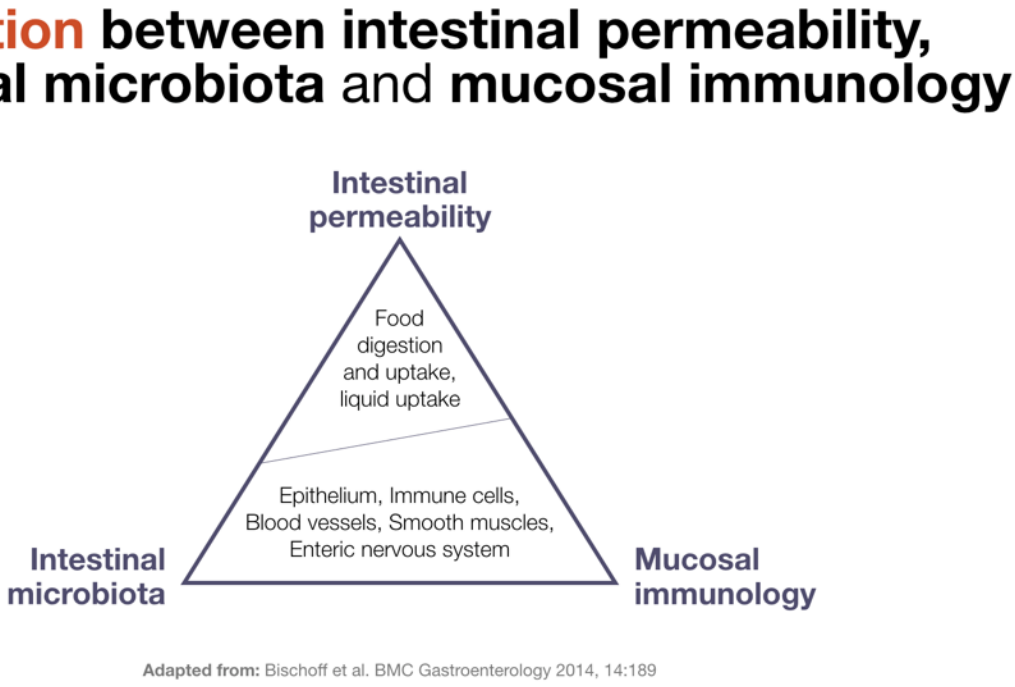
KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Gut: Intestinal Permeability, Part 1

Hey, everybody, in this presentation we're going to talk about intestinal permeability. I'll begin with a brief review of the gut barrier and the pathology of intestinal permeability, and then we'll move into testing. The intestinal barrier covers a surface area of 400 square meters and requires approximately 40 percent of the body's energy expenditure. Compare this to 20 percent required by the brain. This is another indicator of how crucial the gut barrier is to health. The gut barrier prevents against the loss of water and electrolytes and the entry of antigens and microorganisms, and it allows the absorption of nutrients and the exchange of molecules between the host and the environment. It allows a peaceful coexistence between the host and commensal microorganisms, which are the beneficial microorganisms that live in our gut typically, without eliciting chronic inflammation, so it allows us to coexist with these organisms without treating them as if they're foreign invaders. It provides measured inflammatory response as a defense against pathogens, and has an incredibly sophisticated and discerning system for that.



The gut barrier consists of multiple layers. The first is an external physical barrier. The second is an inner, functional physiological barrier. Successful interaction of these two barriers allows appropriate permeability to be maintained, and when either system malfunctions, permeability becomes inappropriate, and this is what we refer to as leaky gut. So, of course, all guts should be leaky to some degree, because that is how we absorb nutrients. If the gut wasn't at all leaky, we couldn't get any of the nutrition that we needed. So when we say leaky gut, what we are actually referring to or what we mean is a gut that is permeable or leaky to the wrong molecules at the wrong times.

Possible causes of impairment of intestinal barrier

Nutrition	e.g. Western diet, lack of fermentable carbohydrates and fermented foods
Infections and toxins	e.g. bacterial, viral, parasitic infections; fungal overgrowth; heavy metals; mycotoxins
Medications	e.g. PPIs, antibiotics, NSAIDs
Lifestyle	e.g. chronic stress, sleep deprivation, inappropriate physical activity
"Hygiene hypothesis"	Inadequate immune stimulation during crucial developmental period
Endogenous factors	Chronic inflammation, SIBO, gut-brain dysfunction, low MSH
Genetic susceptibility	e.g. 70% of asymptomatic relatives of CD patients positive for ↑ intestinal permeability

There are numerous factors that affect the integrity of the gut barrier system. These include nutrition, like Western diet, lack of fermentable carbohydrates and fermented foods; infections and toxins, these could be bacterial, viral, parasitic infections, fungal overgrowth, things like heavy metals or mycotoxins, mold; medications like acid-suppressing drugs, antibiotics, and NSAIDS; lifestyle, like chronic stress, sleep deprivation, inappropriate physical activity, either too little or too much; the hygiene hypothesis, which means inadequate immune stimulation during crucial developmental period; sanitation, which is part of the modern Western lifestyle, has certainly saved numerous lives due to reductions in acute infectious disease, and I'm not suggesting that we go back to a time prior to sanitation, but there's a lot of research recently that has shown some of the dark sides of sanitation, and this is one of them. Some of the stuff we're exposed to in a less sanitary environment actually helps our immune system to develop in a competent way. There are endogenous factors like chronic inflammation, SIBO, gut-brain axis dysfunction, and low melanocyte-stimulating hormone, or MSH, and genetic factors, for example, 70 percent of asymptomatic relatives of celiac disease patients are positive for intestinal permeability.

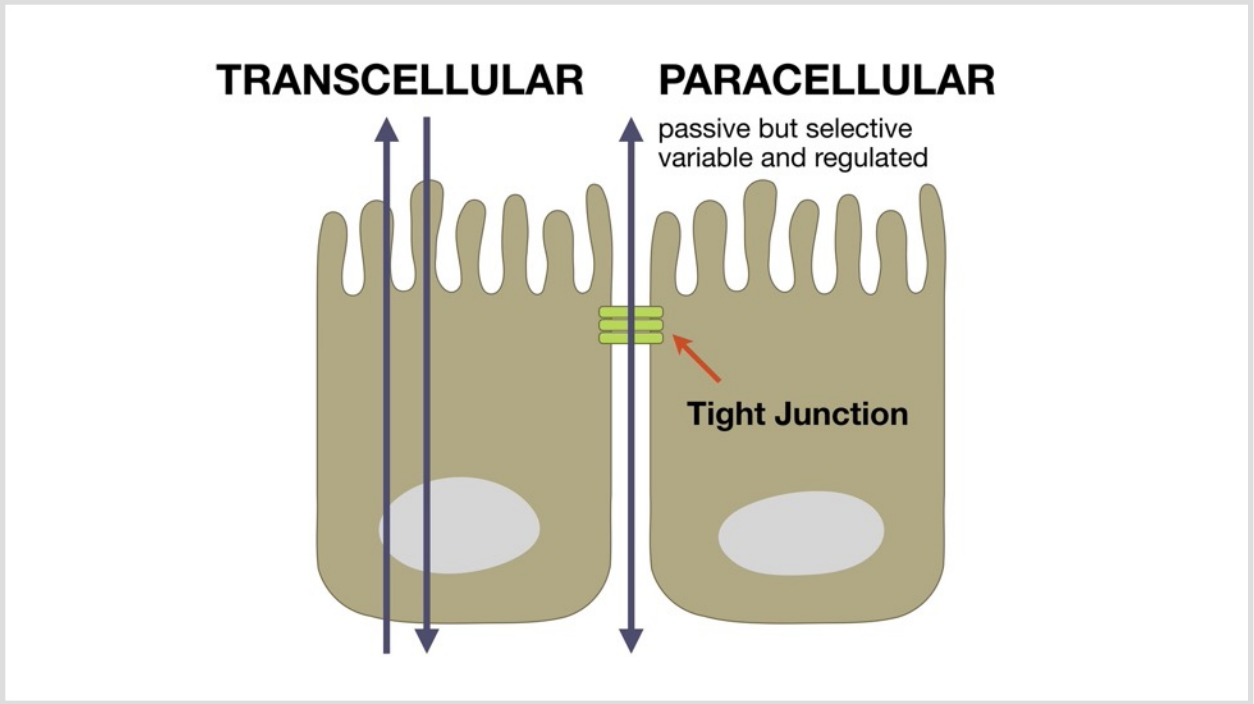
Diseases associated with intestinal permeability

Intestinal	Extra-intestinal
Gastric ulcers	Allergies
Infectious diarrhea	Autoimmune disease
Irritable Bowel Syndrome (IBS) & other functional GI diseases	Arthritis and other inflammatory conditions
Inflammatory Bowel Disease (IBD)	Obesity and metabolic disease
Celiac disease	Parkinson's, Alzheimer's, and other neurological conditions
Cancer (esophageal, colorectal)	Autism Spectrum Disorder, ADHD and other behavioral disorders

Adapted from: Bischoff et al. BMC Gastroenterology 2014, 14:189

Leaky gut used to be the province of so-called "quack" alternative medicine practitioners, probably the fastest way to get yourself laughed out of a room of conventional medicine practitioners if you started talking about it 20 or 30 years ago. Fortunately, that's changed significantly; today there are over 2,000 papers in PubMed on the subject of intestinal permeability, with an increase from 10 publications a year 30 years ago to over 100 per year now. It's become clear that the loss of barrier function can occur abruptly, for example, following a major organ trauma, or it can occur gradually, leading to chronic inflammatory disease. There is a wide range of conditions associated with intestinal permeability in the scientific literature, both intestinal conditions and extra-intestinal conditions, and new ones are discovered all the time. So, I've put a partial list of these conditions on the slide.

In terms of intestinal conditions, we're talking about gastric ulcers, infectious diarrhea, IBS and other functional GI disorders, inflammatory bowel disease, celiac disease, and both esophageal and colorectal cancer. Extra-intestinal diseases associated with intestinal permeability would be allergies, autoimmune disease, arthritis and other inflammatory conditions, obesity, metabolic disease, Parkinson's, Alzheimer's, and other neurological conditions, autism spectrum disorder, ADHD, and other behavioral disorders, to name a few.



There's several important molecules and mechanisms that have been identified that regulate the gut barrier. There are a lot of good resources to learn more about the nitty-gritty biomolecular details if you're interested in them. I'm going to focus on what I think you need to know in the context of testing and treatment to be able to help people with this. So, a combination of genetic susceptibility and environmental triggers causes the mucosal barrier to become permeable, and this leads to enlarged spaces between the cells of the gut wall and disassociation of tight junction proteins. The compromised barrier increases bacterial translocation and increases the concentration of endotoxins in tight junction proteins in the blood. So there are two key transport mechanisms of antigens through the gut barrier: transcellular and paracellular. Transcellular means through the cell, and that's where the antigen passes through the cell itself, whereas paracellular means between cells, where the antigen passes between the cells, and this is illustrated here on the slide:

Endotoxins that pass through the gut barrier into the blood elicit an autoimmune response. Bacterial toxins act as super-antigens to T-lymphocytes or provoke a response through something called molecular mimicry. Many bacteria have antigenic sites that are similar to human tissue antigens, including neuronal and brain tissue. So the body will attack both the endotoxins and the self tissue during the defensive response. This is why you see such a strong connection between autoimmune disease and leaky gut, and in fact, Dr. Alessio Fasano, who I interviewed on my podcast on this topic, and who's a pioneer in research on celiac disease, non-celiac gluten sensitivity, and intestinal permeability, and also the discoverer of zonulin, one of the proteins that regulates tight junction function, believes that intestinal permeability is a precondition of developing autoimmunity. In other words, you can't develop an autoimmune disease without having intestinal permeability, in Dr. Fasano's view. Even when autoimmunity is not triggered by intestinal permeability, leaky gut can result in chronic systemic inflammation, which is the root of

virtually all modern diseases and probably the primary mechanism by which intestinal permeability causes harm.

Methods of testing for intestinal permeability

Method	Test molecules
Lactulose mannitol permeability assay	Oligosaccharides
Antigenic permeability screen	LPS, actomyosin, occludin/zonulin antibodies
D-lactate	Bacterial lactate
Hemolysin	Pathogens (cell culture)
Butyrate production	BPB (PCR)
Zonulin	Tight junction protein

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Okay, let's move on to talk about testing for leaky gut. Before we talk about different types of testing available, let's talk about when to test for intestinal permeability. My opinion is that intestinal permeability is almost always caused by something else: poor diet, gut infections, chronic stress, etc. And consistent with the functional medicine approach, we want to remove all these triggers before addressing intestinal permeability specifically. In many cases, we found that you don't need to address intestinal permeability specifically; once you remove the triggers, the barrier integrity is restored without additional intervention because the intestinal epithelium regenerates itself every five days. So if you remove those triggers, you test and treat for things like SIBO, gut infections, other gut issues, you correct the diet and HPA axis dysfunction, and then if the patient is still having problems after you've done all that, that's when we would go forward and test for intestinal permeability.

In research settings, the common methods of screening are intestinal permeability assays, which we're going to talk about in more detail; assessment of biomarkers of epithelial integrity, such as soluble adhesion molecules; biomarkers of immunity or inflammation; and bacterial markers like circulating endotoxin. As I mentioned in the organic acids presentation, D-lactate is also being investigated as a marker for intestinal permeability. It's produced by acidophilus bacteria that inhabit the small intestine. However, in clinical practice, there are two primary methods of assessing leaky gut, and these are the intestinal permeability assays. So one is a lactulose-mannitol test, and the other is an antigenic permeability screen.