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A BRIEF EVIDENCE-BASED REVIEW OF TWO GASTROINTESTINAL ILLNESSES: IRRITABLE BOWEL AND LEAKY GUT SYNDROMES

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Irritable bowel syndrome (IBS) encompasses a group of functional bowel disorders characterized by a combination of chronic, continuous or intermittent abdominal complaints and abnormal bowel habits.[3,4] IBS accounts for more gastroenterology referrals than any other gastrointestinal disorder,[5] with estimated prevalences of 4.4% in Australia,[6] 21.6% in the United Kingdom,[7] and 20% (using the Manning criteria) in the United States.[8] According to one survey, one fifth of people with IBS or functional dyspepsia used CAM modalities for healing at some point in their life, most commonly because of dissatisfaction with conventional medicine.[9]

PATHOPHYSIOLOGY

The pathophysiology story of IBS has been evolving over the years, and consensus has yet to be reached as to the etiology of this disease. For the most part, IBS is recognized by most clinicians as a discreet clinical entity, although a popular pathology text, *Robbins Pathologic Basis of Disease*, still does not mention IBS in its nearly 1,500 pages.[10] Although some experts still consider IBS an idiopathic disease,[4] a number of pathogenic mechanisms for IBS have been postulated and identified, including altered gastrointestinal motility and increased intestinal sensitivity.[11] Other factors such as psychosocial influences, food exposures, and prior infection have also been implicated in the development or exacerbation of IBS.[11] Advances in the understanding of neurogastroenterology (brain-gut axis) have provided novel and intriguing insights into the pathophysiology of IBS, and a multicomponent model including physiological, behavioral, cognitive and emotional factors has been developed.[12,13] (See Figure 1.)

Several studies have confirmed a relationship between gastrointestinal infection and the development of IBS.[14-16] One of these was a questionnaire of 386 people with confirmed diagnosis of infectious gastroenteritis. Six months later, 20% still complained of abnormal bowel habits and 6% had developed IBS according to Rome II criteria.[14] A different survey compared incidence of IBS in 318 patients with confirmed gastroenteritis to 584,308 control subjects in the general population.[15] One year later, they found confirmed IBS incidence of 4.4% in the post-infectious group compared to 0.3% in the general population, indicating that those with a recent history of gastroenteritis are ten times more likely to develop IBS than those in the normal population. This certainly has intriguing implications for the etiology of IBS, yet it still leaves the question open as to why some people develop post-infectious IBS while others do not. Another study in 94 patients admitted to a hospital with acute gastroenteritis found that 22 developed IBS three months later, while 72 did not.[16] Those that did had scored significantly higher on anxiety, neuroticism, and somatization measures, while rectal hypersensitivity, rectal reactivity, and colonic transit were relatively the same between the two groups.

These findings indicate that psychological factors may be important IBS predictors. For example, it has been widely reported that stress influences activities in the gut.[12,17] Furthermore, although psychological distress does not appear to cause IBS, it does drive patients with IBS to seek healthcare.[18] Also, stressful or traumatic episodes often trigger or exacerbate the symptoms of IBS.[19]

DIAGNOSIS

There are 3 main diagnostic criteria, which partially explains the different published prevalence rates for

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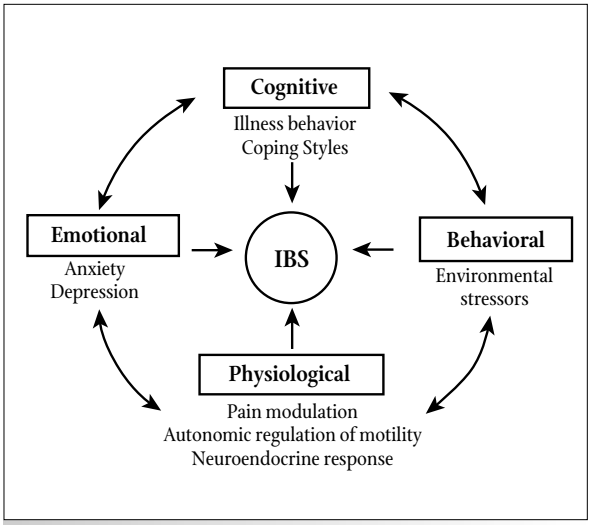

FIGURE 1
DISEASE MODEL OF IBS

IBS. Historically, the Manning criteria were used,[20] although these have since been modified so that the current standards for diagnosis are the Rome and Rome II criteria. The Rome II criteria, developed by a consensus of experts, are the most current tool for diagnosis, providing more stringent criteria for IBS diagnosis than the Manning or original Rome criteria.[3] (See Table 1.) Major differences between the Rome and Rome II criteria are that Rome II requires the presence of both abdominal pain and disturbed defecation. The Rome II criteria also require a minimum duration of 12 weeks of continuous or intermittent symptoms within the past 12 months, while there is no minimum duration of symptoms in the original Rome criteria.[3,21,22] Among the arguments for using the Rome II criteria is that they provide a standard tool for identifying IBS in research subjects in the acquisition and interpretation of scientific data.[3,22]

Symptoms that support, but are not essential to, the diagnosis of IBS include abnormal stool frequency (greater than 3 bowel movements/day or less than 3 bowel movements/week), abnormal stool form (lumpy/hard or loose/watery stool), abnormal stool passage (straining, urgency, or feeling of incomplete evacuation), passage of mucus, and bloating or feeling of abdominal distension.[3]

Patients with IBS generally fall into one of three subgroups: constipation-predominant IBS, diarrhea-predominant IBS, or alternating IBS. The prevalence of the individual subgroups in the general population is equal, although women are more likely to have the constipation-predominant variety.[8]

Currently, no specific diagnostic tests exist for IBS, though tests may be used in the processing of eliminating other diagnoses in the differential.

TABLE 1
MANNING, ROME, AND ROME II DIAGNOSTIC CRITERIA FOR IBS

Name	Criteria
Manning criteria*	• Onset of pain linked to more frequent bowel movements • Looser stools associated with onset of pain • Pain relieved by passage of stool • Noticeable abdominal bloating • Sensation of incomplete evacuation more than 25% of the time • Diarrhea with mucus more than 25% of the time
Original Rome Diagnostic criteria†	Continuous or recurrent symptoms of: • Abdominal pain, relieved with defecation, or associated with a change in frequency or consistency of stool; and/or • Disturbed defecation: two or more of altered stool frequency, altered stool form (hard or loose/watery), altered stool passage (straining or urgency, feeling of incomplete evacuation), passage of mucus usually with bloating or feeling of abdominal distension
Rome II Diagnostic criteria‡	At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three features: • Relieved with defecation; and/or • Onset associated with a change infrequency of stool; and/or • Onset associated with a change in form (appearance) of stool

* Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *Br Med J.* 1978;2(6138):653-4.
† Thompson WG, Dotevall G, Drossman DA, et al. Irritable bowel syndrome: Guidelines for the diagnosis. *Gastroenterol Int.* 1989;2:92-5.
‡ Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut.* 1999;45 Suppl 2:II43-7.

TREATMENT OVERVIEW

Most published sources approach the treatment of IBS in a stepwise fashion. After the diagnosis is established, experts mention the importance of a caring doctor-patient relationship, explanation of the illness to the patient, and provide dietary advice, lifestyle suggestions, and reassurance.[11,23-28] This approach shares some characteristics with the field of integrative medicine that also recognizes the importance of a therapeutic relationship between the clinician and patient in approaching health and healing.[29] Treatment may then progress based on symptoms in the 3 IBS sub-types—constipation-predominant, diarrhea-predominant, and pain-dominant—with any necessary referrals or further work-up for patients who fail initial attempts at treatment.[11] Furthermore, an integrated approach to IBS may incorporate a variety of CAM healing modali-

ties,[30] some of which are described below.

Conventional IBS Treatments

Pharmaceuticals

Numerous literature reviews have discussed conventional IBS treatments, including pharmaceutical and psychological interventions.[28,31-35] These reviews describe the use of many different pharmacological agents for IBS. (See Table 2.)

There has been an evolution in the medical literature with respect to the conclusions that can be drawn about the pharmacological agents used for IBS. For example, one author examined research from 1966 to the mid-1980s and located 43 studies on the use of a variety of medications, including antispasmodics, anticholinergic/barbiturate combinations, antidepressants, bulking agents, dopamine antagonists, carminatives, opioids, and tranquilizers.[31] The author found methodological problems with much of the published research at the time, and concluded that none of the trials were convincing for the effective treatment of entire IBS complex, though perhaps medications may be useful in controlling specific symptoms. Another study updated these results and reviewed 45 randomized studies from 1987-1998, which included the examination of similar medications.[33] Again, methodological quality was an issue; out of the 45 studies, only 6 met minimal criteria for well-designed randomized controlled trials. However, that review concluded that there may be some evidence for the effectiveness of medications in treating specific symptoms, such as bulking agents in IBS constipation, and one antispasmodic (cimetropium bromide) and some antidepressants for IBS pain. More recent reviews echo the flaws in much of the published pharmaceutical research, but concede that there may be some treatments for specific symptoms:[34,35] antispasmodics or tricyclic antidepressants for abdominal pain, bulk forming agents for constipation, 5HT-4 agonists for constipation-predominant IBS in women, and 5HT-3 antagonists for diarrhea-predominant IBS in women. (See Table 2.)

One meta-analysis reviewed the use of antidepressants in functional gastrointestinal disorders, focusing on tricyclic antidepressants and one antiserotonin medication.[36] Twelve randomized, placebo-controlled trials were analyzed: 8 studies of IBS, 2 of non-ulcer dyspepsia, and 1 for both IBS and non-ulcer dyspepsia. The reviewers looked at both dichotomous or continuous measures of outcome with improvement in symptoms such as pain with antidepressant therapy; the number needed to treat was 3.2. There are limitations of this meta-analysis, including the low-to-moderate methodological quality of the original studies and the fact that it is difficult to rule out the improvement being due to the concomitant improvement of depressive symptoms.

TABLE 2
SOME PHARMACOLOGICAL TREATMENTS FOR IBS

Drug Class	Examples	Comments
5-HT3 receptor antagonists	alosetron	For non-constipated female patients with IBS
5-HT4 agonist	tegaserod	Available in some countries for constipated female patients with IBS
Anti-diarrheal agents	loperamide	For diarrhea-predominant IBS
Anti-spasmodics (also called smooth muscle relaxants or myorelaxants)	cimetropium bromide, hyoscine butyl bromide, meberverine, otilium bromide, pinaverium bromide, trimebutine	Primarily useful for pain symptoms. Varying mechanism of action: some act as anti-cholinergics
Bulk-forming agents	bran, psyllium	May be of benefit for constipation-predominant IBS, but may not benefit other IBS patients
Selective serotonin reuptake inhibitors (SSRIs)	paroxetine	Improved physical component in quality-of-life tests
Tricyclic antidepressants	amitriptyline, clomipramine, desipramine, doxepin	Primarily useful for pain symptoms. Useful if comorbid psychiatric disturbances.

Other researchers pooled several different medicines under the term of "smooth muscle relaxants" (also called myorelaxants or antispasmodics; often with an anticholenergic/antimuscarinic mechanism of action) and did a meta-analysis of 21 randomized controlled trials.[37] The researchers examined cimetropium bromide, hyoscine butyl bromide, meberverine, otilium bromide, pinaverium bromide, and trimebutine, looking at the percentage of patients with global improvement in symptoms, as well as subsets of different symptoms during treatment; their analysis showed a benefit with these medicines in IBS.

A recent randomized trial examined the use of a selective serotonin reuptake inhibitor (SSRI), paroxetine, in 257 patients with severe irritable bowel syndrome.[38] The patients were randomized to receive either eight sessions of individual psychotherapy (psychodynamic interpersonal therapy), 20 mg daily of paroxetine, or routine care by a gastroenterologist or family physician. After 3 months, and again at 1 year, the patients were surveyed for abdominal pain, health-

TABLE 3
CAM TREATMENTS FOR IBS (LISTED ALPHABETICALLY)

Treatment	Description
Chinese herbal remedy	Significant improvement of all IBS symptoms; standard formula better for acute symptoms and individual formula better for long-term benefit
Combination patented formula of artichoke leaf extract and other constituents (Hepar-SL)	Possible remedy for constipation-predominant IBS
Enteric-coated peppermint oil	Significant improvement in abdominal pain and discomfort
Gut-directed hypnotherapy	Significant benefits in the normalization of bowel habits
Padma Lax (Tibetan herbal remedy)	Possible remedy for constipation-predominant IBS
Probiotics (i.e. Lactobacillus)	Possible reduction in flatulence and abdominal pain

related quality of life, and the costs of treatment were determined. There was also blinding of the research staff and an intention-to-treat analysis. Paroxetine and psychotherapy both improved the physical component of the health-related quality of life, as compared to routine follow-up; psychotherapy was also associated with a significant reduction in healthcare costs.

Overall, there appears to be some evidence for the use of pharmaceuticals in treating IBS in specific circumstances, though much of the research is difficult to interpret due to low methodological quality. Furthermore, the practical clinical application of some of the research is limited given that few of the drugs mentioned in the literature have been approved for treatment of IBS in the United States, or may not be available in all countries.[34] There is a significant amount of research on new medications for IBS, some of which will take advantage of new understanding about gastrointestinal physiology and muscle-nerve mechanisms.[28]

Psychological Interventions

Psychological interventions have been a part of the treatment of IBS for a long time. For example, psychotherapy has been mentioned as an IBS treatment for nearly 40 years.[39] Research on psychological interventions for IBS has investigated a variety of treatments, including dynamic (interpersonal) psychotherapy, cognitive-behavioral therapy (CBT), pharmaceuticals (as described above) and relaxation techniques.[23,24,26,27] The fact that this body of literature also often includes such interventions as hypnotherapy (see below) illustrates that separation of IBS treatments into the categories conventional and CAM can be arbitrary.

Researchers have commented on the low methodological quality of psychological studies for IBS,[27,28,40] but most experts find the data sufficient for the use of psychological interventions for reducing abdominal pain and diarrhea,[23,27] as well as for the treatment of co-morbid conditions such as depression, anxiety, and panic,[24,34] or sleep disorders, a history of abuse, or current life stressors.[25,26] Several of the studies include a combination of psychological interventions (ie, CBT with relaxation), though there is some research on single techniques, such as meditation.[41,42] Some of the specific details about which interventions work for which patients has yet to be determined. For example, one trial of 105 patients with IBS (Rome I criteria, non-resistant symptoms), showed similar improvements in physical and psychological parameters for all three groups tested: standard care, CBT, and relaxation therapy.[43]

Patients seem to respond better to psychological treatments if their IBS symptoms worsen with stress, are younger than 50 years old, have lower levels of anxiety, and do not have chronic pain.[23,24,28]

There are challenges in the incorporation of the different psychological treatments for IBS patients that include such factors as having an adequate referral network of practitioners well-versed in CBT and hypnotherapy, and insurance coverage for these treatments.[34]

CAM Treatments for IBS

Hypnotherapy

Several studies have found that hypnotherapy is useful in the treatment of IBS[44-49] although the mechanism is still elusive. Hypotheses for how hypnosis may relieve symptoms of IBS include the normalization of the interpretation of aversive intestinal stimuli, the reduction of smooth muscle tone, the modification of bowel functioning through autonomic balance, and/or the amelioration of somatically focused distress that influences symptom experience.[46]

Long-term success with hypnosis has also been found. For example, a follow-up 1-6 years later on 204 patients who had undergone hypnotherapy in an original study[45] found that of the 71% who initially responded to hypnotherapy, 81% had sustained improvement.[50] This work led to the establishment of the first hypnotherapy unit in the National Health Service in the United Kingdom devoted to the treatment of IBS patients. Although it seems to be successful in treating refractory IBS, hypnotherapy can be very time consuming. A solution to this may be the use of audio tapes for self-hypnosis,[44,47] although a pilot study comparing autohypnosis with audio tape to gut-direct-

ed hypnosis by a therapist found gut-directed hypnosis to be significantly superior to autohypnosis in the reduction of symptoms in refractory IBS patients.[47]

Herbs

Chinese herbal medicine has been used for centuries in the treatment of functional bowel disorders, and it is still routinely used as such in China.[51] One randomized, double-blind placebo-controlled study investigated the use of Chinese herbal formulas for the treatment of IBS.[51] The researchers divided 116 subjects into 3 treatment groups: one used patient-individualized treatments developed by a Chinese medicine practitioner, one used a standard Chinese IBS formula consisting of 20 herbs, and one remained as a placebo group. After 16 continuous weeks of treatment, they found that the group on the standard Chinese herbal therapy showed the best results with 44%-59% improvement, followed-by a 40%-42% improvement for patient-individualized treatments, both of which were significantly different than the placebo group (a 19%-22% improvement, P=0.03). At a 14-week follow up, the patients on the individualized therapy showed the greatest improvement (75%), followed by the standard formulations (63%), and the placebo group (32%, P=0.03 compared to the 2 treatment groups). The results of this study seem to indicate that Chinese herbal medicine may be beneficial in the treatment of IBS.

Another herbal remedy, Padma Lax (EcoNugenics), is a Tibetan herbal formula of 13 different herbal constituents that has been commercially available in Switzerland for more than 30 years as a remedy for constipation. This product was evaluated in a randomized, placebo-controlled study for its safety and effectiveness in 61 patients with constipation-predominant IBS.[52] After 3 months, significant improvement of constipation (P=0.0001) and abdominal pain (P=0.09) was demonstrated compared to placebo, as well as a significant global assessment improvement (P<0.002). Loose stools were a side effect in 7 patients, so the product is probably not appropriate for diarrhea-predominant or alternating IBS.

Artichoke leaf extract (ALE) from the artichoke plant (*Cynara scolymus*) may also be useful in IBS symptom management. ALE has been described as a carminative, antiemetic, and spasmolytic.[53] A prospective study using ALE capsules in 279 patients suffering with 3 of 5 symptoms of abdominal pain, right-sided abdominal cramps, bloating, flatulence, or constipation found that 84% of patients improved during the 6-week trial.[54] The extract studied was a patented formulation called Hepar-SL. The other constituents in the formula were lactose, talcum, magnesium, stearate, and silicon dioxide.

Peppermint oil from the peppermint plant (*Mentha piperita*) has a long history of use as a carminative and antispasmodic that has been used for the treatment of IBS for at least three decades.[55-57] It reduces gastric motility[58] by directly acting on gut calcium channels to relax gastrointestinal smooth muscle.[59]

In IBS, peppermint oil is best used for the relief of abdominal pain and discomfort,[60-62] though not all studies agree. A recent meta-analysis of peppermint oil for IBS concluded that the role of peppermint in IBS was not adequately supported,[63] and another found no significant difference between peppermint and placebo in the reduction of IBS abdominal pain.[64] On the other hand, in a randomized, double-blind controlled pediatric trial of 42 children, enteric-coated peppermint oil capsules significantly reduced abdominal pain in acute IBS, though there was little effect on the other symptoms of IBS.[61] A similar study in 27 adults revealed that peppermint oil was superior to placebo in the treatment of abdominal symptoms of IBS.[60] It appears that peppermint oil may help alleviate IBS abdominal pain and discomfort, though it is not recommended for the treatment of abnormal bowel habits.

Probiotics

The role of probiotics, particularly lactic acid bacteria, is receiving increasing attention in IBS literature.[65-67] A probiotic is composed of either a single species, or several species, of microorganisms that are intended to be beneficial to health.[66] Stress of daily life, change in dietary habits, pharmaceutical compounds (ie, antibiotics), and pathogens can all disrupt the homeostasis of the gut flora.[66] One double-blind placebo-controlled trial of 52 patients with IBS found that the administration of the probiotic *Lactobacillus plantarum* DSM 9843 decreased pain and flatulence as compared to placebo.[65] This trial suggests that the use of probiotics has potential in helping patients with IBS symptoms, but other researchers warn that safety from toxicity and virulence must be fully evaluated.[68] Another review article about the possible effects of probiotics in IBS concludes that the evidence for the use of probiotics for IBS is inconclusive and that currently there is no specific organism to be recommended.[67] They do, however, state that "...a probiotic approach will ultimately be justified."

Irritable Bowel Syndrome: Conclusion

IBS is a common gastrointestinal medical disorder with detailed criteria (most recently the Rome II criteria) for diagnosis and with significant morbidity. Some of the pathological mechanisms being postulated for IBS include brain-gut neuromuscular mechanisms, psychological factors, and infectious causes. There is a significant body of literature about IBS treatments, and despite research of varying methodological quality, numerous CAM and more conventional treatments appear effective

in addressing some of the symptoms associated with IBS.

Part II: Leaky Gut Syndrome

Overview

Leaky gut syndrome is a phenomenon of increased intestinal permeability, which is thought to be related to, and perhaps is an etiological factor in a variety of disorders including Crohn's disease, celiac sprue, chronic fatigue syndrome, and fibromyalgia.[69-71] Intestinal permeability refers to the ability of substances to pass between the cells of the intestinal epithelial layer; the size and characteristics of the compounds that can passively cross the barrier is thought to indicate how well the barrier, especially the tight junctions between epithelial cells, is functioning.[72]

Pathophysiology

There are several theories about the order of events in leaky gut syndrome, and many of the proposed mechanisms involved in the development of the disorder are theoretical, though there are some interesting data accumulating that are relevant to the various hypotheses. One hypothesis for the relevance to various clinical conditions is that larger molecules cross an abnormally-functioning intestinal wall and overwhelm the ability of the liver to process them, leading to direct systemic toxicity, as well as secondary responses to these compounds mediated by the immune system.[71] Some authors identify that leaky gut syndrome and several other conditions may have a similar constellation of symptoms or etiology; these related conditions include the overgrowth of bacteria or *Candida albicans* in the small intestine, "yeast syndrome" or chronic candidiasis, and food allergies that may come from a chronic immune hypersensitivity to the absorption of inadequately digested proteins and short-chain polypeptides.[73] Some authors list a variety of causative agents involved in the development of intestinal dysfunction and dysbiosis, including exposure to environmental toxicants, antibiotic use, a low-fiber diet, and other gastrointestinal disorders.[73] (See Table 4.)

Published Scientific Research: Laboratory, Animal, and Clinical Trials

Much of the published scientific research on leaky gut in humans has centered on observation that Crohn's disease patients have an increased intestinal permeability to certain substances. Increased permeability in the intestinal wall allows larger-sized compounds called luminal antigens and commensal gut flora to penetrate the intestinal tissue and contribute to inflammation.[74,75] There also seems to be the involvement of tumor necrosis factor alpha (TNF-α) which disrupts the tight junctions between epithelial cell layers and increases permeability.[74] This led researchers to treat Crohn's disease patients with infliximab (Remicade), an antibody to TNF-α, which decreases TNF-α levels, suppresses bowel inflammation, tightens the intercellular tight junctions, and improves symptoms.[74,75] There is a difference in permeability changes that occur for certain sized compounds in healthy versus diseased intestine, the location along the gastrointestinal tract, and the preference for villous or crypt tight junctions.[74] The order of events is still the subject of scientific discourse about whether the bowel damage and increased permeability occur first and then lead to inflammation and symptomatic Crohn's disease, or if the reverse order is true.

There also seems to be a connection between increased intestinal permeability and endotoxemia, and a pathologically significant role for endotoxemia in various disease processes. For example, in the case of alcoholic cirrhosis, patients with chronic liver disease are also the ones with a significant increase in intestinal permeability; the hypothesis is that endotoxin from commensal gut flora enters into the bloodstream and, via the portal circulation, is able to cause a damaging hepatic inflammatory cascade.[76] In patients with inflammatory bowel disease, endotoxins from intraluminal bacteria are believed to be part of the inflammatory process, and some studies show systemic endotoxemia to significantly correlate with the extent and activity of the clinical disease process in inflammatory bowel disease.[77]

A model of intestinal damage has occurred from human and animal research on the gastroenteropathic effects of non-steroidal anti-inflammatory drugs (NSAIDs), as well as the role of gut bacteria on the pathophysiology of altered intestinal permeability. Epithelial damage caused by NSAIDs seems to lead to increased luminal bacteria concentrations and a resulting inflammatory reaction.[78] An increase in intestinal permeability after administration of NSAIDs such as aspirin, ibuprofen, and indomethacin has been demonstrated in humans[79] as well as animals. This change in permeability appears to be reversible, and may be prevented by certain prostaglandins, such as prostaglandin E_2.[79] There may also be an effect of NSAIDs on colonic permeability.[80] Another study of people taking indomethacin, as compared to control subjects, suggests that the changes in intestinal permeability are due to local effects of the medication (as opposed to systemic effects), and appear to be reversible.[81] A role for enteric bacteria in the inflammatory process is postulated from trials showing a benefit in using probiotics, specifically *Lactobacillus* sp., to improve symptoms in Crohn's disease.[82] A study of *Lactobacillus* strains in an enterocolitis animal model showed reduced bacterial translocation across the intestinal wall, reduced plasma endotoxin, and reduced intestinal permeability.[83] Furthermore, in this same study, oat fiber also decreased the intestinal permeability, though there was

TABLE 4
SOME OF THE PROPOSED CAUSES OF INCREASED INTESTINAL PERMEABILITY

- antibiotic use
- celiac disease
- Crohn's disease
- exposure to environmental toxicants
- hemorrhage
- immunosuppression
- injury/trauma
- intestinal infections (*Giardia lamblia*, salmonella, malaria, *Ascaris lumbricoides*, hepatitis A, Rotavirus, and non-specific gastroenteritis)
- low-fiber diet
- NSAIDs
- sepsis

less of an effect on intestinal microecology. There is data that shows leakiness in the intestinal epithelium to both macromolecules such as bacterial endotoxins, and to the microbes themselves, which may be able to translocate across the epithelial layer.[84] Endotoxins are able to cross the intestinal epithelial layer in cases of bowel ischemia, inflammatory bowel disease, and necrotizing enterocolitis.[85] One animal study indicated that intestinal permeability increased and bacterial translocation occurred within two hours of an episode of shock.[86] Prior treatment with antibiotics in one group was able to prevent the translocation of bacteria across the intestinal wall, but not the mucosal injury or increased permeability. All of these studies point to an interaction between increased intestinal permeability, bacterial translocation across the intestinal wall, endotoxemia, and inflammation, as well as some of the therapies that might be useful in stopping the cascade of events.

There are many possible substances that cause damage to the tight junctions between intestinal epithelial cells and lead to increased intestinal permeability. In addition to NSAIDs mentioned above, increased intestinal permeability has been observed upon exposure to ethanol, clostridial toxin, and gamma-interferon,[72] as well as in situations of injury or trauma, immunosuppression, sepsis, or hemorrhage.[84]

The intestinal epithelial cell tight junctions may not function normally in different disease states. Investigations using animal models and various cell lines demonstrate increased intestinal permeability in celiac sprue, and enterocolitis secondary to *Clostridium difficile*.[87] Also, polyethylene glycol molecules of 2 sizes were used to measure the intestinal permeability in 8 patients with eczema and food allergy, and 10 patients with just eczema.[88] The researchers found that the patients with eczema had an increased absorption of the larger molecules regardless of food allergy status, lending some data to the hypothesis that eczema has some associated gastrointestinal abnormalities. Another study used a permeability test (cellobiose and mannitol) on a variety of human subjects, finding increased permeability in those people with abnormal jejunal biopsy results, and a variety of diagnoses, including idiopathic diarrhea, folate deficiency, post-infectious diarrhea, Crohn's disease, and atopic eczema, some of whom had normal biopsy results.[89] Increased intestinal permeability is associated with a variety of intestinal infections, including *Giardia lamblia,* salmonella, malaria*, Ascaris lumbricoides*, hepatitis A, *Rotavirus*, and gastroenteritis, as well as in some, but not all, cases of food intolerance.[90]

An increase in intestinal permeability has also been demonstrated in patients with Crohn's disease, and perhaps may play a causal role in the pathogenesis of those diseases.[72] For example, Crohn's patients have been found to have an increased intestinal permeability to various compounds, including lactulose, cellobiose, and Cr-EDTA,[72] a phenomenon not seen in ulcerative colitis. This increased permeability may just be the result of the inflammatory process involved. However, some studies of first-degree relatives of Crohn's patients have found an increased permeability to substances such as lactulose and polyethylene glycol, leading to the thought that there is a genetic connection to intestinal barrier dysfunction, which then leads in some cases to the development of Crohn's disease. Possibly due to a genetic abnormality, healthy relatives of Crohn's patients, may also have less of an ability to preserve the function of the intestinal lining in the face of gastrointestinal stressors such as NSAIDs. For example, there is a significantly increased intestinal permeability (demonstrated by lactulose-mannitol ratio and total sucrose excretion) in response to aspirin ingestion in some first-degree relatives of Crohn's patients as compared to controls.[91,92] This has led to the postulation that there may be an etiologic role for increased intestinal permeability in inflammatory bowel disease, given that some asymptomatic first-degree relatives of Crohn's patients have been documented to have increased intestinal permeability.[90]

Researchers studying multi-organ failure that results from shock and trauma have proposed that ischemia in the splanchnic region may lead to increased permeability, and can then allow intestinal bacteria to cross, enter the bloodstream, and cause sepsis and an endotoxin-induced inflammatory reaction leading to shock.[93,94]

Researchers recognize the possibility that increased intestinal permeability to macromolecules could, in theory, lead to disease processes distant from the gastrointestinal tract.[90]

In summary, there is a plethora of research about increased intestinal permeability. As mentioned above, there are substances, such as NSAIDs and alcohol, that can lead to increased intestinal permeability, and the pathophysiology of this change often includes alterations in the bowel flora and perhaps a genetic predisposition. Many disease states, most notably Crohn's and celiac disease, are associated with an increase in

intestinal permeability, though the cause-effect relationship has yet to be definitively determined.

Diagnosis

Various compounds can be given to people orally in order to test the function of the intestinal barrier. These "permeability markers" are hydrophilic, passively cross the intestinal epithelial layer, and are not metabolized. Some examples are lactulose, cellobiose, mannitol, rhamnose, polyethylene glycols, and Cr-EDTA.[72,76,90] However, when assessing intestinal permeability, as with NSAID-induced damage to the intestinal wall, the exact test dose and composition is an important factor in accurately determining permeability.[95] There is also a lack of specificity in many of the permeability tests[90] because there is an increased permeability to test probes in a variety of common intestinal disorders.

In specific clinical circumstances, the diagnosis of altered intestinal permeability can be helpful. There are well-documented intestinal permeability changes in active celiac disease. Permeability tests can be used to assess the successful avoidance of gluten, to confirm the diagnosis, or to determine the effect of treatment.[90] Also, sugar permeability in the intestine can be used to measure disease exacerbations of Crohn's disease, and may be the result of either severe inflammation or an alteration of the gut flora.[96]

Treatment

There is some doubt about the need to treat increased intestinal permeability given that the cause-effect relationship with many disease states is unknown. However, in specific circumstances it may be justified to test for increased intestinal permeability and attempt to treat it if elevated. For example, as mentioned above, research shows that TNF-α is involved in both a "leaky gut" and symptoms of Crohn's disease, and infliximab (Remicade), an antibody to TNF-α, tightens the intercellular tight junctions (among other actions), and improves symptoms in patients with Crohn's disease.[74,75] Another example is in alcohol-induced liver disease, when the minimization of intestinal permeability may help prevent the complication of cirrhosis.[76]

If the goal is to repair or prevent further damage to the intestinal wall and normalize a "leaky gut," there are some other interventions supported by the medical literature. One important recommendation is the avoidance of NSAIDs and ethanol, which are known to increase intestinal permeability. If the hypothesized mechanisms are correct, these substances could start a cycle of increased permeability, inflammation, and immune system response, and lead to yet further altered permeability. Some dietary interventions could be useful. For example, a small trial involving 8 patients with active Crohn's disease tested the effect of an elemental diet on intestinal permeability. The patients on the elemental diet, which consisted of 17% amino acids, 79% dextrin, and 0.6% soybean oil administered by nasogastric tube, led to a normalization of intestinal permeability as determined by lactulose and rhamnose ratios after 4-8 weeks.[97] Though this is not practical for most patients, it is interesting that dietary changes could be connected to permeability improvements in this disease process.

There are some experimental treatments coming out of animal studies. One research trial showed that some of the damage from endotoxins, which includes processes involving lipid peroxidation and free radical formation, can be prevented or reversed by the use of antioxidants such as alpha-tocopherol (Vitamin E) or coenzyme Q_{10}.[98] Also, efforts have been made in animal models to bind endotoxins in the intestinal lumen, addressing one step in the cascade of events involving abnormal intestinal permeability and its connection to various medical conditions. Some of the compounds used to decrease endotoxemia include kaopectate, charcoal, lactulose, oral non-resorbed antibiotics, and bile salts.[85] Research has also shown some benefit using bowel lavage with saline solution, anti-lipopolysaccharide antibodies, and the prophylactic use of methylprednisone to address endotoxemia.[85]

Leaky Gut Syndrome: Conclusions

Leaky gut syndrome, a situation of increased intestinal permeability, is a well-documented phenomenon in cases of exposure to certain substances or with certain disease states. There is some evidence for the use of permeability studies and treatments to normalize intestinal permeability, primarily in Crohn's and celiac disease. More research is needed to clarify the pathophysiology and cause-effect relationship between increased intestinal permeability and other disease states, as well as to demonstrate the clinical efficacy of various treatments in improving not only intestinal permeability, but also clinical symptomatology.

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