

# Understanding the Pathogenesis of Inflammatory Bowel Diseases, and moving towards a “Functional Cure”

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## Disclaimer

First, I want to make it clear that while I am a doctor, I am not a medical doctor – I am a physicist. My interest in IBD (and health overall) comes from having been diagnosed with ulcerative colitis (UC) myself roughly 12 years ago. After becoming a father, I decided I did not want to accept the conventional wisdom that UC is an incurable disease that could at best be managed by immunosuppressants with harsh side effects, and with a high likelihood that eventually they would fail and I would need to have my colon removed.

In 2012, I did a little research into alternative therapies revolving around diet and repopulating the gut microbiota, and ostensibly cured myself through those processes. I was off all medication, and doing better than I had since 2000. But, in the summer of 2013, it came back – and badly. I lost 25 pounds in 2 months. I decided I had to understand exactly what was causing this, why it came back, why I developed UC in the first place, and how to keep it from ever returning. Over the summer, I read well over 150 research papers, with those goals in mind. This paper summarizes my findings, and at the end, the treatment plan that I devised for myself, that so far seems to be working very well.

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One point of frustration I have found when reading through the research is that the focus is often on trying to find one common underlying cause for all cases of either UC or Crohn's disease, and one single thing to treat the disease. As a scientist, I understand the basis for this. For example, for the latter issue, it is desirable to do a comparative study with only one variable between the study group and the control group, to determine the impact of that one variable. However, as a patient, my focus is on developing a treatment program that works, not necessarily something that only involves one medication, one supplement, or one of anything.

Additionally, as IBD is clearly a lifestyle disease, to the extent that certain aspects of our western lifestyle contribute to its development (as I describe in detail below), I think that a successful approach must involve adjusting those aspects of our lifestyle that can contribute to the recurrence of the disease. To date, no studies have been done that incorporate a multitude of treatment supplements (aimed at healing and maintaining the epithelial barrier) as well as lifestyle adjustments – so there is no data on how this overall protocol will work. But, I have done my homework, and I feel it is very well-grounded in science, with each piece of the protocol backed by controlled studies.

In research papers, it is typical for the author to disclose any vested interests that might bias their views. In that vein, I want to clarify that I have a vested interest, which is that I hope to never crap blood again. If what I have learned works, then I hope it works for others as well, so I am publishing it freely for other IBD patients to read and consider.

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#### *Update 1/6/2014*

I started my protocol in August of 2013, and if my memory is correct, within 3 or 4 weeks my symptoms had completely vanished. I had a colonoscopy in late October or early November, which showed no signs of inflammation. When seeing my gastroenterologist (Dr. William Maher of Gastroenterology Professional Associates in Somersworth, NH, who has been very supportive) after the biopsy results came back, his first words were “your biopsies were amazing!”. He took many biopsies to assess the level of inflammation and mutagenicity, and everything was apparently completely normal – no signs of any inflammation, a perfectly normal colon. Woohoo!

I am no longer on any colitis meds – I initially went on a low dose of prednisone and 4 Lialda a day. I started tapering off the prednisone right away though, since it didn't seem to be necessary. I think the Wellbutrin played a big role in helping get the inflammation under control rapidly, and allowing the healing part of the protocol to work. I am still taking Wellbutrin (3 x 100 mg per day), but will likely start reducing the dosage soon. I will continue taking natural TNF-alpha inhibitors, in particular curcumin and quercetin, as well as colostrum to aid with rapid repair of any damage that does occur to the epithelial barrier.

I feel that diet and stress management will play a large role with maintaining a state of good health. I have not written much about diet yet – I will now add in a section about that at the end of this paper. Since I am short on time right now, I may not have time to put in references for everything I say in that section yet. Everything in there though is based on relevant research, and will have references to back it up once I have time to put them all in.

### *Update 12/22/2014*

As of this latest update, I have been completely healthy (no symptoms) for almost 1.5 years, off all UC meds for about a year, and off all medications for over 6 months (I continued taking Wellbutrin for about 6 months after stopping all UC meds).

One issue I have been reading more about is genetic mutations (or variations) in the MTHFR (methylenetetrahydrofolate reductase) gene and other genes related to methylation. The MTHFR gene in particular provides instructions for making the enzyme necessary for methylating folic acid into its usable form, methyl folate. Insufficient MTHFR enzyme impairs the production of Coenzyme Q10, carnitine, phosphatidylcholine, creatine, and SAMe (glutathione precursor), with impaired phosphatidylcholine and glutathione production being particularly problematic in colitis.

MTHFR deficiency results in a build-up of homocysteine, and if our body's sulfonation pathway can not keep up with the homocysteine buildup we get increased sulfite/sulfide production, molybdenum deficiency (needed for making enzymes for the sulfonation pathway and methionine pathway), etc.. Mutations in the MTHFR genes are fairly common, with it generally estimated that around 1/4 of the US population has some form of mutation – with the percent being higher among people with “auto-immune” disorders.

Given the problems from excess sulfur and impaired glutathione and phosphatidylcholine production in colitis (described in detail below), at first glance it seems like it may be wise for any colitis patient to supplement with methyl folate, and NOT folic acid, to ensure sufficient MTHFR production to aid the methylation pathway. But, if a person doesn't have a MTHFR defect, and has a polymorphism in certain other genes (such as SOD genes, which I'll write about more later when I have time), taking methyl folate could be detrimental. So, I highly recommend that anyone with IBD have genetic testing done through 23andme to identify exactly what polymorphisms they have that could be contributing to the dysfunctional immune response, which will help with individualizing their treatment.

Mutations in the CBS and FUT2 genes can also be important. The FUT2 gene is necessary for making an oligosaccharide that friendly gut bacteria feed on, and also regulates the expression of some blood-group antigens. Both of those factors can have a significant impact on the microbiota. In particular, these mutations can lead to very low levels of beneficial bifidobacteria<sup>1</sup>.

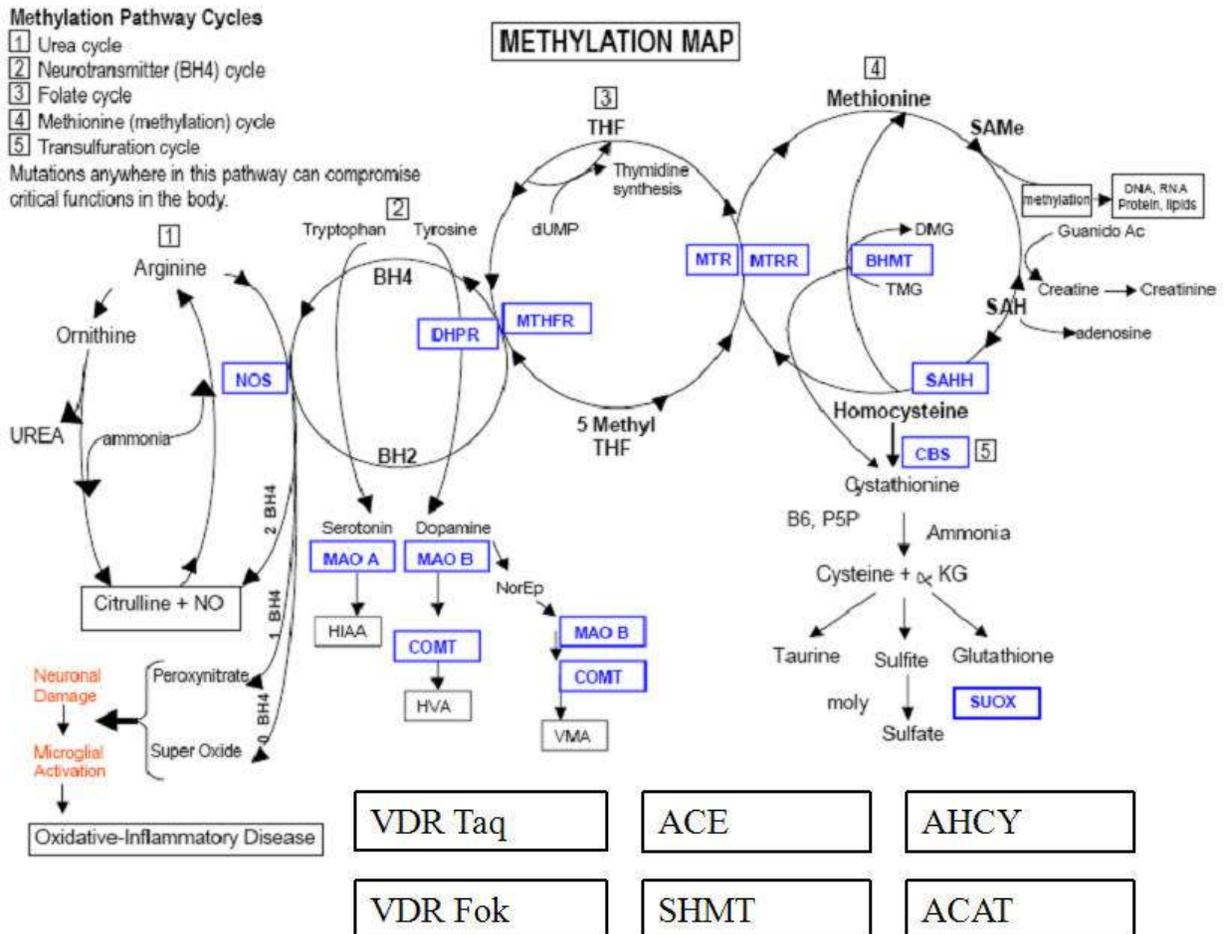
The CBS gene is used for making cystathione beta synthase, an enzyme used for the first step of the transsulfuration pathway, which converts homocysteine initially to cystathione, which can then be used for making either glutathione or taurine. Glutathione is our body's primary anti-oxidant, and extremely critical in so-called “auto-immune” diseases, which revolve around oxidative damage being done to our tissues, with low levels of glutathione playing a pivotal role. People with IBD have low levels of glutathione – so this is an important issue to understand and address.

I highly recommend anyone with any health issues get genetic testing done, which you can get through <http://23andme.com>. People with IBD can have the testing done for free as part of a survey they are doing.

I will put a schematic of the methylation / transsulfuration pathways on the next page to illustrate these processes, as I think defects in them may be significant in IBD, as well as many other diseases – particularly those labeled as autoimmune diseases. It is important though to find out whether

or not a person has any related defects before self-medicating, since over-methylation or over-transsulfuration can be just as bad as the opposite.

The most important gene polymorphisms in my own case I suspect are ones I have in the SOD2 genes. In the next update I'll explain this in more detail....



Update 6/2/2015

Still fine!

## 1. Introduction

By looking at the current state of research in Inflammatory Bowel Disease (IBD), but also other “Western Diseases” (metabolic diseases such as diabetes, obesity, chronic fatigue syndrome, heart and lung disease, etc.), I will try to show how most of these diseases share a similar underlying causative

factor, resulting from our Western lifestyle – especially our diet. The underlying cause revolves around the breakdown of the epithelial barrier of the intestines (a “Leaky Gut”), with a genetically hyperactive immune response to that in some people leading to the symptoms of IBD.

Many of these diseases share similar inflammatory reactions, in particular revolving around the disruption of the metabolism of sulfur in the body to produce oxidants and counteracting anti-oxidants. This plays a key role in the damage induced in IBD after the epithelial barrier is broken down, and in distal IBD (such as ulcerative colitis) it is also likely the source of the initial barrier breakdown – and largely a product of our diet.

Based on this, I will lay out what I feel is a logical treatment, with the goal of achieving a “functional cure” – by this I mean avoiding a recurrence of the disease primarily through the use of diet and supplementation, with only a minimal use of pharmaceuticals (the degree to which this is necessary likely varies individually based on the degree of pre-disposition due to underlying genetic mutations). Current treatment of IBD focuses on anti-inflammatory and immunosuppressive medications to get inflammation under control, and then reliance on lower doses of the same medications to try to maintain remission. I will put forth a possible explanation of why this approach almost always leads to disease recurrence, requiring progressively higher doses of immunosuppressives to get inflammation under control, until eventually “safe” levels of the medications are not able to succeed at that, and the patient is deemed “refractory” to medication and recommended for surgical removal of the colon (or wherever the inflammation is).

What I feel is a better approach is to first use the pharmaceuticals (anti-inflammatories and immunosuppressives as necessary) to get the symptoms under control, in particular inhibiting production of a particular inflammatory cytokine (TNF- $\alpha$ ), and then transition to a strategy of fixing the underlying breakdown of the epithelial barrier (and the factors that lead to the breakdown), and a long-term focus on maintaining that barrier through diet and supplementation.

Note that for the most part I am writing this in the form of a research paper, but I will occasionally interject with my personal experiences when it would be beneficial.

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## 2. Disease Pathogenesis

A variety of illnesses are known to be more common in “Western” societies – Inflammatory Bowel Diseases (IBD), Irritable Bowel Syndrome (IBS), diabetes, autism, chronic fatigue syndrome, etc.. As undeveloped countries become more developed, and take on traits of our western societies, the incidence of these diseases has been shown to rise<sup>13</sup>. Genetics alone can not explain this, so there is presumably some factor in our way of life that contributes to the onset and perpetuation of these diseases. I will make the case for these diseases sharing a common underlying pathology, which revolves around diet-induced imbalance in how our bodies process sulfur.

IBD Research over the past few decades has looked into three potential primary causative factors – a single pathogenic organism responsible, genetic factors, and the role of the microbiome as a whole (the entire makeup of bacteria and other organisms in the intestine). While particular pathogenic organisms can induce colitis, as with *C. Difficile* for example, IBD as a whole does not appear to be caused by a singular pathogenic organism. Instead, research points to a combination of the other two

factors – a bacterial “dysbiosis” (imbalance) that results in a breakdown of the epithelial barrier, which in a genetically susceptible host results in an inflammatory cascade<sup>2, 3, 4, 5, 6</sup>. The earlier belief was that the bacterial dysbiosis observed in IBD was a result of the inflammation, rather than a cause of it, but more recent research is indicating the reverse. In particular, metabolic researchers have shown that a dietary-induced dysbiosis can produce inflammation, and research on mice has shown that a dysbiosis that causes inflammation in mice can be transferred to other mice (which happens largely due to ingestion of feces), with those mice developing inflammation as a consequence of the dysbiosis they acquire from the other mice<sup>7</sup>.

A typical human gut harbors approximately 100 trillion bacteria<sup>8</sup>, and those bacteria are separated from our immune system by a single layer of cells – the “epithelial barrier”. The barrier is held together by “tight junction proteins”, with this barrier being given the task of not only keeping bacteria from migrating through to the other side (the lamina propria), but to simultaneously allow the extraction of nutrients and other beneficial elements from the food we eat to pass through. This barrier has redundant mechanisms for repairing itself after injury<sup>9</sup>, but these mechanisms are limited by the availability of resources. If the rate at which damage is done to the barrier exceeds the capacity to rebuilt it, it will break down, becoming more permeable to substances that are not intended to be allowed through (such as bacteria). Some of the genetic mutations that have been found to be more common in people with IBD are in genes related to the repair of the epithelial barrier<sup>10, 11</sup>,

The breakdown of this barrier, often referred to as “Leaky Gut”, is implicated in a variety of diseases in addition to IBD and Irritable Bowel Syndrome (IBS)<sup>12</sup>, all of which are more common in “western” civilizations<sup>13</sup>, such as autism<sup>14</sup> and diabetes<sup>15</sup>. Cani, et. al. (2007) demonstrated that an increase in plasma concentrations of lipopolysaccharide (LPS, found in the outer membrane of gram-negative bacteria, which elicits a strong immune response) is responsible for metabolic diseases such as diabetes, by showing that a subcutaneous low-rate infusion of LPS induced most, if not all, of the symptoms of metabolic diseases<sup>16</sup>. Further, they showed that putting mice on a highly “westernized” diet – no carbs (thus no fiber), high fat and high protein – produced a bacterial dysbiosis, which then produced a breakdown of the epithelial barrier, allowing bacteria to translocate through the barrier. The result was an increase in LPS in the bloodstream – which they found could trigger the various metabolic diseases. They did not identify exactly how the epithelial barrier broke down, but they did note an increase in the ratio of gram-negative bacteria to gram-positive bacteria with the no carb (no fiber) diet. The addition of fiber to the diet resulted in normalization of that ratio<sup>17</sup>.

How does this relate to IBD? A variety of genetic mutations related to the immune response have been found to be more common in patients with IBD than the general public<sup>18</sup>. Overall, people with IBD appear to have a genetic predisposition resulting from one of a variety of genetic mutations that ultimately result in a heightened immune response to bacterial infiltration<sup>8</sup>, in addition to many IBD patients having an aforementioned mutation related to the repair of the epithelial barrier. For example, in 2011, Kovarik, et. al<sup>19</sup> found that the peripheral blood mononuclear cells of IBD patients – even those in clinical remission – exhibit a hyperresponsiveness to bacterial stimulation resulting in significantly increased production of the inflammatory cytokines IL-12/p2340 and TNF- $\alpha$ . Both of these, but especially Tumor Necrosis Factor alpha (TNF- $\alpha$ ), plays a pivotal role in the inflammatory cascade that characterizes IBD. That is why the anti-TNF antibodies Remicade and Humira can be so effective in treating both types of IBD. Unfortunately, Remicade and Humira are foreign proteins, to which our own

bodies develop antibodies over time – such that those drugs are only effective in patients for a limited amount of time (ranging from a few months to several years).

Taken together, IBD appears to result from the breakdown of the epithelial barrier (“Leaky Gut”) in a patient with a genetic predisposition to an exacerbated immune reaction, likely involving an exaggerated production of TNF-  $\alpha$ . If that barrier is not broken down, allowing bacteria to pass through and trigger the heightened immune response, that should keep the disease from recurring. A multitude of studies on mice bred to have a genetic predisposition towards a hyperactive immune response, have found that if the epithelial barrier of the mice is broken, and “normal” bacteria are present in the intestines, then the inflammatory cascade characteristic of IBD ensues<sup>20</sup>. For example, in IL-10 “knock-out” mice (mice that are deficient in a gene for production of IL-10, a cytokine that acts as a negative feedback for inflammation, inhibiting the production of the inflammatory cytokines, and blocking the important NF $\kappa$ B inflammatory pathway), studies have shown that despite having a dysregulated immune system that predisposes them to a hyperactive immune response (as in humans with IBD), disruption of the epithelial barrier is required as an initial trigger<sup>3</sup>. This initial epithelial barrier disruption is often accomplished in experiments on mice by giving the mice a high dose of a heavily sulfated agent such as Dextran Sulphate Sodium, trinitrobenzene sulfonic acid, or carrageenan<sup>70</sup>.

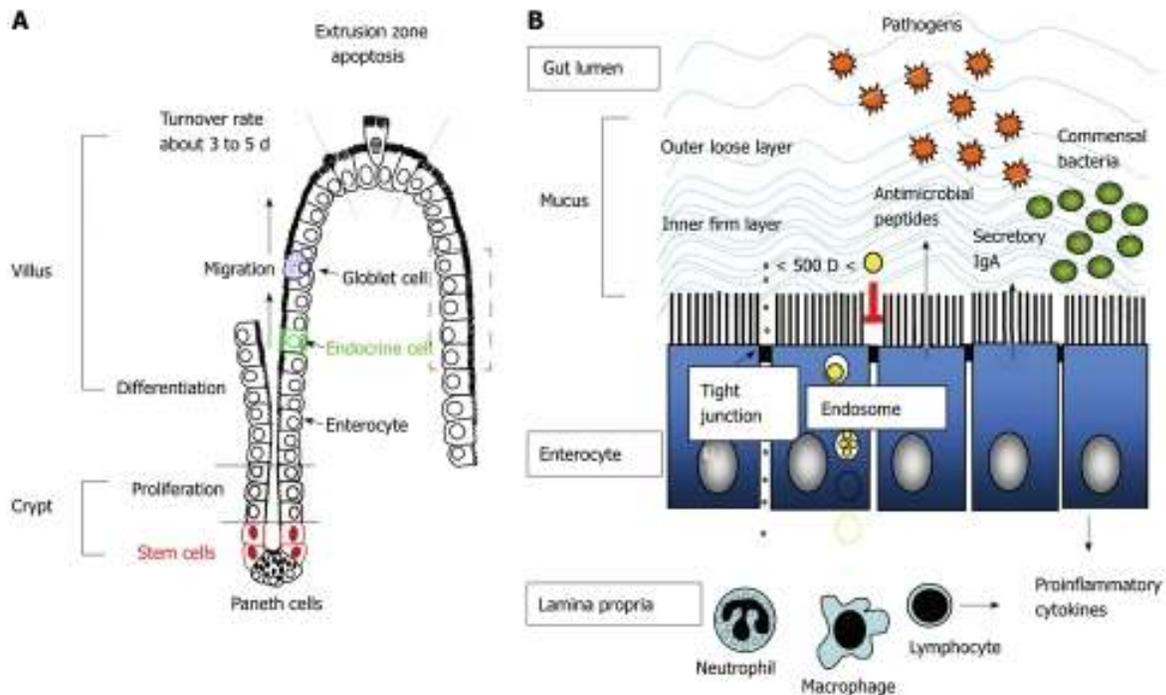
Note that in Crohn’s Disease (CD), one of the IBD’s, there is the additional complication of granuloma formation, which appears to be the result of pathogenic bacteria such as Mycobacterium avium subspecies paratuberculosis(MAP) or an Adhesive Invasive strain of E. Coli (AIEC) entering macrophages through M-cells, replicating within the macrophages, and ultimately the immune response producing the granulomas<sup>21</sup>. However, it was recently found that these bacteria are not able to enter M-cells until after inflammation has already started<sup>22, 23</sup> (from the breakdown of the epithelial barrier and subsequent heightened immune reaction) – so preventing that breakdown should also prevent the characteristic granuloma formation in CD, at least in theory.

Given that CD is likely to involve the infection with an actual pathogenic bacteria, treatment of CD should likely require additional steps in comparison to UC, aimed at eradicating the pathogenic bacteria and re-building the microbiota to prevent them from returning (similar to treating C Diff).

## 2.1. The Intestinal Microbiota and Barrier Breakdown

So – how does the barrier break down? For an excellent overview, I highly recommend the paper “Host-microbial interactions and regulation of intestinal epithelial barrier function: from physiology to pathology” by Yu, et. al,<sup>24</sup>. To help with understanding the process, see the figure on the next page, which is taken without permission from that article.

For our purposes, the key issues are how are bacteria normally prevented from crossing the barrier (and accessing the immune system in the lamina propria), and what leads to them being able to cross, how does that contribute to disease, and how do we stop it. The article mentioned above covers some of this very well, in particular the first one (how it is *supposed* to work). When bacteria are able to cross over, or “translocate”, they can do it in one of two ways – paracellular transport (between cells, through the tight-junctions), or transcellular transport (through the cells)<sup>24</sup>.



In rat models of IBD, it was found that paracellular transport is initiated by some trauma (administration of high levels of indomethacin, a non-steroidal anti-inflammatory), and the maintenance of that paracellular breakdown (through breaks in the tight junction proteins) is the source of the chronicity of the disease, while the occasional triggering of transcellular transport by increased cytokine production results in a greater translocation of bacteria, and corresponds to the active phases of the disease (heavy inflammation)<sup>25</sup>. Human IBD appears to parallel this process, so, presumably, a long-term resolution to the disease must include fixing the underlying breakdown of the tight junctions that allows the ongoing paracellular translocation.

Note: Still working on the paracellular / transcellular distinction....

There can be a variety of factors that can contribute to the weakening of the barrier, and there are likely a variety of factors that come into play in breaking the barrier down (and may also determine where the breakdown occurs, and play a significant role in the presentation of IBD). But there are a few common features that show up not only in IBD, but in most of the “western” diseases. In particular, there are common shifts in the intestinal fauna which has a negative impact on the tight junctions in the epithelial barrier. This particular mechanism for barrier breakdown likely plays a prominent role in the initiation of IBD that starts in the rectum (but as will be explained, is likely less of a factor in IBD that starts in the small intestine or ileum, as is more common with CD).

In general, 90% of the typical human microbiota (a typical person’s intestines contain on the order of 100 trillion bacteria) is composed of bacteria from two phyla, the Firmicutes<sup>26</sup> (gram-positive bacteria, with the primary subgroups being *Clostridium coccoides* and *Clostridium Leptum*) and Bacteroides (gram-negative, with prominent phyla including *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucmicrobia*)<sup>27</sup>. In health, we have a highly symbiotic relationship with our

intestinal flora, ultimately indicating that humans and our microbiota have co-evolved<sup>28</sup>. We rely on the microbiota for digestion of dietary compounds, fermentation of undigestible carbohydrates to produce Short Chain Fatty Acids (SCFAs), inhibiting pathogen invasion (by occupying space and also production of anti-microbial peptides), and various immune modulating functions<sup>2</sup>.

With the various tasks that our microbiota perform for us, it is not surprising that a significant shift in the composition of the microbiota (i.e. a dysbiosis) could lead to health problems. Analyses of the intestinal microbiota of IBD patients has revealed some commonalities, in particular a reduction in beneficial butyrate-producing bacteria (*Clostridium IXa* and *IV groups* in particular) and an increase in sulfate reducing bacteria<sup>2</sup> (the increase in SRB is more typical in IBD that starts in the distal colon than proximal colon). We will look at these two factors separately, and then look at the combined effect.

## 2.2. Short-Chain Fatty Acids

The production of SCFAs, primarily butyrate, acetate, and propionate, from undigestible carbohydrates (fiber and resistant starches) is a vitally important task. They, especially butyrate, serve as the primary energy source for epithelial cells, inhibit the release of inflammatory cytokines such as TNF- $\alpha$ , and play key roles in the expression of the tight-junction proteins<sup>29</sup> where the epithelial barrier can break down. As the primary energy source of cells, a reduction in butyrate oxidation would result in an energy deficiency in epithelial cells, in the form of less Adenosine Tri-Phosphate (ATP) available<sup>30</sup>. And in fact, decreased butyrate uptake is universally observed in patients with IBD<sup>20,29,30,31,37</sup>. As we will see, this plays a vital role in the development of IBD and other western diseases, and is a consequence of our “western diet” being significantly lower in fiber and resistant starches.

Butyrate also increases production of mucin and antimicrobial peptides, and butyrate enemas have been found to be effective in treating distal UC<sup>31</sup>. In a paper about to be published, Smith, et. al, show how the SCFAs regulate homeostasis of colonic T<sub>reg</sub> cells<sup>32</sup>. These T<sub>reg</sub> cells produce the anti-inflammatory cytokines Transforming Growth Factor  $\beta$  (TGF $\beta$ ), and Interleukin-10 (IL-10), and suppress the responses of other immune cells, including those that promote inflammation. TGF $\beta$  plays a critical role in maintaining the epithelial barrier, and preventing increased permeability from various challenges<sup>33,34,35</sup>.

The SCFAs produced from fermentation of fiber and resistant starches clearly play a prominent role in maintaining the health of our intestinal tract – and in fact it has been almost three decades since it was first shown that impairment of SCFA oxidation can be a primary factor in triggering colitis<sup>36</sup>. The aforementioned inflammatory cytokine TNF- $\alpha$ , which IBD patients produce in excess due to stimuli (after epithelial breakdown), directly inhibits butyrate uptake by decreasing expression of the genes involved in the process<sup>37</sup>. So, once the barrier is broken down, and the inflammatory response is triggered, the exaggerated production of TNF- $\alpha$  will also provide a positive feedback mechanism that propagates the inflammatory cascade by further inhibiting butyrate uptake.

Something that I have struggled to understand for a while is why IBD patients generally find that while their IBD is active, eating fibrous foods often makes their symptoms worse. Since SCFAs (butyrate in particular) have many important anti-inflammatory functions, as well as maintaining the epithelial barrier, this initially didn't make sense. However, most (if not all) of the beneficial effects of SCFAs require them first being taken up into the epithelium (for example, the role in increasing T<sub>reg</sub> cells<sup>32,38</sup>).

During active inflammation in IBD patients, production of TNF- $\alpha$  and IFN- $\gamma$  is hyperactive, and these inflammatory cytokines down-regulate<sup>39</sup> monocarboxylate transporter 1 (MCT1), which plays a critical role in SCFA uptake<sup>40,41</sup> – thus the inflammatory cytokines decrease uptake of butyrate and the other SCFAs, inhibiting their ability to exert anti-inflammatory effects and rebuild the epithelial barrier. Additionally, oxidation of butyrate (which happens when epithelial cells use it as fuel) is also inhibited by TNF- $\alpha$ . Overall, butyrate's beneficial effects are largely prevented by high TNF- $\alpha$  production, which is characteristic of IBD. In fact, this is likely why patients with active IBD have higher butyrate levels in their stool<sup>42</sup> - it is not because of excess butyrate production triggering IBD, but rather the inflammation is preventing butyrate uptake and oxidation, so it comes out in the stool.

This would explain why butyrate has had mixed results (at best) at mitigating active IBD, despite the many anti-inflammatory effects it can have<sup>43,44</sup>. But, why would it actually make symptoms worse? One possible explanation arises from the observation by Berndt, et al that butyrate increases production of IL-23 (an inflammatory cytokine involved in the progression of IBD) from stimulated dendritic cells<sup>45</sup>. This role of butyrate (one of its few pro-inflammatory effects) happens without butyrate needing to pass through the epithelial barrier, so it would not be impeded by TNF- $\alpha$ .

So, when the colon is in a state of health, and levels of TNF- $\alpha$  and IFN- $\gamma$  are low, the anti-inflammatory and barrier-building effects of butyrate likely dominate. But as levels of those cytokines rise, butyrate (and the other SCFAs) are inhibited from passing through the epithelial barrier and enacting their anti-inflammatory effects – so the pro-inflammatory effects dominate, particularly with the levels of butyrate remaining high due to the reduced absorption. If this is the case, this would mean that while IBD is active, it would be wise to not try to increase SCFA levels, but to instead first focus on getting the immune response under control – in particular through TNF- $\alpha$  inhibition.

## Hydrogen Sulfide

Sulfur plays a variety of roles in our bodies, in particular in our intestines<sup>46</sup>. To greatly simplify the discussion, overall sulfur metabolism can lead to the production of oxidizing agents and anti-oxidants. The first path can be done purely through enzymatic action, or can be facilitated by sulfate-reducing bacteria, with both paths leading to the production of hydrogen sulfide, a highly toxic gas with roughly the same toxicity as cyanide<sup>47</sup>, which could be viewed as having many effects exactly the opposite of butyrate. Hydrogen sulfide increases production of Reactive Oxygen Species (ROS, which are highly oxidizing), increasing the production of inflammatory cytokines (including TNF- $\alpha$ ), inhibiting butyrate oxidation<sup>48</sup> and uptake by the epithelium, and ultimately weakening the epithelial barrier<sup>49</sup>. In fact, hydrogen sulfide has been suspected of playing a pivotal role in the onset of UC for over 20 years<sup>50</sup>. Consuming sulfite preservatives as well as a high protein diet<sup>51</sup> (containing sulfurous amino acids) results in an increase in sulfate production, driving a weakening of the barrier, and can play a pivotal role in the initiation or recurrence of IBD, particularly that which starts in the distal colon<sup>52</sup>.

As a point of interest - for workplace regulations, workers are allowed to work in air that has up to 10 ppm of hydrogen sulfide for up to 10 minutes. In addition to the deleterious effects of hydrogen sulfide described above, it also inhibits cytochrome oxidase like cyanide. In studies in rats, colonic hydrogen sulfide levels have been found to sometimes exceed 1,000 ppm<sup>47</sup>, a concentration which if inhaled would lead to paralysis, coma, and death within minutes. Clearly our epithelial lining must have a means of rapidly metabolizing this gas into a non-toxic product. It had initially been suspected that this

occurred through methylation of the hydrogen sulfide into methanethiol and then dimethyl-sulfide, but it was found that the process is actually the reverse, with hydrogen sulfide ultimately being demethylated into thiocyanate<sup>47</sup>.

A recent study found that UC patients have an impaired ability to detoxify hydrogen sulfide (into thiocyanate), due to a significant decrease in activity and gene expression of colonic mucosal thiosulfate sulfurtransferase enzyme<sup>53</sup> (TST), which carries out the conversion to thiocyanate. This is likely a consequence of elevated TNF- $\alpha$  levels, since successful treatment with the TNF- $\alpha$  antibody Remicade (Infliximab) resulted in a significant increase in TST gene expression. Since this appears to be a consequence of elevated TNF- $\alpha$ , this impaired ability to detoxify hydrogen sulfide is likely not a primary cause of the disease, but rather an induced effect resulting from the hyperactive immune response (elevated TNF- $\alpha$  production), which acts as a positive feedback to exacerbate the disease. Some patients may have an underlying genetic mutation that inherently reduces the rate at which hydrogen sulfide is demethylated<sup>54</sup>, but as with most genetic mutations, it does not appear in a high percentage of patients. The presence of such a mutation though would likely result in a lowered “threshold” for the breakdown of the epithelial barrier (thus disease recurrence could happen more easily), and perhaps even a more severe presentation of the disease.

Hydrogen Sulfide has been shown to cause direct cleavage of DNA and increase production of Reactive Oxygen Species (ROS)<sup>55</sup>, which are strong oxidizing agents. An imbalance between these strong ROS and antioxidant defenses results in tissue damage<sup>56</sup>, as seen in IBD. The body’s primary anti-oxidant is glutathione, also produced from sulfurous amino acids (methionine and cysteine), as hydrogen sulfide is. A balance in the production of ROS and glutathione is important for maintaining homeostasis. Excess abundance of ROS and impaired glutathione synthesis and action has been found in patients with IBD<sup>57</sup>. This oxidative imbalance likely plays a key role in the tissue damage that occurs in the disease – and I will make a case that this is likely a consequence of the over-production of TNF- $\alpha$  that starts with the initial barrier breakdown.

While the sulfurous amino acids cysteine and methionine can lead to the production of hydrogen sulfide by either enzymatic processes within epithelial cells or by sulfate reducing bacteria, they can also be used for the production of glutathione and S-adenosylmethionine (SAM), respectively<sup>58</sup>. As mentioned, glutathione is the most abundant anti-oxidant in our bodies, and counteracts the ROS produced by hydrogen sulfide. SAM plays an important role in this process, mediating glutathione efficacy by increasing activity of glutathione S-transferase<sup>59</sup> which is involved in quenching oxidative species and elimination of toxic xenobiotics by forming glutathione conjugates<sup>59</sup>. If sulfur is preferentially being used more for producing hydrogen sulfide than the antioxidants, an imbalance between oxidative and anti-oxidant species occurs, resulting in tissue damage.

The pathways for metabolizing cysteine and methionine (the sulfurous amino acids) into glutathione and SAM are dependent on ATP<sup>77</sup> within the epithelial cells, such that if energy reserves are depleted due to decreased butyrate uptake, that would impair production of glutathione and SAM. When butyrate uptake is reduced, epithelial cells can shift to getting energy from glucose, but increasing presence of glucose impairs the expression of  $\gamma$ -GCS, the rate limiting enzyme in the production of glutathione (so glutathione production decreases). Reducing production of glutathione and SAM would leave more cysteine and methionine in circulation for conversion to hydrogen sulfate by SRBs, resulting in an oxidative imbalance that would cause tissue damage. Once the epithelial barrier is disrupted in a

genetically susceptible person, excess production of TNF- $\alpha$  begins. TNF- $\alpha$  reduces butyrate uptake and oxidation by epithelial cells, reducing their storage of Adenosine Triphosphate (ATP, as energy storage), leading to an overly oxidative environment deficient in glutathione and with excess hydrogen sulfide and ROS, exactly as has been observed in IBD patients.

Additionally, an oxidative state itself results in increased production of TNF- $\alpha$  upon bacterial stimulation, and a decrease in production as the environment becomes more reductive due to the presence of anti-oxidants<sup>60</sup>. This creates the possibility that the hyper-active immune response seen in IBD may at least in part be a result of the development of an overly oxidative environment.

While inhibition of butyrate uptake by TNF- $\alpha$  and hydrogen sulfide itself can create this redox imbalance (or push it further in the direction of oxidation), it could also be produced as the result of diet. The enzymatic pathway for producing the anti-oxidants glutathione and SAM requires cellular ATP (stored energy). The primary energy source for epithelial cells (accounting for over 70% of their energy) is butyrate. If intestinal butyrate production is reduced either due to low intake of fiber and resistant starches, or a reduction in butyrate-producing bacteria (although the latter is likely the result of the former), this would result in a decrease in ATP within cells, and a decrease in the production of anti-oxidants from the sulfurous amino acids. That would leave more sulfur available for production of hydrogen sulfide. The enzymatic cellular processes for this may be rate limited, but bacteria (SRB) can carry out this process as well, such that with increasing sulfate availability, SRB will be able to grow in numbers and produce an excess of hydrogen sulfide – creating a damaging oxidative environment, that can break down the epithelial barrier as well as contribute to the inflammatory cascade and tissue damage after the barrier is broken down (which could happen due to another mechanism).

This highly oxidizing environment contributes significantly to the tissue damage seen in IBD, and a deficiency in reduced glutathione (commonly labelled GSH) and increase in oxidized glutathione (labelled GSSG) shows up not only in IBD patients<sup>57,61</sup>, but also in other western diseases such as diabetes<sup>62</sup> obesity<sup>63</sup>, diseases of the lung<sup>60</sup>, etc.. Since this is the case, we might expect that increasing levels of anti-oxidants within the intestines (in particular at the site where damage is occurring) should help ameliorate that damage – and that is exactly what has been observed. Enemas with d-alpha tocopherol (natural vitamin E) have been found to be effective at treating mild colitis (relegated to the rectum and only partway into the sigmoid colon) under control<sup>64</sup>, through both anti-inflammatory and anti-oxidant effects. At the end of the study (12 weeks), all 12 patients had had significant clinical improvement, with 9 of the patients achieving clinical remission. After the study, 10 of the patients chose to continue with the vitamin E enemas, and all remained symptom free up through the 8 months until the paper was published (no information is available beyond that point). The two patients who chose to stop the enemas both had recurrence of the disease, at 4 weeks and 7 weeks after stopping the enemas.

This likely indicates that the anti-oxidant vitamin E was able to inhibit tissue damage by the ROS, and likely also reduce the production of inflammatory cytokines by shifting the redox balance. However, this by itself is not going to heal the epithelial barrier, nor fix the underlying problem that caused the failure of the epithelial barrier – which is likely why patients who stopped the enemas had the disease recur.

Similarly, supplementing with SAM or glutathione itself might be effective in inhibiting tissue damage, and shifting the redox balance. Additionally, oral or rectal administration of the anti-oxidant

ethyl pyruvate has been shown to ameliorate symptoms of experimental colitis in mice<sup>65</sup> through scavenging of ROS<sup>66</sup>. Ethyl pyruvate is a mono-ethyl ester of pyruvic acid, and has been used as a food additive for decades. Ethyl pyruvate has also been found to inhibit damage to the epithelial barrier by the inflammatory cytokines TNF- $\alpha$ , IFN- $\gamma$  and IL-1 $\beta$ <sup>67</sup>, and ameliorate epithelial barrier dysfunction. Unfortunately, it is not readily available to the public, as the only suppliers of the pure chemical are chemical supply companies such as Sargent-Welch (or companies selling it in 55 gallon drums for use as a food additive).

It is interesting to note that one of the classes of drugs commonly used for treating IBD, 5-aminosalicylic acids (5-ASAs) such as mesalazine, were initially used because of its anti-oxidant properties (inhibiting damage from free radicals produced in the inflammatory process), but subsequent research found that they also have a significant effect at inhibiting production of hydrogen sulfide from sulfates<sup>68</sup>. It has also been found that increasing in-situ production of SCFAs by addition of fibers such as oligosaccharides to the diet results in a decrease in hydrogen sulfide production<sup>69</sup>.

It is also worth noting that experimental colitis is typically induced in mice through oral dosage of a heavily sulphated agent such as Dextran Sulphate Sodium, trinitrobenzene sulfonic acid, or carrageenan<sup>70</sup>. However, it has been found that immune-compromised germ free mice do not develop colitis when given these agents, whereas mice with a normal intestinal fauna do<sup>71</sup>. This illustrates a clear role of both hydrogen sulfide and the intestinal fauna in the onset of the disease – or at least one means of breaking down the epithelial barrier and triggering the disease.

### 2.3. Creating the Dysbiosis

This shift in the microbiota common in distal IBD creates a dysbiosis that promotes inflammation and the breakdown of the epithelial barrier. How does this microbial shift occur? Diet is generally a large factor, with the butyrate producing bacteria feeding on certain fibers and resistant starches, which are considerably less common in a typical Western diet than in less developed countries. Additionally, the Western diet is much higher in food sources for the SRBs than in undeveloped countries, in particular sulfite preservatives and protein, particularly the sources with the highest levels of sulfurous amino acids (eggs, dairy, and red meat)<sup>52</sup>. With excess sulfur consumption, particularly combined with reduced fiber intake, it is more likely that the anti-oxidant producing pathway of sulfate metabolism would become saturated, leading to an environment richer in oxidants than anti-oxidants.

In a survey and follow-up of UC patients aimed at identifying potential dietary associations with recurrence of UC, Jowett et. al. found that there was a strong correlation between protein intake (especially red and processed meat) and overall sulfur intake and the relapse of the disease<sup>72</sup>. Multiple studies have found that patients who develop IBD that starts in the distal colon tend to eat a diet higher in protein and lower in fiber and resistant starches than the general public<sup>73, 74</sup>. This trend does not show up often though in patients who develop IBD initially in the ileum or small intestines, indicating a different mechanism is likely responsible for the initial breakdown of barrier function in those instances (impaired butyrate uptake likely still plays a pivotal role, but it may be unrelated to hydrogen sulfide when the disease starts earlier in the digestive tract).

In metabolic research on mice, the diet that was used to develop a leaky gut in the mice was a diet with no carbohydrates, entirely containing fats and proteins<sup>15</sup>. On a personal level, this also matches my own experience. When I first developed IBD (around 2000), I was heavily into weightlifting,

and consuming a diet very high in protein (200-300 grams a day) and low in fiber (probably on the order of 5-10 grams on a typical day). After ostensibly “curing” myself in the late summer of 2012 (through a combination of fecal transplants and a diet high in fiber), I eventually got very heavily back into weightlifting, and roughly 2 months before the recurrence of symptoms I had gone back to my old high protein low fiber diet.

Taken together, this seems to clearly indicate that diet can play a significant role in manipulating the intestinal fauna, and ultimately producing the breakdown of the epithelial barrier – which in a genetically susceptible person can start the inflammatory cascade typical of IBD. This mechanism described above for how the epithelial barrier can become disrupted is presumably not the only way it can happen, but is likely a common mechanism for disease that starts in the distal colon (i.e. rectum, sigmoid colon, etc.) and works its way proximally from there. The reason for this is that as food passes through the intestines, the amount of fiber available for fermentation decreases, and therefore so does the level of SCFAs<sup>75</sup>.

On the other hand, sulfate reduction becomes increasingly more common, as do sulfate reducing bacteria, moving distally in the colon<sup>51</sup>. With the combination of more hydrogen sulfide and less butyrate clearly being capable of disrupting the epithelial barrier, and the concentration of H<sub>2</sub>S increasing and butyrate (and other SCFAs) decreasing distally in the colon, if that is the mechanism causing the breakdown, one would expect it to occur first in the most distal end (the rectum) – as is typical of UC (the disease which is associated with an increased consumption of protein and decreased consumption of fiber prior to disease onset, and is most heavily associated with a reduction in butyrate producing bacteria and increase in SRBs – although that has also been observed in CD). It is also worth noting that SCFAs are thought to be responsible for the lower pH found in the proximal colon<sup>76</sup>, and the butyrate-producing bacteria that are typically diminished in IBD (especially distal disease) have been found to be more tolerant of low pH than the *Bacteroides* and *Proteobacteria* that are more prevalent in IBD. This may be a factor in why increasing SCFA production through increasing fiber intake results in a decrease in hydrogen sulphide production<sup>69</sup>, or it could be because SCFA production itself consumes hydrogen sulfide<sup>77</sup>.

Over-production of hydrogen sulfide and under-production of SCFAs is not the only mechanism by which the epithelial barrier can be disrupted, however. Various pathogenic bacteria have been found capable of doing it individually (such as *C. Difficile*), and medications such as NSAIDs<sup>78, 79</sup>. Food allergies could potentially also play a role, as aberrations in the mucosal IgA immune response is implicated as a possible causative factor in the progression of some IBD<sup>80</sup>. Additionally, emotional stress can cause epithelial damage via mucosal mast cell hyperplasia and activation<sup>81</sup>. Again on a personal note, when I first developed IBD, and when it returned in 2013, leading up to that was two of the most stressful times of my life, which could have played a role in the onset of the disease and its recurrence.

These other issues may be more significant factors in disease that starts further “up” in the intestinal tract, such as the small intestine or ileal region (so possibly more of an issue for CD than UC), and is also implicated in Celiac disease. The mechanism by which the barrier is broken down may in fact play a significant role in the manifestation of the disease. It is generally assumed that a person’s genetics determine whether that person is vulnerable to developing UC versus CD – but perhaps the determining factor is more related to how the epithelial barrier is disrupted. It is worth noting that while mutations in the NOD2 gene CARD15 are suspected of being affiliated more with CD than UC (since the mutation is

more common in patients with CD – although still only at the level of 10-20% of patients having such a mutation)<sup>20</sup>, NOD2 deficient mice who are administered a highly sulfated polysaccharide such as DSS develop experimental colitis starting at the distal region, rather than the characteristic traits of Crohn’s disease (which generally starts in the ileum or small intestine). Additionally, while having a relative with IBD significantly increases a person’s odds of developing IBD themselves, the person may not develop the same IBD as the relative – indicating that other factors than genetics may play a significant role in how the disease manifests.

## 2.4. The Parasympathetic Nervous System

Our autonomic nervous system is split into two divisions – the sympathetic and parasympathetic. The sympathetic system drives the “fight or flight” response and the inflammatory response (to fight pathogens, etc.). The parasympathetic system is the counterbalance to this, sometimes referred to as the “rest and digest” system, or “feed and breed”. While the sympathetic system promotes inflammation, the parasympathetic system produces neurotransmitters like acetylcholine which suppress production of pro-inflammatory cytokines and promote production of anti-inflammatory cytokines.

These two systems are supposed to keep our body in a balanced state of homeostasis. But, our modern life seems to promote the sympathetic system (driven by anxiety, stress, etc.) over the parasympathetic system. The vagus nerve is the channel through which the parasympathetic nervous system acts, and decreased vagus nerve activity has been observed in patients with IBD . Even more significant, increasing activation of the vagus nerve through administration of an inhibitor of the enzyme that breaks down the parasympathetic neurotransmitter acetylcholine has been found to alleviate experimental colitis in mice<sup>82</sup>.

This illustrates that increasing activation of the vagus nerve can play an important role in down-regulating the inflammatory response in IBD. In fact, this may be the primary mechanism by which THC (from marijuana) exerts a beneficial effect in IBD, as it is a competitive inhibitor with the enzyme that breaks down acetylcholine.

Making use of this “cholinergic anti-inflammatory pathway” (CAIP) to suppress inflammation has started to receive a lot of research focus. Most of the research focuses on developing pharmaceuticals to either inhibit the Acetylcholinesterase enzyme, or in some other manner stimulate the parasympathetic system. Some work is also going into electrical implants to directly stimulate the vagus nerve.

Fortunately, there is a much more practical approach – safe stimulation of the vagus nerve to trigger the parasympathetic system. The simplest method is deep, slow abdominal breathing (as in meditation) – taking slow (about 5 second) breaths with your abdomen expanding (not chest), and then slowly exhaling (over 10 seconds or so) through pursed lips as if blowing through a straw.

Another approach is making use of the “dive response”. In all mammals (including humans), sudden immersion of the face in cold water triggers the dive response, which in part stimulates the vagus nerve (this response seems to be aimed at slowing heart rate to conserve oxygen when jumping into cold water). This can be simulated by either immersing your face in cold water (in a bowl for example), or by putting cold water in a large bag, and holding it against your face.

Ultimately, the best approach (in my opinion) is to take up meditation – not only to spend time doing abdominal breathing and making that style of breathing more habitual (rather than the shallow breathing most of us naturally do, which stimulates the sympathetic system), but also to cultivate an inner calm that will help with handling life’s stresses. Ultimately, an imbalance in the sympathetic and parasympathetic nervous systems is likely the primary role by which stress is a prominent factor in IBD and other inflammatory conditions.

### 3. Treatment – “The Briggs Protocol”

Since I am arrogant and self-centered, I will narcissistically label my treatment protocol “The Briggs Protocol”. My primary goal with treatment is not to make the treatment as simple as possible – ie. “just take this one magic pill, and you’ll be good” – but rather to focus on a well rounded treatment plan with the primary goal being getting the patient into remission, and keeping the damn disease from ever coming back. Given that IBD clearly seems to be related to some aspects of our Western lifestyle, we should expect that there might need to be some changes in that regard, in particular with our diet. I don’t want to have to be on any form of extreme diet, and fortunately it does not appear that that is necessary. There is one caveat though: most IBD and IBS patients likely have difficulty with gluten, so avoiding that would be preferable. Research<sup>83</sup> has shown that the gliadin component of gluten induces an immediate leaky gut in everyone (by triggering production of something called “zonulin”, which forces the tight junctions between the epithelial cells apart, allowing protein and bacteria to migrate through). Unfortunately, wheat is now practically omnipresent in our culture, which makes avoiding it very difficult. With the rapid rise in gluten intolerance issues, however, there has at least been a rapid rise in an accommodating “gluten-free” people, so it is fairly easy to avoid it now.

My protocol is broken into three phases:

1. Inducing Remission (stopping the inflammatory cascade)
2. Healing the epithelial barrier, stopping bacterial translocation
3. Maintaining the epithelial barrier (maintaining remission)

Current treatment largely revolves around using anti-inflammatory or immunosuppressant medications to get a person into remission, and then maintaining that remission with the continued use of the same medications, typically at lower dosages. The currently used medications can be effective at inducing remission, but there are a few supplemental points worth making. In general, current treatment of IBD relies almost entirely on some form of immunosuppression and anti-inflammatory, not just to get a patient into remission, but for trying to maintain remission. The problem with this is that suppressing the immune reaction – while necessary for getting the inflammation under control – does not by itself fix the underlying problem, the breakdown of the epithelial barrier (and the source of that barrier breakdown).

For example, prednisone inhibits NFκB gene expression to suppress the inflammatory pathway<sup>84</sup> (but “down-stream” of TNFα production), but it also significantly inhibits<sup>85</sup> expression of TGF-β1, which plays an important role in regulation of tight-junction proteins, and maintaining epithelial barrier function, as previously mentioned. Likewise, sulfasalazine (a 5-ASA) inhibits activation of NFκB<sup>86</sup>. This inhibition can help shunt the inflammatory cascade, but the critical step in that process is the initial over-production of TNF-α, not its subsequent activation of NFκB. Even if TNF-α is prevented from

activating the NFκB pathway, it will still be able to interfere with the demethylation of hydrogen sulfide, and to inhibit uptake and oxidation of butyrate – two critical steps in maintaining the epithelial barrier.

Because of the greatly exaggerated production of TNF-α in IBD patients, once inflammation has started, some form of direct suppression of TNF-α production would be beneficial to not only get inflammation under control, but to also help with rebuilding the epithelial barrier – since continued overproduction of that cytokine plays a pivotal role in exacerbating the breakdown.

In fact, it may be because current treatment largely revolves around anti-inflammatories that suppress NFκB activation that most IBD patients eventually have symptoms recur, generally requiring increasing dosages of immunosuppressants to get back into remission. If the underlying epithelial breakdown is not fixed (as well as compounding factors such as excess hydrogen sulfide production), the breakdown will likely spread, with more and more stimulation of the hyper-active immune system, until eventually the current dose of immunosuppressant can not sufficiently block the over-production of TNF-α from triggering the inflammatory cascade (since NFκB inhibition occurs in a dose-dependent manner), and the disease recurs (and requires higher levels of immunosuppression to get it back under control – until eventually dosages reach the maximal safe level, at which point the patient is deemed refractory to medications, and surgical removal of the colon is recommended).

Direct suppression of the inflammatory cytokine that not only triggers the NFκB pathway, but also plays a pivotal role in furthering the production of hydrogen sulphide and preventing uptake and oxidation of butyrate (which individually can be sufficient to trigger colitis), seems a better approach to take to get inflammation under control. Once the inflammation is under control, instead of just relying on inhibition of inflammatory cytokines to maintain remission, the focus should shift to rebuilding and then maintaining the epithelial barrier (through diet and supplements). Continued inhibition of TNF-α may be advisable, however, so that a slight break in the barrier (and subsequent over-production of TNF-α) is prevented from triggering a recurrence of the disease.

An important factor is rebuilding the microbiota, in particular the bacteria *Faecalibacterium prausnitzii*, which has been found to be deficient in people with IBD<sup>87</sup>. *Faecalibacterium prausnitzii* helps by promoting production of the anti-inflammatory cytokine IL-10 while also secreting metabolites that interfere with the production of the inflammatory cytokines IL-8 and NFκB. The ideal scenario would be able to take a *Faecalibacterium prausnitzii* probiotic, but since it is an anaerobic bacteria, it is very difficult to culture and put in capsular form. Some groups are getting close though. In the meantime, a few things have been found to be effective at boosting the population of *Faecalibacterium prausnitzii*: supplemental riboflavin (B-2) and the probiotic *Bacillus coagulans* BC30<sup>88</sup> (Digestive Advantage Daily Probiotic).

Lastly, personal and anecdotal experience, as well as research papers<sup>89</sup>, agree that emotional or psychological stress are correlated with disease activity in UC. This is not surprising, considering the large number of studies that have shown that psychological stress results in increased oxidative damage throughout the body<sup>90</sup>. It is imperative that IBD patients learn to manage stress. Personally, I have found awareness meditation (aka “insight meditation”) to be an excellent tool in that regard.

### 3.1. Treatment Stage 1

This stage will focus primarily on getting the inflammation under control through a combination of immunosuppression and anti-oxidants. As mentioned above, for the first stage, and potentially longer, some degree of direct TNF- $\alpha$  modulation should be done. Also as mentioned in the section on Short Chain Fatty Acids, so long as there is rampant TNF- $\alpha$  production, increasing fiber intake (to boost butyrate production) may not be wise, since the TNF- $\alpha$  is going to block most of the beneficial effects of the butyrate (by inhibiting uptake and oxidation), and the pro-inflammatory effect of butyrate through enhancing inflammatory production from dendritic cells will remain.

The biological agents Remicade and Humira are effective at dealing with TNF- $\alpha$  (acting as TNF- $\alpha$  antibodies), but since they are foreign proteins, our bodies will ultimately produce antibodies to them, rendering them ineffective (and actually dangerous). So, they do not represent long-term solutions. An alternative that could be used for long-term TNF- $\alpha$  modulation is the antidepressant bupropion (trade name Wellbutrin), which has been found to be an inhibitor of both TNF- $\alpha$ <sup>91</sup> and Interferon- $\gamma$ , another inflammatory cytokine involved in IBD. For some reason that has not been elucidated, the Immediate Release version is more effective in getting IBD symptoms under control than the sustained release versions – perhaps because of the slow release versions not achieving sufficiently high concentrations. In addition to those options, there are some natural inhibitors of TNF- $\alpha$  such as Curcumin and Quercetin<sup>92</sup>, although what dosage level of such agents would be required has not been established.

Traditional 5-ASAs (such as mesalamine) can be helpful also, not only because of their anti-inflammatory effects, but also since they partially inhibit production of hydrogen sulfide, which plays an important role in the onset and exacerbation of IBD, particularly in the colon. Eventually SCFAs will be relied on more for this role, but since butyrate may have a net inflammatory effect until TNF- $\alpha$  production is under control, 5-ASAs can serve that purpose initially.

As a big part of getting inflammation under control initially, and during the process of rebuilding the epithelial barrier, it can be very beneficial to increase levels of anti-oxidants at the site of damage (because of the deficiency in reduced glutathione that shows up in IBD<sup>57</sup>, creating a highly oxidative environment). In UC, since it starts in the distal colon, enemas with anti-oxidant agents can also be helpful at getting inflammation under control – and also at rebuilding the epithelial barrier. As previously stated, vitamin E and ethyl pyruvate have been found effective in distal colitis (although ethyl pyruvate is not currently readily available), and the antioxidants SAM and glutathione or the intermediary methionine derivative N-Acetyl-L-Cysteine<sup>77</sup> (NAC) are also options (orally or as enemas if the inflammation is distal). Oral administration of these anti-oxidants would presumably also be helpful, but moreso in proximal disease than distal as the levels would likely decrease considerably in transit through the intestines. Glutamine can also be delivered both orally and rectally via enemas (more on glutamine in a few paragraphs).

Since oral antioxidants are often absorbed before they make it to the large intestine, and their systemic antioxidant effect is generally weaker than if they made it directly into the colon, approaches for getting antioxidants into the colon are desirable. One approach is making homemade anti-inflammatory enemas (or suppositories). Another interesting approach is supplementing with the bioflavonoid rutin. Rutin is not absorbed in the small intestine, and is broken down by colonic bacteria into the antioxidant quercetin<sup>93,94</sup>. This allows rutin to effectively deliver the antioxidant quercetin to the colon, whereas directly supplementing with quercetin results in it being absorbed before it reaches the

colon. Because of this, rutin has been found to be much more effective at ameliorating (halting and healing) colitis in mice<sup>95</sup>. Personally I have found rutin to be one of the most (perhaps the most) effective natural antioxidants for stopping colonic inflammation.

Also, oral administration and enemas with bovine colostrum have been found effective at getting distal colitis under control<sup>96</sup>, as well as rebuilding the epithelial barrier (due to a boost in TGFβ). It seems like it will be more beneficial for the latter effect than the former, so I think it is more important to emphasize it in stage 2 (rebuilding), and continue using it in smaller doses for long-term maintenance of the barrier (stage 3).

Glutamine is important not only as a potential energy source for epithelial cells, but also for rebuilding tissue (as glutamine can be broken down to make almost any other amino acid, as needed). Not surprisingly, glutamine supplementation (orally and in enemas) has been found to be very helpful for IBD, especially colitis<sup>97,98,99,100</sup>. Some people apparently have a negative reaction to glutamine, however – something I do not fully understand yet. For that reason, people should not jump fully into glutamine supplementation, but instead ramp it up slowly. If no problem is found, initial supplementation at 10-15 grams per day can help with suppressing inflammation (the references explain how) and rebuilding the intestines. Zinc carnosine is also helpful for repairing intestinal lining<sup>101</sup>, and has been shown to be helpful in treating colitis (orally and in enemas).

For the most part, the anti-oxidant options are relatively inexpensive, over-the-counter products that a patient can self-administer with enema bottles, initially on a daily basis to get inflammation under control (the vitamin E study used 8,000 IU nightly, but especially if combined with other efforts described above, a lower level would likely be sufficient), then with decreasing frequency. In the vitamin E study<sup>64</sup>, participants kept doing them nightly throughout the follow-up period to maintain remission. Our goal is to fix the underlying problem, heal the epithelial barrier, and increase in-situ production of the anti-oxidant glutathione as well as the short chain fatty acids. With that approach, it should not be necessary to continue with anti-oxidant enemas, although it may be helpful to supplement with additional anti-oxidants (in particular rutin).

To help get the inflammation under control quickly, getting the antioxidants and other things for healing (N-Acetyl L-glucosamine, zinc carnosine, L-glutamine, colostrum) directly to the colon is imperative. Either enemas or homemade suppositories can work fine. If the inflammation extends far beyond the distal colon, enemas would likely be more effective as a person can do inversions (tilting your body slightly upside down) to allow the ingredients to travel further up into the colon, compared to suppositories. Suppositories can be made by melting some cocoa butter in a glass measuring cup (microwave it), adding the desired ingredients, mixing, and pouring the mix into the fingertips of extra small nitrile gloves (without powder), and chilling it in the refrigerator. The nice thing about this approach is you can make a batch of suppositories fairly quickly, and just use one or two a night until symptoms have been gone for a few weeks.

Since most of these supplements have not gone through clinical trials with humans with IBD taking them as suppositories, there generally are not clearly established dosing guidelines. For suppositories, the approach I used was mixing the following ingredients with enough melted cocoa butter to make about 10 suppositories (to be used one a night, until a few weeks after symptoms were gone to make sure everything was healed up nicely): 1,000 mg L-glutamine, 2,500 mg phosphatidylcholine, 4,000 IU vitamin E, 600 mg quercetin, 500 mg curcumin, 500 mg NAC, 500 mg N-

acetyl L-glucosamine (NAG), 500 mg reduced glutathione, ~100 mg zinc carnosine, 2 grams colostrum, and 800 mg EGCG.

With enemas, you need to mix the ingredients up each night, mixing them with distilled water. It is also harder to retain the enemas since there is a greater volume of liquid (but that does allow it to reach further into the colon). So each of those approaches has pluses and minuses. The third approach is to just use gelcaps directly as suppositories, putting some water-based lubricant on them. This is the easiest approach to do, but the drawback is that you don't really want to do this with powdery supplements (which many of them are), since they wouldn't be well absorbed. It can be done effectively though with vitamin E gelcaps (the large 1,000 IU ones) and phosphatidylcholine gelcaps.

Note that vitamin E seems to have an osmotic effect when given as an enema, which may result in the first stool afterwards being watery (especially if they were administered with a fair amount of water). If the enemas are done just before bed, that can help with retention.

If (and only if) a person has MTHFR mutations, it would be wise to supplement with methyl folate to bypass any deficiencies in the MTHFR enzyme, to allow sufficient methylation and subsequent production of NAC and glutathione as well as aiding in sulfonation by limiting build-up of homocysteine. But, if there are also mutations in CBS genes, it may be necessary to first address deficiencies in the transsulfuration pathway. What a person does regarding genetic mutations would need to be tailored to their individual mutations. There are some growing communities online that are focusing on these issues. Dr. Amy Yasko seems to be a pioneer in this area, the field of "nutrigenomics", so I am currently reading through her work.

At this stage one should also start trying to boost concentration of *Faecalibacterium prausnitzii* by supplementing with Digestive Advantage Daily Probiotic and Riboflavin.

### 3.2. Treatment Stage 2

Once the inflammation is under control, the focus should be on rebuilding and then maintaining the epithelial barrier, rather than relying purely on immunosuppressants to maintain remission. A diet high in fiber, particularly inulin and fructo-oligosaccharides, which are the best food sources for butyrate production<sup>102</sup>. Chitosan oligosaccharide also has many beneficial effects for inhibiting intestinal inflammation, by inhibiting NF- $\kappa$ B activation, production of TNF- $\alpha$  and IL-6, and helping maintain epithelial barrier integrity under stressed conditions<sup>103</sup>. Additionally, sulfite preservatives should be avoided, and protein intake should be kept to modest levels (particularly eggs, dairy, and red meat), and alcohol should also be avoided, as these all have been found to be compounding factors<sup>72</sup>, likely due to the sulfate content. The patient should have food sensitivity (IgA/IgG) testing done to identify foods that could promote an immune response, which could also contribute to barrier weakening. Other issues that promote barrier breakdown (stress, NSAIDs, etc.) should also be avoided.

At the same time, it would be beneficial to supplement with agents that have been proven effective at rebuilding and maintaining the epithelial barrier, such as bovine colostrum<sup>104</sup> and additional butyrate supplementation. During this stage, a high level of colostrum supplementation would likely be beneficial (on the order of 10 grams/day – note that it can be bought in powder form instead of pills for high dosage).

Due to the importance of the microbiota in maintaining homeostasis, attention should also be paid to undoing an underlying bacterial dysbiosis. Diet can play a role in that, as described above, but other methods can help as well. In particular, fecal transplants have been found effective at resolving underlying bacterial dysbiosis in IBD patients, particularly colitis, and providing an effective cure<sup>105</sup>. The Center for Digestive Diseases (CDD) in Australia has pioneered this approach, and has had better success at it than has been seen in more recent studies by other groups<sup>106</sup>. However, this may be a result of significant differences in the methodology used. The CDD not only has patients do repeated transplants often over the course of many weeks or months, but they also require patients to switch to a diet high in fiber (and avoid certain foods such as preserved meats, which tend to be high in sulfates) once starting the process.

Fecal Transplants will be discussed in a little more detail in section 3.2.1.

Speaking from my own experience, getting inflammation under control first, and consuming a proper diet afterwards are key factors. I did fecal transplants (FTs) in the late summer of 2012 while on Remicade (so symptoms fully under control), and subsequently came off Remicade, and I seemed to be perfectly cured. For the first time in 12 years, I not only had a normally functioning digestive system, but I was also off all medication. But after about 6 months I changed my diet to a very high protein and low fiber diet, and my UC returned.

One issue here is that while IBD is active, most patients generally have a willingness to try anything to get their disease into remission (which helps get over the “ick” factor of FTs, particularly self-administered), once in remission our view often switches to not wanting to try anything new that might “rock the boat”. So, IBD patients are most-willing to try FTs at a time that is not the ideal time to try it – and when the time is right (symptoms are under control, and it is now time to fix the underlying dysbiosis problem), their willingness wanes.

There are other options as well for helping to improve the microbiota. In general, it seems that the primary bacterial problem in IBD is not the presence (or lack thereof) of a particular strain, but rather a significant shift in the populations of certain common strains. Both diet and FTs can help resolve that issue. Diet-wise, there should be a heavy emphasis on fiber, in particular inulin, fructo-oligosaccharides, and oligofructose, which are particularly beneficial for SCFA production. A patient should also focus on limiting sulfur intake, which means only moderate levels of protein (and avoiding the highest sulfur sources as much as reasonable: eggs, red meat, shellfish, and cheese), particularly during this rebuilding stage. Carageenan (a sulfated polysaccharide used as a thickening agent in many foods, especially meat and dairy alternatives) and sulfurous preservatives should also be avoided.

As an adjunct, supplementation with various probiotic strains has been found to be helpful in getting IBD under control as well as maintaining remission (generally through the production of butyrate or other SCFAs, or anti-inflammatory cytokines, or suppression of inflammatory cytokines). In particular, *Bifidobacterium Longum* (as a Synbiotic, mixed with inulin to feed the bacteria)<sup>107, 108</sup>, *Lactobacillus Casei*<sup>109,110</sup> (increases production of anti-inflammatory IL-10 and TGF- $\beta$ , decreases levels of myeloperoxidase activity and pro-inflammatory interleukin (IL)-12p40) are good choices. *E. Coli Nissle 1917* has been found to be as effective as mesalamine at inducing and maintaining remission in IBD, but it also is somewhat genotoxic to eukaryotic cells, which may increase the likelihood of developing colon cancer<sup>111</sup>. Additionally, since that strain was initially harvested from human stool (from a soldier who did

not develop dysentery, unlike the other soldiers in his platoon), and the US FDA has labelled stool as a drug, that probiotic can not currently be sold in the US.

The epithelium is normally protected from luminal contents (including bacteria) by a mucus layer containing phosphatidylcholine (PC, phospholipids containing choline). A key manifestation of IBD is lipid peroxidation from the high levels of Reactive Oxygen Species, brought on by rampant inflammatory cytokine production. As a result, patients with IBD have been found to have a reduced thickness of the protective lipid-mucus layer<sup>112</sup>, with reduced levels of PC<sup>113,114</sup>. A consequence of this is reduced levels of PC. In fact, a likely mechanism by which NSAIDs cause gastrointestinal ulceration is due to their affinity for bonding with PC<sup>115</sup>. Supplemental PC can play an important part of helping reduce bacterial translocation (by rebuilding that protective layer) and healing the intestines. Oral supplementation of delayed release PC has been found to be effective at reducing intestinal inflammation<sup>116</sup> and getting UC patients into remission<sup>117</sup>. So, part of my protocol will include supplementation with a modest level (1 gram/day) of PC during the healing process, dropping down to half of that for maintenance. One of the potential issues though is that PC may be too rapidly absorbed in small intestine (in the studies they used PC coated with shellac to delay absorption). So a more effective approach would be to either put PC into homemade suppositories or enemas, or to simply put some water-based lubricant (without carrageenan) on a PC gelcap and use it as a suppository.

### 3.2.1. Fecal Transplants

So far, very few studies have been done on the effectiveness of FMTs (Fecal Microbial Transplants) on IBD, and the few that have have not been well designed (in my opinion). The studies have not imposed any dietary restrictions on participants, so participants may not be properly feeding the new bacteria (eating ample fiber and resistance starches), or they may be consuming foods that by themselves cause intestinal barrier breakdown (such as gluten). Since IBD is not a disease with one lone cause, it is not reasonable to expect fixing one of the underlying problems to cure the disease. Especially if no efforts are taken to ensure that that one problem is truly fixed – i.e. making sure that the transplanted bacteria are able to take root and continue being fed properly.

One potential complicating factor for doing FMTs (Fecal Microbial Transplants) for IBD is that some bacteria build “biofilms” to help protect them and to guard their space. If those biofilms are not broken down, the bacteria can often survive antibiotics, and it also makes it more difficult for transplanted bacteria to establish themselves. The issue of bacteria protecting themselves with biofilms has been studied mostly with regards to pathogenic bacteria that build biofilms on medical devices (implanted or otherwise) to protect themselves<sup>118</sup>, but it is well known that bacteria build biofilms within the gut as well.

When I did FMTs, I first took a supplement (Interfase Plus) designed to break down bacterial biofilms, to help clear the path for transplanted bacteria. After a week of that and antibiotics, my colon should have been a fairly “clean slate” for the transplanted bacteria to take root. This is likely an important component to achieving success,

An additional factor is that fecal transplants are likely to be more successful if done after the inflammatory process has been brought into remission. If the epithelial barrier is broken, and TNF- $\alpha$  production is not inhibited, adding a donor’s stool the colon to be retained for several hours would likely

result in significant bacterial translocation across the barrier, potentially exacerbating symptoms rather than helping.

#### 4. “The Briggs Protocol” Treatment Summary

For more information on any of these, see the more detailed description of the protocol above. Note that I took an “everything but the kitchen sink” approach, meaning I threw a whole bunch of stuff at it to get the inflammation under control quickly. Most likely it is not necessary to do all of this. There is a lot of individual variation in terms of how much inflammation a person has, what genetic polymorphisms they have and how they affect their immune response, how distorted their microbiota is, and other factors. All of the options for getting inflammation under control (whether natural over-the-counter supplements, or pharmaceuticals) work in a dose dependent manner. That means the more inflammation (hence oxidation) is present, the more anti-oxidants / anti-inflammatories are necessary to quench it. Because of that there is likely to be significant variation in how much one person needs versus another to get their inflammation under control. Therefore this should be viewed as a very rough guideline. Some people may not need as much, while other people may need more.

##### ***Phase 1: Induce Remission (quickly)***

- A. Anti-TNF- $\alpha$  therapy: The anti-depressant Wellbutrin (bupropion), in immediate release form, at a dosage of three 100 mg pills a day, seems to be effective at inhibiting TNF- $\alpha$  production. Some natural options are curcumin and quercetin, but no studies have clearly identified what dosage would be required for sufficient inhibition to induce remission (which would likely also vary from person to person based on how much is being produced, based on the level of barrier breakdown and other factors). The anti-TNF antibodies Remicade and Humira are also very effective at this, but with a significant drawback – they are foreign proteins, that your body will eventually develop antibodies to. Also, their mechanism of action seems to include greater side effects than Wellbutrin.
- B. Restart methylation if (and only if) genetic mutations require it: supplement with methyl folate to ensure adequate MTHFR enzyme production, necessary for making N-acetyl L-cysteine, glutathione, phosphatidylcholine, etc..
- C. Hydrogen Sulfide inhibition: 5-ASAs, such as Lialda (mesalamine), are effective at inhibiting bacterial production of hydrogen sulfide, which can help get the redox balance back under control. They are also potent anti-inflammatory agents.
- D. Additional prescription anti-inflammatories *if necessary*: i.e. prednisone. Drugs like prednisone have serious side effects, and should be avoided unless necessary to induce remission. Wellbutrin, mesalamine, and natural anti-oxidants should be tried first before resorting to prednisone.

- E. Additional, natural anti-oxidants: vitamin E, n-Acetyl L-cysteine, glutathione, milk thistle (the active component silymarin has been shown to help with maintaining remission of UC)<sup>119</sup>, EGCG, rutin, curcumin.
- F. Have IgA testing done, and avoid foods that you have a high IgA response to
- G. Avoid fluoridated water (fluoride deplets ATP from epithelial cells, reducing their energy reserves<sup>120</sup>) – ideally drink spring or distilled water, at least until everything is healed.
- H. Phosphatidylcholine (2 grams/day until mucus and bleeding have stopped, then 1 g/day)
- I. Glutamine, 10-20 grams/day (note that some genetic mutations can result in a person having issues with excess ammonia production related to high intake of glutamine or protein in general)
- J. 5-grams of L-glycine<sup>121</sup>
- K. Anti-inflammatory enemas until inflammation has cleared: 3,000 to 7,000 IUs of natural vitamin E, 500 mg of reduced glutathione, 1 gram of colostrum, 500 mg of phosphatidylcholine, and 5 grams of L-glutamine, mixed in ~50 mL of water. These are best done before bed to help with retaining. Note that since inflamed tissue is ineffective at absorbing water, and vitamin E having a mild laxative effect, it will likely result in a loose stool in the morning – but will help with getting inflammation under control. It may be more palatable to instead make suppositories by mixing ingredients in melted cocoa butter and pouring into the fingers of a latex or nitrile glove (then refrigerating). You’ll have to reduce the amount of stuff used though.
- L. Zinc carnosine (Pepzin GI), one or two capsules a day (orally or could be used in enemas)
- M. Probiotics: Lactobacillus Rhamnosus GG (“Culturelle”)<sup>122</sup>, lactobacillus plantarum 299V (Jarrow sells some<sup>123</sup>), and clostridium butyricum miyairi<sup>124</sup> have all been found effective at inhibiting the inflammatory response in IBD. Bacillus Coagulans BC30 (Digestive Advantage Daily Probiotic) and Riboflavin should be taken to help boost concentration of Faecalibacterium prausnitzii. Fecal transplants are best done **after** inflammation is under control (phase 2), but these probiotics can be taken during phase 1.
- N. Practice awareness meditation.

## **Phase 2: Barrier Repair**

Once inflammation has stopped (no more mucus or bleeding):

- A. Diet: Once TNF production is under control, the diet should include significant levels of fiber and resistant starches for production of SCFAs, in particular butyrate. In addition to consuming a significant amount of vegetables (and beans and rice for resistant starches), I also add 15-20 grams of supplemental fiber per day, as inulin, fructo-oligosaccharides, and oligofructose, plus 1-2 grams of chitosan oligosaccharide<sup>103</sup>. It may be preferable to start out low and work up to such levels. Also, the diet should still be relatively low in sulfur (i.e. avoid sulfate and sulfite preservatives, don’t go overboard on protein). In phase 3 it is ok to eat a normal amount of protein, but for now it should be on the low side, but supplemented with L-glutamine.
- B. Maintain the TNF- $\alpha$  and hydrogen sulfide inhibition (ideally Wellbutrin and a lower dose of mesalamine. The latter can be gradually reduced in this stage).

- C. Bovine Colostrum (5-10 grams/day during this phase, with a powder form such as that from Symbiotics being the easiest and most cost effective way of doing this)
- D. Phosphatidylcholine (1 g/day)
- E. Increase glutathione levels with enteric-coated glutathione, or n-Acetyl l-cysteine (NAC, doesn't have to be enteric coated). NOW makes an NAC supplement that contains the selenium and molybdenum necessary for making the enzyme to turn NAC into glutathione.
- F. Commercial products: "GI Revive", which contains mucin (among other things) to help replenish the low levels of mucin found in people with IBD.
- G. Microbiota rebalancing: Depending on how "out of whack" a person's microbiota is, and a person's inclination, this could be done with probiotics and diet, or the addition of fecal transplants (a diet high in fiber and resistant starches would still be beneficial for repopulating with beneficial bacteria, and increasing SCFA production). In addition to those mentioned in Phase 1, Bifidobacterium Longum and Brevis, and Lactobacillus Casei and Reuteri have been found to be beneficial, among others. Natural Factors Ultimate Protec-Probiotic contains the first three of those, and is enteric coated.
- H. Glutamine – 15 grams/day
- I. Selenium, vitamin D

### ***Phase 3: Barrier Maintenance (long-term)***

I don't have a clear timeframe on how long to stay on Phase 2. Phase 3 will ultimately be a reduced version of phase 2 (the supplements that are effective at rebuilding the epithelial layer have mostly also been shown to be effective at helping to maintain it in a prophylactic manner, in lower doses). A good measuring stick for when to progress to this might come from having an lactulose/mannitol intestinal permeability test.

## **5. Diet**

As mentioned in the update at the start of this version, I may not have time to add in references for everything right away.

My protocol overall revolves around minimizing things that have been shown to cause damage to the epithelial barrier, while using supplements (and dietary factors) that have been shown to help maintain and repair the barrier. IBD revolves around a hyperactive immune response to bacteria translocating through the epithelial barrier. So, if the barrier can be maintained, preventing (or at least greatly limiting) bacterial translocation, IBD should not occur.

A variety of non-dietary factors contribute to breakdown of the epithelial barrier, including emotional stress<sup>125</sup>, NSAIDs, alcohol, disruption of the circadian rhythm<sup>126</sup>, high intensity exercise<sup>127</sup>, and bacterial dysbiosis<sup>128</sup> induced by antibiotics. I love exercising, and it is healthy in general, so I don't plan on stopping entirely - but I also won't be doing any marathons.

In addition to the non-dietary factors, there are also a variety of dietary factors that contribute directly to barrier disruption and increased inflammation. Some of those factors have already been discussed above (lack of short chain fatty acid production from fiber and resistant starches, excess

sulfate consumption, lack of commensal bacteria for helping maintain the barrier, and eating foods that you have an allergic response to<sup>129</sup>), but some have not.

The two biggest dietary factors that can help are avoiding gluten and limiting processed foods. The latter issue is largely due to certain additives added to many processed foods. In particular, the common emulsifiers carrageenan, carboxymethylcellulose and polysorbate-80<sup>130</sup> have been shown to produce colitis in pre-disposed mice by altering the microbiota in a manner that promotes bacterial translocation and increased inflammatory response. Consuming some processed foods is ok as long as they don't contain particularly unhealthy additives. The emulsifier carboxymethylcellulose is also often listed as "cellulose gum", and unfortunately shows up in many gluten-free processed foods (but there are also many that don't use it). Carrageenan is used in many dairy alternatives, such as many brands of soy milk, rice milk, almond milk, coconut milk, and dairy and non-dairy ice creams, whipped cream, etc..

There are a few other general dietary factors that I keep in mind:

1. Minimizing damage from dietary lectins
2. Reducing the ratio of pro-inflammatory Omega 6 fatty acids to anti-inflammatory Omega 3 fatty acids

Lectins are a type of protein which are found in practically all types of food, but they are particularly concentrated in seeds, nuts, and grains. All of these can be viewed as plant "offspring", which the plants presumably do not want us eating. Lectins are mild endotoxins that biologists feel are concentrated in these plant offspring to discourage animals from consuming them. The most well known lectin is likely gliadin, a component of gluten found in wheat, barley, rye, and most oats. Gliadin stimulates production of zonulin by epithelial cells, and zonulin results in the tight junctions moving further apart, allowing food macromolecules (whole proteins in particular) and bacteria being able to migrate through<sup>131</sup>. This happens in everyone who consumes gluten containing foods, whether they have a gluten sensitivity or not. Allowing whole proteins to pass through increases the likelihood of developing food sensitivities or allergies, since our immune system is more likely to identify a protein as a pathogen when it starts showing up in our bloodstream.

Modern wheat has been selectively bred for rapid growth, which has unintentionally resulted in high levels of gliadin. Based on this, it seems clear that nobody with IBD should consume gluten-containing foods. In fact, nobody at all should consume them, as this barrier disruption caused by gliadin has been linked to a large variety of diseases, not just inflammatory diseases, but also things like autism and Alzheimer's disease.

The lectins in other grains, legumes, nuts, etc. don't seem to be as bad as gliadin, but they do still cause damage to the epithelial surface<sup>132</sup>. So, for that reason, an effort should be made to reduce lectin intake. Note that we also want to feed our intestinal microflora, which requires a good deal of fiber and resistant starches – many of the best sources of which are lectin-containing foods (grains and legumes especially). So, what are we to do?

The approach of some diets (paleo, for example), is to completely exclude lectin-containing foods – which eliminates many otherwise very healthy foods from the diet. The Paleo diet eliminates these based on the argument that Paleolithic man did not eat them (grains, etc.). One thing that bugs me about this is that they seem to be assuming that we stopped evolving at some point during the

Paleolithic era, which is absurd. Not only have we continued to evolve, we have continued to *co-evolve* with our microbiota. Modern humans rely on our intestinal microflora to perform a variety of functions for us, and in order for them to do so, we need to feed them – with fiber and resistant starches, which are found in foods the Paleo diet specifically excludes (as does the Specific Carbohydrate Diet).

Humans have eaten grains, legumes, nuts, and seeds for thousands of years. What has changed is how we grow, harvest, and process those foods. Traditionally, grains were allowed to sprout before being milled into flours. The sprouting process breaks down anti-nutrients like phytic acid and lectins. Also, prior to the development of rapid rise yeast, breads required several hours to properly rise – during which time fermentation by the yeast and bacteria further broke down lectins and phytic acid. While modern agricultural and culinary practices have greatly simplified and expedited food related activities (allowing only a small percentage of the population to be involved in agriculture, for example), there have been unintended side effects – in particular high lectin consumption.

We can minimize this by using traditional food preparation processes – in particular using sprouted flours and soaking legumes in a slightly acidic medium for several hours. Additionally, lectin damage can be mitigated with certain sacrificial carbohydrates. Lectins exert their damage by binding to particular carbohydrates inside us. For example, gliadin binds to n-Acetyl L-Glucosamine, which is found in our epithelial cells. By supplementing with n-Acetyl L-Glucosamine when eating a food containing a lectin that binds to it, the lectins will instead bind to the ingested n-Acetyl L-Glucosamine, sparing our cells from damage. A few products are available that contain a variety of lectin binders – “Lectin Lock”, Lectin Control Formula”, and “GI Revive” (which also has other things).

Limiting consumption of lectins (by using sprouted grains or fermenting doughs, soaking and thoroughly cooking legumes, etc.) and taking lectin binders when lectins are consumed will reduce damage to our epithelial cells by lectins – this damage likely plays a significant role in the increase in inflammatory bowel disease and other ailments in developed civilizations. Avoiding modern wheat alone can go a long way towards reducing damage.

The other dietary factor revolves around fats. The mechanisms are messier than I have time to get into right now, but ultimately omega 6 fatty acids are pro-inflammatory (increased production of prostaglandins,  $\text{tnf-}\alpha$ , etc.), while omega 3 fatty acids are anti-inflammatory. The ratio of omega 6 to omega 3 fatty acids has a significant effect on the production of inflammatory cytokines<sup>133</sup>. It is becoming fairly well accepted<sup>134</sup> that humans traditionally had a close to 1:1 ratio of omega 6 to omega 3 fatty acids in our diet, but the modern American diet is around 16:1. Much of this appears to be due to a greatly increased consumption of certain vegetable oils. For example, corn oil has a ratio of 83:1.

Surprisingly, the much-demonized canola oil actually has a very appealing omega 6:3 ratio of about 2.2:1. About 80% of the canola oil sold in the US is GMO, but it is possible to find non-GMO, cold-pressed canola oil. Anyway – there is a lot of information available online about how to improve your omega 6:omega 3 ratio, so I’m not going to duplicate that here. Some Paleo diet advocates also emphasize this heavily, so there are several Paleo sites with a lot of information about it. One caveat to this – many of these sites advocate avoiding most nuts, since they have high ratios of omega 6 to omega 3 (except walnuts and macadamias). I disagree with this though, since most nuts primarily contain healthy monounsaturated omega 9 oils, so the total amount of both omega 6 and 3 (the polyunsaturated fatty acids) are actually pretty low. Peanuts on the other hand, which are legumes, not nuts, are high in omega 6s, and worth avoiding or at least limiting.

There are a variety of diets that have become popular among people with inflammatory conditions (especially IBD), in particular the Specific Carbohydrate Diet and Paleolithic Diet. There are some aspects of the Paleolithic Diet that I like (in particular limiting lectin consumption and improving omega 6:3 ratio), but I have a significant problem with one aspect of the diet – and it is the same problem I have with the Specific Carbohydrate Diet (SCD). Both diets ignores the importance of our microbiota for our health. The Paleo diet is based on the assumption that our digestive system has not evolved any since the Paleolithic era, which is a rather absurd assumption – particularly when you consider the significant changes in agricultural practices of humans over the past several thousand years, and how our microbiota co-evolves with us. Dozens, perhaps hundreds of studies (many of which are referenced below) have demonstrated the importance of our microbiota to our overall health – so a diet that ignores that, and makes no attempt to properly feed the microbiota, is in my view not ideally designed.

Some Paleo advocates have recently started advocating the consumption of some resistant starches (in particular potato starch) to help feed the bacteria – this is a wise move on their part. Advocates of this are finding a significant improvement in their microbiota and overall health with this adjustment. Personally, I'd say that they could instead lift their strict ban on grains and legumes (which are banned based on the argument that Paleolithic man did not eat them), and instead focus on proper preparation of those foods.

The SCD has had considerable success in helping many people with IBD and other intestinal issues, but with caveats. Based on what I have seen from my own experience on it, as well as what people on SCD mailing lists say who have been on the diet for many years, there is a significant flaw. The diet is based on the idea that these digestive problems are purely the result of a bacterial dysbiosis, which needs to be fixed by “starving off the bad bacteria” (practically an SCD mantra). The problem that is completely ignored is that the so-called “bad bacteria” feed on the same things as “good bacteria” – complex carbohydrates, especially fiber and resistant starches. The diet focuses on removing complex carbohydrates to starve off the bad bacteria, but the unavoidable result is starving off **all** of the bacteria, essentially a slash and burn of the microbiota similar to what antibiotics do.

Since we rely on our microbiota for many important functions – including maintaining the epithelial barrier – starving off all the bacteria does not seem like a good approach to repairing that barrier (and ultimately it is the breakdown of that barrier that is the crux of the problem). As mentioned earlier in the paper, studies in mice have shown that if the barrier is broken down, but negligible bacteria are present (as in the “germ free” mice), there will be no inflammatory response – since the inflammatory response is a reaction to bacterial translocation through a disrupted barrier. It may be that the mechanism by which SCD works is simply creating a near “germ-free” state by starving off the entire microbiota.

The SCD forbids many probiotics, but does allow Lactobacilli. Studies on the rate of translocation of different types of bacteria found the lowest rates for Lactobacilli. So, it may be that the reason Lactobacilli are allowed under SCD is that the barrier remains broken, and any other strains of bacteria will cause inflammation due to translocation through the broken barrier. Indeed, this may be why many people who have been ostensibly cured by SCD find that they have to remain on the diet indefinitely, as eating any complex carbohydrates leads to the return of symptoms. This may be because the complex

carbohydrates feed any remaining bacteria in the intestines, including non-Lactobacilli, causing a temporary “bloom” of strains that translocate through the barrier, triggering an immune response.

Note that these are just my own personal thoughts on these two diets, and why I have chosen to not follow either of them. I was on SCD for a while, including when my UC returned, and I remained on the first stage of SCD for weeks while my symptoms got worse and worse (as I was simultaneously doing fecal transplants, which was just putting in plenty of bacteria to translocate through my broken epithelial barrier).

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