Small Bowel Bacterial Overgrowth and Fibromyalgia (FMS)

• Lactulose breath tests: 153 patients (42 FMS, 111 IBS) and 15 healthy controls
• All 42 FMS and 93 (84%) of IBS had an abnormal LBT, but only 3 (20%) of controls.
• Breath hydrogen correlated with the degree of pain in FMS.

• Cross-reactivity to bacterial antigens leads to immune-mediated damage
• Antibodies against microbes bind to cells carrying HLA antigens
• Inflammation from complement or cytokine cascades, T cell activation e.g. RA
Low Fermentation Diet

• Basic diet: no wheat, sucrose, lactose
• Additional restrictions
  - no glutinous grains
  - no cereal grains, potatoes
  - restrict fruits, juices, honey
  - avoid legumes
  - cook all vegetables
Tight Junction

- Microvillus
- Tight junction
- Adherens junction

0.5 µm scale bar
The intestinal epithelium is the site of vectorial transport...between the intestinal lumen and the circulation. The net effect of transport is regulated by the tightness (or leakiness) of the barrier and vice versa. Both transport and barrier functions are physiologically regulated, and both can be dramatically altered under disease conditions.”
MECHANISMS WHICH SUPPORT NORMAL INTESTINAL PERMEABILITY

• Intestinal mucus
• Secretory IgA
• Mucosal epithelium
• Intramural macrophages
• Intramural lymphocytes
  – intra-epithelial
  – in Peyer’s patches
TWO TYPES OF EPITHELIAL PERMEABILITY

• Trans-Cellular

• Para-Cellular
TRANS-CELLULAR PERMEABILITY

• The principal route for the absorption of solutes, fluid and macromolecules
PARA-CELLULAR PERMEABILITY IS LIMITED BY CELL ADHERANCE MOLECULES (CAMs)

- Tight junctions contain claudins
- Adherens junctions and desmosomes contain cadherins
- Contraction of the cytoskeleton opens junctions (glucose absorption is a stimulus)
FIGURE 3. Schematic representation of adhesive cell–cell contacts by classical cadherins, desmosomal cadherins, and LI-cadherin in the intestinal mucosa (tj, tight junctions; aj, adherens junctions; d, desmosomes).
CAUSES OF INCREASED PARA-CELLULAR PERMEABILITY

• Infectious agents
  – Parasites
  – Bacteria
  – Viruses
  – Yeasts

Continued
CAUSES OF INCREASED PARA-CELLULAR PERMEABILITY

• Enterotoxins
  – Ethanol
  – NSAIDs*  
  – Cytotoxic drugs

• Dysoxia
  – Ischemia
  – Reactive oxygen species
PSYCHOLOGICAL STRESS CAN INCREASE GUT PERMEABILITY THROUGH A CHOLINERGIC MECHANISM

• Rats: cold stress increases para-cellular permeability.
  - This effect is greater when cholinesterase activity is weak
  - The effect is blocked by atropine
  - It may depend upon vagal activation of mast cells

• Similar effects occur in humans
DIET ALTERS INTESTINAL PERMEABILITY

• Fasting:
  – Controls: Increased I.P.
  – R.A.: Decreases I.P.
• Mucosal Inflammation increases I.P.
  – Food allergy
  – “Idiopathic” (celiac disease)
• Increased I.P. induced by:
  – Low-fiber diets
  – Carrageenan
  – Pectin/guar gum
  – Castor oil
  – Alcohol
  – Allergens

Continued
Intestinal Permeability

- Incomplete protein digestion (hypo/achlorhydria, pancreatic insufficiency)
- Pathogenic bacteria produce polyamines (toxic forms of amino acids)
- Polyamines induce damage to integrity of intestinal cells - inflammation
- Tight junctions become ‘leaky’
Other factors

- *Dysbiosis* – bacterial imbalance
- *Chronic Stress* - inhibits peristalsis, reduced IgA, immune suppression,
- *Parasites* - irritation to intestinal cells
- *Candida* - fungal form grows through GIT
- *Alcohol consumption*
- *Low fibre diet* - slow transit, promotes dysbiosis
- *NSAID’s* - damage intestinal cells
- *Contraceptive pill, steroid drugs* - promote fungi overgrowth
Leaky Gut Symptoms

- Abdominal pain
- Bloating
- Flatulence
- Diarrhoea
- Constipation
- Indigestion
- Skin rashes

- Fatigue
- Poor immunity
- Anxiety
- Mood swings
- Recurrent UTI’s
- Chronic joint pain
- Chronic muscle pain
Associated conditions

- Auto-immune diseases
- Allergies
- Celiac disease
- Crohn’s disease
- Malabsorption
- Skin irritations
- Asthma
Tests

- Intestinal permeability test - urine (lactulose/mannitol)
  - Low mannitol/normal lactulose = possible malabsorption
  - Elevated lactulose or elevated ratio (>0.03) = possible inflammation
Allergies

• Intestinal barrier broken down
• Substances passing into blood from gut
• Cytokines initiate immune response
• Antibodies formed
• IgG mediated food intolerance
• Usually proteins (gluten, casein etc)
Leaky Gut & the Liver

- Increased P450 enzyme activity
- Increased free radical synthesis in liver
- Potential damage to hepatic cells
- Toxic by-products in bile
- Bile released into GIT. Exacerbates inflammation and permeability
- GSH levels affected by extra detoxification
The Vicious Circle of Chronic Toxic Overload

- Liver Overload
  - Alcohol
  - Cigarette Smoke
  - Rich Foods
  - Chocolates

- Intestinal Permeability
  - Candida
  - Dysbiosis

- Detoxification Problems
- Oxidative Stress
- Free Radical Production

- Health Problems
  - Joint / Muscular
  - Cardiovascular
  - Gastrointestinal
  - Chronic Fatigue
  - Infections

- May treat with Drugs
  - NSAIDS
  - Painkillers
  - Antibiotics
  - etc.
Leaky Gut & NSAIDS

- NSAID’s shown to increase permeability between cells
- Disruption to metabolism of anti-inflammatory prostaglandins
- Damage to intestinal cells
Leaky Gut & Stress

- Stress states induce increased cortisol secretion from adrenals
- High cortisol states depress IgA levels
- Tissue repair and healing slowed by high cortisol
LEAKY GUT SYNDROMES

• Enteritis, colitis
  Infectious/inflammatory
• Arthritis, chronic
  inflammatory
• Food allergic disorders
• AIDS

• CFIDS
• MCS
• Chronic pancreatic disease
• Chronic non-infectious hepatitis
• Acne
• Psoriasis
Intestinal Permeability and Food Allergy

- Increased baseline permeability
- Marked increase after challenge
- Increase blocked by sodium cromoglycate
ABNORMAL INTESTINAL PERMEABILITY IN FOOD ALLERGY

• 42% of children with eczema had reduced jejunal villus: crypt ratios (malabsorption)
• Increased PEG-4K absorption (leakiness)
• Increased PEG absorption blocked by cromolyn pre-treatment
• Increased fasting lactulose absorption in adults with food allergy (eczema, hives); further increase with offending food blocked by cromolyn 300mg
• “Evaluation of I.P… provides an effective means of diagnosing food allergy”


Continued
INTESTINAL PERMEABILITY AND CROHN’S DISEASE

- Patients have increased I.P.
- First degree relatives have high I.P. and excessive increase in I.P. when exposed to aspirin
- Patients have abnormal reactivity of mucosal lymphocytes to normal gut flora and Candida antigens
- Permeability index in patients with Crohn’s disease (n=72) and controls (n=30).
• Probability of a relapse within 1 year
HYPER-PERMEABILITY IN RHEUMATOID ARTHRITIS

• NSAIDs increase intestinal permeability
• Increased I.P. allows sensitization to gut flora
• Bacterial sensitization causes enteritis and formation of circulating immune complexes
HYPER-PERMEABILITY IN RHEUMATOID ARTHRITIS (continued)

• I.P. is further increased
• Systemic inflammation exacerbates
• Metronidazole and minocycline break the cycle
PROTEUS AND RHEUMATOID ARTHRITIS (RA)

- Frequency of HLA-DR4 in RA patients: 50 to 75%. Those without HLA-DR4 usually have DR-4 + mothers.
  - Controls: 20% HLA-DR4 positive

- RA patients often have elevated serum IgG titers to Proteus spp that cross-react with HLA-DR4
TREATMENT OF HYPER-PERMEABILITY

• Avoid enterotoxins e.g. Lectins
• Treat intestinal infection/bacterial overgrowth with antimicrobials
• Diet: high nutrient density
  – non-irritating
  – allergen-free
HELPING TO REPAIR THE DAMAGED INTESTINE

• Glutamine
• Essential fatty acids
• Antioxidants
  – Glutathione
  – Bioflavonoids
  – Vitamin E
  – Gamma-oryzanol
• Epidermal growth factor
• Colostrum
Treatment protocol

- Elimination diet (establish allergens)
- Remove alcohol/NSAID’s if possible
- Chew food - stimulates saliva that contains epidermal growth factor (EGF). Purified EGF has been shown to promote healing of ulcers
- Anti-candida programme?
Supplements

- Betaine Hydrochloride/Histadine
- Pancreatic enzymes
- EFA’s (EPA and GLA)
- Fibre (psyllium, flax seed meal)
- Probiotics (dependent on patient, minimum 4 strains, preferably 6-8) - inhibition of pathogenic bacteria responsible for polyamines
- L-Glutamine. (7mg/kg/day)
- Zinc (25-100mg/day)
- Vitamin D3 (S-T:4-8000iu/day, L-T:2-4000/day)
- Turmeric (curcumin) (100-240mg/day)
- Goldenseal - Mucous membrane soothing, anti-microbial properties
- Magnesium - cell replication/energy metabolism
- Zinc. - tissue repair
- Vitamin A. - cell repair
Glutamine

• Major source of metabolic fuel for intestinal epithelial cells

• Major source of fuel for intestinal immune cells (SIgA, macrophages, lymphocytes etc.)

• Animal fed a glutamine free diet found to have depressed SIgA levels