Leaky Gut and Inflammation

Brenda Powell MD
University of Washington
Cleveland Clinic

Disclosures

I have no relevant financial relationships to disclose

I will not discuss any off-label use and/or investigational use in my presentation

Objectives

- 1. Determine the importance of the microbiome to health
- 2. Describe the factors causing intestinal permeability and inflammation
- 3. Understand importance of treating intestinal permeability to restore health

The Gut in Our Lives

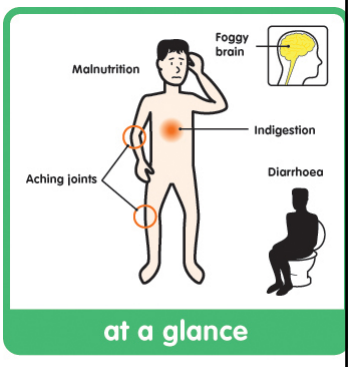
- To have a gut feeling
- To have a gut response
- Go with your gut
- Have a gut reaction
- Have a strong stomach
- Have a knot in your stomach
- To have guts
- My gut tells me
- Like a kick in the guts
- Gut wrenching
- Gut instinct
- No guts, no glory

Enlightenment and the Gut

- "Having awoken to unsurpassed, perfect enlightenment–I am endowed with a stomach whose digestion is regular, by means of which everything I eat, drink, chew and enjoy is digested with perfect ease, and I am free of disease and have left illness behind"

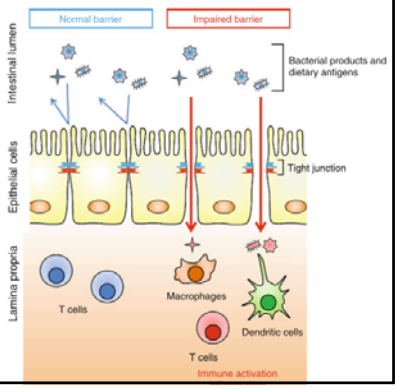
Patient Terminology

Doc, I think I have leaky gut with systemic candidiasis making me feel achy and causing brain fog and fatigue. Can you help me?



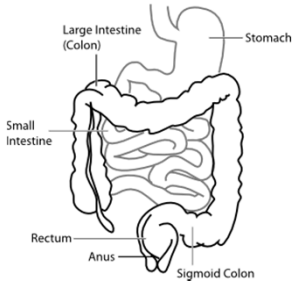
Medical Terminology

Doc, I think I have increased intestinal permeability allowing bacteria and endotoxin translocation through damaged tight junctions causing a chronic inflammatory response. Can I repair this?



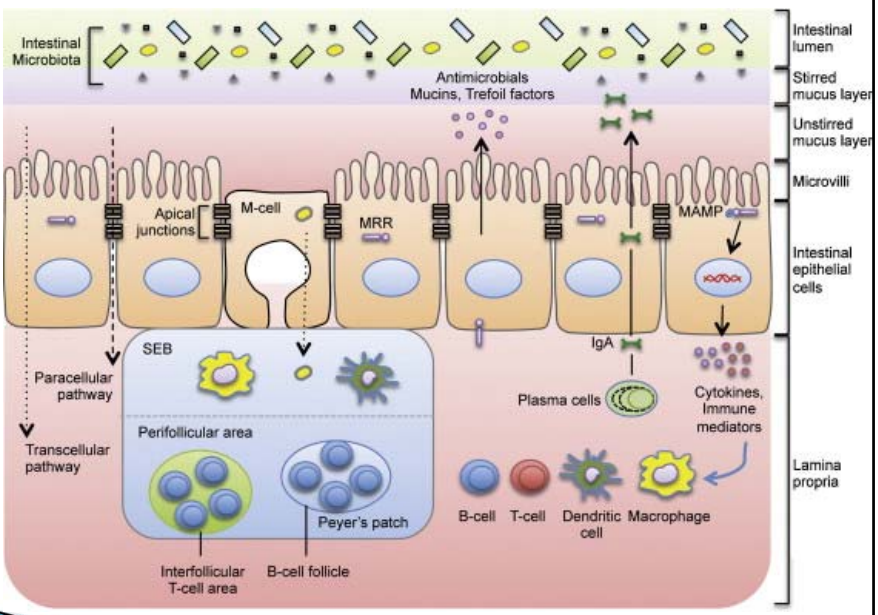
Intestinal Function

- Nutrient absorption
  - transcellular and paracellular transport
- Barrier to antigens and pathogens
- Secretion of enzymes and hormones
- Neuroendocrine function
- Immunologic function



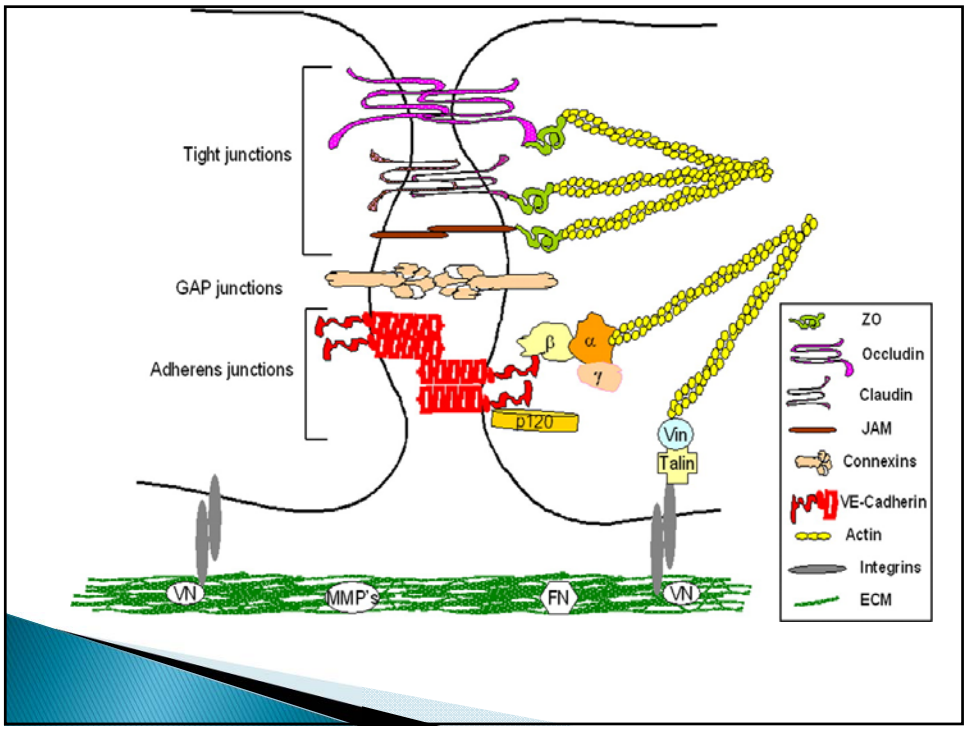
Epithelial Barrier Composition

- Lining of enterocytes, turnover every 4-5 days, just a single layer
- Barrier between the external environment and internal milieu by tight junctions between cells
- Mucus Layer
- Bacterial layer



Tight Junctions

- Claudin proteins are considered to be the structural backbone of TJ
- Claudins determine the selective permeability of the barrier
- Zonula occludens are the intracellular scaffold for the tight junction



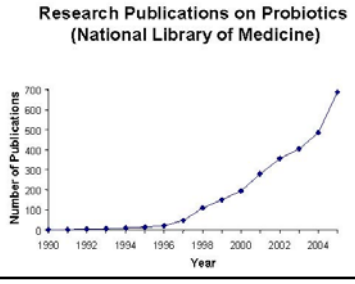
Mucus Layer

Goblet cells secrete mucin glycoproteins and MUC2

MUC2 is the major mucin making up the mucus coat of the intestinal epithelium

Microflora

- Friend, foe and bystander
- Host and microbe interactions bidirectional
- Immune modulators, nutrition, inflammation
- Diet is the primary modifier of the microbiota

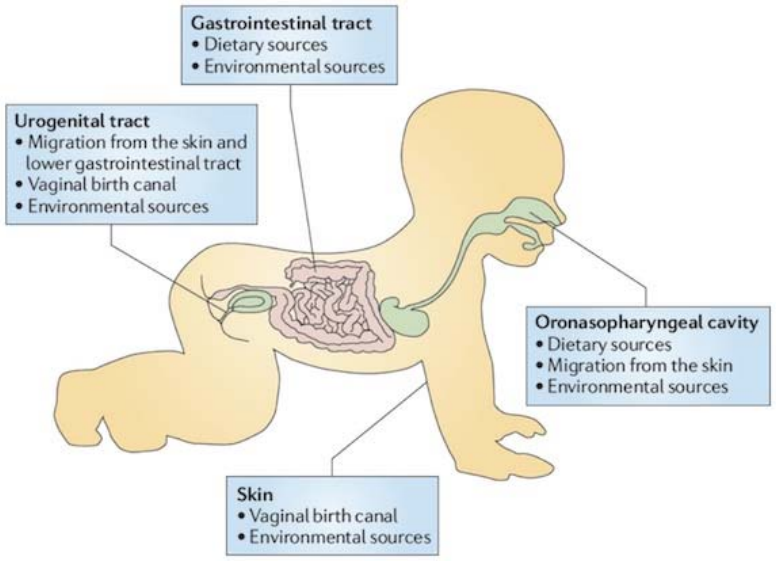


Bacterial Layer

- Inhabited by 10^{14} microbes
- Competes with pathogens for nutrients
- Fermentation of non-digestible carbohydrates to Vitamin K, biotin, folate, riboflavin, cobalamin
- Production of SCFA butyrate and acetate
- Improved tight junctions
- Improved UGI motility
- Production of satiety hormones

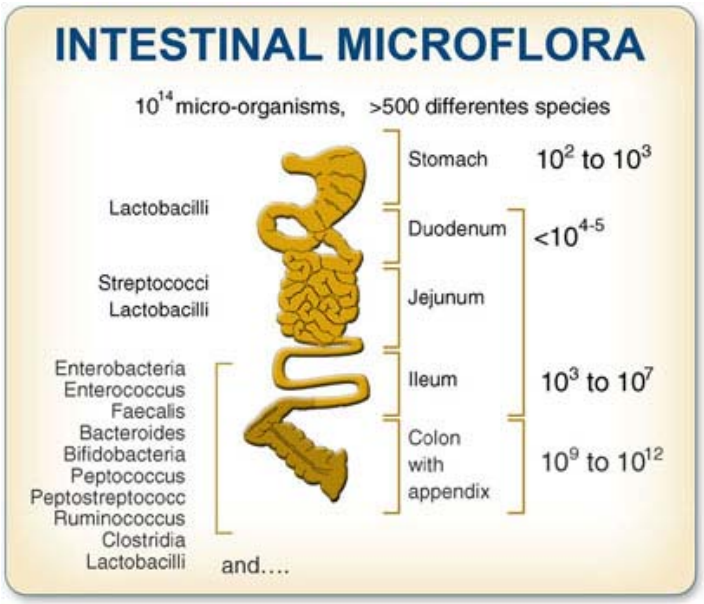
Bacterial Colonization

- Colonization begins at birth, lactobacillus from the vaginal canal
- The infant is exposed to several environmental sources of bacteria (e.g. skin, mouth, mother's milk)
- Gut microbiota has fully matured by the first 1-2 years of life
- 5-day course of oral antibiotics modifies human gut microbiota for up to 4 weeks



Gut Bacteria

- Firmicutes (~75%)
  - Tolerates pH< 5.5, produces butyrate
- Bacteroidetes(~20%),
  - Tolerates pH >6.5
- Lesser contributions from Proteobacteria and Actinobacteria
- Lowering carbohydrate/soluble fiber reduces butyrate production



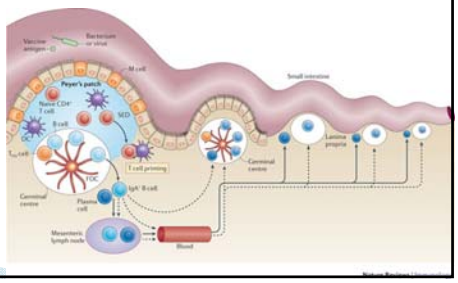
Intestinal Barrier to Dysbiosis

- Degradation of bacteria and antigens by gastric acid, bile acids and digestive enzymes
- Commensal bacteria inhibit colonization of pathogens by production of antimicrobial substances, enhance enterocyte function by producing SCFAs acetate and butyrate
- Water, glycocalyx, and mucus layer prevent bacterial adhesion and produce antimicrobial substances

GALT

Gut-associated lymphoid tissue (GALT) is comprised chiefly of aggregated (Peyer's patches, PPs) and isolated lymphoid follicles (ILFs)

70% of the immune Tissue is in the gut



Oral Tolerance

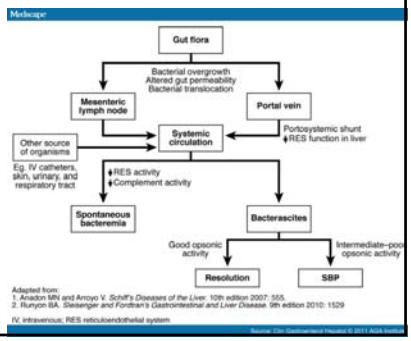
- At birth the intestines have high permeability
- Exclusive breast feeding provides protection over the next 6 months of maturation
- During this time the immune system is maturing, recognizing self and commensal bacteria
- Thought that exposure to immunogenic foods at this time can initiate food allergies

Intestinal Permeability

- Loss of the tight junctions and the epithelial layer
- Bacteria and endotoxins translocate through the paracellular route
- Then detected by dendritic cells
- Immune reaction in Peyer's patches
- General inflammatory reaction
- Possible autoantibody production or antibody cross reaction with self

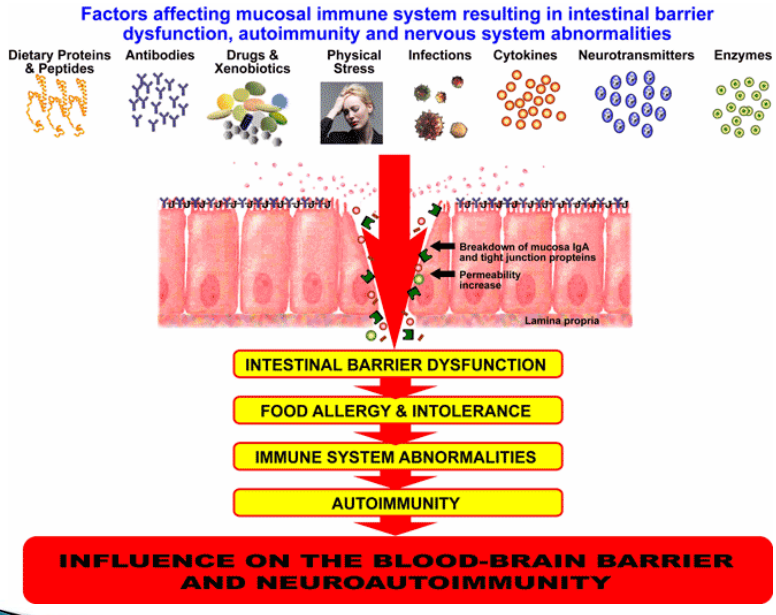
Serious Causes/Consequences

- Cause of sepsis and death in burn patients
- Cause of sepsis in post-op patients
- Seen in HIV
- Observed in inflammatory bowel disease



Disruption of the Barrier

- Food allergies
- Bile acid malabsorption
- High-fat diet
- Stress and inflammation,
  - Mast cell receptors to cortisol
  - Genetic predisposition to increased inflammatory response
- Dysbiosis
  - Impair through release of inflammatory mediators
- Smoking breaks down the barrier
- Alcohol breaks down the barrier

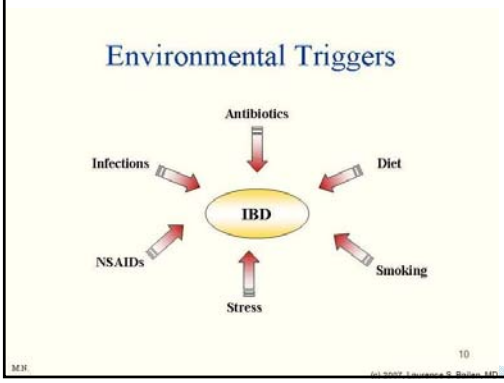


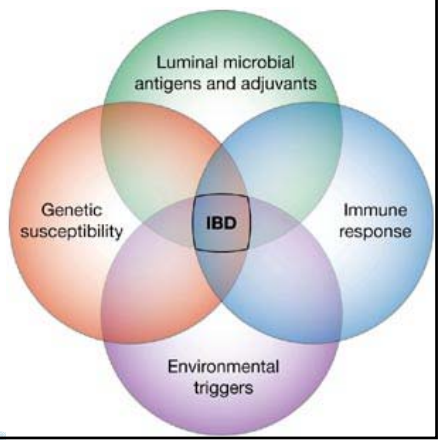
Intestinal Permeability

- Increased intestinal permeability is implicated as a cause of autoimmune, inflammatory, and atopic diseases
- Increased with aging and stress
- Combination of genetics and antigens
- Associated with deficiencies of Vitamin D, Zinc, Magnesium, Calcium, B12, and Vitamin A

Gastrointestinal Disease

- Ulcerative colitis, Crohn's disease, celiac disease and irritable bowel disease are examples of diseases of the GI tract with increased permeability



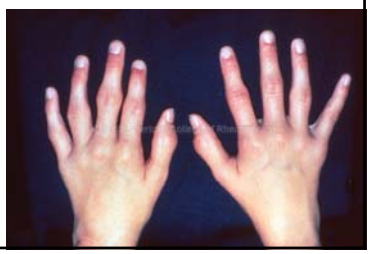


Disease Associations

- Crohn's
  - *seronegative spondyloarthropathy*, erythema nodosum, autoimmune hemolytic anemia, uveitis
- Ulcerative Colitis
  - *seronegative spondyloarthropathy*, erythema nodosum, autoimmune hemolytic anemia, uveitis
- Celiac Disease
  - diabetes mellitus type 1, non-Hodgkin's lymphomas
- Irritable Bowel Disease
  - interstitial cystitis, fibromyalgia, endometriosis

Diseases Associated with Increase Intestinal Permeability

- Diabetes mellitus type 1
- Multiple sclerosis
- Rheumatoid arthritis
- Ankylosing spondylitis
- Irritable bowel disease
- Schizophrenia



Type 1 Diabetes

- ~50% have increased serum zonulin levels associated with increased intestinal permeability
- 25% of unaffected family members have increased zonulin levels
- Suggests loss of intestinal permeability a part of this process, but needs an exposure to antigen
- Association of Ab to Glo-3a wheat protein and islet cell auto-immunity

Progression to Disease

- The host must have a genetic susceptibility
- The host must be exposed to the antigen in the intestinal lumen
- The antigen must be presented to the GALT through paracellular transit
- The permeability of the intestine must be altered to allow this
- The key modulator is upregulation of zonulin, opening the gates previously closed by tight junctions

Intestinal Permeability and Autoimmune Diseases

- Autoimmune diseases involve a miscommunication between innate and adaptive immunity
- The continuous stimulation by nonself-antigens seems to be necessary to perpetuate the process
- Loss of the protective function of mucosal barriers that interact with the environment is necessary for autoimmunity to develop

Celiac Disease as an Example

- Genetic predisposition through HLA genes
- The gliadin antigen
- A highly specific humoral autoimmune response against tissue transglutaminase auto-antigen
- An early loss of tight junctions mediated through increase of zonulin
- Reversed with the removal of the environmental antigen

The Digestive Tract and Obesity

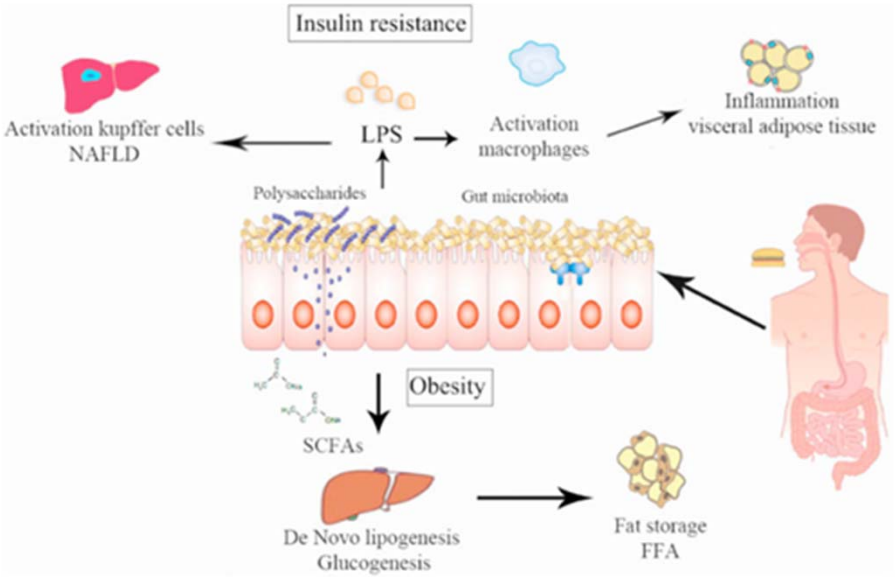
- Toll-like receptors activated by bacterial lipopolysaccharides
- TLR present in adipocytes, immune cells, epithelial cells and create an inflammatory response
- Diet alters the gut microbiota: protein vs. vegetables
- Altered gut microbiota, increased gut permeability

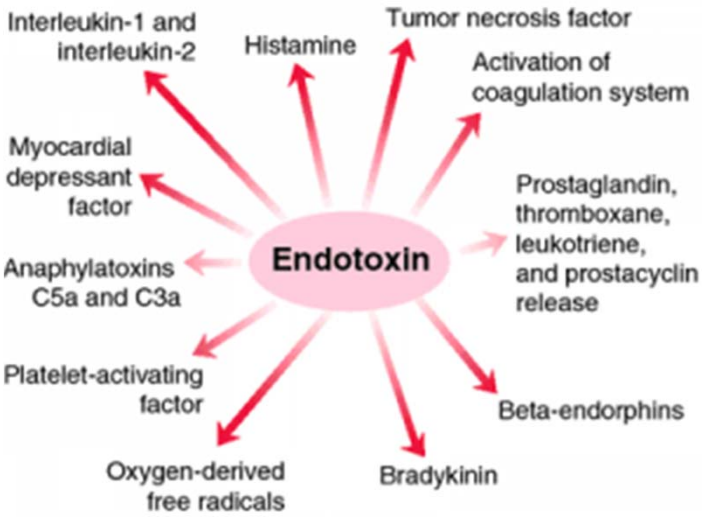
Mediterranean diet decreases inflammatory disease without weight loss

Endotoxemia and Inflammation

- Bacterial lipopolysaccharides cause inflammation in the obesity state
- High-fat meals increase intestinal permeability through changes in occludin and zonulin
- Bacterial lipopolysaccharides increased after a high fat meal via translocation
- Increase in inflammatory markers

such as NF-kB


Insulin resistance
Activation kupffer cells
NAFLD
LPS
Activation
macrophages
Inflammation
visceral adipose tissue
Polysaccharides
Gut microbiota
Obesity
SCFAs
De Novo lipogenesis
Glucogenesis
Fat storage
FFA


Interleukin-1 and
interleukin-2
Histamine
Tumor necrosis factor
Activation of
coagulation system
Myocardial
depressant
factor
Endotoxin
Prostaglandin,
thromboxane,
leukotriene,
and prostacyclin
release
Anaphylatoxins
C5a and C3a
Platelet-activating
factor
Beta-endorphins
Oxygen-derived
free radicals
Bradykinin

IBS and Permeability

- Studies have shown increased permeability
- Increased number of mast cells in IBS
- Mast cells have corticotrophin releasing factor receptors
- Increased permeability as measured by L:M ratios correlated to increased severity of pain
- Increased number of mast cells correlated with fatigue
- Decreased glutamine synthetase in IBS

IBS and Inflammation

- An abnormal IL-10/IL-12 ratio in patients with irritable bowel syndrome is indicative of a proinflammatory Th-1 state; has been shown to be normalized by Bifidobacterium infantis

Atopy and Probiotics

- Lactobacillus given to pregnant women reduced atopy in infants
- Lactobacillus given to infants reduced the incidence of atopy
- Probiotics given to infants with atopy reduced the severity of disease

Treating Increased Permeability

- Probiotics
  - increase barrier function
  - butyric acid, acetic acid, propionic acid
  - Treat the dysbiosis
- Glutamine
  - energy source for the rapidly dividing enterocytes,
  - improves the tight junction

Elimination Diet, 4 weeks

- Oranges
- Egg
- Dairy
- Gluten
- Beef, pork, shellfish
- Soy
- Corn
- Alcohol, coffee, soda
- Sugars, artificial sweeteners

Conclusion

- The intestine is a barrier to antigens
- The microbiome improves this function and the health of the enterocytes
- 70% of the immune system lines the gut
- Integrity of the tight barriers prevent translocation of antigens and endotoxins
- These then can stimulate an innate or adaptive immune reaction
- Causing inflammation and subsequent disease

References

- N Engl J Med. 2012 Oct 25;367(17):1626-35. doi: 10.1056/NEJMra1207068.
- Peripheral mechanisms in irritable bowel syndrome.
- Camilleri M.
-
- Handb Exp Pharmacol. 2012;(214):473-97. doi: 10.1007/978-3-642-30726-3_21.
- Treatment of irritable bowel syndrome: sex and gender specific aspects.
- Voß U, Lewerenz A, Nieber K.
-
- Nat Rev Microbiol. 2012 Nov;10(11):735-42. doi: 10.1038/nrmicro2876. Epub 2012 Sep 24.
- The interplay between the intestinal microbiota and the brain.
- Collins SM, Surette M, Bercik P.

References

- Am Fam Physician. 2012 Sep 1;86(5):419-26.
- Diagnosis and management of IBS in adults.
- Wilkins T, Pepitone C, Alex B, Schade RR.
-
- Curr Gastroenterol Rep. 2012 Oct;14(5):439-45. doi: 10.1007/s11894-012-0284-2.
- Antibiotics for irritable bowel syndrome: rationale and current evidence.
- Sachdev AH, Pimentel M.
-
- BMJ. 2012 Sep 4;345:e5836. doi: 10.1136/bmj.e5836.
- Irritable bowel syndrome.
- Ford AC, Talley NJ.

- *Physiol Rev* • VOL 91 • JANUARY 2011
- Zonulin and its regulation of intestinal barrier function: the
- biological door to inflammation, autoimmunity, and cancer
- Fasano A.

References

- Curr Gastroenterol Rep. 2012 Oct;14(5):446-52. doi: 10.1007/s11894-012-0281-5.
- The colonic microbiota and colonic disease.
- Shanahan F.
-
- Am J Physiol Gastrointest Liver Physiol. 2012 Oct;303(7):G775-85. doi: 10.1152/ajpgi.00155.2012. Epub 2012 Jul 26.
- Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome.
- Camilleri M, Lasch K, Zhou W.
-
- Expert Opin Drug Saf. 2012 Sep;11(5):841-50. doi: 10.1517/14740338.2012.708732. Epub 2012 Jul 27.
- Safety evaluation of lubiprostone in the treatment of constipation and irritable bowel syndrome.
- Chamberlain SM, Rao SS.

References

- J Clin Gastroenterol. 2012 Oct;46(9):748-51. doi: 10.1097/MCG.0b013e31825a2ff2.
- The role of effective clinician-patient communication in the management of irritable bowel syndrome and chronic constipation.
- Di Palma JA, Herrera JL.
-
- Curr Opin Clin Nutr Metab Care. 2012 Sep;15(5):489-93. doi: 10.1097/MCO.0b013e328356662d.
- Intestinal gas: has diet anything to do in the absence of a demonstrable malabsorption state?
- Serra J.
-
- Am J Gastroenterol. 2012 Oct;107(10):1486-93. doi: 10.1038/ajg.2012.194. Epub 2012 Jul 10.
- Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights.
- Strate LL, Modi R, Cohen E, Spiegel BM.

References

- Curr Gastroenterol Rep. 2012 Aug;14(4):283-9. doi: 10.1007/s11894-012-0268-2.
- Meditation over medication for irritable bowel syndrome? On exercise and alternative treatments for irritable bowel syndrome.
- Asare F, Störsrud S, Simrén M.
-
- Expert Rev Gastroenterol Hepatol. 2012 Jun;6(3):383-98. doi: 10.1586/egh.12.9.
- Intestinal microbiota, pathophysiology and translation to probiotic use in patients with irritable bowel syndrome.
- Almansa C, Agrawal A, Houghton LA.
-
- Curr Gastroenterol Rep. 2012 Aug;14(4):290-6. doi: 10.1007/s11894-012-0270-8.
- When is irritable bowel syndrome not irritable bowel syndrome? Diagnosis and treatment of chronic functional abdominal pain.
- Grover M.

References

- Cochrane Database Syst Rev. 2012 May 16;5:CD005111. doi: 10.1002/14651858.CD005111.pub3.
- Acupuncture for treatment of irritable bowel syndrome.
- Manheimer E, Cheng K, Wieland LS, Min LS, Shen X, Berman BM, Lao L.
-
- Neurogastroenterol Motil. 2012 Jun;24(6):503-12. doi: 10.1111/j.1365-2982.2012.01921.x.
- Intestinal barrier function in health and gastrointestinal disease.
- Camilleri M, Madsen K, Spiller R, Greenwood-Van Meerveld B, Verne GN.
-
- Am J Med. 2012 Jun;125(6):538-44. doi: 10.1016/j.amjmed.2011.11.006.
- Review: Management of postprandial diarrhea syndrome.
- Money ME, Camilleri M.

References

- Nat Rev Gastroenterol Hepatol. 2012 Feb 28;9(5):295-9. doi: 10.1038/nrgastro.2012.15.
- New understanding of gluten sensitivity.
- Volta U, De Giorgio R.
-
- Clin Rev Allergy Immunol. 2012 Jun;42(3):279-87. doi: 10.1007/s12016-010-8223-1.
- Cutting-edge issues in celiac disease and in gluten intolerance.
- Bizzaro N, Tozzoli R, Villalta D, Fabris M, Tonutti E.
-
- Clinics (Sao Paulo). 2010 Jun;65(6):635-43. doi: 10.1590/S1807-59322010000600012.
- Possible links between intestinal permeability and food processing: A potential therapeutic niche for glutamine.
- Rapin JR, Wiernsperger N.

References

- Expert Opin Investig Drugs. 2009 Mar;18(3):349-58. doi: 10.1517/13543780902780175 .
- Review of rifaximin as treatment for SIBO and IBS.
- Pimentel M.
-
- Ann Pharmacother. 2008 Mar;42(3):408-12. doi: 10.1345/aph.1K345. Epub 2008 Feb 26.
- Rifaximin treatment for symptoms of irritable bowel syndrome.
- Fumi AL, Trexler K.
-
- Am J Clin Nutr. 2007 May;85(5):1185-96.
- Histamine and histamine intolerance.
- Maintz L, Novak N.

References

- Regulation of tight junction permeability by intestinal bacteria and dietary components. J. Nutr. 141: 769–776, 2011
- Diet, microbiome, and the intestinal epithelium: an essential triumvirate?. Biomed Res Int 2013;2013:425146
- Leaky Gut and Autoimmune Diseases. Clinic Rev Allerg Immunol (2012) 42:71–78
- Potential mechanisms for the emerging link between obesity and increased intestinal permeability. Nutrition Research 32 (2012) 637–647
- Regulation of intestinal epithelial permeability by tight junctions. Cell. Mol. Life Sci. (2013) 70:631–659