CF Natural Health

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eBook

Understanding Cystic Fibrosis:
A Deep Dive into CF Pathophysiology

Table of Contents

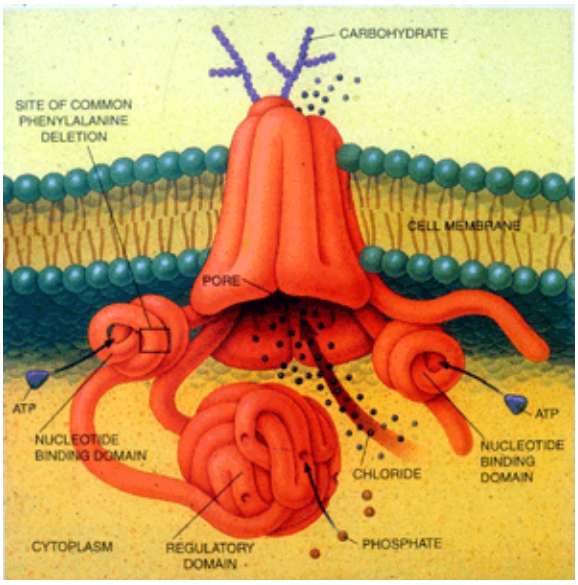
I. Introduction

CF 201: Know Thyself

The following is an intermediate-level course in the pathophysiology of cystic fibrosis. If you need a basic overview of the disease before you continue with CF201, check out the info here. There are many things about CF that every person needs to know in order to embark on a path of self-healing. The more informed you are about your disease, the more empowered you will become to make your own health decisions. So I have put together some info below as a kind of intermediate course on your health.

Genetic Mutation

At the cellular level, the fundamental problem is that a protein embedded in the membranes of our body's epithelial cells (i.e. lungs, skin, digestive tract, etc.)--the CFTR (cystic fibrosis transmembrane conductance regulator) protein--is mutated and thus does not function properly. A healthy, unmutated CFTR channel transports sodium and chloride ions across the cell membrane efficiently to maintain the correct balance of electrolytes inside and outside of the cell. This is a very important function in epithelial cells that ensures our mucus has enough water in it, and is not too thick and sticky. A normal CFTR protein moves chloride and thiocyanate ions (both with a negative charge) out of the cell and into the mucus covering the cell. Positively charged sodium ions follow these anions out of the cell to maintain the electrical balance, or gradient. This increases the total electrolyte concentration in the mucus and results in the movement of water out of cell and into the mucus via osmosis, thus thinning the mucus out.



CFTR protein 1

A mutated CFTR protein[1] (coded for by a number of different mutations of the CFTR genes on chromosome 7) does not allow these ions to flow across the cell membrane effectively, and this results in water retention in the cell. When water is retained in the cell, it means the mucus is not getting enough water and it becomes thick and sticky. The mucus is so thick and so sticky that the cilia (cute little hairs on the outside of the cell that move mucus in the respiratory tract) cannot move. That means the mucus cannot be effectively moved out of the airways and can attract pathogens (viruses, bacteria, fungi) that just sit there and

[1] *CFTR Mutations: A Guide.* <https://www.cftrscience.com/a_guide.php>

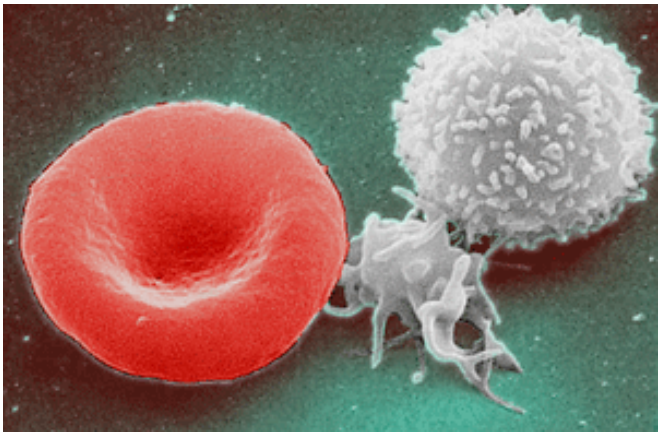
proliferate.

The purpose of mucus is to catch pathogens in the body, neutralize them, and carry them out via your orifices (think of a runny nose when you've got a cold). But when the mucus can't move, the pathogens don't move either, and soon you've got an infection. There are new drugs available and in development that correct this defect in the CFTR protein in certain mutations (e.g. Kalydeco in G551D mutations; Orkambi, Symdeko, and Trikafta in deltaF508 mutations). Each CF genetic mutation causes a different problem for the CFTR protein in the cell membrane (either a lack or absence of them, or change in their functions) so CFTR-correcting drugs have to be targeted to specific mutations. Their first drug was able to correct the "easiest" of the CF mutations (i.e. CFTR proteins are present but have a "gating" problem = the G551D mutation), and the next drugs in development are targeted at fixing the more difficult mutations, which cause a lack of enough CFTR proteins (i.e. the deltaF508 and G542X mutations).

So at the roots of it all, we've got a mucus problem due to improper ion transport through faulty CFTR proteins. One way to treat this mucus problem in the lungs is through the use of osmotic drugs, i.e. inhaled hypertonic saline or a sugar called mannitol. The point of both of these drugs is to artificially increase the electrolyte load in your mucus so that water is drawn out of the cells via osmosis into the mucus, thinning it and allowing us to cough it up and out of our lungs. Simple, safe, and effective! Our digestive tissue also has this problem with mucus thickening, and so the use of miralax (an osmotic laxative used in CF-related constipation) also uses this concept to induce bowel movements in CFers with constipation. Natural alternatives to pharmaceutical laxatives may also be effect for this issue.

There are many other things that we can expose ourselves to that can exacerbate this mucus problem, primarily foods, food-like substances (i.e. junk food), and digestive deficiency. I am particularly concerned with what foods and food-like substances can make our mucus problems worse, setting us up for more serious infections and worsened symptoms overall.

II. Inflammation and Infection



Red and white blood cells 1

Inflammation is an important contributor to an increased mucus load. There are special cells scattered throughout the epithelial linings of certain organs (lungs and digestive tract in particular), called goblet cells, that secrete mucin (the main constituent of mucus). When goblet cells detect pathogens nearby, they secrete more mucin in order to try to flush them away and out of the body. But in CF, our little cilia are not working and our cells are not secreting enough water to combine with that mucin to thin it out, so those goblet cells are just making the problem worse! Furthermore, in bronchitis and chronic lung infections, the number of goblet cells in the airways increases! Now we've got too much thick, sticky mucus on our hands in addition to whatever pathogens the immune system detected. Soon we've got clogged up lungs and an infection brewing. Not good. Goblet cells can also be triggered to secrete more mucus if they detect toxins or allergens in the airways such as pollution, cigarette smoke, or compounds that the immune system has inappropriately created antibodies against.

Interestingly, the intestines also secrete mucus as part of their normal functions, but they secrete excess mucus when they encounter pathogens and allergens in the gut, or irritating/hard-to-digest foods. Both the lungs and the digestive tract are innervated by the vagus nerve, and so when the guts are producing excess mucus due to digestive irritation, mucus secretion will increase in the lungs as well. Therefore, eating inflammatory or difficult to digest foods can increase lung mucus! Have you ever noticed that certain foods make your nose run or your lungs produce more mucus? I have, and so have many of my clients. This is a naturally physiological response to digestive irritation, but unfortunately few mainstream doctors are aware of this connection and may dismiss it when their patients explain this to them. In fact, there is a method of herbal application called acupharmacology that exploits this vagus nerve connection between the guts and lungs to sooth and calm the airways! This is essentially how elecampane can increase respiratory expectoration, or how marshmallow root tea can sooth a dry, hacking cough.

Mucus production is a non-inflammatory immune response. It is our first line of defense against pathogens and irritating particles. But if pathogens or allergens are not cleared away, the body will mount either of two immune responses that are inflammatory: 1) an

innate immune response mediated predominantly by neutrophils, and 2) an *acquired* immune response mediated by antibody creation (like IgE) and detection by B cells and T cells. These inflammatory responses may kill pathogens, but they also cause fever, swelling, heat, and pain. And when there is chronic infection, white blood cells are more likely to get over-excited and begin damaging our own tissue cells too, usually by accident. When pathogens or our own cells are being destroyed by white blood cells, particles of that tissue can get into the blood, triggering a further immune response. Furthermore, when a type of leukocyte (white blood cell) called a neutrophil gets called in to kill infection, in CF these are not very effective (in large part because they lack enough of our body's primary antioxidant called glutathione [1]) and die in huge numbers, signaling more neutrophils to be called in to clean up the mess, which makes the whole situation worse.

Neutrophils also secrete an enzyme called neutrophil elastase that can break down the proteins that make up our airways, leading to airway remodeling and destruction. Even though it's true that infection causes inflammation, it may be a more complex situation than that. One well-known study documented that CFers had high levels of inflammatory markers even before their infections with pseudomonas became significant. In other words, there is evidence that inflammation makes CFers more susceptible to infection [2]. Chicken or egg? A higher basal level of inflammation has many cascading systemic effects, but in relation to infection or allergy, it can make the immune system hyper-responsive, which can cause worsened airway destruction and prolonged recovery time. Inflammatory responses cause the release of oxygen free radicals or "reactive oxygen species"/ROS (those things that antioxidants neutralize), which cause further tissue damage, and can even cause pseudomonas to mutate into more harmful strains! Yikes! Some pathogens prefer an inflamed tissue environment to colonize. Chronic inflammation can lead the acquired immune response to shift to a more hyper-inflammatory state (i.e. a shift from Th1 to Th2, which I will discuss in the next section).

Elevated basal levels of inflammation in CF are due in part to faulty CFTR function. Intracellular antioxidants which reduce inflammation, such as glutathione and superoxide dismutase, cannot move out of the cell in sufficient quantity because the mutated CFTR cannot push them out, leaving the space outside of the cells more vulnerable to damage by oxidation/ROS. In addition, the faulty CFTR cannot move critical antimicrobial chemicals (such as hydrogen peroxide) out of the cell to mount a proper immune response when confronted with pathogens. This means that people with CF have a reduced ability to properly neutralize oxidation, and also have less effective cell-mediated immune responses [3]. Furthermore, CF lung fluid is known to be excessively acidic due to inadequate bicarbonate release by CFTR channels in the airways [4]. Excessively acidic airways prevent proper immune responses to infection, and bicarbonate is a key component in keeping mucus thinned out [5]. The CF community is now experimenting with inhaled bicarbonate, and some are having very good results. Researchers are also trying to find ways to block the proton pumps in the airways.

The discovery that CFers have a higher baseline level of inflammation prompted the experimentation in CF clinics with administering high-dose ibuprofen at a young age, before infection became significant, and also other anti-inflammatory drug therapy such as

steroids (i.e. prednisone). But both of these drugs have harmful side effects. Ibuprofen can cause stomach ulcers, and steroids essential dampen or shut down part of the immune response, which would of course inhibit our natural ability to fight infection--not a good idea! A better long-term solution is to eat foods, take supplements, and use herbal medicine to regulate the harmful aspects of the immune dysregulation while boosting the beneficial aspects of the immunity. These foods I will outline in the What to Eat section.

Whole foods and herbs can be more helpful long-term with fewer negative side effects than some pharmaceuticals. Many immunological pharmaceuticals suppress *all* immune responses indiscriminately, the good and the bad. We need our immune system to help us fight off infection, so we need to be more precise and respectful when dealing with our immune system. It's a precious tool, let's *nurture* it!

More and more research shows that gut flora play a huge role in regulating the immune system, and an imbalance in the flora (called dysbiosis) can lead to inappropriate immune responses, indigestion, and chronic inflammation. By eating more healthfully and rebalancing our gut flora, we can reduce markers of systemic inflammation, benefiting the entire body. Therefore, the decisions we make about what we eat can have a huge impact on our overall inflammatory load. This is good news! It means we have the power to control certain aspects of our health with simple, natural solutions.

Sources:

[1] Tirouvanziam, Rabindra et al. “High-dose oral N-acetylcysteine, a glutathione prodrug, modulates inflammation in cystic fibrosis.” *Proceedings of the National Academy of Sciences of the United States of America* vol. 103,12 (2006): 4628-33. doi:10.1073/pnas.0511304103
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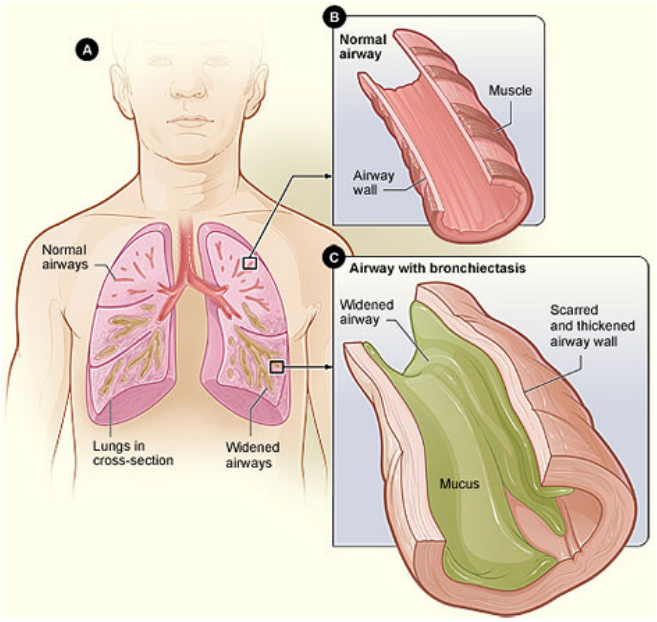
III. Bronchiectasis

Cystic Fibrosis is described as a classic example of chronic inflammatory disease. Bronchiectasis, the main characteristic of CF lung disease, is the result of out-of-control inflammation. It is described as the over-dilation of our airways to the point where they lose their elasticity and scarify. This causes the airways to become fragile and increases the risk of them collapsing or breaking, which can lead to hemoptysis (bleeding of the bronchial arterioles into the airways leading to coughing up of blood). Our airways over-dilate in part because they are filled with mucus, and in order to move any air through a clogged up airway they must widen themselves. But bronchiectasis is also caused by neutrophilic inflammation and the airway scarification and restructuring that results.



The inflammatory processes that cause bronchiectasis are complicated and not fully understood, but much of the problem has to do with over-recruitment of neutrophils into the airways. Neutrophils are white blood cells that are part of the innate immune system and their job is to kill pathogens and help clean up infection or tissue damage. Under normal circumstances, these guys are wonderful and target infection quickly, clean it up, then move on. But in situations of chronic infection, neutrophils (NTs) never really move on. In CF, the situation is even more complex. It turns out that CF lungs have higher than normal levels of NT elastase (an enzyme that NTs use to kill pathogens and break down tissue) *even without pathogenic colonization* [1,2]. We don't know why this is for sure, but I postulate that it is a result the Th2 part of the acquired immune response becoming dominant, which is linked to allergies and autoimmunity. The Th1/Th2 response can be rebalanced with a diet low in modern, processed foods and high in anti-inflammatory foods and phytochemicals found in wild plants and herbs. Neutrophils and the inflammatory mediators that they secrete (e.g. NT elastase, IL-8) cause further neutrophil recruitment, tissue damage, and airway remodeling (i.e. bronchiectasis) [1]. It has been found that the greater the level of NT elastase in CF sputum, the lower a person's FEV1 will be [3]. Not only does NT elastase break down the elastin, collagen, and proteoglycans in the tissue of our airways, but it also makes our mucus thicker and harder to expel. This is a problem because thick mucus provides an even better home for pathogens to breed. In addition, thick mucus makes it harder for the NTs to move around in the airways, so they get stuck, die, and cause mucus pooling. Airways widen even more to get around the mucus pooling,

causing further bronchiectasis. Pulmozyme (DNAase) works by breaking apart neutrophil elastase in the airways, making the mucus thinner and easier to cough out.

Another problem with neutrophilic inflammation in CF is that although the NTs are called in to kill pathogens, they don't actually do a very good job cleaning up infection, and when they release cytokines and ROS, the body has a reduced ability to neutralize that oxidation with its own antioxidants. In CF, epithelial cells have a hard time secreting glutathione (our most prevalent antioxidant) into extracellular space because of the faulty CFTR channel, so neutrophil free radicals are not quenched effectively. Furthermore, it's been found that in CF the neutrophils themselves have low glutathione (GSH) reserves. Because there is a lack of native antioxidants in CF, and because neutrophils that try to kill bacteria behind their biofilm fortresses are ineffective and produce increased amounts of ROS, neutrophils have more of a negative effect on the CF lung than a positive one [4]. Several studies have looked into reducing systemic inflammation by boosting neutrophil GSH levels with NAC supplementation. N-acetylcystine (NAC) is a molecule necessary for the synthesis of glutathione in the body, essentially being a glutathione precursor. Direct supplementation with glutathione is largely ineffective because it is easily oxidized (and neutralized) by environmental factors. It's been shown that oral supplementation with NAC increases NT glutathione in the lungs, and also reduces neutrophil recruitment to the site of infection in the lungs. Oral NAC significantly reduces IL-8 (an inflammatory marker) in the airways, and significantly reduced NT elastase in the sputum [3]. This means that instead of dealing with systemic inflammation through palliative treatments like steroids, high-dose ibuprofen, and azithromycin, NAC supplementation can help address the root of the problem with a completely harmless treatment that has virtually no side-effects and no known level of toxicity! A small pilot study showed that high dose oral NAC (2400mg per day) was safe and increased systemic levels of the antioxidant vitamin C [4]. A larger multi-center study on oral NAC in CF using PharmaNAC showed that after 6 months at a dose of 900mg 3xday, patients' lung functions were prevented from declining or were improved compared to placebo [5]. That said, I do not believe NAC to be a cure-all, though it may help reduce CF lung inflammation. Efficacy will vary from person to person. A standard dose for oral NAC is 600 mg three times a day. It is very cheap over the counter, but your doctor may also be able to write you a prescription for it. It is used in modern medicine to treat acetaminophen (tylenol) poisoning and interstitial lung disease. There is a lot of interest in the CF community about a supplement called PharmaNAC, which is a powder containing NAC that can be added to drinks. Some of my clients have said it has helped thin their mucus.

The liver is the body's major producer of glutathione. Milk thistle seed contains silymarin, a phytochemical that triggers epigenetic changes that cause the liver to produce more glutathione. In fact, *one* unit of silymarin causes the liver to produce *ten* units of glutathione! That's more efficient than taking NAC! Studies have not been done to see if milk thistle has a positive effect on increasing neutrophil GSH or reducing neutrophil recruitment, but theoretically, it could be possible. I take milk thistle everyday for this purpose and for general liver support. I also want to mention that there is an older inhaled drug out there called Mucomyst, which is inhaled NAC. It breaks the disulfide bonds in mucus, making it more liquidy and easier to cough out. It does not, however, increase GSH

levels in the lungs because in order for NAC to be converted to GSH, it has to be metabolized in the liver. Only oral NAC can increase systemic GSH levels in the body, because oral NAC is absorbed through the intestines, metabolized by the liver, then circulated in the blood.

Given all this, I have decided to focus on improving my lung symptoms by targeting inflammation and reducing the amount of inflammatory substances I put into my body by cleaning up my diet. I struggled with bouts of significant hemoptysis for several years, and had a pulmonary embolization in May 2013. I have noticed that I get hemoptysis when I am particularly inflamed, caused either by a bad lung infection, inflammatory foods, and/or environmental irritants (e.g. campfire smoke or heavy pollen). Thus, in addition to adhering to an ancestral diet like Paleo, I got my doc to give me a prescription for NAC, and I take many herbs that help me reduce my level of systemic inflammation.

To treat systemic inflammation one must consider the role of gut inflammation, which is at the root of many inflammatory diseases. Targeting the root cause of my systemic inflammation by focusing on the gut through improving my diet and cultivating a more balanced intestinal bacteria community has yielded very positive results so far.

Sources:

[1] Jackson, Patricia L., et al. "Human neutrophil elastase-mediated cleavage sites of MMP-9 and TIMP-1: implications to cystic fibrosis proteolytic dysfunction." *Molecular medicine* 16.5 (2010): 159-166.
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[3] Tirouvanziam, Rabindra et al. “High-dose oral N-acetylcysteine, a glutathione prodrug, modulates inflammation in cystic fibrosis.” *Proceedings of the National Academy of Sciences of the United States of America* vol. 103,12 (2006): 4628-33. doi:10.1073/pnas.0511304103
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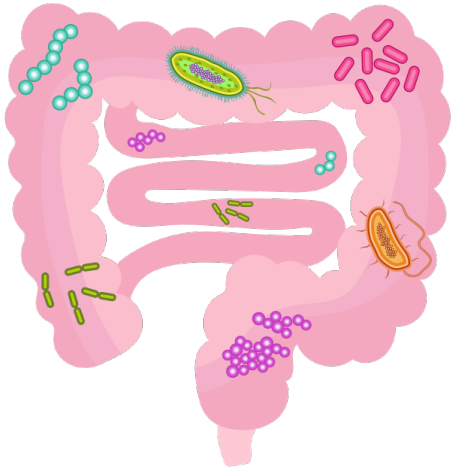
IV. The Microbiome: The Gut's Influence on Immunity

The gastrointestinal tract is a central part of the immune system. The digestive system is linked either directly or indirectly to every organ system in the body, and part of its role is to kill pathogens we swallow with stomach acid, produce protective mucus, or trigger an evacuation response upon exposure to harmful substances. The gut's lymphatic tissue (called peyer's patches) trap and kills pathogens as well. By improving our gastrointestinal (G.I.) functions we can make significant progress in addressing our other disease symptoms in the lungs, immune system, liver, endocrine system, and other organ systems.



Much of this has to do with eliminating toxins, irritants, allergens, and inflammatory foods from our diets. My experimentation in this realm has led me to some incredible discoveries about my diet's effects on all my organ systems. Of all the thousands of medical systems in the world, it is only modern Western techno-medicine that believes that what you eat has little bearing on your overall health--and even this belief is being disproven and rejected as outdated and myopic. It is a leftover of the harmful and false belief that the human body is a machine, a machine that runs on "fuel". Many doctors still in practice today were educated in this belief system, yet fortunately the new generations of practitioners are coming to realize the truths that traditional medical systems have always known: that food is medicine. As Hippocrates (the father of Western medicine) once said, "Let thy food be thy medicine and medicine be thy food". The mechanical model of modern medicine has adopted the delusion that the organ systems are isolated from one another, but neither good science nor clinical observation backs up this belief. Everything is connected, and the gut is that center.

So gut health is connected to everything else in the body. But how? In several ways. Firstly, all of the epithelial cells in our body (cells in organ systems that have some kind of exposure to the "outside", i.e. G.I. tract, sinuses, pancreas ducts, certain reproductive organs, skin, lungs, etc.) are linked to each other via the central nervous system. When you eat a really spicy food have you ever wondered why your eyes start to water, your nose starts to run, you cough and start to sweat? You surely didn't get any spice in your eyes, up your nose, or on your skin. Many of our epithelial tissues are connected through central nervous system via the vagus nerve, including the lungs and GI tract. When we eat something very irritating, our tongue or stomach or small intestine detects that something is not right (it thinks: "this spicy chemical could be dangerous!") and so the small intestine starts secreting mucus in order to flush the irritant away. But again, when your body

detects the irritation it doesn't necessarily know where it is coming from (your mouth, the air, your nose, etc.) so it produces mucus in all the hollow tubes that could have imbibed the irritant, just to be safe. These tubes include the bronchi and the sinus chambers. This is why eating irritating foods, toxins, or allergens can cause or exacerbate lung infections or post-nasal drip: because secretion of gut mucus can trigger secretion of respiratory mucus. I can tell you that whenever I eat something that upsets my digestion, one of the first symptoms I get is an increase in my lung mucus and more coughing.

Secondly, the human stomach environment is highly acidic, with a healthy pH of under 3 (the lower the pH, the more acidic a substance). It is very important that we have a low stomach pH and enough acid to destroy any bacteria that may enter in our food, and to properly break down proteins and trigger the digestion of carbohydrates and fats in the small intestine. For a number of reasons, which I explain in this blog post, we can develop low stomach acid (i.e. develop a stomach pH of over 5). Having low stomach acid can cause many issues including heartburn/GERD/reflux (this is, by the way, the opposite of what antacid commercials tell you), gas, constipation, diarrhea, carbohydrate malabsorption, bacterial overgrowth of the upper GI tract, increased risk of developing GI infections like *Clostridium dificile*, gastroparesis (delayed gastric emptying), bone fractures, vitamin B12 deficiency, asthma, vocal chord dysfunction, and further susceptibility to bacterial infections in other parts of the body, including the lungs [1]. I believe CFers are at higher risk for developing low stomach acid than our peers because of excessive pharmaceutical use and poor diet choice, so we should pay close attention to this issue. Low stomach acid is corrected by lowering the stomach pH through supplementation with betaine HCL, apple cider vinegar, or a digestive bitters tincture before meals, and of course stopping use of all antacids and PPIs. I discuss all this in depth in the aforementioned blog post.

Another way your G.I. tract is linked to the rest of you is that it is responsible for absorbing nutrients and energy from what you ingest, which is used by all of your other organ systems to function properly. We are, quite literally, made up of what we eat. So if what you eat is lacking in essential nutrients and energy, your whole body will slowly cease to function properly. Malnutrition can be caused in two primary ways (or a combination of both):

1. Not eating enough nutrient-rich foods, either by:
    a. simply not eating enough (as in starvation or famine);
    b. by eating foods that lack nutritional value (what happens primarily in America, where junk food is a cultural staple. Modern society has invented a new phenomenon--simultaneous obesity and malnourishment);
    c. by orthorexia, that is following a popular diet in attempts to lose weight or "get healthy" but which is actually is harmful;
    d. by eating too many foods with *negative* nutritional value (food-like-substances/toxins that bind to nutrients, flush them out of our bodies, or store them in inaccessible places. These include refined sugars, phytic acid, and transfats).
2. Not being able to adequately break down, digest, or absorb the nutrients consumed.

CFers naturally have problems with number 2, but due to the toxic diets that Americans in general eat, plus the harmful nutritional advice that many CF docs give us, we also end up having problems with number 1. CFers have higher than average levels of oxidative stress [2], due in part to our disease processes, chronic infections, and inflammation but also as a result of our doctors telling us to eat less healthy foods (as in vegetables naturally high in antioxidants and anti-inflammatory nutrients) in favor of higher calorie foods such as junk food and dairy. Many low-quality, high calorie foods are inflammatory and can increase oxidative stress load, so we must choose them very wisely according to their nutrient density, their inflammatory or anti-inflammatory characteristics, how they were raised or harvested, and our individual reactions to these foods.

In addition, the entirety of the intestines is lined with lymphatic tissue that samples the lumen and sucks up pathogens and allergens into the lymph (the fluid that circulates through the lymphatic system flows in special channels and interacts with the blood). When in the lymph, pathogens or allergens are detected and neutralized by immune cells. The Gut Associated Lymphatic Tissue (GALT) also sends immune cells and inflammatory chemicals directly into the intestinal lumen to fight perceived infection. The GALT constitutes the largest amount of immune tissue in the body, and its ability to remove and kill pathogens before they get into the blood is critical to our health. The immune cells associated with the GALT, predominantly T and B cells, are responsible for telling our immune system to differentiate between organisms and antigens that are harmful, and those that are harmless. The bacteria in our guts (microbiota) are responsible for educating these T and B cells about which incoming antigens are safe, and which ones are enemies to the body [3]. When the gut microbiota is disrupted and the ecosystem becomes unhealthy (which can be caused by poor diet, excessive pharmaceutical use, antibiotics, stress, lack of exposure to healthy environmental bacteria, etc.) the gut microbiome can no longer educate the immune system properly and we can develop a variety of immunological diseases including immunodeficiency, allergies, asthma, and autoimmunity. An improperly educated gut microbiota can result in inflammatory over-reactions to environmental challenges that are not dangerous (i.e. pollen or food allergies) and over-reactions that target our own tissues (i.e. autoimmunity).

The human body is an ecosystem that harbors over 400 species of bacteria just in the intestines themselves. But the whole body is populated by bacteria; the skin, eyes, nose, mouth, ears, genitals, lungs, etc. In fact, we have more bacterial cells in and on our bodies than we do human cells! In reality we are more bacteria than human. We are walking, talking ecosystems, and our bacteria keep us happy and healthy... if we keep *them* happy and healthy. Beneficial bacteria in the gut help us break down and digest foods, particularly complex carbohydrates, and synthesize a number of nutrients that we cannot create ourselves including vitamin K2, folic acid, vitamins B1, B2, B3, B6, B12, and various amino acids. They also help us metabolize certain xenobiotic substances including plant constituents, pharmaceuticals, and toxins. But with our modern toxic lifestyles, it is becoming harder and harder to keep our beneficial bacteria healthy and our internal ecosystem balanced. It is very important to keep our friends happy by eating prebiotic fibers in plants. This includes fibers contained in roots, green vegetables, nuts/seeds, and

whole grains. When beneficial bacteria in the colon ferment upon these fibers, they release short-chain fatty acids that directly feed our intestinal cells. These beneficial bacteria are competitive inhibitors of colonization by pathogenic species, and also have the ability to directly kill pathogenic species or stimulate our immune system to kill them [4]. This role that beneficial bacteria play in the gut microbiome is very similar to the role that native plant species play in a forest. When human disruption (clear-cutting, pesticide use, etc.) or natural disaster reduce the natural biodiversity in the forest, invasive species have an easier time taking over, crowding out native species and imbalancing the ecosystem. But if there is a healthy population of native species, this invasion is less likely. As above, so below.

As a result of the modern obsession with germ theory (the idea that all disease is caused by catching germs), the public and medical institutions alike have become obsessed with sanitation. While germ theory is a valid idea and has very useful in controlling communicable diseases by preventing and treating infections, it has been taken to the extreme in some situations. Over-treating for infectins or over-sanitizing our modern lives has led to two major problems: 1) declining diversity of the human microbiome, and 2) drug-resistant infections. Regarding the former, in a traditional lifestyle connected with Nature our ancestors spent much of the day outdoors and in contact with wild or domesticated animals. By being in constant contact with Nature we carry the bacteria, fungi, viruses, and parasites in the world around us, which when balanced, protect and educate our immune systems. We are now finding that people who live hyper-sanitized modern lives have the lowest microbiome diversity and the highest incidence of modern diseases such as autoimmune diseases, allergies, obesity, and so on [5]. Secondly, when antimicrobial drugs and cleaners are mis-prescribed and over-used, pathogens can develop resistance to those drugs and chemicals, leading to an arms race between pathogens and modern science [6]. Because Nature is far more intelligent and far more creative than modern science can keep up with, pathogens will always win that race. Better to avoid that contest whenever possible!

The role of the gut microbiota in CF is getting more and more attention these days. Recent research has found that the bacteria that inhabit the *gut* early in life determines, in part, the bacteria that inhabit the *lungs* later in life. (As a side note, breast-feeding ensures an infant develops a healthy and diverse intestinal flora, so breastfeed your babe as long as possible!). The healthier the intestinal ecosystem is, the more resilient the lungs are to pathogenic bacterial infection. Thus, the guts and lungs are directly connected via their bacterial populations: "these findings are consistent with previous reports, with identification of bacteria in the respiratory tract in CF that are typically associated with the intestinal cavity and are theorized to contribute to the continuum of interactions between the host and microbial community in CF that relates to both the lung and gut microbiota" [7]. Although the biota of the guts and lungs are different, many species are shared between them, and this is especially true of pathogenic bacteria, like S*taph.* Healthy lungs host far fewer bacteria than the guts, and the healthy respiratory microbiome is not particularity diverse. However, in CF low diversity in the lung microbiome corresponds to increased disease severity and lower lung function. We could also say that since the microbiome of the lungs are connected to the guts, a less-diverse gut microbiome could mean a less-

diverse lung microbiome. This is very similar to measuring the health of an ecosystem (like a rainforest) by its biodiversity, i.e. the number of species that inhabit it. A decline in CF lung microbiota diversity is associated with antibiotic use, therefore overuse of antibiotics may set up a vicious cycle of declining diversity and dependence on antibiotics: "[research has] identified that diversity decreased over time in parallel with progressive disease and remained stable in patients with milder lung disease; however, they identified antibiotic use rather than lung function as the most significant driver of decreased microbial diversity in sputum samples. Additionally, based on sputum samples, Stressmann et al. corroborated similar findings for 14 patients with CF that antibiotic use was most associated with decreased microbial diversity and that overall decreased diversity was correlated to more-severe lung disease, as well as abundance of *Pseudomonas aeruginosa*" [7].

Thus, it's important for us to use antibiotics sparingly and only when necessary, as they are particularly detrimental to the intestinal bacteria that keep us healthy and balance our immune systems. So what are the implications for CFers who often have to rely on regular courses of high-dose antibiotics their whole lives? It will of course disrupt the intestinal ecosystem and increase the risk of developing problems associated with dysbiosis (e.g. leaky gut syndrome). However, refusing to use antibiotics for the sake of preserving protecting gut health may have its own negative consequences as I have personally experienced. Avoiding taking antibiotics when I needed them may have caused me unnecessary lung damage. So it is a fine balance. Inhaled antibiotics (e.g. tobramycin or colistin) have far less impact on intestinal flora, and certain IV antibiotics like vancomycin also have minimal impact. All oral antibiotics impact the gut flora, and most IV antibiotics do as well (e.g. tobramycin, meropenum, ceftazadime, linezolid, etc.). Unfortunately, most CF docs are not educated on the importance of a healthy gut microbiome for overall health. Most CF docs are pulmonologists by training, and modern Western medicine generally sees organ systems as separate and independent from one another. Both the latest research and traditional medicinal paradigms blow this belief apart. Don't be surprised if you have to remind your doctors of this point!

Even more exciting is the research being done on treatment of the lungs through supplementation with oral probiotics. One study found that oral supplementation with only a single strain of *Lactobacillus* (GG) significantly increased CF children's FEV1, increased body weight, reduced the number and duration of hospitalizations, reduced the number of pulmonary exacerbations, and reduced the number of inflammatory markers (IgG). LGG and other *Lactobacillus* strains have direct action against P*seudomonas* and have a systemic anti-inflammatory effect [8]. Thus, taking oral probiotics is very important for CFers, not only to restore intestinal microbial diversity, but to fight systemic inflammation and lung infections as well. But in order to restore ecological diversity in the intestines and the lungs, we should choose probiotics with as many strains of beneficial bacteria as possible.

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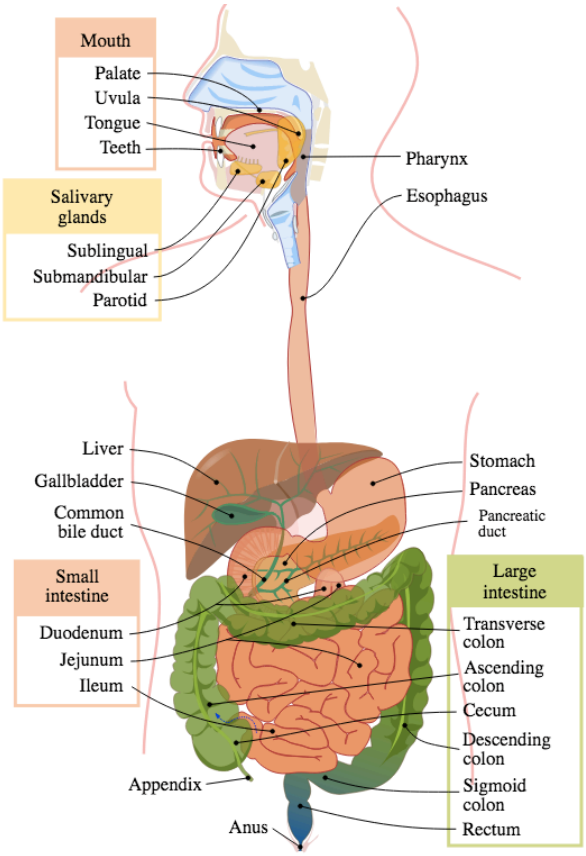
V. Carbohydrate Malabsorption, Gut Flora, and Leaky Gut Syndrome



The human lower intestine is inhabited by over 400 species of bacteria that help us break down food and allow us to absorb nutrients we can't on our own. Our gut bacteria provide us with innumerable services that scientists have only just begun to discover in the last several years. These services including the regulation of our immune systems, producing hormones and neurotransmitters (e.g. serotonin), and directly feeding the cells of our intestines with butyrate. There are trillions of bacteria down there and in a healthy colon and distal ileum they are all living in harmony, keeping each other in check and preventing overgrowth or dominance by one species or another. The collective community of microorganisms living in the gastrointestinal tract is what is referred to as our gut microbiota. The microbiota's collective genome is called the microbiome (though many people use these two words interchangeably). Microorganisms also inhabit many other parts of our bodies including the skin, respiratory tract, and genitals, each of which has its own unique microbiota.

However, fewer and fewer people have healthy gut microbiomes nowadays due to our unhealthy modern diets and lifestyles. CFers are especially likely to have an unhealthy gut microbiome (also called dysbiosis) because we are constantly on and off antibiotics, have functional malabsorption issues, and are often given poor dietary advice from mainstream doctors. Thus, it is a good idea for CFers to be aware of microbiome science and take good care of our precious bacteria. We may not be able to avoid taking antibiotics, but we can choose to take probiotic supplements (which I discuss here), eat fermented foods (e.g. sauerkraut, kombucha, and yogurt/keifer if you tolerate dairy), and eat foods high in prebiotic fibers. In addition, we should consider removing foods from our diets that contribute to harmful bacterial overgrowth. This past piece is the focus of this page.

The Standard American/Westernized Diet contains significant amounts of refined carbohydrates (especially sugar), rancid vegetable oils, factory-farmed animal foods, and

very few fruits and vegetables. The resulting gastrointestinal and systemic inflammation contributes to the development of increases intestinal permeability, commonly referred to as leaky gut syndrome, which in turn can lead to the develop of other diseases and imbalances including allergies, autoimmunity, mental imbalances, blood sugar irregularities, obesity... and the list goes on. By eating too many inflammatory foods and too few anti-inflammatory foods (i.e. berries, vegetables, and wild or pastured animal foods) our bodies' systems of self-healing and self-regulation can be stressed and fall into dysfunction. This process is mediated through the gut via the GALT (mentioned in the previous section). Several important aspects of the diet, including quality of the carbohydrates we eat, have a profound impact on the microbiome for good or ill.

Gut Dysbiosis, Carbohydrate Malabsorption, and Leaky Gut Syndrome
Several factors can disrupt the balance of bacterial, fungal, viral, and parasitic species which make up the human gut microbiota. These may include: inheritance of a parent's imbalanced microbiota (via the birth canal, breast feeding, and touch), frequent antibiotic or other pharmaceutical use, chronic physical and/or psychological stress, unhealthy diet, pollution, etc. In situations such as these, the populations of beneficial bacteria which protect the health of our digestive systems diminish, and the populations of pathogenic bacteria and fungi (including fungi like *Candida albicans)* are flourishing.

More specifically, a common dietary cause of dysbiosis is the over-consumption of refined carbohydrates such as sugar, soda, pastries, bread, pasta, etc. These are the preferred foods for many pathogenic bacterial and fungal species, especially those who wish to creep higher into the upper intestines where they are not supposed to be. Complex carbohydrates with significant amounts of fiber (from whole root vegetables, grains, fruits) preferentially feed the beneficial gut flora lower down in the distal ileum and colon. By eating too many refined carbohydrates and not enough fiber, we feed the opportunistic bacteria, favoring the proliferation of pathogenic species while starving the beneficial species. If this style of eating is maintained for a longer period of time, gut dysbiosis will result. Unfortunately, since the post-WWII era, modern low-nutrient "foods", especially refined carbohydrates and industrial seed oils, have become a staple of the Western diet. Since microbiomes are inherited from the parents and we are now moving into the fourth generation of modern industrialized dietary habits since that era, the Western microbiome is shrinking in diversity and causing a growing number of diseases never before seen, as evidenced by the epidemic of autoimmune diseases [1].

Antibiotics also have a profound effect on the microbiome. Antibiotics are broad-spectrum killers of gut microbes, whether the species are helpful or harmful. Beneficial gut bugs often have a harder time bouncing back from an assault by antibiotics compared to pathogenic flora, which can recover more quickly. Every use of antibiotics must be accompanied by probiotic foods and/or supplements plus prebiotic fiber supplementation or else dysbiosis may occur. Dozens of clinical studies have demonstrated the benefit of taking probiotic supplementation with or after antibiotic therapy to reduce negative gastrointestinal side effects of antibiotics and to reverse the long-term health of our microbiomes [2, 3].

Many Americans, CFers included, are prescribed long-term courses of antacids or proton-pump inhibitors (PPIs). These drugs lower stomach acid, a secretion critically necessary for protein digestion, killing pathogens in our food, absorbing nutrients, and triggering a cascade of important digestive secretions lower down in the GI tract such as sodium bicarbonate, bile, and pancreatic enzymes. Adequate levels of stomach acid help prevent gut infections and prevent flora in the lower intestines from traveling upward and colonizing the upper intestines. Bacterial colonization of the upper intestine is called small intestine bacterial overgrowth (SIBO). PPIs were not designed for long term use, and yet they are often improperly prescribed this way, leading to many serious side effects. I discuss PPIs at length in this article.

When pathogenic bacteria dominate the microbiota, our gut tissue can become inflamed by the exotoxins that they produce and by the undigested proteins in the gut lumen. Undigested proteins can act as antigens (i.e. compounds that stimulate an immune response) and when detected by the GALT lead to an inflammatory response. Inflammatory compounds such as cytokines can cause the enterocytes (intestinal cells) to separate, allowing pathogens, undigested proteins (food antigens), and bacterial toxins to enter the blood stream. When this happens, the body's immune response gets even more ramped up in order to attack and neutralize those antigens which should not be in the blood stream. At this point a wide range of symptoms can present, such as fever, body pain, mood swings, cognitive issues, fatigue, skin eruptions, hormone imbalances, and much more [4, 5]. In some cases, an antigen from an invading pathogen or undigested food protein may look very similar to the structure of a human tissue. This is called molecular mimicry, and can lead to the body creating antibodies against itself, which is called autoimmunity. Dr. Alessio Fasano, head of the Maryland Center for Celiac Research and world leader in the field of autoimmunity, believes that leaky gut is a necessary precursor to the development of many autoimmune diseases [6]. The food antigens that are the most common culprits of molecular mimicry are gluten (the protein in wheat and several other grains) and casein (the protein in dairy). Unfortunately, an antibody created against gluten can have cross-reactivity with casein, meaning that if you're sensitized to gluten (as are people with Celiac disease or gluten sensitivity) dairy can cause a similar immune reaction.

If this gut inflammation lasts long enough, the process of digestion begins to degrade and we may see diarrhea, constipation, gas, bloating, undigested food in the stools, malabsorption, clay-colored stools, mucus in the stools, or even bloody stools. In situations of more serious dysbiosis and digestive disease, the villi on the enterocytes can be destroyed, and the enzymes that are produced by those villi (e.g. lactase, sucrase, and maltase) disappear. This means that the ability to break down lactose (milk sugar), sucrose (table sugar), and maltose (sugar in beer and other malted foods) declines and digestive upset can result. Thus, it is common to see lactose intolerance develop in those with chronic gut inflammation, and this is one reason why I recommend that CFers avoid dairy unless their digestive capacity is excellent and have no associated digestive symptoms. Without these brush-border enzymes doing their jobs, carbohydrates like lactose and sucrose are no longer absorbed across the intestinal membrane so they are flushed down to the lower intestines where they can feed pathogenic bacterial

fermentation further causing gas, bloating, and other uncomfortable symptoms.

Carbohydrates and Evolution

Evolutionarily, a diet high in simple or refined carbs is very new, less than 200 years old. Archaeological and anthropological evidence shows us that the diets we have evolved to eat over 1.3 million years of hominid evolution were generally low in concentrated sugars (wild honey being one of the few exceptions) and lower in all carbohydrates compared to modern peoples. The carbohydrates that our hunter-gatherer ancestors ate were always high in fiber, nutrients, and medicinal phytochemicals. Depending on our ethnic backgrounds, our ancestors may not have been practicing intensive agriculture or eating grains for very long. Many peoples throughout the world still do not practice agriculture, and others have only been practicing intensive farming for a few hundred years or less. This is certainly not a long enough time for our digestive systems to adapt to well to heavy reliance on carbs from grains and refined sugars. Such adaptation takes hundreds of generations to occur, which would increase the prevalence of genes that code for increased insulin secretion and the production of certain digestive enzymes. Furthermore, we must remember that all of our foods were wild or lightly cultivated (i.e. not heavily bred or hybridized) until the Neolithic period less than 10,000 years ago. Wild foods are much higher in nutrients than modern hybridized crops, including vitamins, minerals, antioxidants, medicinal phytochemicals, and prebiotic fibers. Although modern fruits and vegetables (which have been heavily bred to increase their size and sugar content) are "healthy" compared to processed foods, they are nowhere near as nutritious as wild foods [7]. Our modern diets of the Western world are extremely heavy in carbohydrates, specifically sugars and simple starches, which are very difficult for our digestive systems to handle in large quantities. Given the long length of time evolution takes, the human body still operates as if it is in the Paleolithic era when we were all hunter-gatherers. Some human populations (such as those in the Middle East and East Asia) have been relying on intensive agriculture the longest, thus have had a longer time to adapt to carb-heavy diets than other populations such as the Indigenous peoples of the Americas and many populations in Africa. When we are poorly adapted to these high-carb modern diets the refined carbohydrates we eat can feed pathogenic bacteria and fungi and overwhelm the pancreas's ability to produce insulin, causing diabetes (which I discuss in the next article). Incidence of diabetes is significantly higher in populations with shorter historical exposure to carb-heavy diets.

Yet not all carbohydrates are harmful for those with gut dysbiosis or leaky gut. Depending on the type of infection (i.e. where it is located and what species are overgrown) certain carbohydrates are preferable to others. In some cases of SIBO where bacteria from the lower intestines has invaded too high up, any type of carbohydrate including monosaccharides, disaccharides, and complex carbohydrates can feed bacterial fermentation and cause distress. In other types of SIBO, monosaccharides are tolerated but not complex carbohydrates, especially FODMAPs (fermentable oligo-, di-, monosaccharides, and polyols). In dysbiosis lower down in the colon, simple sugars like mono- and disaccharides and simple starches can be tolerated but not any fibers that may be fermented upon by colonic pathogens. So each case of dysbiosis needs to be assessed based on the individual case, thus it's important to consult a qualified health care practitioner (i.e.

herbalist, naturopath, functional medicine practitioner, etc.) on how to proceed. Often times the client may require some combination of antimicrobial therapy (preferably herbal) alongside a dietary protocol with multiple stages. In addition, some fibers and phytochemicals in whole foods as well as food additives can be irritating to certain people's guts if they have significant inflammation or tissue damage. This may include lectins in grains; phytic acid in grains, legumes, and some nuts; oxalic acid in certain vegetables like spinach and rhubarb; histamines; compounds in the nightshade family (tomatoes, potatoes, bell peppers, etc.); sulfites in wine; nitrites in cured meats; and other food preservatives and additives. Once the dysbiosis is addressed and the tissue begins to heal, often these things no longer produce irritation for the individual.

Carbohydrate Digestion

In order to be absorbed into the blood, all sugars and complex carbs that we ingest must be broken down into their single-sugar elements, called monosaccharides, which include glucose, fructose, and galactose. Monosaccharides are used by our cells for energy or can be turned into glycogen or fat by the liver to store for use at a later time. There are a number of ways healthy bodies break down sugars into monosaccharides. In the saliva and in the pancreatic juices, amylase is secreted, an enzyme that breaks down certain carbs into monosaccharides. Because CFers with pancreatic insufficiency secrete little to no digestive enzymes at all, you'll see that our supplemental enzyme lists three classes of enzymes: lipase to break down fats, protease to break down proteins, and amylase to break down carbs.

But amylases only breaks down certain carbs, such as starches. There are other enzymes needed to break down other types of carbs and sugars in the small intestine, and not all of them are secreted by the pancreas. Lactase breaks down the milk sugar lactose and is secreted by the microvilli on small intestinal cells. However, you must be genetically predisposed to produce lactase in your gut past childhood (called "lactase persistence"), yet only about 35% of the world's population has this trait. In other words, 65% of the world is lactose intolerant [8]. You had no idea, huh? Neither did I! Many people of European, Middle Eastern, and South Asian descent have lactase persistence and therefore can tolerate and breakdown lactose to some extent because their ancestral diets have included dairy. However, even if we do have lactase persistence, we depend on the microvilli in our guts to be healthy enough to produce lactase, but the microvilli can be damaged due to inflammation and gut dysbiosis. Thus, it is my belief that the ability of CFers to tolerate lactose is very often compromised because our microvilli may not be healthy enough to produce lactase. This may explain the dairy sensitivities I commonly see in CFers, including myself. Have you ever heard someone suggest not to eat dairy when you've got a cold? This is why. A cold creates excess mucus production in all of your epithelial tissues (since they're all connected via the vagus nerve) including your intestines, which is inhibiting the production of lactase and the ability to break down lactose. In conclusion, most CFers have trouble digesting lactose-containing dairy (e.g. milk, store-bought yogurt, soft cheeses) and they exacerbate our mucus problems and gut inflammation. The microvilli produce other disaccharidases such as sucrase and maltase, so digestion of sugar (sucrose) and foods containing maltose may be compromised in people

with significant gut inflammation.

Humans can only digest and absorb a narrow scope of carbohydrates, while other animals can digest a wider variety. For example, beavers can digest tree bark and horses can digest grass, but humans can do neither. There are other types of carbohydrates that humans digest only partially, giving beneficial gut bacteria the opportunity to use them for their own fermentation inside the human gut. These complex carbohydrates are called prebiotic fibers because they preferentially feed our beneficial gut bacteria in the colon. These symbiotic bacteria ferment upon the prebiotic fibers in certain plants, producing short-chain fatty acids to feed our enterocytes and secreting compounds that calm the immune system. In a healthy gut, prbiotic fibers in plants are very important for mainting a healthy gut ecosystem. These fibers include oligosaccharides, soluble and insoluble fibers, and resistant starches. Eating enough fiber is a good way to prevent dysbiosis. The best way to obtain these prebiotic fibers is to eat fibrous vegetables and fruits like cabbage, garlic, onions, leaks, dark-colored potatoes, sweet potatoes, sunchokes, root vegetables in general (especially wild ones like burdock), leafy greens, celery, apples, berries, and many more. You can even use prebiotic fiber powders (e.g. burdock root, dandelion root, ground flax seed, or raw potato starch) to add to smoothies, drinks, herbal formulas, or foods. The modern Western diet is very low in fiber, essentially starving the microbiota and setting up long-term problems.

If the diet has been deficient in prebiotic fibers for long enough (several years to several generations) a person may become susceptible to infection by gut pathogens leading to leaky gut, colitis, IBS, and more. When pathogenic species have taken hold they can sometimes use certain plant fibers for their own nefarious purposes, and their fermetation produces compounds that irritate and inflame the gut. Some persons with dysbiosis find that eating certain plant fibers (especially FODMAPS) causes GI upset. These individuals may find using a low-FODMAP diet or a specific carbohydrate diet like the GAPS protocol [9] alongside an herbal protocol may help to re-regulate the microbiome. The best way to do this is to work with a health care practitioner who knows a lot about the gut, the microbiome, and holisitic herbal inteventions. Ultimately, the goal is to correct the dysbiosis, improve microbiota diversity, and add prebiotic fibers back into the diet for long-term gut health. It is a common mistake for people to stay on a low-FODMAPS or low-fiber diet for too long without thinking about the end-game of eventually eating a high-fiber diet. This can keep the micrbiota in a low-diversity state and may not allow the body to come back into balance.

In a healthy gut, enzymes secreted by the pancreas and upper digestive tract break down certain carbohydrates like starches and disaccharides into monosaccharides for absorption through the walls of the small intestine. But if these enzymes are not secreted in proper amounts corresponding to the kinds of foods eaten (i.e. sucrase production for sucrose, lactase production for lactose, etc.) then sugars, starches, and fibers can pass into the colon to feed bacteria lower down. These bacteria often produce methane and hydrogen in the process of their fermentaiton causing gas and flatulence. Excessive gas production may be a sign of carb malabsorption and dysbiosis. If the fermentation is significant enough to stimulate an immune response, this may eventually lead to leaky gut syndrome. It is very

important for people with gas and bloating or dysbiosis generally to minimize their consumption of sugars and refined carbohydrates! For those with healthy guts, simple sugars can be eaten as an occasional treat, but never as a daily staple for eventually this would select for bacterial and fungal species that could do long-term harm.

Yeast Infections

Another problem associated with carb malabsorption is C*andida* overgrowth. This most often takes the shape of vaginal yeast infections or oral thrush, though in severely immunocompromised individuals (e.g. those on chemotherapy, long-term immunosuppresive drugs, or those with AIDS) a systemic Candida infection may occur, though rarely. One of the most effective ways to control Candida overgrowth is to strictly restrict intake of simple sugars. Having an imbalance of the bacteria and fungi in the gut allows certain opportunistic pathogens to dominate, including the common yeast *Candida albicans.* Candida is a normal commensal fungus in the human gut, but only if it is overgrown does it cause trouble. Yeasts are a kind of fungus, and they LOVE to eat simple sugars. Eating a significant amount of sugars, especially sugars you may not be breaking down or absorbing entirely like sucrose, lactose, or fructose, may feed an overgrowth of Candida in the gut and the tissues at the "in" and "out" ends of the tube: the mouth and genitals. Transient dysbiosis caused by antibiotics and other antimicrobial pharmaceuticals may trigger a sudden yeast infection of the mouth or genitals causing painful white patches in the mouth, white discharge of the vagina, itching, and pain. Pharmaceutical antibiotics kill beneficial flora in the gut (especially the good ones like *Lactobacillus* species that dominate in the vagina) but do not kill fungi, thus yeast are left untouched and the ecosystem is cleared of the competitors which usually keep them in check. I have gotten oral thrush many times in my life when taking IV antibiotics.

Mainstream modern docs treat oral thrush or vaginitis with a prescription for antifungal medications, but disregard the importance of reducing sugar intake. Some antifungal medications have troublesome side effects and are hard on the liver. I prefer to address the root cause by reducing sugar intake, increasing probiotic foods and supplements, and using certain antifungal herbs. Many antimicrobial and vulnerary herbs can be used in mouth washes (for thrush) and creams (for vaginitis), including calendula, goldenseal (or other less-endangered berberine-containing plants like barberry or oregon grape), thyme, yarrow, and more. To treat oral thrush I have compared the use of a nystatin oral rinse (NOT swallowed) and a tea of calendula flowers with a little goldenseal powder mixed in. Both were effective at clearing up the thrush within 3-4 days, but the calendula tea was a bit quicker and didn't taste as bad. In addition, I recommend rinsing or douching with probiotic yogurts to rebalance a healthy oral or genital flora. An added perk is that cold yogurt feels nice and soothing to inflamed nether-regions.

For certain individuals, fructose can also be a factor in feeding yeast and bacterial infections. Fructose is not as well absorbed in the small intestine as glucose, so foods and food-like-substances (e.g. sodas and candy) with high amounts of fructose can directly feed bacterial and yeast overgrowth. High-fructose corn syrup, agave syrup, dried fruit, and fresh tropical fruits with a high ratio of frustose to glucose should be avoided by people

who have trouble with fructose absorption. A great tool to assess the fructose content of foods is this database [10]. I highly suggest reading up on fructose malabsorption [11] if you experience chronic yeast infections or excessive gas or bloating when eating fruit.

CF and Leaky Gut Syndrome

Leaky gut syndrome, also called "increased intestinal permeability", is not a common term in the CF lexicon. Yet it should be, since more research is elucidating the importance of a healthy gut flora in CF and the hidden prevalence of leaky gut syndrome in the CF population. Research has shown that "the intestinal microflora of [CF] children is often abnormal due to massive exposure to antibiotics, and in addition their intestinal permeability is increased suggesting disruption of intestinal barrier function". Furthermore, "the disruption of the intestinal epithelial barrier is central to the pathogenesis of several inflammatory diseases. Interestingly, an increase in intestinal permeability has been reported in atopic dermatitis and IDDM (insulin-dependent diabetes mellitus), as well as in CF. These findings suggest that probiotics may contribute in several ways to the first line host defence to environmental challenges" [12]. In addition, research is finding that gut inflammation is very common in CF: "intestinal inflammation is another typical feature of CF and is much more common than previously thought. Recently, we reported that fecal calprotectin concentration and rectal nitric oxide production are increased in virtually all children with CF, suggesting that intestine is a target organ in CF and is constantly in an inflammatory state" [12].

As I have written in previous articles, gut inflammation is a central part of the pathogenesis of leaky gut syndrome, and maintaining a healthy gut microbiota via good diet and probiotic supplementation is essential to maintaining lung health. As one study reported: "our findings suggest that nutritional factors and gut colonization patterns are determinants of microbial development in the respiratory tract in infancy and present opportunities for early intervention in CF" [13]. From my communication with other CFers around the world, I've found that many of us are presenting typical symptoms of leaky gut syndrome which include low secretory IgA, high systemic inflammatory markers, comorbidity with IBS, Celiac's, and Crohn's disease, chronic bloating and gas, achy joints and bones, food sensitivities, and more. However I have found it quite rare for CF docs to discuss the importance of healthy microbiota with their patients, let alone suggest dietary interventions. I believe leaky gut and dysbiosis is more common the CF population than not. In the future, I hope mainstream docs will be treating CF with much more attention paid to the maintenance of healthy intestinal and lung microbiomes. We should expect this transition to take decades, so in the meantime it's up to us to take charge of our microbial health in this way. I discuss herbal and dietary interventions in the rest of the literature on this website.

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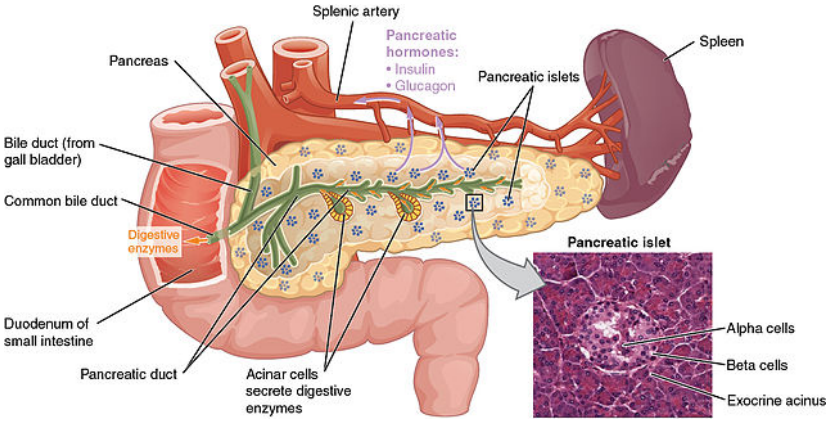
VI. CF-Related Diabetes and Impaired Glucose Tolerance



The pancreas has two primary functions in the human body: to produce digestive enzymes (called the *exocrine* pancreas*)* and the secretion of insulin (called the *endocrine* pancreas). Cystic fibrosis often has trouble with both these pancreatic functions. In CF, trouble with the endocrine side of the pancreas can lead to impaired glucose tolerance or CF-related diabetes (CFRD). Approximately 50% of CF adults over the age of 30 develop CFRD, more common in the severe mutations [1]. CFRD is our own special kind of diabetes: it is similar to type 1 diabetes in that the pancreas has trouble excreting insulin into the blood stream, and is also similar to type 2 diabetes in that we may have some degree of insulin resistance. Here I'd like to explain how blood sugar regulation is supposed to work in healthy individuals and how it gets out of balance in some people with CF.

The Physiology of Blood Sugar Regulation

Glucose is a monosaccharide (single sugar) and is the preferred energy source of cells. Much of the carbohydrates that we eat in our food are broken down into glucose by enzymes and gut bacteria. Glucose is absorbed from food through the walls of the small intestine into the blood stream, and cells that need energy absorb that glucose from the blood. The body detects the amount of carbohydrate ingested, which triggers the release of an appropriate amount of insulin from the endocrine pancreas. The body detects how much carbohydrate is ingested in multiple ways: the sweet taste receptors on the tongue are stimulated, and once the food enters and moves through the stomach, glucose begins to be absorbed and is detected in the blood stream by glucose sensors in the pancreatic beta-cells. There are also peripheral glucose-sensing neurons in the small intestine, hepatic portal vein, carotid artery, and parts of the brain [2].

Insulin is a hormone secreted by the pancreas's beta-cells (part of the endocrine pancreas). Once the body has detected glucose in the blood stream, the pancreas excretes insulin. Insulin facilitates the movement of glucose out of the blood and into the cells, thus lowering the blood sugar (a.k.a. blood glucose). The beta-cells secrete insulin in two ways: a little bit all the time to maintain a basal level of glucose movement into the cells, and in response to carbohydrate ingestion at mealtime. Once insulin has moved glucose into the cell it is used in one of three ways: 1) immediate conversion into ATP (the basic unit of cell energy) and used to power the cell's processes, 2) conversion to glycogen, which is a multi-branched

polysaccharide (complex sugar) and is stored inside the liver and other tissues for later use, 3) conversion to triglycerides (free fatty acids) for storage in liver, fat, and muscle cells. Storage of glucose is very important, because it acts as an emergency supply when our blood sugar may be too low. When insulin levels are too low in the blood, the alpha-cells of the pancreas secrete glucagon, a hormone which acts in the opposite way of insulin. Glucagon causes glycogen stored in the liver and other tissues to be converted into glucose and excreted into the blood stream, thus raising the blood sugar (which can then be utilized by our cells).

In addition to glucose-dependent metabolism, the human body has evolved a secondary and alternative metabolic system for maintaining constant energy for the body's cells: ketosis. Ketones are a small molecules produced by the liver from fatty acids in times that the body does not have adequate access to carbohydrates as a fuel source. We've adapted this metabolic pathway as a response to the possibility of famine or prolonged periods of fasting. Certain traditional cultures who eat very little plant foods either seasonally or year-round dwell in a state of ketosis. For most people with adequate endocrine pancreas function, ketosis is a safe and healthy way to live. In fact, many people are using dietary ketosis to treat a variety of health issues associated with carbohydrate consumption (e.g. type 2 diabetes, autoimmunity, gut issues, etc.). One can induce ketosis by eating very few carbs (20-40g per day or less) for a long period of time. I myself use a ketogenic diet to treat my reactive hypoglycemia (it's the only thing that's worked)--more on that in this blog post. Ketones must stay within a narrow range to be considered safe. When ketones levels become too high they can acidify the blood causing seizures, coma, and death. This is called ketoacidosis and only occurs in people with type 1 diabetes if they do not use insulin. Thus insulin is always necessary for human survival, even in a state of ketosis.

Pancreatic Malfunction

In CF-related diabetes this normal physiological process of carbohydrate utilization breaks down. The main problem with CF glucose intolerance is that our endocrine pancreas slowly begins to malfunction, in addition to the malfunctioning exocrine pancreas for which we must take supplemental enzymes. We don't yet know exactly why or how the endocrine pancreas stops working properly. The old theory was that because the ducts that move the pancreatic juices into the small intestine get clogged with mucus, these enzyme-containing juices get backed up and the pancreas inadvertently starts digesting itself. Yet newer research has theorized that the CF genetic mutation itself is responsible for causing the malfunctions of the beta-cells in the pancreas [3, 4]. I think this new theory is more likely, as I have personally worked with clients whose exocrine pancreases work normally (i.e. they don't need to take digestive enzymes) but have diabetes. So as the pancreas degrades, the ability for its beta-cells to produce insulin (and reflexively its alpha-cells to produce glucagon [2]) declines and we may need to take supplemental insulin injections. In CFRD we can have both hyperglycemia (blood sugar too high) and hypoglycemia (blood sugar too low).

Glucagon is produced in two ways as well: in small amounts all the time, and in response to hypoglycemia. But in CFers with pancreatic exocrine insufficiency (i.e. reduced ability to

excrete pancreatic enzymes into the intestines) glucagon production is impaired for unknown reasons [5]. This could either be a direct result of CFTR mutation, or could be the result of a broken feedback mechanism in relation to insulin production. Insulin and glucagon are supposed to counter-balance each other. In type 1 diabetes, where insulin production is also impaired, glucagon production is lacking not due to any physical malfunction of the alpha-cells, but because glucagon is released in response to *both* hypoglycemia (blood sugar below about 70 mg/dL) *and* falling insulin production. But for insulin-dependent type 1 diabetics, hypoglycemia induced by overdosing with injectable insulin does not trigger this feedback mechanism correctly because high insulin in the blood stops the release of glucagon, even if the blood glucose is too low [2]. Being in a state of hypoglycemia too often can increase our tolerance for hypoglycemic episodes so that it becomes harder to detect when we're getting hypoglycemic, further increasing the risk of life-threatening hypoglycemic episodes. This is called "hypoglycemia unawareness", and it was very troublesome to me for many years before I started the ketogenic diet; sometimes I wouldn't be able to tell that I was hypoglycemic until I got brain fog and a subtle weakness around 40-50 mg/dL. That's dangerous--if we can pass out, go into a coma, and if not rescued quickly enough we can die. These days I am dependent on using a continuous glucose monitor, and always have a glucometer with me as back up in case the continuous glucose monitor fails. We can increase our sensitivity to hypoglycemia if we control the diet and prevent hypoglycemic crashes, as I have done with a low-carb diet. However, I always keep a snack with me as well as glucose tablets, just in case. For regular people, they might feel "hypoglycemic" even when their blood sugar is normal (70-100 mg/dL), so what they actually mean is they feel weak and hungry. I discuss hypoglycemia and reactive hypoglycemia further in this article.

For some CFers, the process of pancreatic degradation is so slow that they can go their whole lives without developing diabetes or endocrine problems. For others, the process of degradation is quicker and they might be diagnosed with CFRD in childhood or adolescence. Most CFers get diagnosed with CFRD in early adulthood. I developed diabetes when I was 24 but I had glucose intolerance for at least 5 years preceding. One study suggests that treating glucose intolerance with insulin injections *before* it becomes outright diabetes may preserve a person's health for longer than waiting until CFRD develops [6]. I personally believe this to be true and I wish I had done more work to control my blood sugar at an earlier age, as the negative physiological impacts of hyperglycemia are significant, which I describe below. It is possible that controlling the blood sugar earlier in this process with carb control and medication, putting less stress on the pancreas, may preserve endocrine function for longer.

Insulin Resistance

Insulin resistance is when the body develops a reduced capacity to use insulin to transport glucose into our cells. In a person with insulin resistance, the cells down-regulate the number of insulin receptors on cell membranes. This can happen in type 2 diabetes when a person eats so many carbohydrates that the pancreas secretes an extremely high amount of insulin into the blood in order to deal with the onslaught of glucose in the blood. The body thinks the extremely high amount of insulin circulating in the blood must be some kind of mistake, so it essentially begins to reduce the number of "ears" (i.e. insulin receptors) it has

to listen to the insulin. In CF and other chronic diseases (and also with long-term corticosteroid use, like prednisone) insulin resistance can develop when cortisol levels are very high, as when someone experiences significant emotional or physical stress (like chronic infection or illness) [7]. In both cases the body blocks the ability for insulin to work to remove glucose from the blood, leaving the blood stream with high levels of both insulin and glucose. Insulin resistance in CF can fluctuate with changing levels of infection and inflammation, and can also be modulated by exercise and avoiding excessive carbohydrate intake. One of the reasons why it is bad practice to perform a glucose tolerance test when someone is sick with a lung infection or in the hospital is that insulin resistance temporarily increases during that time of stress and can lead to a false positive for diabetes. So get a glucose tolerance test when you are healthy or in between lung infections. Cinnamon, bitter melon, and several other herbs can increase insulin sensitivity. Taking cinnamon with a high carb meal can help lower blood glucose, but should not be used if you experience reactive hypoglycemia.

Cortisol plays a big role in insulin resistance. Cortisol is a hormone that keeps us awake and alert, and it reduces inflammation in the body. Because humans are diurnal (awake in the day) cortisol is produced in the daytime in opposition to melatonin, the sleep hormone produced at night. This is called the circadian rhythm. Cortisol levels are highest in the morning and midday, if the circadian rhythm is normal. I recently had an "aha!" moment when I realized that for some, reactive hypoglycemia is more common in the morning when cortisol levels are highest. There are other factors involved with this, including that the typical Western breakfast contains a lot of carbs, and that eating carbs on an empty stomach can cause a rush of glucose into the blood when a malfunctioning pancreas cannot keep up with producing insulin on time (in CFRD, insulin production may be delayed). Having hypoglycemia in the morning 1-2 hours after breakfast is one of the first signs of glucose intolerance and insulin resistance. One solution is to avoid eating carbohydrates, especially sugars, in the morning and instead choose a breakfast rich in protein and fat.

Early on in my diabetes journey, I took glucose readings for several days eating various quantities of carbs in the morning for breakfast. What I found was that if I ate more than about 15 g of carbs, my blood sugar would spike at about 120-180 mg/dL. If I was sedentary, my blood sugar would crash about 2 hours later below 70 mg/dL, leaving me weak, shaky, and hungry. The more carbs I ate, the longer it took to crash but the harder the crash became. Taking insulin with breakfast would not change my blood glucose *at all*. That was the biggest clue in this puzzle. I could take double the amount of insulin I usually take for that amount of carbs and it wouldn't reduce the peak, but it would make the crash deeper. So what I hypothesized from this information is that my AM cortisol spike made my insulin resistance worse in the earlier hours of the day, but once the cortisol circulating in my blood went back down to a lower baseline level, my insulin sensitivity was normal again, usually by 1 or 2 pm. If I ate a lot of carbs in the morning, my pancreas would produce the right of amount of insulin but delayed, and due to insulin resistance it would be ineffective until a little later in the day. I have found that having reactive hypoglycemia in the morning sets up a roller coaster of multiple peaks and crashes for the rest of the day. This can be prevented by avoiding carbs in the morning. As my diabetes got worse over the

years, and after starting Symdeko and then Trikafta (CFTR modulating drugs), my reactive hypoglycemia only got worse, leading to multiple crashes throughout the day (up to four) where I used to only have one in the morning. A ketogenic diet fixed this. In addition, it's important for diabetics of all types to have an active lifestyle with daily exercise because exercising muscles uptake glucose from the blood without the use of insulin. So, many times when I expect that a meal will cause me hyperglycemia (and then a crash afterward) I go on a walk immediately afterward to burn off some of those carbs.

Hyperglycemia

I've explained why hypoglycemia is bad, but what about *hyper*glycemia? Hyperglycemia is when the blood sugar goes above the normal physiological range (70-120 mg/dL) for too long. Healthy people can have occasional, transient blood sugar above 120 mg/dL if they eat a lot of sugars all at once, but it usually doesn't last for more than an hour. Chronic high blood sugar can cause and exacerbate a number of problems including inflammation, infection, and damage to capillaries (very small blood vessels) in the eyes, kidneys, fingers, and toes [8]. Sugar is an oxidative substance, meaning that it introduces free radicals (radical oxygen species, ROS) into the body, binding to molecules and causing damage. The damage that sugar oxidation causes to the tissues triggers an inflammatory response in the body to clean up the damage and battle the culprit. This is especially problematic in heart disease when the oxidative damage that sugar does to our blood vessels causes the body to respond to this damage by patching the wounds in the blood vessels with cholesterol, a process called atherosclerosis. A sad fact is that for more than 70 years mainstream medicine has misdiagnosed atherosclerosis and heart disease as problems caused by dietary cholesterol and fat, when in fact they're primarily caused by sugar! Controlling carbohydrate intake is an effective treatment for reducing and preventing cardiovascular disease [9, 10]. Heart disease is much more common in diabetics due to the link with chronic hyperglycemia [11].

The alveoli of the lungs are surrounded by capillaries which are responsible for oxygen exchange, and I suspect that hyperglycemia may negatively impact these capillaries. This could be an additional reason why blood sugar must remain under control in cystic fibrosis--we don't need anything else to harm our lungs! The barrier between the capillaries that exchange gases in the bronchioles and alveoli is very thin and permeable, which puts it at higher risk of damage by oxidative forces like hyperglycemia. Hyperglycemia may have some connection to hemoptysis (the breakage of blood vessels in the lungs causing coughing up of blood), a common complication of bronchiectasis (I discuss hemoptysis further in this article). More research needs to be done on this connection. One study showed a correlation between hyperglycemia and risk of developing pulmonary tuberculosis in which hemoptysis is common [12]. Another study showed "that hyperglycemia in mice lacking functional CFTR disrupts airway glucose control, exaggerates pulmonary neutrophilic infiltration in response to a bacterial challenge, and reduces lung bacterial clearance over time"--in other words, in a mouse model of CF, hyperglycemia led to increased inflammation, infection, and reduced mucus clearance in the lungs [13]. High blood glucose has been shown to raise the glucose concentration in CF lung fluid (i.e. mucus), which is very dangerous because that can directly provide sugar for the bacteria that live in our airways. In a 2007 study, people with

CF had significantly higher levels of glucose in their lung fluids than normal people, and patients with CFRD and hyperglycemia had even more glucose in their lung fluid that non-diabetic CFers. Not only that, but the inflammation caused by the hyperglycemia leads to the weakening of the junctions between our respiratory epithelial cells, allowing further infiltration of glucose into lung fluid [14] and possibly even contributing to the development of hemoptysis.

In the early stages of glucose intolerance and diabetes, we can better regulate our blood sugar by controlling our diet and limiting sugar and carbohydrate intake. I discuss this more in the Blog and the sections on diet and nutrition.

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VII. Conclusion

I hope this eBook has helped you understand a little more about cystic fibrosis. The more we know about our own bodies, the better we are able to make informed healthcare decisions regarding both holistic and conventional choices.

If you wish to gain an in-depth, comprehensive understanding of all aspects of holistic healthcare for CF, consider taking my online course, **Herbal Medicine and Holistic Care for Cystic Fibrosis**. You may also wish to become a member of my **Patreon** to gain access to a host of benefits to deepen your understanding, including a private Facebook group, an invitation to a monthly Q&A, monthly one-on-one consultations with me, and more.