# Loss of Glutamine, the Th2 Shift, and loss of oral tolerance

Connecting Key Factors in Persistent GI Problems.

## Cogence Clinical Pearl

***What the research says…***

In this Clinical Pearl, we continue our discussion of intestinal immunology with remarkable papers from *Nature Immunology, Clinical Nutrition, Nutrition & Metabolism,* and *Nature Reviews Immunology.* The papers make **three powerful points:** 1) inflammation, not diet, determines glutamine level, 2) intestinal inflammation drives Th2 polarization, 3) arabinogalactans are fermented to short chain fatty acids (SCFA's), which are known to improve oral tolerance.

***Application…***

Inflammation lowers glutamine levels. Low glutamine drives leaky gut, which yields food sensitivity reactions, which drives inflammation, creating a loop.

Inflammation ⇒ low glutamine ⇒ leaky gut ⇒ food sensitivity ⇒ inflammation (loop)

And, when intestinal epithelial cells get inflamed, they produce TSLP, IL-25, and IL-33.

Epithelial inflammation ⇒ Th2 cytokine production ⇒ Th2 dominance ⇒ loss of Th1 ⇒ loss of immune surveillance against pathogenic organisms ⇒ dysbiosis ⇒ epithelial inflammation (loop)

To address food intolerances, many people eliminate grains and other foods that contain fiber that the body ferments to short chain fatty acids that promote oral tolerance, the mechanism by which we tolerate our food. Loss of SCFA's yields greater intolerance of food, driving more inflammation.

To address this, four steps are necessary: 1) restore glutamine levels, 2) promote oral tolerance, 3) modulate Th2 and support Th1, 4) quiet GI inflammation.

1) restore glutamine levels – this is done by giving **glutamine**;

2) promote oral tolerance – this is done by increasing SCFA's through the fermentation of **arabinogalactans and other fibers**. And, because arabinogalactans also promote NK cell activation and interferon gamma, they also help promote Th1 response;

3) modulate Th2 – with **perilla, astragalus, quercetin, NAC**; and support Th1 – you'll get some help for this from the **arabinogalactans. Add berberine, baicalin, ginger, sulforaphanes;**

4) quiet GI inflammation – this is done with **curcumin, glutathione, and other substances** we're all familiar with.

***The Research…***

**Inflammation rather than nutritional depletion determines glutamine concentrations and intestinal permeability.**
Clin Nutr. 2004 Oct;23(5):1209-16. Hulsewé KW, van der Hulst RW, Soeters PB, et al.
***(Color and bold added.)***

**Abstract**
AIM: Nutritional depletion has been correlated with low plasma and mucosal glutamine concentrations and with increased intestinal permeability. Since nutritional depletion often is associated with (chronic) inflammatory stress, this study was designed to establish the influence of depletion and inflammation on glutamine concentrations and gut barrier function.
METHODS: Anthropometric parameters were calculated from 26 patients who required artificial nutrition. Glutamine concentrations in plasma and gut mucosa, gut permeability and mucosal morphology were assessed. For determination of the degree of inflammation erythrocyte sedimentation rates and (pre)albumin concentrations were measured. On the basis of these parameters patients were divided into two groups having significant inflammatory stress or not. Similarly, a depleted and a non-depleted group was formed based on percentage ideal body weight, fat-free mass index (FFMI) and percentage weight loss. Glutamine concentrations, gut permeability and villus morphology were compared between the groups.
RESULTS: **The presence of inflammatory activity had significant negative effects on glutamine concentrations in contrast to the presence or absence of nutritional depletion. Similarly, intestinal permeability increased during active inflammation but not in depleted patients. FFMI but not inflammation was related to villus height.**
CONCLUSIONS: **The presence of inflammation significantly affects glutamine concentrations and gut permeability, in contrast to the presence of depletion of body cell mass per se. On the other hand, villus morphology is not influenced by changes in systemic inflammatory activity whereas nutritional status possibly does affect villus height.**

**Sensing the outside world: TSLP regulates barrier immunity.**
Nat Immunol. 2010 Apr;11(4):289-93. Ziegler SF, Artis D.
***(Color and bold added.)***
**Abstract**
Thymic stromal lymphopoietin (TSLP) is an interleukin 7 (IL-7)-like cytokine originally characterized by its ability to promote the activation of B cells and dendritic cells (DCs). Subsequent studies have shown that TSLP promotes T helper type 2 (TH2) cell responses associated with immunity to some helminth parasites and the pathogenesis of many inflammatory diseases, including atopic dermatitis and asthma. This review will focus on recent findings indicating that in addition to influencing B cell and DC function, **TSLP can promote TH2 cytokine-associated inflammation by directly promoting the effector functions of CD4+ TH2 cells,** basophils and other granulocyte populations while simultaneously limiting the expression of DC-derived proinflammatory cytokines and promoting regulatory T cell responses in peripheral tissues.

**Does larch arabinogalactan enhance immune function? A review of mechanistic and clinical trials.**
Nutr Metab (Lond). 2016 Apr 12;13:28. Dion C, Chappuis E, Ripoll C.
***(Color and bold added.)***
**Abstract**
The common cold is a viral infection with important economic burdens in Western countries. The research and development of nutritional solutions to reduce the incidence and severity of colds today is a major focus of interest, and larch arabinogalactan seems to be a promising supportive agent. Arabinogalactan has been consumed by humans for thousands of years and is found in a variety of common vegetables as well as in medicinal herbs. The major commercial sources of this long, densely branched, high-molecular-weight polysaccharide are North American larch trees. The aim of this article is to review the immunomodulatory effects of larch arabinogalactan derived from Larix

laricina and Larix occidentalis (North American Larix species) and more specifically its role in the resistance to common cold infections. In cell and animal models, larch arabinogalactan is capable of **enhancing natural killer cells and macrophages** as well as the secretion of pro-inflammatory cytokines. In humans a clinical study demonstrated that **larch arabinogalactan increased the body's potential to defend against common cold infection. Larch arabinogalactan decreased the incidence of cold episodes by 23 %.** Improvements of serum antigen-specific IgG and IgE response to Streptococcus pneumoniae and tetanus vaccination suggesting a B cell dependent mechanism have been reported in vaccination studies with larch arabinogalactan, while the absence of response following influenza vaccination suggests the involvement of a T cell dependent mechanism. These observations suggest a role for larch arabinogalactan in the improvement of cold infections, although the mode of action remains to be further explored. Different hypotheses can be envisaged as larch arabinogalactan can possibly act indirectly through microbiota-dependent mechanisms and/or have a direct effect on the immune system via the gut-associated lymphoid tissue (GALT).

**The Gut Microbiota from Lean and Obese Subjects Contribute Differently to the Fermentation of Arabinogalactan and Inulin.**
PLoS One. 2016 Jul 13;11(7):e0159236. Aguirre M, Bussolo de Souza C, Venema K.
***(Color and bold added.)***
**Abstract**
BACKGROUND: An aberrant metabolic activity or a compositional alteration of the gut microbiota has been proposed as a factor that makes us more prone to disease. Therefore, we explored the effect of two dietary fibers (arabinogalactan and inulin) on the microbiota from lean and obese subjects during 72 h in vitro fermentation experiments using the validated TNO dynamic in vitro model of the proximal colon: TIM-2. Metabolically, arabinogalactan fermentation showed a higher production of propionate when compared to n-butyrate in the obese microbiota fermentations. In general, lean microbiota produced more n-butyrate from the fermentation of both substrates when compared to the obese microbiota. Furthermore, the obese microbiota extracted more energy from the fermentation of both fibers.
RESULTS: Compositionally, bacteria belonging to Gemmiger, Dorea, Roseburia, Alistipes, Lactobacillus and Bifidobacterium genera were found to be highly abundant or stimulated by the prebiotics in the lean microbiota suggesting a potential role in leanness. Furthermore, a significant correlation between known butyrogenic strains including B. adolescentis, an unclassified Bifidobacterium and F. prausnitzii with this metabolite in the fermentation of inulin in both microbiotas was found.
CONCLUSIONS: Although supplementary in vivo studies are needed, the current study provides more evidence for the consumption of specific ingredients with the aim of modulating the gut microbiota in the context of obesity.

**How are T(H)2-type immune responses initiated and amplified?**
Nat Rev Immunol. 2010 Apr;10(4):225-35. Paul WE1, Zhu J.
***(Color and bold added.)***
**Abstract**
CD4(+) T helper (T(H)) cells have crucial roles in orchestrating adaptive immune responses. T(H)2 cells control immunity to extracellular parasites and all forms of allergic inflammatory responses. Although we understand the initiation of the T(H)2-type response in tissue culture in great detail, much less is known about T(H)2 cell induction in vivo. Here we discuss the involvement of **allergen- and parasite product-mediated activation of epithelial cells, basophils and dendritic cells and the functions of the cytokines interleukin-4 (IL-4), IL-25, IL-33 and thymic stromal lymphopoietin** in the initiation and amplification of T(H)2-type immune responses in vivo.