patients with RA, possibly because fasting in these patients is accompanied by discontinuation of NSAIDs, avoidance of food allergens and decreased activation of enteric lymphocytes.

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 fibre sources, such as fruit pectin or guar gum, has a biphasic effect. At low levels it reverses the hyperpermeability of low residue diets, probably by a mechanical bulking effect which stimulates synthesis of mucosal growth factors. At high levels of supplementation, it produces hyperpermeability, probably by inducing synthesis of bacterial enzymes that degrade intestinal mucins[148-151]. For maximum benefit with regard to intestinal permeability, dietary fiber supplementation should therefore contain a predominance of insoluble fiber.

INFLAMMATORY BOWEL DISEASE

Both dysbiosis and hyperpermeability play central roles in the immunopathology of the inflammatory bowel diseases, Crohn's disease in particular. Small intestinal permeability is increased in healthy first degree relatives of patients with Crohn's disease, suggesting that a predisposition to

hyperpermeability may be a risk factor for its development. Aspirin causes an exaggerated increase in intestinal permeability in these individuals, compared to controls. The rate of relapse among Crohn's disease patients who have entered remission is directly related to the meaurement of small intestinal permeability using the lactulose/ mannitol probe described above. (see Figure...) Hyperpermeability may be the result of microscopic inflammation, but it also increases exposure of the intestinal immune system to luminal antigens. IEL of patients with Crohn's disease are abnormally sensitive to antigens derived from indigenous bowel bacteria and yeast. SBBO may aggravate inflammation in patients with Crohn's disease, and has been identified in 30% of hospitalized patients in one study. The immune response underlying the pathology of Crohn's disease, as in other granulomatous diseases, is driven by TH-1 lymphocytes and their cytokines: IL-2 and g-IFN. These TH-1 products promote a self-sustaining cycle of activation with macrophages, that includes IL-12, which further increases TH-1 activity, and IL-1, IL-6 and TNF-a, which promote a broader inflammatory response. Inflammation increases oxidative stress in the bowel mucosa with increased levels of reactive oxygen intermediates (ROIs) and DNA oxidation products and decreased levels of the anti-oxidant enzyme, copper-zinc superoxide dismutase (Cu-Zn SOD). A growing body of research indicates that the normal intestinal microflora is essential for provoking inflammation in Crohn’s disease and one study has shown adherent

strains of E. coli bound to the ileal mucosa. Using the language of Patient-Centered Diagnosis, the predominant theory of Crohn's disease holds that the key mediators (IL-12, g-IFN, TNF-a and ROIs) are activated by exposure to triggers derived from the normal gut flora and that the usual antecedents are genetic predisposition and/or the occurrence of a precipitating event that damages intestinal mucosal integrity, such as acute enteritis. High sucrose intake has been shown to predispose to Crohn's disease in one study. The control of Crohn's disease is enhanced by dietary avoidance of sucrose and other refined carbohydrates, suggesting that the sugar/disease relationship may be significant, not coincidental.

The hygiene hypothesis has been invoked to explain the increasing prevalence of Crohn's disease during the past century. The most intriguing incarnation of this theory attributes the increase to lack of exposure to helminths. Helminth infestation has been virtually universal among humans until the late Nineteenth Century; its prevalence has declined substantially at the same time and with the same demographics as the increased incidence of IBD. Helminth infestation provokes an immune response that is TH-2 mediated, with the main cytokines being IL-4, IL-5 and IL-11. TH-2 activity naturally down-regulates TH-1 activity. Furthermore, IL-11 is immune suppressive and anti-inflammatory; its synthesis may explain the low levels of clinical allergy in children with heavy parasitic infestation. Researchers at the University of Iowa

have induced remission in patients with refractory Crohn's disease by administering the eggs of a pork roundworm that ordinarily does not colonize humans.

Various studies have identified other triggers for patients with Crohn's disease. Psychological stress may activate quiescent disease. A potential mechanism is the stress-induced, vagally-mediated increase in small bowel permeability mentioned before. Food presents numerous triggers. Patients with Crohn's disease often show immunologic hypersensitivity to a component of *Saccharomyces cerevisiae* (baker's and brewer's yeast). Feeding a suspension of *S.cerevisiae* may provoke symptoms in asymptomatic patients. The East Anglican Multicentre Controlled Trial, conducted under the auspices of Cambridge University, evaluated the value of diet in the treatment of patient's with active Crohn's disease. The first phase consisted of two weeks of a defined elemental diet, during which 84% of the patients achieved clinical remission accompanied by a significant decrease in ESR and C-reactive protein and an increase in serum albumen. Patients were then randomized to receive treatment with prednisolone or treatment with a specific food exclusion diet. To determine which foods each patient needed to avoid, a structured series of dietary challenges was conducted. Foods that provoked symptoms are listed in Table..... . At six months, 70% of patients treated with diet were still in remission, compared with 34% of patients being treated with prednisolone.

After two years, 38% of patients treated with specific food exclusion were still in remission, compared to 21% of steroid-treated patients. Patients who did not comply with their diets were regarded as treatment failures, even if they remained in complete remission. In previous uncontrolled studies, some of the same authors had used a diet consisting of one or two meats (usually lamb or chicken), one starch (usually rice or potatoes), one fruit and one vegetable instead of the elemental diet, in order to induce remission. Compliance with the specific food elimination diet was associated with a rate of relapse of under 10% per year.

Help with maintenance of remission has also been demonstrated in a randomized blinded trial, using an enteric-coated fish oil extract that supplied 1800 mg of EPA and 900 mg of DHA per day. Based upon clinical symptoms and laboratory indices of inflammation, 59% of those receiving fish oil remained in remission at one year, compared to 26% of those receiving placebo. The main side effect of fish oil was reversible diarrhea, which occurred in 10%. The effect of fish oils in Crohn's disease patients may involve more than pharmacologic suppression of inflammation. The leukocytes of patients with Crohn's disease have abnormalities in the uptake and metabolism of EFAs, which correlates with low levels of zinc. Zinc deficiency is common among patients with Crohn's disease, as is selenium deficiency, another mineral important for normal EFA

metabolism.

The author has used the clinical science just reviewed to develop a practical, individualized approach for treatment of patients with Crohn's disease, which was associated with induction of complete clinical remission with discontinuation of all medication in 30% and varying degrees of improvement in symptom scores (range 40-90%, mean 65% improvement) and laboratory parameters in the remainder. This approach is divided into three phases:

Phase One: Initial Exclusion Diet. Although the few foods elimination diet of the Cambridge researchers may be utilized, a broader and easier initial nutritional intervention is a modified paleolithic diet, free of cereal grains, milk and soy products and potatoes and very low in disaccharides such as sucrose, described in a book, *Breaking the Vicious Cycle* and referred to as the specific carbohydrate diet (SCD; for more information go to www.scd.org). In the author's experience, this diet alone has improved symptoms in 55% of patients, being most effective in those with ileitis. [Of note, the diet permits the use of certain cultured dairy products].

Phase Two: Modified Exclusion Diet. In those patients responding with a 50% or greater reduction in symptoms over 30 days using SCD, a slight expansion of the initial diet is permitted, within the guidelines detailed in *Breaking the*

Vicious Cycle. In those patients who do not show a 50% reduction in symptoms, further dietary changes are made, on an individual basis. The most common changes are: (1) elimination of all milk-derived products, (2) reduction in dietary yeast and monosaccharides by eliminating honey, fruit, vinegar and any fermented foods, (3) substitution of rice and potatoes for nut flours (the major source of complex carbohydrate in the SCD).

Phase Three: Nutritional Supplementation. Delayed-release fish oil capsules supplying 2700 mg of n-3 fatty acids a day and a multivitamin and mineral supplying folic acid 800 mcg, zinc 25 mg, selenium 200 mcg and vitamin E 400 mg. For those with ileitis, glutamine 3000 to 6000 mg per day is also used, usually in a formulation that includes either gamma-oryzanol 300 mg/day or EGF derived from a glandular extract.

Probiotics and prebiotics must be used with caution in patients with Crohn's disease, because their effects are highly unpredictable. Although occasional small studies have shown benefits from administration of non-pathogenic bacteria, induction of remission by elemental diet, in fact, has been associated with a reduction in fecal Lactobacillus concentrations, and all bacteria, even friendly flora, may activate TH-1 responses.

Various antibiotic regimens are used in conventional therapy for Crohn's disease, either to treat acute exacerbations or induce remission of chronic

disease. Their use is compatible with the strategy outlined above, with one exception. Some patients experience an exacerbation of symptoms when taking antibiotics, perhaps as a result of the yeast sensitivity which is common among patients with Crohn's disease. These patients may require anti-fungal therapy instead of or in addition to antibiotics.

Case report. A twenty-one year old woman experienced the sudden onset of severe right lower quadrant abdominal pain and diarrhea following a trip to France. Radiologic evaluation revealed an ileocolic fistula and a diagnosis of Crohn's disease was made. Stool examination showed showed cysts of *Entamoeba histolytica*. Her gastroenterologist began treatment with ciprofloxacin and her abdominal pain steadily increased, so she sought an alternative therapy. During her initial interview, she revealed that she had suffered a respiratory infection while travelling and had received an antibiotic from a French physician. The onset of symptoms following one antibiotic and the aggravation of symptoms while taking another, suggested that the antibiotics were the triggers for her symptoms, perhaps by encouraging the overgrowth of antibiotic-resistant organisms. *Clostridium difficile* was not found in stool, but there was a high level of yeast seen in stool. Ciprofloxacin therapy was immediately discontinued and fluconazole 200 mg/day was started. A low sugar, low yeast diet was recommended. Within four days she was pain free. She continued to follow a yeast elimination diet for a peeriod of

two years, observing a transient return of abdominal pain upon consumption of bread or beer. She continued to use diflucan intermittently for several months for control of symptoms, with no other medication. As of 2002 she has been in complete clinical and laboratory remission for 3 years. She has not been compliant with the use of nutritional supplements.

Ulcerative Colitis

Compared to Crohn's disease, the immunopathology of ulcerative colitis is not as clearly understood and the role of intestinal permeability is less certain, because colonic permeability is extremely difficult to measure. Microbial triggers appear to be equally as important, however, with effector cells throught to be atypical TH-2 lymphocytes, which produce transforming growth factor beta (TGF-B) and IL-5. Researchers at the University of Leeds have identified adherent *E.coli* in the colonic crypts obtained at surgery from patients with ulcerative colitis but not from controls. *E. coli* are not normally adherent to colonic epithelium and adherance is considered to be a sign of potential pathogenicity. Treatment of patients with antibiotics, followed by the administration of non-pathogenic, standardized *E. coli* strains, may induce and help to maintain remission. Other probiotic therapies have not been tested in controlled trials, although pouchitis (post-colectomy inflammation of the ileal pouch) has been shown to respond to very high doses (450 billion CFUs/day or

more) of a mixture of lactic acid and bifidobacteria. This preparation is now being tested as an aid to maintenance of remission in patients with ulcerative colitis. Several natural products have shown promise as aids to inducing remission in ulcerative colitis. Fish oils, supplying about 2400 mg of EPA/day, decrease symptoms and lower the levels of leukotriene B4 (LTB4) in stool, with improvement demonstrated after 12 weeks of therapy. The Ayurvedic herb, Boswellia, 450 mg three times a day, was as effective as 5-ASA derivatives in reducing symptoms of active ulcerative colitis. An extract of Aloe vera, concentrated to a mucopolysaccharide (MPS) concentration of 30% of solid weight, was demonstrated to reduce symptoms and indices of inflammation in controlled studies. Butyric acid nourishes the colonic epithelium, encouraging differentiation of cells. Butyrate enemas are beneficial for healing distal ulcerative colitis and post-surgical diversion colitis.

Compared to patients with Crohn's disease, patients with ulcerative colitis are less likely to have specific food intolerance and more likely to harbor intestinal protozoa. Controlled studies of diet for ulcerative colitis have not been performed, but observers who have published uncontrolled studies have estimated that 15 to 20% of patients with ulcerative colitis have food allergy or specific food intolerance, with cow's milk protein being the leading offender. Colitis caused by *Entameba histolytica,* and occasionally other protozoa, may be confused with ulcerative colitis. Protozoan infection is more likely in

patients with recent onset, onset after the age of 30, or poor response to conventional anti-inflammatory medication. The boundary between infectious and "idiopathic" colitis is very fuzzy, however. Acute gastrointestinal infection often precedes the development of IBD and patients with ulcerative colitis are at greater risk of intercurrent colonic infection than controls, possibly because the inflammation already present increases susceptibility. Spontaneous overgrowth of *C. difficile*, without antecedent antibiotic exposure, is not unusual in patients with ulcerative colitis and may be a cause for a sudden onset of rectal bleeding. Stool testing for protozoan infestation is more likely to be accurate when performed by a laboratory that specializes in tropical medicine or parasitology than when performed by a general laboratory. The presence of protozoa in stool of a patient with longstanding, stable mild to moderate ulcerative colitis is most likely to be significant if the patient has experienced a recent exacerbation.

In the author's previously unpublished case series of patients seeking integrative treatment of ulcerative colitis (see Table....), almost 40% of patients were infested with an organism, the majority harboring *E. histolytica*. In 18%, eradication of the organism produced a long-term clinical and pathologic remission, indicating that these patients may indeed have been suffering from an infectious colitis. In 22%, eradication of the organism ended the acute exacerbation and returned the patient to his or her previous state of

stable ulcerative colitis. The following questions are most useful in gauging the likelihood that a patient may respond to specific antimicrobial therapy:

(1) How long ago was a diagnosis of ulcerative colitis made?

(2) How long have you bee experiencing gastrointestinal symptoms?

(3) Was the onset of your symptoms preceded by any other following? Foreign travel, acute gastroenteritis, the use of antibiotics, intimate contact with a person suffering from gastrointestinal symptoms?

(5) Since the onset of your gastrointestinal symptoms, have you been treated with antibiotics for any reason? Which ones? Did your gastrointestinal symptoms change during or after antibiotic use; if so, how?

More recent onset of symptoms, or recent exacerbation, onset associated with high-risk situations for acquiring enteric or colonic infection and improvement of symptoms when using antibiotics all increase the likelihood of a specific microbial trigger. Exacerbation of symptoms associated with antibiotic use suggests the presence of *C. difficile* toxicity or a fungal trigger for inflammation (as described in the case report above in a patient with Crohn's disease).

After the identification and treatment of specific microbial triggers and control of possible dietary triggers, administration of probiotics, fish oils, aloe MPS and Boswellia may be helpful for patients with chronic disease, in addition

to or sometimes in place of conventional therapies. Active involvement of the patient is critical. A team at the University of Manchester designed a “patient-centered alternative” to conventional management of ulcerative colitis. During a 15 to 30 minute consultation, physicians designed personalized self-management strategies for each patient. The goal was to ensure that patients could recognize relapse and that patients and physicians could agree on a mutually acceptable treatment protocol for the patient to initiate at onset of a relapse. Physicians specifically asked patients about the symptoms they had experienced during past relapses and reviewed past and current treatments that had been used to control symptoms, emphasizing the specific effectiveness of each and its acceptability to the patient. Compared to a control group that received customary care, the intervention group required one-third as many doctor visits and one third as many hospitalizations. The difference in outcome was not related to specific treatments employed but rather to the empowerment of patients to be actively involved in managing their own care.

“FUNCTIONAL” DIGESTIVE DISORDERS

Conditions such as Irritable Bowel Syndrome (IBS), non-ulcer dyspepsia and biliary dyskinesis are often grouped together as functional bowel disorders with a high mutual co-morbidity and frequent association with other painful

conditions such as fibromyalgia, migraine headache and vulvar pain syndromes. Various explanations have been put forward to explain the association. In France and Germany, what knits these conditions together is often thought of as “latent tetany” or “spasmophilia”, a condition that involves calcium or magnesium deficiency and the effects of stress. In the U.S. and U.K., the concept evoked is one of visceral hypersensitivity or hypervigilance. Two recent reviews in the *Lancet* emphasize the inadequacy of all concepts about the nature of these disorders and of the “functional” label applied to them. Many patients with IBS have evidence of inflammation on colonoscopy, many dyspeptic patients show mild to moderate gastritis on endoscopy and sphincter of Oddi dysfunction (which is part of the construct of biliary dyskinesis) may be associated with severe cholecystitis and/or pancreatitis. One problem with basing a diagnostic system upon observed pathology is that histology may lack sensitivity in assessing the role of inflammation as an illness mediator. In all hospitals, for example, some percentage of appendices removed because of suspected appendicitis will be histologically normal. A British research team found that a third of these contained elevated concentrations of inflammatory cytokines, indicating that inflammation was occurring without its characteristic microscopic changes.

The fuzzy border between “functional” and “organic” bowel disease reveals itself in the similar responses to nutritional therapies. The Cambridge

group employs the same dietary strategies to treat patients with IBS as with Crohn's disease (described above). In their hands, specific food intolerance is present in almost 50% of patients with diarrhea predominant IBS and the majority of these patients can achieve complete control of IBS symptoms by adhering to a diet that eliminates their triggers. The commonest food triggers for patients with IBS are similar to the food triggers for patients with Crohn's disease: wheat, corn, cow's milk and yeast are high on the list, with most patients having more than one food trigger. They have found that patients with diarrhea-predominant IBS have increased concentrations of PGE2 in stool (a presumed mediator of diarrhea and intestinal cramping in these patients). They believe that food intolerance in IBS results from altered gut microbial ecology (dysbiosis). Patients with food-intolerant IBS have marked instability of the fecal flora with an increased aerobe:anaerobe ratio and excessive colonic fermentation. Employing a whole body chamber for measuring hydrogen and methane production, they observed that patients with IBS produced more hydrogen and methane than controls. The exclusion diet they employed reduced hydrogen and methane production of IBS patients to normal but had no effect on the hydrogen and methane production of the control group. The mechanism for the relationship between specific food intolerance, excessive PGE2 production and abnormal colonic fermentation has not been clearly explained, but treatment of the condition with a permanent exclusion diet has

remained a mainstay of treatment.

Others have suggested that food intolerance in IBS has an immunologic basis and may represent food allergy. Although patients with IBS have a higher than average prevalence of atopic reactivity to intradermal allergy testing with food antigens, the relationship between skin test results and food-induced symptoms is poor and often not confirmed by blinded food challenge. Non-atopic hypersensitivity may be present, especially to wheat and milk proteins. The typical western diet contains large amounts of wheat, 10-15% of which is not digestible by human enzymes and can contribute to abnormal colonic fermentation. About 2% of the population has occult celiac disease and some patients with IBS have increased enteric IELs in a pattern suggesting celiac disease with normal villous architecture. Lactose intolerance occurs in 10% of people of northern European extraction, 40-90% of Asians and 60-80% of Africans. French researchers have shown that lactose intolerance is positively associated with milk protein allergy. They theorize that bacterial lactose fermentation in the gut impairs the normal barrier function, permitting sensitization to protein ingested along with lactose. Type I hypersensitivity to *Candia albicans* has been described in a group of patients with IBS. Ingestion of an extract of *C. albicans* produced cramps and diarrhea in these patients, during a double blind challenge. Most *Candida* allergic patients were also hypersensitive to food yeasts contained in bread, beer, wine, vinegar, fruit

juices and dried fruits. A yeast elimination diet cleared IBS in 40%; an additional 40% needed additional treatment with oral nystatin to eliminate symptoms.

Not only have multiple types of food intolerance been described in patients with IBS, varied types of abnormal gut fermentation have also been described. A team at Cedars-Sinai Medical Center used breath testing for hydrogen and methane to identify the presence of SBBO in patients who met the Rome criteria for IBS (described in Table…). In their patient population, 78% had breath tests suggesting SBBO and were treated with antibiotics; repeat testing indicated that SBBO was no longer present in slightly over half. Antibiotic therapy improved diarrhea and abdominal pain in these patients; 48% of patients who responded to treatment no longer met criteria for IBS by the end of the study. British researchers have used blood ethanol concentration in response to oral glucose loading as a way to measure abnormal gut fermentation. Although they have not studied this phenomenon in relationship to IBS specifically, many of the polysymptomatic patients studied have chronic gastrointestinal symptoms, including abdominal pain and distension and alterations of bowel function. In their study populations, most patients respond better to antifungal drugs than antibiotics, indicating that fungal dysbiosis may be as likely to cause symptoms of IBS as bacterial dysbiosis.

Other frequently described triggers for IBS include parasitic infection,

exposure to environmental chemicals and psychological distress. *Giardia lamblia* and *Blastocystis hominis* have been identified in stool specimens of 20 to 40% of patients diagnosed with IBS. Anti-protozoan therapy improved symptoms of the majority treated, in these studies. The combination of digestive complaints with symptoms of reactive airways disease has been termed Reactive Intestinal Dysfunction Syndrome. Environmental chemical triggers described are listed in Table… Inhalation of these substances was associated with abdominal distension, abdominal pain, diarrhea, vomiting and constipation. The researchers who described this syndrome speculate that activation of neurotransmitters in the lung and the GI tract by the offending chemicals is the mechanism. The relationship between bowel symptoms and emotional distress has long been noted by patients and physicians. Cognitive-behavior therapy has been beneficial and self-hypnosis was shown to induce a sustained remission of symptoms.

An integrated approach to the problem of IBS is much like an integrated approach to the problem of IBD and requires answering a series of questions:

(1) Are there microbial triggers?

(a) Parasites. Examination of stool for O & P by a lab that specializes in parasitology will produce a positive response rate of 7 to 48%, depending upon the laboratory, the selection of patients and the time of

year. Parasitic infection is most likely to be important in patients with a distinct onset of altered bowel habits at onset. Long dsuration of symptoms and the presence of chronic constipation do NOT exclude protozoan infection. Chronic giardiasis, responsive to antimicrobial therapy, is as often characterized by constipation s by diarrhea. The author has encountered patients in whom severe gastrointestinal symptoms present for as long as twenty years has totally cleared upon treatment of giardiasis or amebiasis. Initial treatment options include a number of anti-protozoan drugs and herbs (see Table…) and *S. boulardii*, which stimulates SIgA secretion.

(b). Yeasts. Patients who have developed IBS after exposure to antibiotics, or whose IBS is exacerbated by antibiotics, are likely to have dysbiosis as a trigger. Yeast overgrowth, sometimes associated with yeast hypersensitivity, depletion of normal flora or, occasionally Clostridial overgrowth, are possible. Examination of stool for *C. difficile* toxin and microscopic stool examination for yeast can be helpful. Several studies have described intestinal candidosis as a cause of chronic diarrhea, with diarrhea responding to anti-fungal medication. In one interesting study, the yeasts seen on microscopic stool exam failed to grow on culture and were described as “dead fecal yeasts”. This observation is consistent with unpublished observations of the author, using rectal swabs. The

growth of yeast from culture of a rectal swab was a poor predictors of symptomatic response to anti-fungal drugs. Patients whop showed abundant yeast on microscopic examination but had negative cultures were highly likely to report symptomatic improvement with anti-fungal drug therapy. Rectal mucus from these patients was capable of inhibiting the growth of a standardized culture of *C. albicans* on nutritive agar. This research has two implications: (1) Stool cultures for fungus are unreliable tests for predicting which patients with chronic GI symptoms will respond to anti-yeast therapy. (2) Pathogenesis of yeast-associated intestinal disorders involves a vigorous or hyperactive host response, such that rectal mucus contains anti-fungal factors not present in patients without yeast-associated illness (see Figure….). In addition to antifungal drugs or herbs, dietary restriction of simple carbohydrates and administration of *Lactobacilli* and other probiotics may be helpful.

(c) Bacterial overgrowth. Patients whose IBS symptoms improve when taking antibiotics may be suffering from bacterial overgrowth. Timed breath analysis for hydrogen and methane after a glucose or lactulose challenge may be helpful in confirming this diagnosis, if available, and if precautions are taken to avoid the many causes of false readings. (see Table…). Foods and herbs with anti-microbial activity are potentially useful as adjuncts to treatment. These include uncooked oils of garlic,

oregano, thyme, and rosemary. Achlorhydria is a potential contributor to SBBO, allowing bacteria and yeast to grow in the stomach and duodenum. The commonest causes of achlorhydria are prolonged use of proton pump inhibitors (PPIs) and chronic atrophic gastritis, a complication of infection with *Helicobacter pylori* and possibly a result of normal aging. Alternatives to the use of PPIs and strategies for *H. pylori* eradication are discussed below. If normal gastric pH cannot be restored, there may be value in administration of hydrochloric acid supplements to aid in control of SBBO. Because bacterial proteases can destroy brush border and pancreatic enzymes, symptoms associated with bacterial dysbiosis may also be relieved by the administration of supplemental digestive enzymes.

(2) Are there dietary triggers?

Food may influence IBS in two ways; to apply either, a thorough dietary history should be taken:

(a) Specific food intolerance may provoke symptoms. This intolerance may be pharmacologic (e.g. caffeine or other alkaloids in coffee increasing gut motility), digestive (e.g., lactose intolerance), immunologic (e.g., gluten intolerance), or allergic. A few foods exclusion diet of the type employed by

the Cambridge group (described above for Crohn's disease), may be of value.

(b) The physical/chemical composition of food may alter GI function by increasing bile flow (fats and oils), increasing microbial growth (carbohydrates) or stimulating intestinal baroreceptors (fiber). Increasing dietary fiber can be helpful for chronic constipation but has no consistent effect in IBS, probably because IBS is not a single entity. There is no single diet for IBS.

A practical strategy begins with an analysis of the patient's eating habits. Patients whose habits reflect the lowest common denominator among U.S. adults or children (high fat and sugar, low fiber, fast food eaten quickly) should be counseled in a healthier dietary pattern of a type that has been shown to prevent chronic disease: decreased sugar, fat, and refined carbohydrates, increased consumption of vegetables, fruit and whole grains, substitution of water for coffee and alcohol, more leisurely meals, eaten with friends and family. Form many patients, these simple and obvious changes will reduce symptoms markedly. Patients who become worse with such changes should be asked what foods

they are eating more. If more complex carbohydrate and fiber are associated with worsening of symptoms, a lower carbohydrate diet or the SCD should be considered. Patients who do not benefit from a healthier dietary pattern may be candidates for an exclusion diet

(3) What are the sources of stress in this person's life?

People often know what these are, when asked directly. The response to a few simple, open-ended questions may reveal other sources of stress. These include: How are things going for you at work/in school/at home? How well do you get along with your spouse/parents/children/close friends/co-workers? Are you satisfied with work, family life/social life? Are there people you can confide in or trust? Do you feel financially secure? What are your main sources of pleasure? Identifying major life stressors may allow appropriate interventions that dissipate the impact of stress. As important, knowing the patient in this way enables the doctor to treat the patient empathically, which enhances the quality of the interaction. A strong and trusting relationship between doctor and patient has a significant impact on the long-term management of IBS, independent of any specific treatments employed.

(4) Are there other disorders present which may be contributing to chronic GI symptoms?

By definition, chronic GI symptoms caused by a systemic illness, such as hypothyroidism, are not IBS. The Latent Tetany Syndrome (LTS), however, bears discussion, because it is not recognized in North America. LTS is a state of neuromuscular hyperexcitability characterized by clearly defined electromyographic abnormalities and symptoms caused by spastic contraction of skeletal or smooth muscle. Although LTS can be produced by calcium deficiency, alkalosis and hyperventilation, most individuals with LTS do not show these features. As a group, individuals with LTS have lower levels of serum or erythrocyte magnesium than a control population and abnormal responses to parenteral magnesium challenge suggesting magnesium deficiency. LTS is associated with IBS, fibromyalgia and migraine headache and administration of physiologic doses of magnesium improves symptoms in most cases. The administration of magnesium to a patient with IBS can be difficult; patients with diarrhea may be sensitive to the cathartic effect of magnesium. On the other hand, patients with constipation and abdominal pain, who show other manifestations of LTS, such as anxiety, skeletal muscle spasms, fatigue and delayed sleep onset, may benefit from RDA doseas of magnesium (300-400 mg/day).

Once these four questions have been answered and appropriate

treatments implemented, there remain numerous therapeutic options for control of specific symptoms. Peppermint oil can relieve abdominal cramping, possibly working as a calcium channel blocker in the gut. Fructooligosaccharides (FOS), a mixture of complex fermentable carbohydrates from various vegetable sources, especially chicory, has been shown to relieve constipation and enhance the growth of Bifidobacteria. Other natural products which may help with chronic constipation include ginger, which enhances motility, and triphala, a mixture of herbs used in Ayurveda. Side effects of these are minimal, but both peppermint oil and ginger extracts may aggravate esophageal reflux. Atractyloides rhizome, a component of many traditional Chinese medicines, is another motility enhancer. An intriguing study published in JAMA, demonstrated that a mixture of herbs employed in traditional Chinese medicine (TCM), could effectively relieve symptoms of IBS. The study design permitted a striking observation. Patients with IBS were evaluated by a practitioner of TCM, who wrote each of them an individual prescription based upon the tenets of Chinese diagnosis. Treatment was randomized and blinded. One third received the specific herbal formula prescribed, one third received a standard herbal formula which the group of practitioners had agreed in advance would relieve symptoms of most patients with IBS, and one third received placebo. During the six months of the study, the two groups receiving herbal therapies showed a comparable and significant relief of symptoms compared to

the placebo group. After the herbs were discontinued, the group receiving the standardized formula slowly relapsed, so that six months later they were as symptomatic as the placebo group. The group receiving individualized therapies, however, did not relapse after treatment was discontinued. The unheralded implication of this study is that TCM, when practiced according to its own principles, does not merely relieve symptoms of IBS, but enables a change in the individual being treated.

The principles of evaluation and treatment for IBS may be successfully applied to other "functional" GI disturbances, as illustrated in the following case report:

A second opinion was sought by the parents of a two year old girl who suffered from sever constipation and abdominal pain. The infant had always seemed to have some difficulty with bowel movements, but the problem was accentuated after her first birthday and had become progressively worse. Stool was scanty and dry, bowel movements were infrequent and stooling was slow and associated with crying. The pediatrician suggested milk of magnesia and fruit juice, which helped for about two weeks, and then prescribed a polyethylene glycol (PEG) laxative and a stool softener, which relieved symptoms for a month and then all treatments became ineffective. A pediatric

gastroenterologist rendered a diagnosis of redundant, atonic colon and prescribed senna along with PEG. His rationale was that the child had to move her bowels painlessly every day, or the situation would worsen. The parents were told that she would need to continue this regimen indefinitely.

The first step in re-evaluating the problem was to take a chronological feeding history. She had been nursed for two months and fed a cow's milk formula until twelve months. Solid food had been slowly introduced beginning at five months and cow's milk had become a dietary stable when formula was discontinued, about the same time as constipation became problematic. Cow's milk hypersensitivity is an established cause of childhood constipation. The parents reluctantly eliminated cow's milk from the child's diet, but were afraid to discontinue senna because the specialist had warned them against doing so. FOS and *Lactobacillus GG* were added as supplements. When her stool became loose, senna and then PEG were slowly discontinued. After two months of milk avoidance, FOS and lactobacillus, the child had daily, soft, painless bowel movements and required no further medication.

ACID-PEPTIC DISEASE

Hydrochloric acid produces much of the cellular damage and symptomatology of peptic ulcer disease (PUD), gastritis and gastroesophageal

reflux disease (GERD). The major etiologic factor in duodenal ulceration now appears to be *H. pylori* infection, which destroys somatostatin producing antral cells that down-regulate HCl production. Cigarette smoking contributes to duodenal ulceration by impairing duodenal bicarbonate secretion. *H. pylori*'s effects on the stomach are complex. It causes gastric inflammation by stimulating production of platelet activating factor (PAF) and other inflammatory mediators. In addition to PUD, *H. pylori* may cause or contribute to antral gastritis, NSAID gastropathy, atrophic gastritis, hypertrophic gastritis, gastric adenocarcinoma and gastric lymphoma. The varied diseases provoked by the single trigger reflect the variety of physiological responses evoked by its presence. Eradication of *H. pylori* with antibiotics and PPIs has revolutionized conventional treatment of these conditions. Several natural products have been advanced as alternatives to antibiotics, but evidence to support their use is minimal. The most intriguing, at present, is *Pastitia lentiscus* resin, or mastic gum, which is used as a food component in the Mediterranean and as treatment for gastric disorders by traditional healers. Mastic gum kills *H. pylori* in vitro at concentrations equivalent to administration of 1000 mg twice a day. In the author's unpublished personal series, mastic gum was effective in eradication of *H. pylori* using the stool antigen test in 75% of cases; the cure rate with conventional therapy at present is 96%.

With the decline in gastric disease caused by *H. pylori* has come a

substantial increase in GERD. Some researchers believe that some strains of *H. pylori* actually work to prevent GERD; others that the association is coincidental. GERD results from esophageal exposure to gastric contents, including HCL, pepsin and bile and it may be complicated by esophageal metaplasia (Barrett's esophagus), dysplasia and carcinoma. PPIs reduce symptoms and cure esophagitis in up to 90% of cases, but do not diminish reflux. They appear to replace acid reflux with non-acid reflux. Reflux itself is caused by transient relaxation of the lower esophageal sphincter (LES) not related to swallowing. These are motor reflexes pre-programmed in the brainstem in response to gastric vagal mechanoreceptors. Post-prandial gastric distension is an important trigger for LES relaxation by this mechanism. A more physiological mechanism for reducing reflux is to reduce post-prandial gastric distension by consumption of small meals eaten slowly in a relaxed fashion. Calcium ions increase contraction of the LES, so calcium salts in powdered, chewable or liquid form with meals may also prevent reflux. Calcium used this way is not functioning as an antacid but as a tonifying agent. High fat meals delay gastric emptying and may aggravate reflux, although in individuals with gastric fermentation due to bacterial or yeast overgrowth, fat may be less provocative than carbohydrate, which increases post-prandial gastric distension through fermentation. There are numerous uncontrolled anaecdotal reports of supplementation with hydrochloric acid (betaine HCl) and/or digestive enzymes

reducing symptoms of GERD. These may achieve their effect through enhanced gastric emptying, which decreases gastric distension.