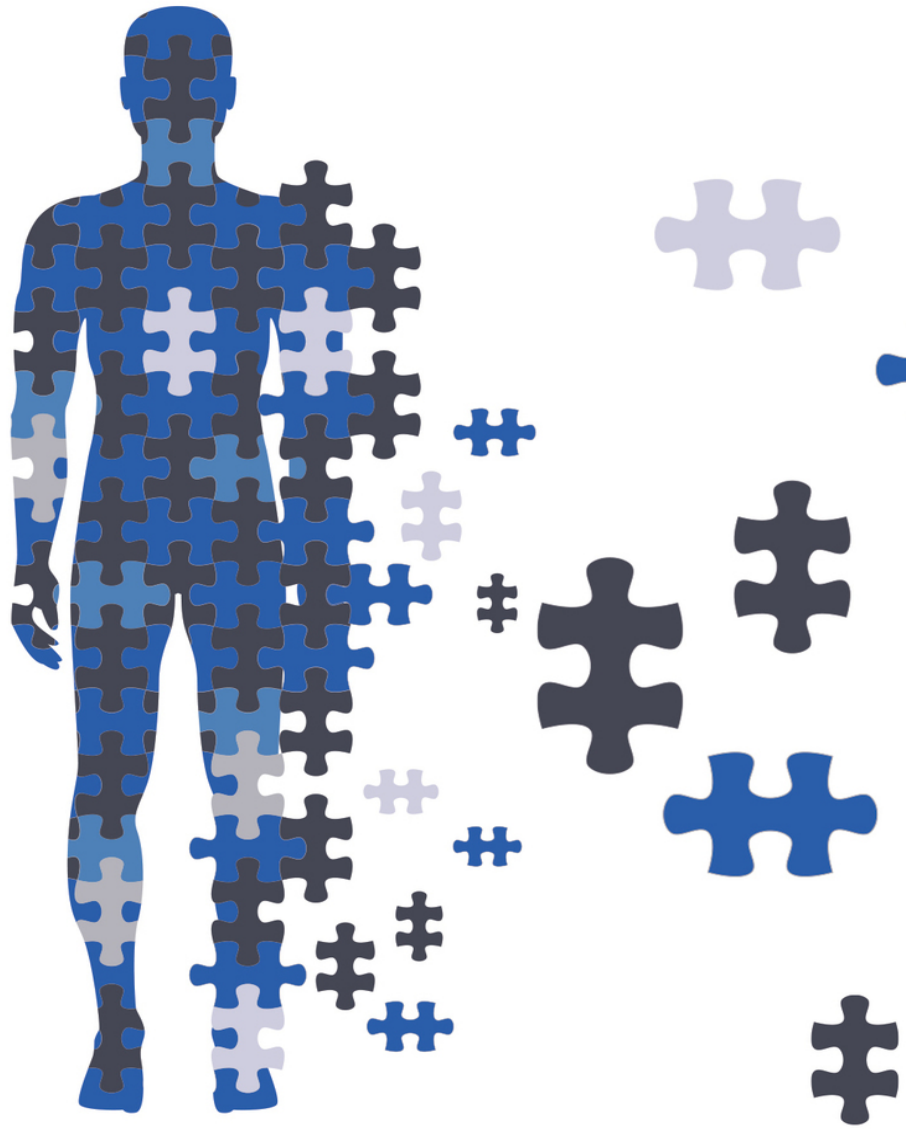
THE

AUTOIMMUNE ANSWER



Using Functional Medicine to address the cause, eliminate symptoms, and optimize quality of life.

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Foreword by Dr. Alex Vasquez

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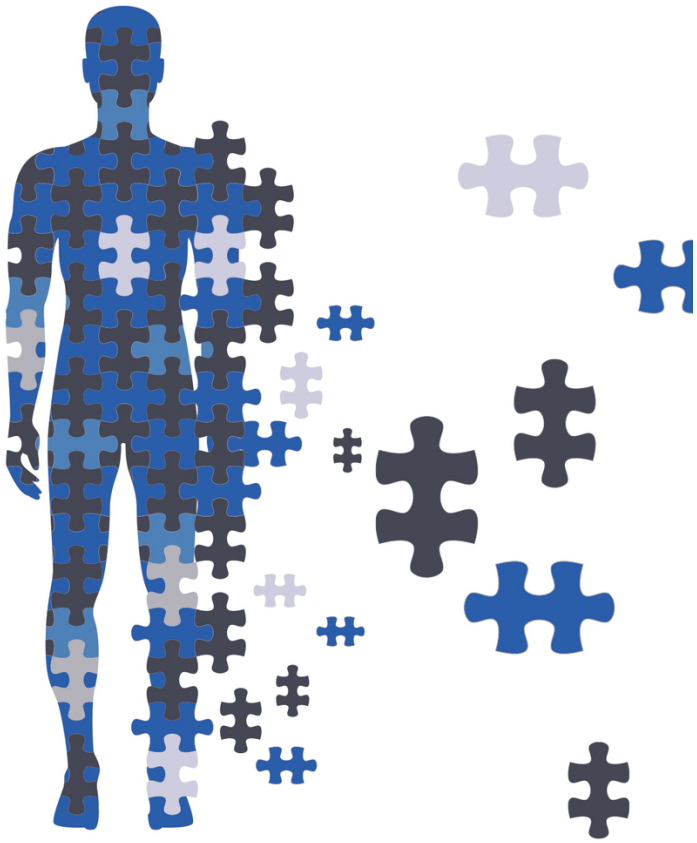

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The Autoimmune Answer

Using Functional Medicine to Address the Cause, Eliminate Symptoms, and Optimize Quality of Life

by

Dr. John Bartemus

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Foreword

This new book by Dr. Bartemus will help many people to understand some of the available solutions to their health problems, but also — and perhaps more importantly — to understand the thought process that leads to finding those solutions. Not all options are available to help patients through all practitioners, as most practitioners are limited to whatever they learned in whichever graduate program they attended. Through the eclectic approach of functional medicine, health professionals from various backgrounds can learn how to ask the right questions and ultimately — per his detective metaphor — find the right pieces to the puzzle and put them in the right places to allow the materialization of the desired final and complete result.

In addition to the useful diet and health information contained within the book, three other very important ingredients for a successful clinical encounter and outcome are also demonstrated.

Firstly, and perhaps most importantly, a patient needs to look for and ultimately find a clinician who actually cares and who is willing to put forth the effort necessary to see their case as unique and find the corresponding unique solutions. Lazy doctors don't solve problems, they typically just medicate them or use whatever solution is most readily available, and that's usually not the customized solution that the patient needs. However, willingness and curiosity can only take us so far; what is needed is a structured approach within which we can apply our energy and knowledge.

Secondly, the model that is used for the understanding of health problems is essentially the same model from which the clinician selects the therapeutic interventions. Functional medicine, like naturopathic medicine, works from a broad perspective and employs a wide range of therapeutic options. In contrast, in medical school, we only learned about drugs, surgery, radiation, and vaccination so of course those are the interventions we reach for in medical practice. However,

contained within that educational model is a flawed therapeutic assumption: namely that the most appropriate solutions to health problems are those same four interventions. According to the medical model, the appropriate treatments for obese and diabetic patients are drugs to lower their blood sugar and surgery to remove part of their digestive tract so they can no longer eat normally and absorb nutrients efficiently; and thereafter live in a state of semi-starvation and surgically-induced malnutrition. Fortunately for all patients, the naturopathic, chiropractic and functional medicine healthcare communities have worked hard to survive and resist the hegemonic power of the so-called medical establishment in order to persevere professionally and to provide patients with more reasonable therapeutic options – in this case, the reversal of obesity and diabetes through diet, exercise, and targeted nutritional supplementation to result in normalization of inflammatory responses and metabolic processes. Patients wanting personalized healthcare solutions need to find clinicians who are willing to think outside of their educational boxes, who continually learn and read and study, and who ultimately have a wide range of talents and therapeutic options from which to select. Hardly anyone these days wants cookie-cutter prefabricated healthcare delivered in a fast food format from a menu that only provides the four options of drugs, surgery, radiation and vaccination; despite its superficial simplicity and efficiency of delivery, that outdated model of medicine delivery provides a reflux of consequences in costs, adverse effects, and poor long-term health outcomes.

Thirdly, as demonstrated in this book, the patient and the practitioner both have to appreciate the process of engagement in the discovery of problems and implementation of solutions. Whiners won't make the cut. A successful athlete requires a good coach, and a good coach can only succeed with a willing and engaged player.

I'm hopeful and confident that John's book will help inform many patients and practitioners to stay the course in constant learning and to continually explore options both near-at-hand and within our reach and those on the horizon that are still coming into clearer focus.

Dr. Alex Vasquez DC ND DO FACN

Author of *Inflammation Mastery: Textbook of Clinical Nutrition and Functional Medicine*

www.InflammationMastery.com

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Dedication

To all those who suffer unnecessarily due to a "health care" system that puts profits over people.

Medical Disclaimer

The information in this book is not intended to replace the advice of the reader's own physician or other medical professional. It is intended for informational purposes only and not for self-treatment and/or diagnosis. You should consult a medical professional in matters relating to health, especially if you have existing medical conditions. You should also consult a medical professional before starting, stopping, or changing the dose of any medication you are taking and before beginning any new diet, exercise, or health program. Individual readers are solely responsible for their own health care decisions. The author and the publisher expressly disclaim any responsibility for any adverse effects individuals may claim to experience, whether directly or indirectly, from the information contained in this book. The information published in this book is not intended to replace or prevent medical treatment and diagnosis.

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The names and identifying characteristics of any patients have been changed to protect their privacy.

What others are saying

"With warmth, wit, and wisdom, Dr. Bartemus gives the reader insights into the complex world of autoimmune disease. Using the world around us and within us, he explains how everyday decisions, big and small, influence how we feel and heal!"

Amy Cross RN, MS
Medical Relations Coordinator
Moleculera Labs, Inc.

"Health detective work at its best. A perfect example of what Functional Medicine is all about - completing the puzzle. Perfectly clear and thorough. A must-read for all who wish to understand this subject better."

Mathieu Bouchard ND, CFMP
Member, International College of Human Nutrition
and Functional Medicine (ICHNFM)

"Dr. John Bartemus offers a compelling glimpse behind the curtain of Conventional Care and shows us what is possible with a deeper dive into Functional Medicine. He has an impeccable ability to arrange the puzzle pieces of human physiology and demonstrate how our health can be influenced by nutrition, epigenetics, microbiome, and toxins. The end result is a holistic masterpiece as he paints a picture of hope for all who suffer from chronic disease."

Lara Salyer DO, IFMCP
Right Brain Rescue

"Dr. Bartemus demonstrates how he is intimately aware of the deep complexities of a variety of autoimmune diseases. Marked off with real-life stories, he illustrates his approach to each case by finding the puzzle pieces of their health history and follows with a plan of attack to resolve symptoms. It provides hope and a motivational boost to search for root causes. This book is a must-read for anyone who is dissatisfied with their current treatment and is seeking to resolve symptoms, not just suppress symptoms with medication."

Achina P. Stein DO, DFAPA, ABIHM, IFMCP
Author of *What If It's Not Depression?: Your Guide to Finding Answers and Solutions*

"In reading this book, it quickly becomes evident why Dr. John Bartemus is a leader in the field of Functional Medicine. Thoughtful, thorough, and well-researched, this text will quickly become a go-to reference for other practitioners looking to incorporate a more holistic and functional paradigm into their patient care model, or patients looking for REAL answers outside of our traditional medical system."

Abbie Ballard DC, CACCP
Ballard Family Chiropractic

"The first step in any journey is understanding the lay of the land, and within the first few pages, you'll get a more understandable explanation and education than you will ever get from 'Dr. Google' or your 'regular' doctor. Dr. Bartemus sets the stage beautifully for empowering the reader with real and actionable knowledge."

Cameron Bearder DC
Keystone Chiropractic

"Dr. John Bartemus is without a doubt one of the most brilliant minds in his field. He has done incredibly extensive research and is sharing his findings in this book that can be a catalyst for an enhanced life. You owe it to yourself to dive deep into this gold mine of knowledge and take your health and life experience to the next level."

Ronnie Doss, America's #1 Teamwork and Performance Specialist
Author of *Leading Lions* and *Dig*

"This book will help you change the way you think about chronic health conditions and how to heal from them. Dr. Bartemus breaks down complicated health topics into an easily digestible format so you can take back control of your health."

Ryan Cedermark DC, NP, DABCN

"In an overwhelmed, broken, and fiscally irresponsible health care environment, we the patient, have been victim to the

failures of mediocre conventional medicine for far too long. Thankfully, there is hope for us! Dr. John Bartemus is one of the brightest minds you will ever encounter who not only has dedicated his life to putting the pieces of your health puzzle together but whose expert approach is the answer to many of our unanswered questions and burdensome health concerns."

Alexandria Bearder RN
Critical Care Nurse

"This book shines light into the way of thinking that is required to create health and to change chronic illness rather than just treating symptoms through medication. Dr. Bartemus takes the complexities of the body and breaks the concepts down in a way that anyone can understand."

Russell Hulbert DC
Premier Family Healthcare, LLC

"Dr. John Bartemus, my colleague and dear friend, is on his way to putting the pieces together. This book is epic! Get ready to take a tour through the mind of a one-of-a-kind healthcare practitioner and his journey into the world of Functional Medicine."

Dylan DeLorenzo DC
Applied Kinesiology Center of NJ

"Dr. Bartemus's book blends the best of both worlds- the science of modern medicine and real healing from the natural world. This book is sure to help anybody with an autoimmune disease- no matter the diagnosis."

Nicole DiNezza DC, NTP
Infinity Holistic Healthcare

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I have been blessed with wonderful people at every age and stage of my life. It is not possible to put every name worthy of mention in this book. If I left you out, please know that it was not due to any bad will. I am grateful for all of you.

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Thank you, Dr. Cameron Bearder, for your spirit, zest for life, and desire to change the world. You are the next big thing, and I am excited to walk with you.

Thank you, Dr. Sam Yanuck, for your passion for immunology and teaching. Your work has changed my life as a clinician and resulted in a significant positive impact on every person I work with.

Thank you, Dr. Alex Vasquez, for your friendship, mentorship, and integrity. It is your combination of integrity and literary genius that has left an indelible mark on my professional and personal life.

Introduction

"Learn how to see. Realize that
everything connects to everything."

—Leonardo da Vinci

Do you remember doing puzzles as a kid? I loved puzzles. I remember sitting with my grandmother (we called her Mama) at her kitchen table and putting together 300, 500, and 1000 piece puzzles with her.

I remember looking for all of the edge pieces first, putting them together, and then filling in the inside once I had a framework to go by. There's a certain detective work to it that made me excited. I remember watching *Matlock* and *Columbo* ("whodunit" shows of the '70s and '80s) with Mama.

The movie *Dick Tracy* also came out during my childhood, and I loved the 1989 Michael Keaton version of *Batman* . Many of my heroes were detectives or people tasked with taking clues and putting them together to find the result, the bad guy, or both. I believe these early experiences in puzzle solving and detective work informed how I view the world, how I set goals, and my approach as a clinician. In everything I did, and in everything I do, there is a puzzle-constructing component. Puzzles are everywhere—they are principles of life.

Maybe you are like me, at least a little bit or at least in certain situations. Do you see the puzzles all around you? If you have a goal, do you ask yourself: *What are the steps or puzzle pieces that need to be put together in order to achieve my goal?*

What was your first major life goal? Mine was to play in the NFL. I used puzzle-solving when trying to achieve my NFL goal —what were the pieces of a perfect, natural plan to get me to the NFL, and how could I put them together in such a way that I achieve that goal?

Nutrition was a puzzle. Maximum strength, speed, and skills were also a puzzle. They were all puzzles for me to put together in order to optimize my performance and help me achieve my goal of making the league. Leveraging the nutrition and fitness puzzles got me to college football and a Division 1-AA team,

but I was unable to ultimately achieve my goal of a pro football career.

As Napoleon Hill said, “Every failure brings with it the seed of an equivalent success.” Out of my failed NFL career came the seeds, which blossomed into my success as a clinician. My puzzle-solving in the fields of nutrition and performance had set the stage for my current role as a clinician and solver of human puzzles.

What perceived failures are you dealing with or have you dealt with in life? Is one of them your current struggle with an autoimmune disease? Do you feel depressed or intimidated because you have been suffering from chronic symptoms that your doctor cannot explain, and when they run tests and diagnostics, all results say you are “normal”?

You are not a failure—you are a puzzle. More detective work needs to be done on your case so that the missing pieces (or the pieces that are in the wrong place) can be discovered and put right. Just like putting the pieces of a puzzle together requires the proper border or framework, health is achieved by putting the pieces together inside an optimal framework. This book is going to show you the ideal framework to use to understand why you have the symptoms you’re having, why conventional medicine says you’re “normal” even though you don’t feel normal, and how to create optimal health.

In order to determine the proper framework to work from, you must first have the proper worldview or paradigm. All of us look at our world through a certain lens or, as motivational speaker Ronnie Doss says, “A certain pair of glasses.” The glasses through which you see your world are yours.

Conventional medicine looks at your health through glasses that show you as a machine made up of interchangeable parts. How is that working for us as a society or you as an individual?

As Wendell Berry describes in his book:

- “Where the art and science of healing are concerned, tl machine metaphor works to enforce a division that falsifies tl process of healing because it falsifies the nature of the creatu needing to be healed. If the body is a machine, then its diseas

can be healed by a sort of mechanical tinkering, witho reference to anything outside the body itself."

- "The modern hospital…undoubtedly does well at surgery ar other procedures that permit the body and its parts to be treate as separate things. But when you try to think of it as a place healing – of reconnecting and making whole – then the hospit reveals the disarray of the medical industry's thinking abo health."

- "In healing, the body is restored to itself. It begins to live aga by its own powers and instincts, to the extent that it can do s To the extent that it can do so, it goes free of drugs ar mechanical helps. Its appetites return. It relishes food and re The patient is restored to family and friends, home ar community and work." [1]

The U.S. has some of the best drugs, technology, and surgeons in the world, but we don't have the best health. Will more drugs and surgeons make us healthier? No. The answer to better health is a change in our paradigm or the pair of glasses through which we view health.

Einstein defined insanity as doing the same thing over and over and expecting a different result. Trying to fix your health by wearing the glasses that allowed your sickness to occur in the first place is insanity. You—and we as a nation—need a new pair of glasses, and that new pair of glasses through which to practice health care is known as Functional Medicine. Functional Medicine is 21st century healthcare and provides us with a framework we can use to construct and fill in your puzzle.

A quick "heads up" …

When an author sets out on the journey of writing a book, the advice typically given is to keep the subject material as close to a "6th grade reading level" as possible. This strategy is recommended so that the majority of readers can understand the message being conveyed.

I'll get to the point. This book is not written at a 6th grade level. Some parts are significantly higher. DON'T WORRY! When the subject becomes complex and the difficulty increases, I will

always follow it with an easy-to-understand translation, analogy, or metaphor. You see, the ability to understand a concept and then explain it in a simple way is one of the most powerful tools I can offer. My goal is not to confuse you or sound heady, but rather to educate you and empower you, so that you have the BEST chance to heal! To quote Sir Francis Bacon, famed English scientist and philosopher, "Knowledge itself is power."

Now let's get healing!

Exposome, epigenome, and microbiome

There are three main pieces to the functional medicine framework:

- The **exposome** represents all exogenous (outside) ar endogenous (inside) environmental exposures that begin preconception and carry on throughout life. [2] This includ exposures such as diet, alcohol, tobacco, chemicals, drug vaccines, infections, UVA/UVB, stress, socioeconomic statu hormones, metals, nutrient status, microbiome, soci relationships, etc. Specific to autoimmune diseases, tl exposome has also been termed "the Autoimmune Ecology." [3]

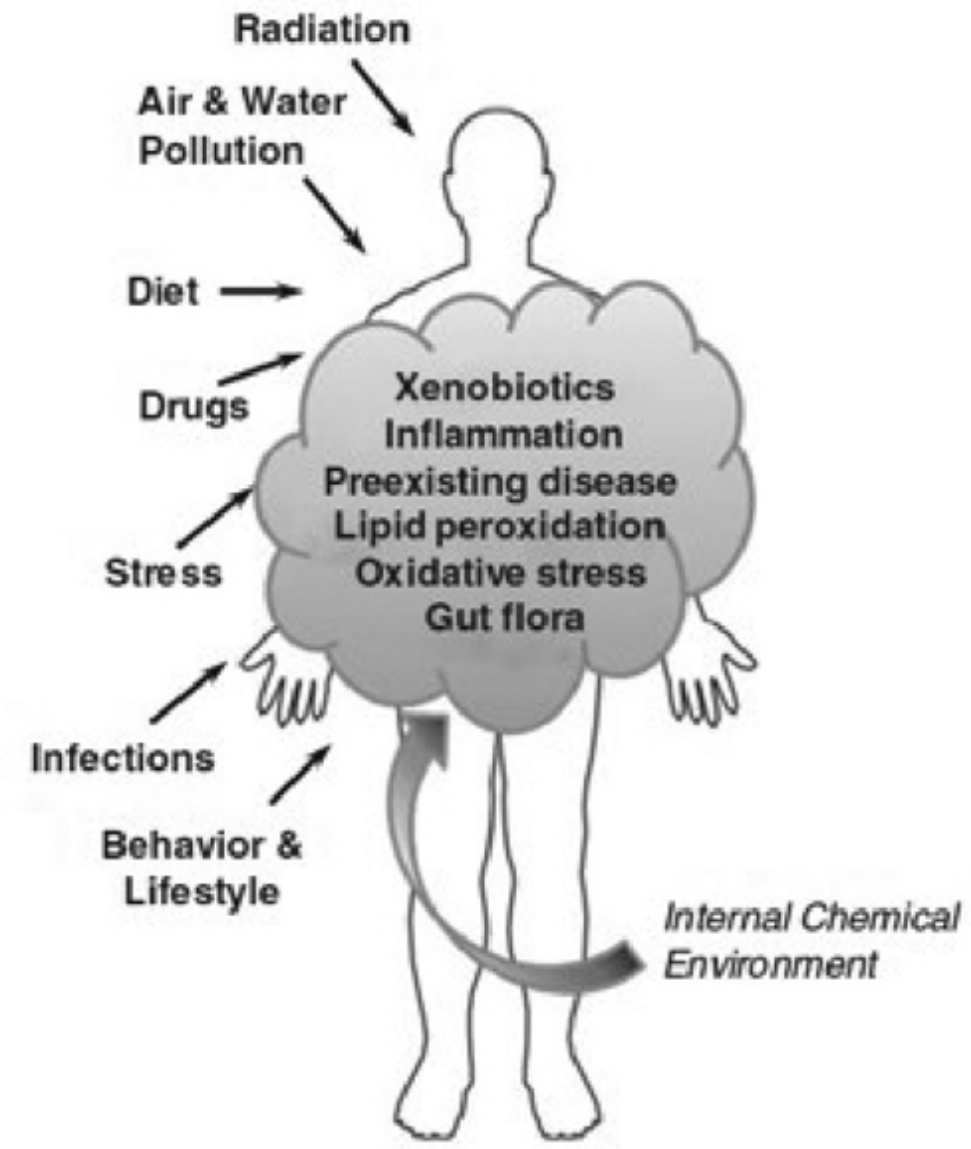


Figure compliments of the open access article from *Journal of Exposure Science and Environmental* Epidemiology [4]

Wendell Berry described the exposome before the term was created: "The body alone is not, properly speaking, a body. Divided from its sources of air, food, drink, clothing, shelter, and companionship, a body is, properly speaking, a cadaver, whereas a machine by itself, shut down or out of fuel, is still a machine…the body lives and moves and has its being, minute by minute, by an interinvolvement with other bodies and other creatures, living and unliving, that is too complex to diagram or describe. It is, moreover, under the influence of thought and feeling. It does not live by 'fuel' alone."[1]

The exposome offers clinicians an avenue for integrating research that is currently fractured along lines related to particular diseases and risk factors and can thereby promote discovery of the key exposures responsible for chronic diseases (including autoimmune disease). Said another way, the exposome is the science proving Da Vinci's statement that "everything is connected to everything."

- The **epigenome** is the total of potentially heritable changes gene expression and function that do not involve alterations your original DNA. Epigenetic regulation plays a crucial role various life processes including the growth, development, a aging of your cells. It also plays a crucial role in your immu response. Epigenetics provides a better understanding of ho environmental triggers (aka, your exposome) can alter ge expression and disturb immune homeostasis. It is also implicat in the pathogenic mechanisms of many complex diseases (i.e cancers and autoimmune diseases). [5]

The difference between your genome (genes) and epigenome (genetic expression) is that your genes cannot be changed. However, the expression of your genes can. Long, et al. state this quite well in their 2018 study titled, "The Epigenetics of Autoimmunity-An Overview" [6] :

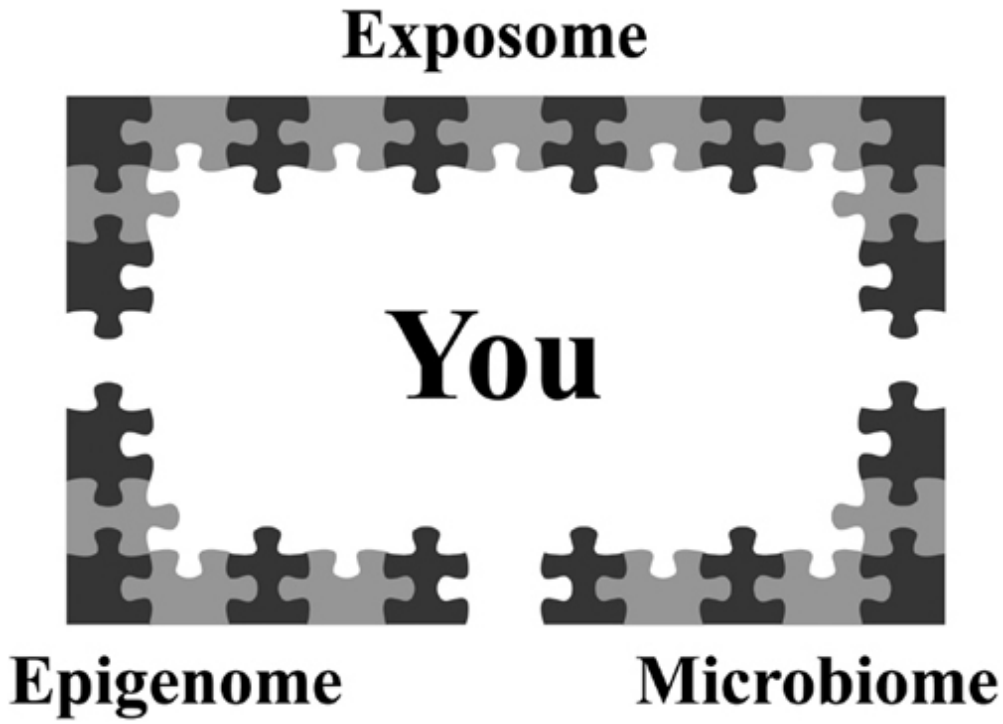
"Unlike gene mutations and chromosome anomalies, epigenetic abnormalities are REVERSIBLE and thus have the potential to be 'corrected.' The number of research publications regarding epigenetic modifications in autoimmune diseases has increased exponentially in recent decades, highlighting the attractiveness of epigenetic research in this field."

Do you see the importance of this statement? Epigenetic issues *are* reversible! In other words, THERE IS HOPE FOR YOU AND YOUR AUTOIMMUNE DISEASE! Genetics is the science of hopelessness. If a disease is genetic, there is no hope because you cannot change your genes. Thankfully, only a few diseases are truly genetic such as trisomy 21 (Down syndrome), cystic fibrosis, and sickle cell anemia. [7] In fact, current evidence suggests that

non-genetic factors contribute to 90% of chronic disease risk.[4] Epigenetics is the science of hope because your epigenome can change. What determines your epigenetic expression (your state of health or disease)? Your exposome, or, your total environmental exposure.

- The **microbiome** is all the microbes—bacteria, fungi, parasite protozoa, and viruses—that live on and inside the human bod The total number of genes that make up the human microbion is two hundred times the number of genes in the human genom In other words, the microbes that inhabit us have two hundr times the total genetic load that we have. These microbes help digest our food, influence and regulate our immune system, ou compete disease-causing pathogens for our body's real estat and produce nutrients for us such as vitamins B1, B2, B12, ar K. [8] They also produce short-chain fatty acids (SCFAs) nourish our large intestine and have an anti-inflammatory effe Autoimmune diseases such as type 1 diabetes, rheumato arthritis (RA), psoriasis, and multiple sclerosis (MS) a associated with dysfunction in the microbiome.

Together, these three "-omes" create the border, or framework, of your puzzle. These are the major factors contributing to your state of health or disease and help detectives like me fill in the rest of your puzzle to determine how to "reverse" or "correct"[5] your autoimmune disease.



What is autoimmunity?

We need to address what autoimmune disease is before we jump into the next chapter. Before we dive in, let me first say that the immune system is very complex, our knowledge of it is continually evolving, and entire textbooks are written on it. I am not trying to compete with what you could learn in an immunology textbook. My goal is to simplify it in order to empower you with an understanding that allows you to better conceive what is going on in your body if you are suffering with an autoimmune issue.

Autoimmunity is defined as a "dysregulated immune state that causes loss of immunological tolerance to self-antigens and damage to normal cells and tissues…characterized by the presence of autoreactive immune cells and/or the development of autoantibodies. These disorders include not only organ-specific autoimmune diseases but also various systemic autoimmune diseases."[5]

Fundamentally, the key thing to understand about autoimmunity is that it is a "dysregulated immune state." It doesn't matter what specific organ or system is being attacked, the dysregulated or imbalanced immune response is the cause. Metaphorically, the

organ or system that the symptoms are manifesting in is the victim, while the immune system is the criminal.

For example, in Hashimoto's Disease (a thyroid autoimmune disease) the thyroid symptoms of hair loss, weak nails, cold hands and feet, inability to lose weight, etc. are the victim (the thyroid gland) crying out for help. The criminal is the immune system. Giving Levothyroxine (thyroid hormone replacement medication) will just put duct tape over the victim's mouth and keep them from screaming. Meanwhile, the criminal will continue to assault the victim. It is not until we apprehend the criminal that the victim will stop crying for help.

How does the immune system become dysregulated? The answer to that question is different for everyone. As stated above, major drivers of disease in general and immune dysregulation specifically are going to come from issues found in the exposome, epigenome, and microbiome.

You will learn in this book that there are many potential drivers of immune dysregulation. There are also many directions in which the immune system can become dysregulated or inappropriately polarized. Polarization applies to our T cells.

Conventional immunology teaches that our immune system is made up of two main responses: the innate immune response and the adaptive immune response. [9] The innate immune response is the acute response. If your tissue is damaged or infected, the cells of the innate immune system are on the scene almost immediately. The adaptive immune response is a delayed response and takes 3 to 5 days to arrive on the scene. Think of the innate immune system as the local police and the adaptive immune system as the national guard.

While working to clean up the scene, the innate immune cells (primarily dendritic cells) will take samples of self-tissue and foreign tissue to the lymph nodes and present it to adaptive immune cells called T cells and B cells. T cells have the ability to respond in many different ways, whereas B cells lead to antibody production. [10]

Based on the information presented to it, a naïve T cell in the lymph node will become polarized (similar to going from a police officer right out of boot camp to becoming a national

guard specialist in a specific area such as bomb squad, sniper, etc.) and travel from the lymph node back to the scene of damage or infection and produce a more specific response. [11]

To keep it as simple as possible, here is a list of the seven T-cell polarizations science is currently aware of and how they function [12] followed by a visual representation of the handoff in the lymph node between the dendritic cell and the naïve T cell:

Th- stands for T-helper cell.

Th1 cells – primary killers of viruses, bacteria, and other pathogens that infect our cells (intracellular infection).

Th2 cells – produce the allergic response. They are primary responders to extracellular pathogens (such as parasites, worms, yeast) that infect hollow organs such as the gut, lungs, bladder, and sinuses.

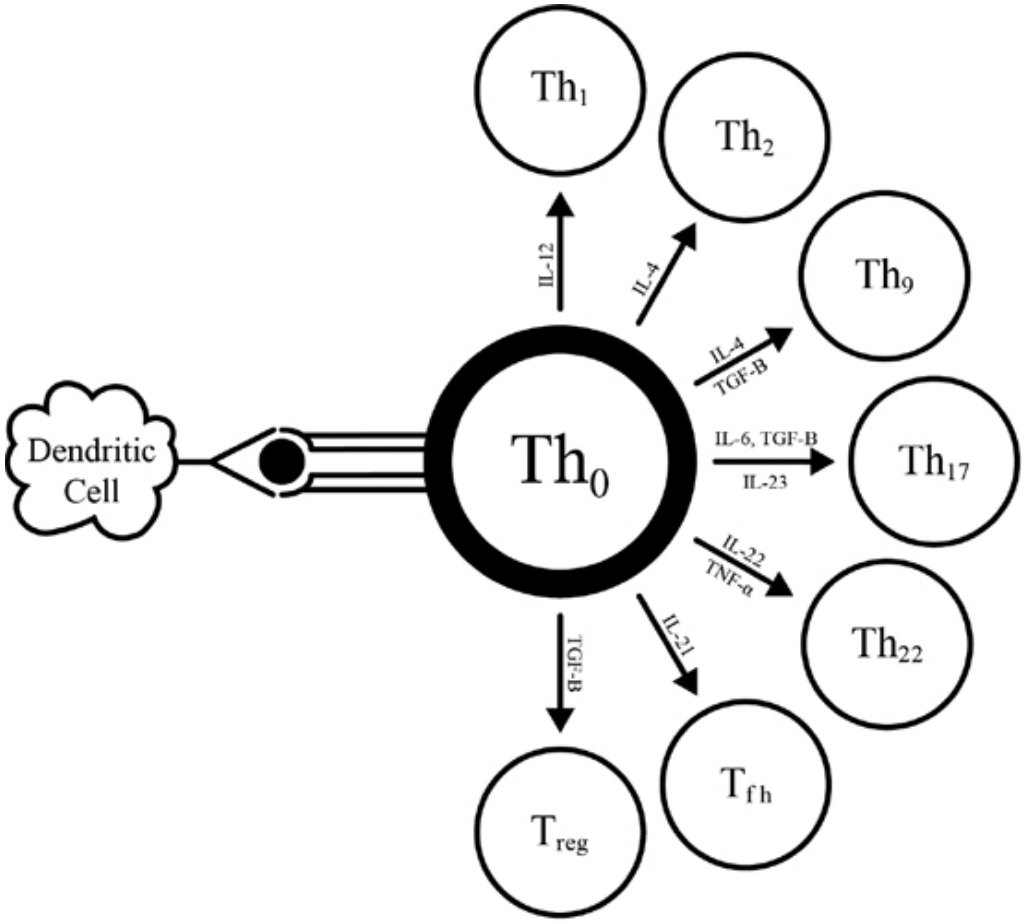
Th9 cells – essentially a more intense version of the Th2 (allergic) response.

Th17 cells – also respond to hollow organ damage and infection.

Th22 cells – promote robust tissue inflammation.

Tfh cells – (T-follicular helper cells) promote antibody production.[12]

Treg cells – (T-regulatory cells) promote resolution of inflammation (anti-inflammatory) and immune tolerance. [13]



T cells differentiate into the various polarizations depending on multiple factors, including the vitamin status and presence of other immune chemicals in the local microenvironment. [14]

Each of these T-cell polarizations is beneficial when the response is of appropriate timing, duration, and intensity. Problems arise when the response time, duration, and/or intensity is inappropriately long or intense. If your immune system becomes dominant or hyperpolarized in one direction, that can be pathologic.

For example, you will learn in this book that a Th17 dominance is known to drive the tissue damage seen in many autoimmune diseases. [15]

Autoimmunity occurs when your immune system begins to lose its ability to recognize the difference between you and not you (i.e., self vs. non-self). For example, your immune system should clearly discern between what is causing strep throat

(streptococcal bacteria) and you. It should then only attack and kill the strep and minimize the damage to your tonsils. In this situation, if your immune system has lost self-tolerance (the ability to differentiate you from not you, the self from the non-self), then your strep infection may result in rheumatic fever. Rheumatic fever is an autoimmune attack of the heart tissue due to the fact that the heart tissue looks (to a non-discerning immune system) like streptococcal bacteria. This is a mechanism known as molecular mimicry. [16]

How do you know you have an autoimmune disease, and how is it diagnosed? This is an area that you must understand when you suspect you have an autoimmune disease, but your doctor reports that you are "normal."

Autoimmune process vs. autoimmune disease

Deciphering between an autoimmune process and an autoimmune disease can be confusing. Many people have experienced the following scenario: They go to their doctor with a self-diagnosis (based on online reading) of a suspected autoimmune disease and request the doctor run lab tests to confirm or deny their suspicion. Let's use thyroid autoimmunity as an example.

A woman has recently experienced fatigue, hair loss, cold hands and feet, and perhaps some brain fog. After a Google search of her symptoms, she suspects that she has a thyroid problem. So she goes to her medical doctor, tells her what she has found, and requests thyroid labs. The doctor agrees to run thyroid testing (which is woefully inadequate, as will be discussed in Chapter 7, but for right now just go with it), and when the results come back, the patient is told her thyroid is normal.

Does this mean she does not have thyroid autoimmunity? No.

Does this mean she does not have a thyroid autoimmune disease? Yes.

"What?!" you ask incredulously. "How?! How could you say we cannot rule out autoimmunity and in the next sentence say that she does not have an autoimmune disease?"

Great question. The answer is in the details.

The answer is in understanding the difference between an autoimmune *process* and an autoimmune *disease* .

Merriam-Webster dictionary defines process as “a natural phenomenon marked by gradual changes that lead toward a particular result.”

Medically speaking, a specific disease is defined or diagnosed when it meets concrete diagnostic criteria that have been determined by various medical institutions, governing bodies, and/or expert consortiums. In conventional medicine, if you don’t meet the defined diagnostic criteria, you don’t have a disease.

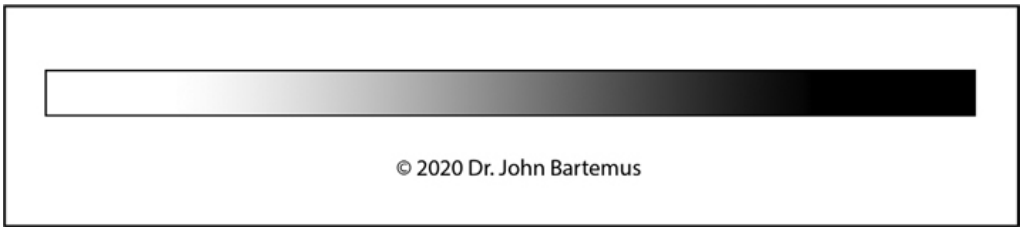
Does that mean you are healthy, and there is nothing wrong with your physiology?

Any coherent human would say no. But conventional medicine acts as if the answer is yes. You don’t fit diagnostic criteria for a given disease, so you must be normal.

In our example, to diagnose hypothyroidism, the doctor would have to see a lab high value for thyroid stimulating hormone (TSH) in your blood. Since that biomarker came back normal, our example patient was told she was normal. No doubt, she left the office frustrated because even though she was told she was “normal,” she still didn’t feel normal and left suffering from the same abnormal symptoms that she had walked in with.

Medicine is black and white. Black meaning you fit diagnostic criteria and have a disease. White meaning you do not fit diagnostic criteria, and you are normal. The frustration and suffering arise from the fact that the conventional medical model has no room for gray.

In reality, there is a continuum from health (white) to disease (black). You cannot get to black from white without first going through gray. The continuum could be viewed graphically like this:



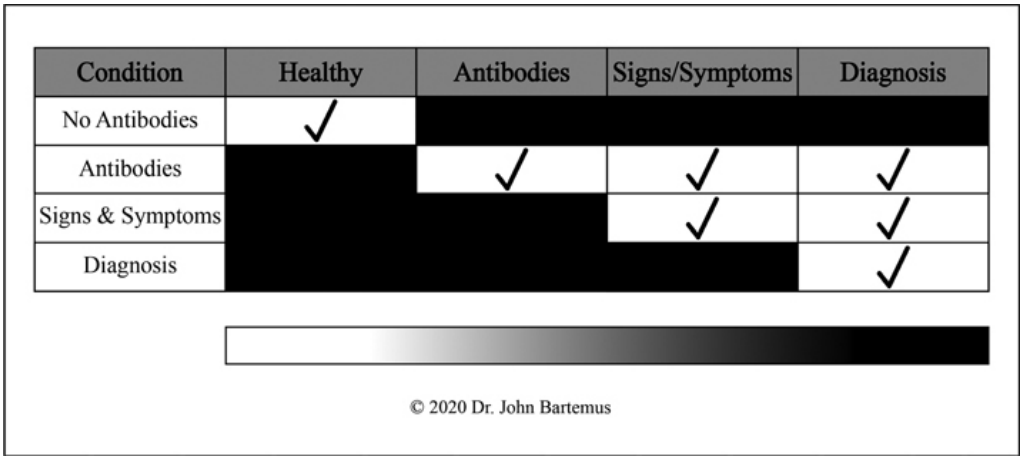
White is health, gray is suboptimal or sick, black is diagnosable disease.

Guess what, most people are gray; meaning, they are in process. And as our definition above states, a process is marked by "gradual changes that lead toward a particular result."

Our example patient does not meet diagnostic criteria, so she is not black. Her symptoms make it obvious that she is not white, so that leaves her in the gray area without the necessary knowledge or support to move herself back to white.

If her thyroid symptoms are due to thyroid autoimmunity (as 90 percent of hypothyroidism cases in the US are) [17] , then she is currently gray but heading toward a "particular result" of diagnosable disease (black). It is not until her TSH is lab high (meeting diagnostic criteria for hypothyroidism, aka black) that her doctor will acknowledge her problem. Even when that happens, the doctor will not know or care whether autoimmunity is behind the diagnosis. In order to know for sure, thyroid antibodies would need to be tested and lab high. We will get much more in-depth regarding thyroid testing and diagnosis in chapter 7.

Let's apply our example patient's experience to the following Autoimmune Process vs. Autoimmune Disease graphic:



As you can see in the graphic, someone who is truly healthy has no symptoms and no lab evidence of potential autoimmunity. This person is white. If a person has positive antibodies but no signs and symptoms, they are early on the gray scale. Research reveals that antibodies are the first detectable sign of autoimmunity [18] and may be predictive of disease 5 to 10 years down the road. [19], [20], [21]

If a person has positive antibodies and signs and symptoms, they are further down the gray continuum toward disease (a "particular result"). These people are sick and suffering, but they are told they are normal by their doctor because they don't fit diagnostic criteria. A person could be spinning their wheels in this part of the continuum for years, seeing many doctors and receiving no help.

Finally, when a person has positive antibodies, signs and symptoms, and enough damage has occurred to their biology and physiology that they finally meet all diagnostic criteria, they are diagnosed with a specific autoimmune disease (black) and offered a medication. That medication will do nothing to improve immune function or reverse the disease. Its only purpose is to decrease symptoms.

We can do better. We *MUST* do better.

Better starts with finding the dysfunctional biology sooner [22] and taking action immediately[20] . Better means honoring the possibility that most cases are gray, not black or white. Better starts with a new pair of glasses.

I hope you are excited about diving further into this book. This introduction has pieced together the borders of the puzzle, and we can now build chapter by chapter toward educating you on what you need to do to heal from your autoimmune disease and optimize your health.

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CHAPTER 1

Current State of Health Care—
Functional Medicine vs. Conventional Medicine–Parkinson's Disease Case Study

"Do they even cure you, or is it just to humor us before we die?" – "Accidents,"

—Alexisonfire

Wanda was sixty-seven, retired, and married. She was obese when I met her. She had been suffering for four years from Parkinson's disease that was diagnosed by her medical doctor. She had associated symptoms of stiffness, tremors, brain fog, and a lack of mental clarity and had been prescribed the typical medication—Levodopa—four times a day for Parkinson's.

Wanda had also been suffering for sixteen years from restless leg syndrome and insomnia. Her legs kept her up at night to the point where she said she would be up pacing the floor until 4:00 a.m. I don't know about you, but if I were doing that each night, I would not be performing too well the following day.

In addition, Wanda had a ten-year history of high cholesterol and high blood pressure and had been diagnosed with sleep apnea three years before meeting me. She had back surgery and a total knee replacement two years before I met her, and in the previous year, she had gained forty pounds. Her most recent complaint was that she had developed pain in her hips.

Wanda presented with nine medications, some of which were for high blood pressure, high cholesterol, pain, and acid reflux. When I ran a medication interaction check on the prescriptions she was taking, it came up with sixteen possible interactions that could drive weight gain and raise her blood pressure even higher, which was counterintuitive because she was on medications to lower her blood pressure. There was also a risk of motor impairment via the drug interactions, which was a problem as she had Parkinson's disease and was already motor-impaired.

Wanda had seen five medical doctors that were managing her symptoms—a neurologist, a neurosurgeon, her primary care provider, a cardiologist, and a pain management doctor. When she asked them, "What's wrong with me?" they told her, "Well, you have Parkinson's disease, and some of your issues are due to the side effects of your medications. There may also be possible side effects from your back surgery, and, of course, old age."

By this point, Wanda had seen a chiropractor. She was then referred to me because she was not getting better beyond the initial benefit from chiropractic care. She wasn't enjoying the quality of life that she wanted.

Do you believe this is how Wanda envisioned her golden years? Is this how you plan on spending yours? I'm betting it isn't, but if you are trusting conventional medicine to keep you healthy so that you can enjoy your retirement, statistics show that, like Wanda, you're going to be disappointed.

A study in *The New England Journal of Medicine* [1] looked at the quality of care in America and declared, "Medical care in the United States is uniformly mediocre." Patients in the study were found to receive only 55 percent of the recommended standard of care. This means that a typical American going to the doctor is only going to get half of the recommended care that is considered the standard for their particular ailment.

Why is health care in America so mediocre?

As we discussed earlier, we are wearing the wrong pair of glasses. Conventional medicine sees Parkinson's as a progressive, neurodegenerative disease that has no chance of cure or reversal. How much hope does that definition offer a person diagnosed with the disease? Not much, but it fits perfectly into the current medical framework of "there's nothing you can do, so just take this drug," which in this case is Levodopa for "managing symptoms." As you continue to get worse, you'll just get more drugs, until you end up with a combination of symptoms and side effects that you can live with. At which point, your condition will be deemed by the medical community as "well managed."

Levodopa is the “gold standard” of Parkinson’s medications in the U.S. [2] It targets only motor symptoms like tremors and slowness, but ignores the documented, broad range, systemic, non-motor symptoms. It is also well known that the use of Levodopa to alleviate Parkinson’s symptoms leads to high homocysteine levels. Patients with the highest levels of homocysteine deteriorate faster than those with lower levels. [3] As you will learn in the following pages, homocysteine creates high amounts of free radicals, which promote destruction of brain tissue.

I suspect that the creators of conventional medicine did not grow up solving puzzles. If they did, they used children’s puzzles that had just four giant pieces. The framework of a four-piece puzzle *is* the puzzle—there’s not a whole lot of detective work going on there.

Parkinson’s is currently approached from a four-piece puzzle perspective in America. However, researchers in the UK have changed their glasses. [4] They say, “Considering Parkinson’s disease only in terms of progressive, self-perpetuating degeneration relegates any environmental influence to being, at best, remote hit-and-run. Classification as ‘non-communicable’ reinforces this. Regarding any systemic illness in Parkinson’s disease as an ‘intercurrent event,’ as opposed to a co-morbidity, compounds the problem.”

The authors go on to give their vision for an accurate framework from which to approach Parkinson’s. “It is envisaged that Parkinson’s disease will be reclassified as a systemic condition in response to immune-inflammatory activation, influenced by microbiota, tempered by human genetics, within a spectrum of neuropsychiatric and gastroenterological conditions…where drivers, perpetuators, and mediators remain active, attempts at neuronal replacement, repair and regeneration, and symptomatic treatment may underperform.”

Translation—Parkinson’s disease should be viewed from the perspective of exposome, epigenome, and microbiome. If environmental, lifestyle, and mental-emotional drivers are not considered and addressed, then symptomatic treatment will underperform. Not only will treatment underperform, but there is also no hope for healing.

The functional medicine framework of exposome, epigenome, and microbiome provides that hope—it honors the fact that exposures which contribute the development of Parkinson's may occur years or even decades before diagnosis. [5]

Another quote from the UK researchers provides a thorough definition of the functional medicine approach: "What is sure, in a disease peculiar to man, is that re-evaluating the patient is a good starting point. Detective work is needed, where subtle clues are uncovered and statistical analysis builds on meticulous clinical observation. In such exploratory studies, it is necessary to understand what is measured and what influences it, explore effect modification, examine biological plausibility, and seek corroborative evidence. Not until a large number of clues have been assimilated will their position within a causal scheme become more certain. A scientifically challenging causal pathway does not preclude a clinical solution sufficiently simple to be assimilated into practice. Grassroots opinion, from people with the chronic disease who want a cure, is important in influencing professional consensus."[4]

Translation—good clinicians (i.e., "detectives") should consider any and all factors (i.e., "clues") in the patient's life that did, are, or could contribute to their current condition, including the opinions of the patient. I trust that you are beginning to see the framework we need to operate from if we hope to heal from autoimmune disease and optimize our quality of life.

I can hear the questions now: "Wait a minute, doc—Parkinson's is not an autoimmune disease. Why are you talking about it?"

That's a very astute question, young Skywalker! I have a question for you—what glasses are you wearing? Various authors have reported on associations of Parkinson's disease with HLA-DR loci, [6], [7] which suggest that classical autoimmune mechanisms are involved. Another study connected infections to the cause of Parkinson's disease: "Our data are in line with the hypothesis of a possible involvement of the immune system, in particular autoimmunity in the pathogenesis of Parkinson's disease, and that HSV-1 infections may lead to a progression of the disease." [8]

Early-onset Parkinson's is associated with mutations in the genes that encode the enzymes PINK1 kinase and PRKN ubiquitin ligase. [9] These enzymes are responsible for clearing damaged mitochondria from our cells. They have also been shown to play a key role in our adaptive immune system by preventing our immune cells from recognizing our damaged mitochondria (ourselves) as an enemy .

As I teach you in my video on the topic https://www.FunctionalMedicineCharlotte.com/Parkinsons mutations in PINK1 and PRKN genes promote inefficient suppression of immune recognition of damaged mitochondria fragments, leading to autoimmune attack in the periphery and the brain.

The authors conclude, "Our data provide evidence that an autoimmune response engaged in the absence of PINK1 during intestinal infection participates in the aetiology (cause) of Parkinson's disease."

Remember, good detectives must consider all the evidence when building the case. These findings mean we can consider the possibility that Parkinson's has autoimmune mechanisms as drivers of the disease process and move forward. As Stanley Prusiner said in 1982, "The best science often emerges from situations where results carefully obtained do not fit within the accepted paradigms." [10]

Applying the functional medicine framework to Parkinson's disease

Before jumping in, let's address another question that is likely floating around in your head—is Parkinson's genetic? According to Samuel Goldman of the Parkinson's Institute: "Although at least fifteen genes and genetic loci have been associated with Parkinson's disease, identified genetic causes are responsible for only a few percent of cases. Ninety percent of Parkinson's disease patients have no family history of Parkinson's disease."[5]

The American Chemical Society weighed in on the question in the scientific journal, *Chemical Neuroscience* : "While some early onset forms of Parkinson's disease are hereditary or

genetic, the sporadic or late-onset cases are believed to result from lifestyle and environmental factors." [1 1]

Translation—genetics by itself is not the reason Parkinson's is the second most common neurodegenerative disease in the world (Alzheimer's is first).[3]

Now that we have that out of the way, let's look at what is really behind Parkinson's disease. In order to keep it organized, we'll break the contributors down to their respective spots in the framework and then go through them in more detail. The framework, remember, is the combination of exposome, epigenome and microbiome.

- **Exposome** contributors to Parkinson's disease include viruse high homocysteine, vitamin insufficiencies or deficiencie vaccines, metals, chemicals, head injury, body inflammatio and poor quality and/or quantity of sleep.

- **Epigenome** contributors include gene-environment interaction aluminum-gene interactions, and DNA hypomethylation.

- **Microbiome** contributors include dysbiosis and gut-brain ax dysfunction.

Exposome contribution

- **Viruses:** Multiple studies have linked viral infection and tot infectious burden to Parkinson's disease risk. A 2015 study *Parkinsonism and Related Disorders* found that the higher person's infectious burden with common viruses such cytomegalovirus, Epstein–Barr virus, herpes simplex virus typ 1, and other microbes such as Borrelia burgdorferi (or Lyme Chlamydia pneumoniae, and Helicobacter pylori, the high their risk of developing Parkinson's. [12] The reason for this is th infectious burden increases inflammatory chemicals th promote Parkinson's and the processes that result in the damag to brain. [8]

There is a causal theory called the "dual hit theory," which shows Parkinson's often begins in the nerves in the nose, the stomach, or in the enteric (gut) nervous system.

The dual hit theory states that viruses with viremic potential—meaning they infect the whole body—can simultaneously attack both the nervous system of the gastrointestinal tract and of the nose, and travel via those nerves into the brain. [13]

Other studies have shown that enteroviruses, which are viruses that infect the gastrointestinal tract, are associated with neurologic syndromes. There's recent evidence of an enterovirus as a cause of encephalitis lethargica and postencephalitic Parkinsonism.[4]

Hepatitis C virus has also been associated with Parkinson's disease risk. A 2017 study in *The Journal of Neurological Sciences* stated, "Hepatitis C virus can penetrate and replicate within the brain immune cells, increasing their production of inflammatory chemicals and causing direct toxicity to neurons." Other studies have shown that interferon, which is a treatment that used to be used for hepatitis C can increase the risk of Parkinson's disease by inhibiting dopamine transmission in the midbrain and inducing brain inflammation. [14]

- **Vitamin insufficiency or deficiency:** Many vitamins are neede for optimal brain function and for prevention of Parkinson disease, and studies have shown that lacking certain vitamii increases risk of the disease. High homocysteine is a result many possible factors, but a major contributor is the methylatic process. Methylation processes require B vitamins, specifical B12 and folate. When we lack these, studies have shown th there is increased homocysteine, which is a risk factor f Parkinson's.

High homocysteine leads to Parkinson's by multiple mechanisms.[3] It creates an inflamed brain and increases oxidative stress or free radicals, which also promote brain inflammation, nerve cell death, and protein aggregation or protein clumping. [15] It also leads to epigenetic changes, and as previously stated, the drug Levodopa is known to increase homocysteine. A 2017 study in *Neuroscience Letters* found that Parkinson's patients with cognitive dysfunction have higher homocysteine levels and lower

vitamin B12 and folate levels. By lowering homocysteine, the study's authors said, "We can provide hopeful treatment to improve cognitive disorders in Parkinson's disease." [16]

Blood homocysteine levels reflect the functional status of three B vitamins: folate, vitamin B12, and vitamin B6. As homocysteine levels increase, the status of these B vitamins declines. The *Journal of Alzheimer's Disease* published an international consensus statement in 2018 on the relationship between homocysteine levels, age-related cognitive decline, and dementia. The authors concluded:

"The findings are consistent with moderately raised plasma total homocysteine (>11 umol/L), which is common in the elderly, being one of the causes of age-related cognitive decline and dementia." [17]

Lastly, a 2019 study published in the journal *Neurological Sciences* found a close association between higher homocysteine levels, lower folate levels, and white matter hyperintensities in the brain on MRI. Parkinson's Disease patients with these findings exhibited the worst balance and most difficulty walking. [18]

- **Melatonin:** Melatonin is a potent antioxidant and plays neuroprotective role in aging and Parkinson's disease via the antioxidant effects. Studies have found that exposure glyphosate, the active ingredient in Monsanto's Roundup, ca lead to impaired antioxidant protection by suppressing melaton production. [19]

- **Vitamin D:** Vitamin D has neuroprotective effects ar antioxidant capacity. It regulates neuron calcium levels, th immune system, and helps with nerve conduction ar detoxification mechanisms. If vitamin D is lacking, all of the benefits are lacking, and many of these can contribute Parkinson's disease development. Vitamin D receptors are foun in high levels in the dopaminergic (dopamine-producin neurons of the midbrain. If you lack vitamin D, then tho neurons don't function well, and those are the neurons that a impacted in Parkinson's. [20]

In people with Parkinson's, vitamin D was found in a 2019 study [21] to significantly correlate with the risk of non-motor symptoms. The study found that Parkinson's patients had significantly lower vitamin D levels compared to people without Parkinson's, and low levels of vitamin D significantly correlated with a high frequency of falls and insomnia. Low vitamin D also resulted in worse outcomes on measures of depression and anxiety.

- **Vaccines:** Vaccines have been implicated both directly ar indirectly in Parkinson's disease. There is direct association v post-vaccine Parkinsonism induction in patients—there's a ca report of a five-year-old boy who, after receiving a measl vaccine, developed the disease. [22] Although he improved wi Levodopa, his Parkinson's was associated with the vaccine.

Vaccines contribute indirectly to Parkinson's via their heavy metal contents, specifically aluminum. Dr. Russell Blaylock is a neurosurgeon who has written extensively on aluminum and how it damages the brain. He says, "It is of significant concern that low levels of environmental aluminum are sufficient to induce neurotoxic outcomes. Moreover, experimental evidence shows that aluminum preferentially accumulates in the mitochondria, or the powerhouses of our cell, and the cell nucleus, which makes this metal very resistant to removal by chelation. [23]

"Obviously, long-term intracellular persistence of aluminum is likely to exacerbate its toxic effects. The difficulty of removing brain intracellular aluminum will lead to its progressive accumulation over a lifetime, eventually reaching a neurotoxic threshold sufficient to trigger neurodegenerative disease processes of which Parkinson's disease is one."[23]

"The greatest aluminum exposure from vaccines occurs during initial vaccinations soon after birth and during early childhood. Should a child follow the recommended vaccine schedule for the United States, they will receive a total of five milligrams of aluminum by age two from a total of seventeen aluminum-adjuvant pediatric vaccines.

Such repetitive and continuous exposure to aluminum from vaccines could induce prolonged activation of microglia cells and subsequent release of glutamate and pro-inflammatory cytokines."[23]

Microglia cells are the immune cells of the brain, and astrocytes are the structural cells of the brain. Both of those types of cells are sites of preferential aluminum accumulation and toxic action. Microglia and astrocytes are principal sources of glutamate and immune chemicals in the brain and play significant role in immunoexcitotoxicity[23] , which is a big word for immune-induced neuron death. Learn more about excitotoxicity by viewing this video: https://www.FunctionalMedicineCharlotte.com/Excitotoxicit y

It's indisputable that aluminum can increase levels of both inflammatory chemicals and glutamate in the brain. Aluminum adjuvants like those in vaccines are known to activate some 312 genes, 168 of which play a role in immune activation and inflammation. This is aluminum's epigenetic contribution to the Parkinson's puzzle. Activated microglia are present in large numbers, causing a condition known as microgliosis, which strongly implicate the cells and disease pathology of Parkinson's.[23]

Metals: Many epidemiological studies have found an association between Parkinson's and exposure to metals such as mercury, lead, manganese, copper, iron, aluminum, bismuth, thallium, and environmental zinc. The main sources of exposure to these metals include occupational exposure, pollution, contaminated seafood, medications, vaccines, and dental amalgam fillings.

The authors from a 2018 study in the journal *Current Medicinal Chemistry* [24] concluded, "While most metals might contribute to the pathology of PD, mercury seems to be the most toxic metal. Mercury is neurotoxic in every chemical form and appears to be of particular importance in the development of PD. There are many similarities between the effects of mercury exposure/ingestion and the symptoms/consequences of PD…Nigral (basal ganglia)

dopaminergic neurons are very sensitive to mercury… Metals such as iron, copper, and lead do exert a synergistic effect when in combination with mercury."

- **Iron:** Altered iron homeostasis is clearly related to Parkinson disease pathogenesis and plays a role in neurodegeneration. Tl accumulation of iron in neurons of the basal ganglia in peop with Parkinson's has been firmly established, and multip studies have reported that iron concentration in the basal gangl of people with Parkinson's correlates with disease severity. However, it's not clear whether iron dysregulation occurs pri to (or as a consequence of) disease onset.[5]

- **Pesticides, herbicides, and insecticides** : Organochlori pesticides constitute the pesticide class most common associated with Parkinson's, the best known of which is DD DDT has been banned in the U.S. since the 1970s, but it and tl other organochlorine pesticides are extremely persiste compounds that bioaccumulate in the food chain and are st found ubiquitously in human tissues. High organochlori pesticide loads in tissue create an approximate doubling Parkinson's disease risk.[5]

PCBs and organophosphates have also been implicated in Parkinson's disease as they can damage the enteric nervous system (the nervous system of the GI tract – you will learn more about this in chapter 3), which might be sufficient to induce Parkinson's-like progression and reproduce the features of Parkinson's staging or traveling from the GI tract to the brain.[2]

Studies on glyphosate (the active ingredient in Roundup) in Parkinson's disease in humans have not been done. However, many studies do reveal the biological plausibility of it—those exposing the roundworm C. elegans to glyphosate reveal development of pathology in the brain regions analogous to the human midbrain, the region associated with Parkinson's disease. [26]

Glyphosate [19] is a popular herbicide and is used in agricultural practices in the U.S. and throughout the world. Its usage rate has accelerated significantly in the

last twenty years due to two factors. One, its patent expired in 2000, which greatly reduced the cost, and two, the adoption of GMO crops that are resistant to its toxic effects allows for higher exposure with little loss in harvest yield.

Despite its popularity, many of the health issues that appear to be associated with the Western diet could be explained by biological disruptions that have already been attributed to glyphosate, and Parkinson's falls within that list. Glyphosate promotes Parkinson's by interfering with the recycling of mitochondria, which are the powerhouses of our cells. If they are not properly broken down and recycled in a process called mitophagy, they become large, aged mitochondria. Large, aged mitochondria are sources of free radicals that contribute significantly to neuron damage in the brain. Picture your brain as a pinball machine, the pinball bouncing around is the free radical bouncing around and damaging brain cells.

As discussed previously, glyphosate suppresses melatonin production by depleting tryptophan stores. This creates a free radical double-whammy in Parkinson's. Glyphosate inhibits mitophagy, which creates free radicals that destroy neurons, and it impairs melatonin production and its role as a brain-protecting antioxidant.

Glyphosate exposure disrupts the body's ability to detoxify it and other chemicals by interfering with the CYP family of enzymes in the liver. Therefore, in addition to other toxins such as organochlorine and organophosphate pesticides, and/or PCBs, glyphosate exposure creates a synergistic enhancement of toxicity.

MIT's Dr. Stephanie Seneff lists the following mechanisms by which glyphosate exposure may result in many possible brain pathologies, including Parkinson's: "Glyphosate's induction of excess synthesis of ammonia in the gut, combined with depletion of zinc through impaired absorption, depletion of serotonin through dysbiosis of its substrate, tryptophan, depletion of dopamine through impaired synthesis of its substrate, tyrosine, depletion of vitamin D3, due to impairments in

the CYP enzyme responsible for its activation, and depletion of sulfate through interference with its synthesis, can all lead to…a multitude of pathologies in the brain, including Parkinson's disease."[19]

- **BPA:** Another chemical that has been associated wi Parkinson's as recently as May 2019 is bisphenol A (BPA). BP is a chemical used in plastics like water bottles and grocery bag and it is found ubiquitously in our environment. Patients wi Parkinson's have an increased susceptibility to BPA exposu since they have impaired detoxification capacity. Once the non-detoxified BPA chemicals bind to proteins in the body, the become misfolded and look like a Frankenstein-type molecule our immune system, which then produces antibodies again them and starts attacking. A recent study showed that the high the level of these BPA-associated antibodies, the higher the ris of developing alpha-synuclein antibodies, which are th antibodies found in Parkinson's. [27]

Body inflammation promotes brain inflammation via microglia priming : There is now overwhelming evidence that prolonged and/or chronic activation of the peripheral immune system and inflammatory pathways provokes the development of chronic brain inflammation and microglial activation. [28] Research in people with Parkinson's reveals increased levels in highly pro-inflammatory immune messengers such as tumor necrosis factor alpha (TNF-a), inducible nitric oxide synthase (iNOS), and interleukin-1 beta (IL-1b). Experimental models of Parkinson's show that dopaminergic neurons are particularly vulnerable to these inflammatory factors. [29] Any metabolic dysfunction (infection, dysbiosis, medical illness, chronic stress, obesity, metabolic syndrome) leading to chronic low-grade inflammation can induce a direct reduction in basal ganglia dopaminergic neuron function. [30] Excessive stimulation of the innate immune system resulting from gut dysbiosis and intestinal hyperpermeability ("leaky gut") has been hypothesized to contribute to the initiation of alpha-synuclein misfolding. As you will learn below, alpha-synuclein is a protein

found in your brain cells that is genetically and pathologically linked to Parkinson's. [31]

Translation—the more inflamed you are, the higher your risk of brain inflammation, and the higher the likelihood that you activate the microglia. As Dr. Blaylock discussed above, activated microglia leads to increased glutamate and inflammation in the brain, which leads to neuron death and promotes Parkinson's.[23]

- **Brain injuries** : Head injuries have been associated with a increased risk of Parkinson's disease in many studies. [32] This likely due to a combination of direct microglial activation due the physical trauma of the head injury and indirect bra inflammation promoted by brain-gut axis dysfunction caused b the head injury [33] (you will learn more about the Brain-Gut Ax and TBI in chapter 5).

- **Sleep deprivation** : People with Parkinson's have been show to take longer to fall asleep, have less efficient and restorati sleep, and less REM sleep. They also show associate dysfunction in cortisol and melatonin levels; evidenced b elevated serum cortisol and decreased circulating melaton levels. [3] [4]

Epigenome contribution

As previously stated, epigenetics is involved in Parkinson's by high homocysteine levels leading to decreased DNA methylation and decreased genetic expression. Also, aluminum-gene interactions are involved in Parkinson's, as discussed above. Lastly, gene-pesticide interactions are also involved. Studies have shown that joint effects of pesticide exposure and polymorphisms (individual differences) in genes affect the pesticide absorption, distribution, metabolism, and excretion by the body.[5]

Microbiome contribution

The microbiome is implicated on multiple levels in Parkinson's disease. We've already discussed several factors that impact the enteric nervous system (the nervous system in your GI tract).

The total amount of microbes (bacteria, viruses, yeast, parasites) in our GI tract, otherwise known as the gut microbiome, is involved as well. We have beneficial bacteria (probiotics), and we have commensal bacteria, which are bacteria that could be good or bad, depending on the environment around them (aka, the peer pressure).

Studies have shown that in patients with Parkinson's disease, there are differences in their microbiome makeup and the way that their bacteria metabolize different products. A 2017 study in *Genome Medicine* concluded, "Our data revealed differences in colon bacteria and of bacteria metabolism between Parkinson's patients and patients without Parkinson's at an unprecedented detail." They concluded that differences in gut bacteria are an unappreciated aspect of Parkinson's. [35]

Intestinal barrier function and immune function are involved in the gut-brain axis, and multiple studies have implicated this as it applies to Parkinson's. In fact, in 1817, the namesake of Parkinson's disease, James Parkinson, noted in his "Essay on Shaking Palsy": "Although unable to trace the connection by which a disordered state of the stomach and bowels may induce a morbid action in a part of the brain, little hesitation need be employed before we determine on the probability of such occurrence." [36]

Translation—a little over two hundred years ago, even James Parkinson could intuit a gut-brain connection in Parkinson's disease. Today, there's a plethora of studies that have teased out this gut-brain connection. One such study talks about how the enteric nervous system is an integrated network of neurons in the gastrointestinal wall and a major player in the gut-brain axis, which is a bidirectional communication system between the nervous system and the gut.[2] The gut talks to the brain, the brain talks to the gut, and these interactions are influenced by the gut microbiome—your gut microbes.

Authors have said during the first stages of Parkinson's, neurons of the enteric nervous system and the olfactory bulb (the nerves in your nose) were found to contain aggregates of alpha-synuclein, which is the protein that accumulates and creates Lewy bodies, a diagnostic sign of Parkinson's disease. [37]

The gut nervous system and nerves in the nose are gateways to the external environment. New evidence suggests that alpha-synuclein deposition in these neurons is where a toxin or a pathogen and associated immune response might start spreading from the gut to the brain via the vagus nerve or from the nose to the brain via olfactory nuclei.[1]

In conventional medicine, gastrointestinal symptoms of Parkinson's disease are largely ignored. However, since 1817, the gut has been implicated in Parkinson's. Back then, it was guessed at. Today, it is well defined but remains untreated. An international study showed that 62 percent of non-motor symptoms (ex: constipation, drooling, nausea) are not reported by Parkinson's patients due to embarrassment or because they are unaware that these symptoms are related to Parkinson's. [38]

There's also a prevalence of GI symptoms in up to 80 percent of Parkinson's patients, including bloating, drooling, constipation, nausea, or delayed gastric emptying. [39] Constipation is the most prominent, and it might precede motor symptoms by over a decade. [40] The occurrence of constipation before the manifestation of motor symptoms in Parkinson's patients was reported 87 percent of the time. [41] Based on this, constipation is assumed to be a harbinger of what's to come and is therefore associated with an increased risk of developing Parkinson's disease. [42]

Lastly, it's important to note that gut-initiated pathology in Parkinson's does not require a pathogen; an environmental toxin or an imbalance in the gut microbiome (aka dysbiosis) may trigger it. [43] This is a significant finding because it emphasizes the importance of having optimal probiotic levels and non-pathogenic species in your gut.

Putting Wanda's puzzle together

Wanda's lab work revealed high inflammation, as indicated by lab-high calprotectin and C-reactive protein. She had very high homocysteine levels at 15.4 umol/l. She also had an autoimmune process against the parietal cells in her stomach. Once you have one autoimmune process, it tends to snowball and accumulate if you don't take care of yourself.

Wanda had poor blood sugar regulation due to poor insulin regulation. She had gut dysbiosis. She was deficient in healthy probiotics, and she had lab high overgrowth of Candida, Streptococcus, and the parasite Blastocystis hominis. Of course, she had ubiquitous exposure to BPA and glyphosate.

With these findings, we created an individualized and specific plan of care for Wanda based on her framework. After six weeks, I received a message from her chiropractor, and it said, "I just saw Wanda. She's the best I've seen her in two or three years. She is dumping inflammation, and her eyes have unbelievable clarity. Thank you so much for your gift and talent. She has her life back." I responded, "Thank you. I appreciate it," and he replied, "Not as much as she appreciates it. I'm serious! The change today was one of the most significant improvements I've ever seen in someone in this short a time."

At twelve weeks, Wanda filled out a subjective progress evaluation form, which means she was rating her improvement across multiple symptoms in her own words. In regard to anxiety and depression, she reported a 50 percent improvement. She said, "My periods of anxiety have decreased, which means I feel better because my tremors have also decreased." She rated her energy level as 75 percent improved. She said, "I have more energy and can get through the day with less fatigue."

Her digestive complaints improved 50 percent, and her brain fog was 100 percent improved. She said, "[I have] clearer thinking and better memory, which decreases my anxiety." Her chronic pain had decreased 75 percent, and her sleep was reported to be 50 percent better. She said, "I haven't walked the floor until 4:00 or 5:00 in the morning lately. Using the strategies you provided me, I'm now able to sleep seven hours a night without waking."

All of these improvements obviously led to an improvement in her attitude and outlook on life, which she rated as 75 percent better. Wanda then had a follow-up with her primary care physician who said, "This is the best you've ever looked since I've been taking care of you. Keep seeing the functional medicine doctor. It is working."

What were Wanda's twelve-week lab changes? She had a 40 percent reduction in her inflammatory markers, C-reactive protein and calprotectin. She had a 5.7 umol/l drop in

homocysteine. She went from lab high to normal range, and that large of an improvement, the research says, creates a 33-49 percent reduction in all-cause mortality [44] , which in plain English means her risk of death from all causes dropped by up to 49 percent.

Wanda's insulin levels were normalized, so her blood sugar was optimized. In her gut, we eliminated Strep, Candida, and Blastocystis. Big changes in her exposome and microbiome led to epigenetic changes as well. Wanda became a new woman, and she is finally living the life that she desired in her retirement.

Reader action steps

Speak with your provider about supplementing with N-Acetyl Cysteine (NAC). A 2019 study [45] found that oral doses of NAC of 500mg twice per day for three months improved dopamine transporter binding and "significantly improved PD symptoms."

Get moving! Exercise triggers improved plasticity in the human PD brain. [46] This means that it improves neuron growth and communication via increased brain-derived neurotrophic factor (BDNF).

To learn more about the Functional Medicine approach to Parkinson's Disease, view my Parkinson's video playlist here: https://www.FunctionalMedicineCharlotte.com/Parkinsons

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CHAPTER 2

Psoriasis

"Beauty is only skin deep, but lethal is to the bone."

—Agent Scarlett from *G.I. Joe*

Psoriasis was ruining Abby's life. Abby is twenty-three and came to my office after receiving a psoriasis diagnosis six years earlier. On a hot North Carolina day, she wore clothes that would make you think it was cold outside—the only skin that was exposed was her head and hands. She had seen three dermatologists in the six years since her diagnosis, but none of the typical treatments had helped her. In fact, she stated that she felt like the medications increased her toxicity and her disease process.

She complained of amenorrhea, which means she was not having a menstrual cycle and had also been gaining weight for two years. She took no prescriptions, but she had been on supplements—she was taking fish oil, vitamin D, vitamin K, methylation support, digestive enzymes, probiotics, and natural antimicrobials.

That's a pretty solid list of supplements, so shouldn't she be improving? You would think so, but this is an example of why you can't Doctor Google yourself to health because diseases are multi-factorial and complex. Just reading the latest blog on what vitamin is best for a certain disease is reductionist and uses a conventional medicine pair of glasses .

Abby had a history of strep infections, and she had been on multiple courses of antibiotics throughout her infancy and into childhood. She had a history of depression and was depressed when she came to my office. She was under high stress from work, high financial stress, and said her social life was essentially non-existent. She was somewhat anxious and humiliated by this.

Psoriasis is not only skin deep

Psoriasis affects eight million Americans and starts as early as age fifteen. Factors such as genetics, the immune system, the environment, depression and anxiety disorders, infections, drugs, smoking, and alcohol are thought to be involved in the pathogenesis of psoriasis. [1]

For mild to moderate psoriasis, the cornerstone first-line treatment is a topical steroid. If your case is more severe, then a systemic prescription medication like methotrexate, cyclosporine, or Otezla is recommended. As immune suppressants, these medications come with side effects such as liver damage, birth defects, hypertension, and skin cancer. [2]

Newer age drugs for psoriasis (called biologics) are given through subcutaneous or IV injection, and these drugs target specific parts of the immune system.[2] Instead of suppressing the immune system globally (methotrexate), biologics target specific inflammatory molecules such as tumor necrosis factor alpha (TNF-a). Examples of biologics include Enbrel and Remicade. Methotrexate, Enbrel, and Remicade are the three highest-selling autoimmune drugs in history. [3]

Psoriasis is not only a skin disease, it has multiple immune and metabolic components associated with it. Yes, you can see the skin disorder, but hypertension (high blood pressure), atherosclerosis, cardiovascular disease, insulin resistance, depressive disorders, inflammatory bowel disease (including celiac disease), non-alcoholic fatty liver, osteoporosis, and others may be lying underneath. [4]

Conventional medicine looks at psoriasis as the inflammatory disease that it is but only takes it for face value. Functional medicine also sees psoriasis as an inflammatory disease but does the detective work necessary to reveal all the pieces of the puzzle that create the picture of psoriasis in a given person. Based on each individual's exposome, epigenome, and microbiome, each person's puzzle is different. Before we apply the functional medicine framework to psoriasis, let's establish the autoimmune nature of the disease.

Is Psoriasis an autoimmune disease?

Autoimmunity is characterized by the breakdown of self-tolerance and abnormal antibody and or T-cell mediated immune responses against self-tissue. [5] Essentially, what happens is your immune system starts to lose its ability to discern between what's you and what's not you and it attacks both. Identification of genetic risk variance, the discovery of multiple antibodies, and immune dysfunction provide strong support for the concept of psoriasis as an autoimmune disease.

For a long time, science has known that streptococcal throat infections (strep throat) are known triggers of acute guttate psoriasis, with an incidence of preceding infection between 56 percent and 97 percent, [6] but how does a throat infection trigger a skin autoimmune disease?

The mechanism is called molecular mimicry. That means that the strep microbe shares similar amino acid sequences with the keratin in your skin. When the immune system looks for strep, and it sees a similar amino acid sequence in your skin, it attacks your skin, as if your skin were strep, and now you're off to the races with psoriasis.

Another potential molecular mimicry autoantigen is cathelicidin or LL37. This is an antimicrobial peptide produced by your skin cells and by the cells of your immune system in reaction to infection or trauma to the skin. Seventy-five percent of patients with moderate to severe psoriasis have been found to have anti-cathelicidin antibodies in their blood. [7]

Other antibodies found in psoriasis are calpastatin antibodies [8] , heat-shock protein 65 antibodies [9] , stratum cornea antibodies [10] , and squamous cell carcinoma antigen antibodies [11] . Their clinical significance has yet to be determined, but their presence suggests an autoimmune pathology.

There's also supporting evidence for psoriasis as an autoimmune disease in that Th17 cells are identified in the dermis of psoriasis plaques. Th17 cells are the cells of the immune system that cause damage to tissue in autoimmune disease. They're responsible for downstream activation of genetic transcription factors that lead to skin hyperplasia, recruitment of the immune system to the skin, and increased skin inflammation. [12]

As you can see, there are multiple studies citing the strong evidence that psoriasis is an autoimmune disease. Now that we've established this, let's look at the factors that influence or cause psoriasis from the perspective of the functional medicine framework—the exposome, the epigenome, and the microbiome. In psoriasis, the major exposome factors are going to be medications, vaccinations, stress, glyphosate exposure, diet, wheat/gluten intake, vitamin A levels, vitamin D levels, and homocysteine levels.

The exposome in psoriasis

- **Medications** : A study in 2017 was quoted as saying that v should not underestimate the consequences of medication us whether beneficial or harmful in psoriasis. [13] Vario medications have various potential impacts that could promo or exacerbate psoriasis, and one major mechanism for this through impacting the microbiome. We'll discuss tl microbiome further, but the short story is that if medicatio create an imbalance in your probiotics, then that can promote a inflammatory GI tract, which promotes psoriasis via a gut-sk axis mechanism. See below for further detail.

- **Vaccination** : A 2015 study in the *Journal of Immunolog Research* [14] further investigated the findings of multip researchers that had found a possible association between f vaccines and new onset or exacerbation of psoriasis. The autho of the 2015 paper studied forty-three people suffering fro psoriasis that had been triggered after influenza vaccinatic during the 2009-2010 season. The authors concluded, "The sho time intervals between vaccination and psoriasis flares in o patients and the lack of other possible triggers suggest th influenza vaccinations may have provocative effects c psoriasis."

In 2013, the journal *Cutaneous and Ocular Toxicology* [34] published a case report on a 50 year old white male whose psoriasis was triggered by the tetanus and diphtheria immunization (Td vaccine). The authors suspected the following mechanism:

"Studies have shown that the Td vaccine, due to high diphtheria toxoid, induces IL-6 production, which, in turn, stimulates Th17 cells which have a key role in psoriasis pathogenesis."

Translation - the authors suspect that the diphtheria toxoid in the vaccine promoted a Th17 polarization which triggered psoriasis in the recipient.

- **Stress** : Cortisol and stress physiology have been shown in mar studies to be involved in psoriasis development ar exacerbation. Psoriasis patients have been found to have a loc cortisol deficiency in the epidermal layer of skin. Th deficiency promotes inflammation in keratinocytes (skin cells) , which further promotes autoimmunity [16] . As far as perceiv stress is concerned, research shows that higher stress levels people with psoriasis predicted an increase in the severity disease a month later [17] . Another study of one hundred and tw people with psoriasis found a direct correlation between bedtin cortisol and psoriasis severity [18] .

- **Glyphosate exposure:** This has been proven to cause psorias in some cases. There are case studies in the literature whe people did not have psoriasis or any history of skin disorder, ar after exposure of glyphosate on their skin, they develope psoriasis. One case report showed that expert medic assessment was brought in to establish scientific and leg causation of the glyphosate exposure causing psoriasis in th person. The case was approved, and glyphosate was blamed f causing psoriasis. [19]

- **Diet:** A 2017 study that was a national survey in the Unite States queried over 1200 people to observe the dietary impact c psoriasis. [20] And the study revealed that the percentage patients reporting skin improvement was greatest when the reduced alcohol intake, reduced gluten intake, and reduce nightshade intake. Nightshades are foods such as tomatoe peppers, eggplants, et cetera. Beneficial introductions in the die which decreased psoriasis, or improved skin were; fish o increasing vegetable intake, and increasing vitamin D intak

69% of people who switched their diet to a Paleo diet reporte improved skin response.

- **Wheat and gluten;** Many association studies have connected associated psoriasis with celiac disease.[4] And the link establishing this association include vitamin D deficiency, a Th immune response, having a genetic susceptibility to the diseas and increased intestinal hyperpermeability, also known as leak gut.

Celiac disease is known to have blood evidence of tissue transglutaminase antibodies, which is the target of the immune system in the gut. Psoriasis patients show eight times higher levels of skin tissue transglutaminase (see chapter 6 for more detail) than people without psoriasis. Essentially, this is the celiac mechanism in the skin. Studies have shown that psoriatic patients with high levels of skin tissue transglutaminase can cut their levels in half by adopting a gluten-free diet, which, in turn, also leads to significant decreases in immune activation in psoriasis patients. [21]

Even if a psoriasis patient doesn't have tissue transglutaminase antibodies, studies have found that many do have higher levels of antigliadin antibodies (on average). Gliadin is a protein found in wheat, and its antibodies represent gluten sensitivity. Psoriasis patients that have anti-gliadin antibodies have higher psoriasis sensitivity scores. This is the outcome assessment used in clinical practice to determine how severe a person's psoriasis is.

When patients with anti-gliadin antibodies follow a gluten-free diet, they have significant reductions in their psoriasis severity scores and significantly decreased levels of skin proliferation in their psoriasis plaques, meaning the plaques are healing. Sixty percent of people who reintroduce gluten into their diets reported deterioration of their skin condition and a worsening of their psoriasis.[21]

- **Vitamin D deficiency:** This can promote psoriasis in multip ways. Vitamin D is a very important immune modulator—

creates balance in the immune system. If you have a vitamin deficiency, you are more susceptible to an imbalanced immu system, and a Th2, Th22, or Th17 immune response, whi promotes psoriasis [22] .

Vitamin D is a powerful anti-inflammatory. Studies have shown that it specifically inhibits matrix metalloproteinase 9 (MMP9). [23] MMP9 is a key pro-inflammatory driver of psoriasis—if you have a vitamin D deficiency, and you're not inhibiting MMP9, that can be promotional of psoriasis.

Vitamin D is also known to promote the integrity of the intestinal barrier [24] , so a deficiency may make you more susceptible to leaky gut, which can then potentially promote a gut-skin axis imbalance and psoriasis.

- **Vitamin A deficiency:** Vitamin A, like vitamin D, pla multiple important roles from an immune and anti-inflammato standpoint. In fact, these two vitamins should be in a balanc ratio to each other in order to prevent psoriasis. If you ha optimal levels of vitamin D, but deficient levels of vitamin this can be promotional of psoriasis as well. "How?" y ask.Vitamin A prevents immune cells from homing to the sk and promoting skin inflammation[22] , which can promo psoriasis. Sufficient levels of vitamin A keep the immune ce in the gut, prevent them from going to the skin, and there prevent skin inflammation and psoriasis.

- **Homocysteine levels** . Homocysteine can be a factor from exposome perspective, and from an epigenome perspective- we'll address both:

From an exposome perspective, a 2019 study from *The British Journal of Dermatology* found that patients with psoriasis have higher homocysteine levels and lower folate levels than patients without it. [25] As discussed in the previous chapter on Parkinson's disease, homocysteine is a significant promoter of oxidative stress, inflammation, and tissue damage.

The epigenome in psoriasis

Remember, epigenetic modifications are changes in the expression of your genes—the gene itself is not the important part, but whether or not that gene is turned on or off is. Since epigenetic alterations are reversible, they are reasonable targets for therapy and should be clinical targets for us.

Whether the gene is turned on or off depends on the epigenetic modification to that gene. Specific modifications include DNA methylation, histone modification, and non-coding RNA action [26] . Relevant to our conversation is DNA methylation; when a gene is methylated, it's the methylation that turns it on or off. A gene can be *hyper* methylated, which means it's over methylated, or *hypo* methylated, meaning it's under-methylated. Neither is good.

Hypermethylation or hypomethylation may contribute to the development of autoimmune disease. Homocysteine plays a key role in the methylation cycle[1] , or the physiologic process of methylating genes. High homocysteine levels can lead to global DNA hypomethylation, which is closely associated with the pathogenesis of psoriasis. Researchers have found 96 genes in psoriasis that were hypermethylated and 234 genes that were hypomethylated. [27]

Homocysteine levels correlated directly with the psoriasis area severity index score. The higher your homocysteine levels, the more severe your psoriasis. The mechanism of this connection is hypomethylation of the HLA-DRB1 gene[1] , and the lower the methylation of that gene, the higher the severity of psoriasis .

Many people in the alternative medicine world are familiar with the MTHFR gene, which has been associated with psoriasis, but it has not been found to be a causal factor at this point. Having the MTHFR polymorphism does not cause psoriasis, but it has the potential to influence the severity of the disease once it has developed.[1] The MTHFR gene requires folate to function, and when it functions optimally, it promotes optimal methylation and recycling of homocysteine. If you have a MTHFR gene variant that results in the gene working inefficiently, then the methylation cycle may be less efficient and result in less efficient homocysteine recycling. This leads to higher homocysteine levels. Remember, as we discussed, higher

homocysteine levels promote higher disease severity in psoriasis.

The microbiome in psoriasis

How does the microbiome influence psoriasis? First, let's define it. The human microbiome, or the collection of the microbes that are on and within us, plays an important role in providing us with nutrients, regulating our immune system, and maintaining overall health [28] . Dysregulation of the microbiome and disruption of the symbiotic relationships we normally have with our microbiota may allow for the overgrowth of pathogenic species and leave us predisposed to certain diseases.

The gut microbiome is shaped by several environmental factors, including diet, infectious agents, antibiotic use, and factors associated with inflammation and autoimmunity.[28] A healthy microbiome prevents psoriasis.

If you take a healthy microbiome and create an imbalance, that is called dysbiosis, which is defined as an imbalance between the microbiota (or all of the microbes in the microbiome) and its host. This dysbiosis can be considered a form of impaired homeostasis in which the microbes shift towards a less complex and less varied pathological spectrum.[2 1]

You can have dysbiosis of the skin. You can also have dysbiosis of the gut, sinuses, lungs, mouth, or anywhere in or on the body where microbial species colonize. Relevant to psoriasis, skin and gut dysbiosis are key factors. The microbiome is seeded at birth as the baby passes through the vaginal canal and takes that first inhalation of mothers' flora. It then continues to be seeded via breastfeeding (learn more about this in chapter 8).

Relevant to skin dysbiosis, there are many factors that directly influence the balance of your skin microbiome. One is your external environment. Others are the immune system, your lifestyle, and underlying medical conditions. Psoriasis is a chronic, multifactorial, inflammatory skin disorder, which has a microbiota distinct from healthy, unaffected skin.[21] Many studies have shown that psoriatic lesions have different bacterial makeup than unaffected skin on the same person and compared to people without psoriasis. These studies have found that

psoriasis lesions have higher levels of strep in them, as well as higher levels of Staphylococcus aureus.[28]

Staph aureus, a staph infection, is known to evoke a pathogenic Th17 immune response.[28] Earlier in the chapter, we discussed how the Th17 immune response promotes the tissue damage of autoimmunity, and we also discussed how tonsil infections with strep often precede the onset of psoriasis. That is true, however, once you already have psoriasis, exacerbation is associated with skin colonization by Staph aureus, by the fungus Malassezia, or by Candida albicans.[5]

In the gut microbiome, the ratio of *Firmicutes* and *Bacteroidetes* was perturbed in psoriatic individuals and there was an under-representation of Actinobacteria. The decrease in Actinobacteria includes the decrease in Bifidobacterium species, which have been shown to reduce intestinal inflammation, suppress autoimmunity, and induce T-regulatory cells in your immune system.[2 8]

T-regulatory cells are immune modulators—they are the conductor of the immune symphony. One study showed that reintroducing Bifidobacteria in psoriasis patients that were deficient for six to eight weeks resulted in a decrease in systemic inflammatory markers C-reactive protein and tumor necrosis factor alpha. [29] Remember, tumor necrosis factor alpha is the target of biologic drugs such as Enbrel.

It has been established in research since 1990 that gut dysbiosis is a promoter of psoriasis. In one study, Patricia Noah [30] listed many organisms thought to provoke psoriatic attack, including Streptococcus, Klebsiella, E-coli, Enterobacter species, Proteus species, Citrobacter, Morganella, Pseudomonas, Staphylococcus, and Candida.

Too many pathogens can drive psoriasis and so can a lack of beneficial species. One of those species is the beneficial yeast Saccharomyces cerevisiae. Psoriasis patients have been found to be deficient in this yeast (also known as baker's yeast or brewer's yeast). Saccharomyces cerevisiae is known to have anti-inflammatory properties and to be inhibitory of tumor necrosis factor alpha. Interestingly, a variant of Saccharomyces cerevisiae known as Saccharomyces boulardii is already used as

a probiotic for diarrhea. Using Saccharomyces cerevisiae as a probiotic might be a potential candidate for psoriatic patients. [31]

Lactobacillus species have also been shown in mice models to suppress psoriasis-related inflammation in Th17 cells. Overall manipulation of the gut microbiome with probiotics looks like a promising natural treatment for psoriasis patients.[21]

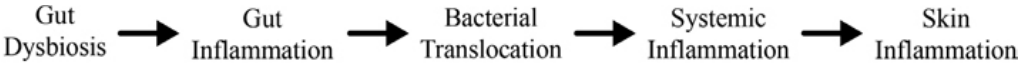
The gut-skin axis in psoriasis

"Psoriasis is considered [to be] a systemic condition and may co-exist with numerous GI pathologies, especially [in] those with established immune-related mechanisms." [4]

As we've gone through the chapter, we've established that psoriasis is a systemic disease and often includes co-morbidities such as cardiovascular disease risk, inflammatory bowel disease, et cetera.

Further studies have found that psoriatic patients have an increased level of bacterial DNA in their blood. [32] What that means is bacteria are penetrating the gut, entering the blood, and traveling systemically to the whole body. They initially enter the body through the gut via intestinal hyperpermeability (leaky gut) mechanisms. Once inside, they jump into the bloodstream, and they're on the super highway to infect the rest of the body and create systemic inflammation. This is termed the gut-skin axis.

The mechanism looks like this: gut dysbiosis leads to gut inflammation, which leads to bacterial translocation, which leads to systemic inflammation, and ultimately, skin inflammation. Bacterial translocation in psoriasis is not induced by just one specific microbe—it can be created by having a microbial imbalance (dysbiosis) in the different groups of microbes in the gut.



Patients with higher levels of bacterial translocation in the blood, require more aggressive treatment. Studies have shown that stool testing allows us to observe the level of dysbiosis in these patients and the level of bacterial translocation. We can use stool

testing to establish a baseline and then to follow patients to determine efficacy of treatment.[3] [2]

Abby's results

So what did Abby's initial testing look like? We discovered that she was systemically inflamed as evidenced by the lab high, high sensitivity C-reactive protein (hsCRP) marker, with a value of 16.5 milligrams per liter. Abby was also vitamin D insufficient—she did not have sufficient levels to put out that systemic fire.

Abby had mentioned amenorrhea, which is infertility. Upon testing, she had lab low progesterone. If you don't have progesterone, you are not going to ovulate, and therefore you will not be able to get pregnant.

Her stool test revealed gut dysbiosis. She had no growth of the beneficial species, Bifidobacterium or Lactobacillus; as mentioned above, both of those are anti-inflammatory for the gut and promote immune balance. Lacking these species promotes inflammation and immune imbalance—the perfect recipe for developing psoriasis in a genetically susceptible person.

Her stool also revealed overgrowth of pathogenic microbes associated with psoriasis, specifically Streptococcus, Citrobacter, and Candida. However, Abby's homocysteine was normal, and she had the normal MTHFR gene, not an MTHFR polymorphism.

We moved forward in a care plan for Abby. We addressed these findings, as well as lifestyle factors such as her high stress, social relationships, sleep, et cetera. After six weeks, Abby reported, "My psoriasis has cleared almost entirely." Lab testing revealed that her systemic inflammatory marker high sensitivity C-reactive protein had dropped from lab high at 16.5 to an optimal 0.6 milligrams per liter, a massive reduction in body-wide inflammation.

Her vitamin D at six weeks was also optimal, which means she was inhibiting MMP9 levels, which led to decreased tissue damage and inflammation. At her 12-week re-test, her progesterone levels were normal, she was wearing weather

appropriate clothes, and confidently showing her skin. Shortly after that visit, she called and said she was pregnant.

Reader action steps

Based on the studies discussed in this chapter, the following options should be considered:

- ✓ Adopting a gluten-free, alcohol-free, nightshade-free diet
- ✓ Supplementing with methylfolate and other antioxidants. (The caveat there is if you don't have high homocysteine levels, and don't have an inefficient MTHFR gene, taking too much methylfolate may lead to hypermethylation, which you don't want to do, period.)
- ✓ Using prebiotics, probiotics, and beneficial yeasts to optimize your microbiome, making sure your vitamin D and A levels are sufficient.
- ✓ Lastly, a recent study has shown that cannabinoids from Cannabis sativa may be useful in psoriasis to suppress inflammation and vascularization known to cause the damage in psoriasis. [33] CBD oil may be useful in certain patients with psoriasis.

However, it is better to work with a detective to figure out which of these factors are necessary in your puzzle and address them that way. To just haphazardly take folate, vitamins D and A, CBD, and probiotics without knowing if you actually need them may lead to symptoms you don't have and/or you may overdose with a given nutrient or nutrients. Work with your functional medicine detective to determine what's right for you .

Learn more at my Psoriasis video playlist:
https://www.FunctionalMedicineCharlotte.com/Psoriasis

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CHAPTER 3

GI Disorders

"Health is an all-inclusive concept. A concept that involves soil, water, plants, animals, ecosystems, individuals, families, cities, and nations. The moment at which one of these elements is pitted against another is the moment of decline."

—Norman Wirzba

Donny was twelve when his mother brought him in to see me. He had been diagnosed with Crohn's disease and failure to thrive. He only weighed 69 pounds, and his skin was gray. The constant diarrhea and bleeding from his GI tract had him spending more time in the bathroom than he spent in class. His accumulated school absences were raising the risk of him having to repeat sixth grade.

Doctors presiding over Donny's case recommended high-powered immune-suppressing drugs and a 90 percent liquid Ensure diet for the rest of his life. His mom vehemently disagreed and told herself there must be better strategies out there. That is when she discovered Functional Medicine.

How did you become so sick?

Donny was vacuum-extracted at birth and had an associated neck injury. He was also jaundiced at birth. As a child, he had multiple strep infections, ear infections, chronic seasonal allergies, chronic eczema, and was malnourished. He was anemic multiple times and had multiple courses of antibiotics associated with the strep and ear infections. How does a twelve year old become so sick?

As the quote at the beginning of this chapter implies and as research proves, our environment, society, and bodies have been polluted with toxic chemicals, foods, and messages that lead to the breakdown of the whole. As the functional medicine framework of exposome, epigenome, and microbiome shows us, Donny became sick due to the combination of many factors, not just one or two. This is why conventional medicine could not

help him and likely why the doctors you've seen can't help you. Your puzzle has far too many pieces, and conventional medicine is not trained to put them together or find the pieces that are missing or out of place and correct them. In Donny's case, they were simply trained to see Crohn's disease and treat it. The world of conventional medicine is very black and white—medical doctors are trained to see pathology, diagnose it, and medicate it.

As many people that I've worked with and many readers of this book have experienced, reality is not black and white, but many shades of gray, and it is in these gray areas where most people with chronic health challenges who are told they are normal live. These areas are where functional disorders exist. This is where conventional medicine fails miserably and where functional medicine shines.

This is not opinion—it's in the research. Chronic intestinal inflammatory diseases, including Crohn's disease and ulcerative colitis, the two major manifestations of inflammatory bowel disease (IBD), affect nearly one percent of Western societies, and the incidences of IBD continue to rise. [1] A considerable burden of disease is accounted for by functional gastrointestinal diseases (FGIDs), which are defined by characteristic patterns of symptoms in the absence of classic organ pathology .

Functional GI diseases include irritable bowel syndrome (IBS) and functional dyspepsia, which are among the most commonly encountered symptom complexes in most adult populations. In Western society, over one-third of the population has chronic gastrointestinal disorders, dominated by irritable bowel syndrome and functional dyspepsia.[1]

Do you see the epic importance of that research? Over one-third of the U.S. population complaining of GI symptoms has a functional gastrointestinal disease! This means over a hundred million people in the United States suffer from GI complaints that put them in the gray area, meaning their doctor will tell them they are normal or give them a drug like a proton pump inhibitor that will, at best, do nothing to affect the cause of disease or, at worst, they'll suffer adverse effects from the treatment.

This is yet another example of how the conventional medical model is not set up to address the major issues in U.S. health care: the gray area diseases, the chronic diseases, the diseases that fester for a decade or longer before they ever meet black and white diagnostic criteria.

Waiting for the disease process to fit the diagnostic criteria is going to get you recommendations and results that you do not want, like immune-suppressing drugs and a 90 percent liquid diet. Research reveals that people that have functional GI diseases such as functional dyspepsia (indigestion) or irritable bowel syndrome (IBS) and have symptoms such as stomach pain, nausea, bloating, belching, or chronic constipation have a significantly higher prevalence of autoimmune disease. [2]

Did you catch that? Your constipation, bloating, and stomach pain may be early signs of autoimmune disease developing that your medical doctor won't catch for years because it's too gray to fit his or her black and white diagnostic criteria. One example is Parkinson's disease. Remember that constipation shows up decades before the Parkinson's diagnosis and is considered a harbinger of the disease .

We can do better—we MUST do better. Science agrees: "A pressing need now exists to understand the pathophysiology of chronic gastrointestinal diseases and the key factors that influence their clinical course to improve patient outcomes."[1]

How can we do better?

We must first have a better understanding of the GI tract and all that went wrong with it. When you think of your GI tract (your gut), how do you define it? I bet most people would respond with eating, digestion, food, waste elimination, stomach, etc. Those answers reveal what we were taught in grade school about the functions of the GI tract.

If you gave those answers, you would not be wrong, but you are not in grade school anymore. It is time to bring your understanding of the GI tract to an appropriate level—a postgraduate level. Having a basic postgraduate understanding of the GI tract will help you and your doctor to be much better detectives. It will also help you understand why and how the GI

is so important, and that there are many disorders and diseases which don't appear to have anything to do with your gut, digestion, or stool quality, but are intimately related to them.

The Dr. Seuss definition of the gut is equivalent to a one-piece puzzle—

Each time that you eat,
the first thing that you do
is put food in your mouth
and that's when you chew.

Food goes into your stomach
(where juices are flowing),
turns into a paste-then
the paste keeps on going .

A tube-the intestine-
is what food moves through.
This food feeds your blood,
which then feeds all of you." [3]

Many doctors still view the gut and its role in health like Dr. Seuss, but it's time to view it like the complicated puzzle that it is.

Let's lay Dr. Seuss aside and be more like Dr. House of the hit series *House M.D* .

As we learned early in life, the gut is a long tube from the mouth to the anus that functions as a digestion and elimination organ. What you are about to learn is that the same long tube exists in an inseparable relationship with the nervous system and a microbial soup called the gut microbiome. The gut has two nervous systems controlling it—the central nervous system (CNS) and the enteric nervous system (ENS).

- **CNS** control of the GI tract is largely dominated by the vagı nerve. The word *vagus* is Latin for "wanderer," and the vagı nerve acts as a massive bidirectional highway. Think of it as tl largest highway in LA between the brain and the gut, formir the gut-brain axis. When your brain is functioning properly, stimulates optimal function of the vagus nerve to the gut. This called the vagal motor outflow.

The vagus promotes optimal GI function in the areas of secretion (think stomach acid and digestive enzymes), motility (constipation—not too little and diarrhea—not too much), and inflammation—optimal vagus function is anti-inflammatory. The vagus also opposes the stress response (aka, the fight or flight response) .

By influencing the total inflammatory load and stress physiology in the GI tract, the vagus nerve has a direct impact on autoimmune disease risk and disease severity. Research has shown that healthy vagus function leads to a decreased antibody release from the spleen. This is important because antibodies mark your body tissue for destruction in autoimmune disease, and decreased vagus function leads to an increased antibody release. [4]

- **The ENS** can function separately and autonomously from tl CNS, but is also closely integrated with and reactive to it. Tl ENS is made up of over a hundred million neurons that contr gut motility, hormone functions, fluid movement, and loc blood flow. The ENS also directly communicates with the cel of the intestinal barrier (the wall that separates your outside fro your inside) and gut immune cells.[1]

The gut is the headquarters of the immune system, as up to 70 percent of the immune system resides there. [5] Picture your gut as a castle and the mucus that lines your GI tract as the moat. Your immune system is sitting just inside the castle walls waiting to respond to anyone—friend or foe—who may try to enter.

The moat around the castle doesn't contain alligators or piranhas, but it is a microbial soup (your gut microbiome). The bacteria in your moat in a healthy state are your immune system's allied forces. They help protect your castle, provide nutrition for it and its inhabitants, and alert your castle to danger. The gut microbiome also assists in food digestion, fat metabolism, blood flow, and ENS function. [6]

Do you see why Dr. Seuss had to simplify his explanation of the gut? It would have been too confusing if you were told ,

Your gut is your gut
but it's also your brain
with immune system and microbes
communicating over mucosal membranes.

(That's my best attempt at rhyming like Dr. Seuss).

Let's see how this all plays out in a real disease such as Donny's Crohn's. The Mayo Clinic defines Crohn's as an idiopathic disease (meaning there is no known cause), but one that is characterized by skip lesions and transmural inflammation, which can affect the entire GI tract from mouth to anus. Presenting symptoms are variable and may include diarrhea, abdominal pain, weight loss, nausea, vomiting, and in certain cases, fever or chills. In some cases, extra-intestinal manifestations also develop. [7]

"A Crohn's diagnosis is typically made with endoscopy and/or radiologic findings. The goal of management is to control inflammation and induce a clinical remission with pharmaceutical drugs, but most patients will eventually require surgery. Unfortunately, surgery is not curative and patients will still require ongoing therapy even afterward to prevent disease recurrence."[7]

As you can see from the definition given by the Mayo Clinic, Crohn's is largely looked at as a GI tract disease from the perspective that Dr. Seuss may have taught. The Mayo Clinic views it as having an unknown cause and no cure. Would you expect anything different from such an elementary school approach?

Let us put on our detective glasses and apply the postgraduate education we just received to determine whether Crohn's disease is truly idiopathic (has an unknown cause) or if the conventional medical approach is just idiotic.

Yes, it is true that there is a GI tract component to Crohn's because the disease occurs there and damages the GI tract. This damage leads to malabsorption and malnutrition, hence Donny's diagnosis of failure to thrive and the lame recommendation of a lifelong liquid diet. As you learned in the previous pages, the gut also has neurological, immune, and microbial components to it that are inseparable from it. Perhaps conventional medicine

idiopaths are missing the keys to what causes Crohn's and how to prevent it and treat it because they are leaving out these components.

Scientific research has proven that chronic GI disorders and diseases exhibit neuroplasticity, which is the adaptive response of the central nervous system to learning, structural damage, or sensory deprivation. Put simply, neurons that fire together, wire together. The more you fire a certain pathway, the stronger that pathway becomes, and the more likely that pathway becomes reinforced.

Picture a virgin grass field that has never been driven over. If you drive over it once in a tractor, you will bend some grass, but in a day or two, no one would know you were ever there. If you drive the tractor over that same path multiple times a day, every day, for months to years, you will clear the grass along that path and develop ruts, and an observer could clearly see where you've been.

Neuroplasticity is similar—the more you use a group of neurons, the more grass you clear, and the more obvious the path. It becomes habit or a new normal, and it doesn't take conscious effort to perform the task, much like driving, throwing a football, or playing piano. Once you've done it so many times, you could do it in your sleep. (Disclaimer, do not attempt to drive to work in your sleep!)

The ENS develops neuroplasticity too. [8] This means, the longer you have GI symptoms, a GI disorder or GI disease, the more it becomes habit or a new normal to your enteric nervous system, it becomes a learned pattern. Medication or surgery will not change your ENS habits. You must teach it new habits and be resolutely consistent .

Let's go back to the grass metaphor. If you have created the ruts in the grass, do you think driving a different path for one day, one week, or one month is going to eliminate those ruts and allow grass to grow in and cover them? Not a chance. You have to drive the new pathway for months to years to create new ruts and allow the others to be grown over. Medications for Crohn's disease do nothing to impact the ENS or neuroplasticity of your disease. They just seek to decrease inflammation. Meanwhile, the learned habit (of Crohn's disease in this example) continues

to be practiced by your ENS day in and day out, driving those same ruts.

Optimal vagus nerve function is key for Crohn's disease. If the vagus is not working optimally, you are missing a key anti-inflammatory and immune-modulating component. This promotes increased inflammation and immune attack on cells, as well as imbalanced smooth muscle contractility, which can contribute to diarrhea or constipation. [9]

The immune system cannot be ignored in Crohn's, any functional GI disease, or pathologic GI disease. As stated above, 70 percent of your immune system resides in your gut. "The gastrointestinal system plays a central role in immune system homeostasis. It is the main root of contact with the external environment and is overloaded every day with external stimuli, sometimes dangerous in the form of pathogens (like bacteria, parasites, fungi, or viruses) or toxic substances. In other cases, the external stimuli are very useful (food or commensal flora)."[5]

Although idiopaths consider Crohn's disease idiopathic, the more accurate way to describe it would be multifactorial and complex because it is caused by different combinations of genetic predisposition, epigenetic interactions, environmental influences, microbial influences, and immune responses in different people. [10]

Immune-related mechanisms in Crohn's disease

Research has documented three immune-mediated mechanisms which may result in Crohn's disease—autoinflammatory, autoimmune, and viral trigger. It is possible to have all three mechanisms or some combination involved in the same person. Let's look at them one at a time.

- **Autoinflammatory Crohn's disease:** "Originally, the ter autoinflammation was coined to describe the occurrence apparently unprovoked episodes of inflammation in the absen of self-reactive T-cells or high titers of autoantibodies, as well the absence of any detectable infectious agents."[10] In oth words, autoinflammatory diseases do not fit the criteria f

autoimmune disease, which have self-reactive T-cells and/ high autoantibody levels. This is true in general, but you a about to see that Crohn's is one exception.

"Autoinflammatory diseases include a few multifactorial complex diseases such as Crohn's, which not only involve the participation of multiple genetic alleles, but also a number of environmental factors."[10] In autoinflammatory diseases, a failure in the regulation of the defense mechanisms of innate immune cells leads to high levels of inflammation. Basically, you have housecleaning mechanisms inside your cells called inflammasomes. Under healthy conditions, they create inflammation inside our cells to clear out inefficient organelles. Think of people at your job that do more sitting around than work; they are inefficient. By cutting the dead weight in the form of inefficient organelles or pathogens, the cell increases its efficiency and performance at doing whatever its specific role is.

When inflammasomes are hyperreactive (i.e., out of control), they don't just clear out the inefficient organelles, they set the whole cell on fire. This results in autoinflammation or, said another way, setting you on fire. Hyperreactive inflammasomes are at the core of autoinflammatory diseases.[10]

Crohn's disease can result from an autoinflammatory mechanism, as a healthy intestinal barrier depends on healthy inflammasome functioning. In a healthy state, inflammasomes regulate tissue repair and growth of the intestines. They also regulate the healthy composition of your gut microbiome and the host-microflora interaction, or how well you and your bugs get along. Hyperreactive inflammasomes lead to autoinflammation of the intestine mediated by changes in the microbiota, local elevation of inflammation, and tissue damage. [11]

What triggers a hyperreactive inflammasome in the first place? Stress—more specifically environmental stress and/or metabolic stress. Environmental stressors that promote inflammasome activation include infection,

trauma, and hypoxia or lack of oxygen (think iron deficiency or high altitude), asbestos, silica, and UV radiation. [12] Metabolic stressors that promote inflammasome activation include high concentrations of sugar, fat, cholesterol, and/or uric acid crystals like those in gout. [13]

- **Autoimmune Crohn's disease:** Crohn's can also manifest fro an autoimmune mechanism. I bet you're saying, "But wait minute, doc! You said above that Crohn's is a autoinflammatory disease and autoinflammatory diseases do n exhibit characteristics of autoimmune disease such as sel reactive T-cells and/or autoantibodies." You are correct, your Skywalker! I'm impressed by your synthesis of this ne information. I also said that Crohn's is an exception to the rul One mechanism for Crohn's disease is autoimmune—there a no blood or stool markers that are diagnostic of Crohn's, b there are two autoantibody markers that have been identified have sufficient sensitivity and specificity to be effective for u in clinical practice. [14] They are anti-Saccharomyces cerevisia antibodies (ASCA) and anti-neutrophil cytoplasmic antibodi (ANCA).

Anti-Saccharomyces cerevisiae antibodies are found in approximately 75 percent of patients with Crohn's disease, according to the nationwide laboratory Quest Diagnostics. High antibody titers increase the likelihood of the disease and are associated with more aggressive disease states. A study in the journal *Nature Reviews Immunology* found that ASCA levels correlate with Candida albicans (yeast/fungus) colonization. They concluded, "These findings suggest that altered sensing of Candida albicans colonization could contribute to aberrant immune responses in Inflammatory Bowel Disease." [15]

According to Quest, ANCA antibodies, specifically atypical P-ANCA antibodies, are observed in inflammatory bowel disease and 5 to 25 percent of patients with Crohn's disease. These findings support an autoimmune mechanism of Crohn's, at least in some patients.

- **Viral Crohn's disease** : Research on mice has revealed possible mechanism for Crohn's development related to vir infection. [16] The researchers have coined the term "virus pl susceptibility gene interaction." In plain English, the autho found that mice have a gene analogous to one that we huma have that increases susceptibility to Crohn's.

  When the researchers exposed mice with that gene to a specific virus, many of them developed Crohn's disease, but mice without the genetic susceptibility that were exposed to the same virus did not. The authors were quick to point out that, "in combination with additional environmental factors and commensal bacteria," virus plus susceptibility gene interaction can result in the disease. Additional factors include immune dysfunction, inflammation, and the health or lack thereof of the gut microbiome. In other words, to trigger Crohn's via the virus plus susceptibility gene interaction, a person must have those two factors, as well as additional contributing factors from the exposome, epigenome, and microbiome.

What you have learned so far in this book is also true for this chapter—mainly, all pathologies including Crohn's and all functional GI diseases include unique combinations of factors from the exposome, epigenome, and microbiome as part of their causes. Each puzzle is different, but the framework is made up of those three components.

Putting together the pieces of the puzzle

Let's now apply the functional medicine framework to Donny's case and layer on his initial laboratory test findings so that you can see how I put the pieces of his puzzle together.

- **Exposome factors** : As mentioned earlier in the chapte exposome factors in Donny's case include vacuum extraction birth with associated neck injury, jaundice in infancy, multip strep infections and ear infections, chronic seasonal allergies a eczema, malnutrition, bouts of anemia, and multiple courses antibiotics. These factors combined to suggest a history chronic inflammation with a Th2 immune dominance (a pr

allergy, pro-histamine immune phenotype). His labs confirme this.

Upon initial testing with me, Donnie had lab high high sensitivity C reactive protein, which indicates systemic inflammation. He had lab high uric acid, which indicates inflammasome activation and an autoinflammatory mechanism for his Crohn's. His anti-Saccharomyces cerevisiae antibody (ASCA) levels were lab high, indicating an autoimmune mechanism for his Crohn's Disease. He had lab high platelets, which is a nonspecific inflammatory marker. He had lab high hemoglobin A1C, which indicates hyperglycemia or a pre-diabetic state. He also had lab low C-peptide, which is low insulin and potential for type 1 diabetes. Lastly, he had iron insufficiency, which promotes a relative hypoxia and is pro-inflammatory.

- **Epigenome factors:** Testing revealed that Donny had multip single nucleotide polymorphisms (aka, SNPs or "snips") genes that code for antioxidant capacity. In other words, there an abnormality (a genetic variant), which increases tl likelihood that he cannot produce optimal levels of antioxida enzymes to combat pro-inflammatory free radicals. The SNPs his case were GSTP1, SOD2, and NAT2.

Donnie's chronic malnutrition promotes negative epigenetic changes via nutrient insufficiencies and deficiencies. The proper expression of our genes requires proper enzyme function, and this requires optimal nutrient co-factor levels. Insufficient or deficient levels of vitamins and minerals lead to insufficient gene and/or enzyme function and resulting epigenetic changes (aka, poor genetic expression).

A classic example that many readers will be familiar with is the gene methylenetetrahydrofolate reductase (MTHFR). The MTHFR gene requires methylfolate (vitamin B9) to function properly. Insufficient or deficient levels of methylfolate will lead to suboptimal MTHFR function, whether or not the person has an MTHFR SNP. A poor MTHFR gene may result in poor methylation

leading to increased homocysteine levels. As discussed in the first two chapters, high homocysteine can wreak havoc on your physiology and increases risk of cardiovascular disease and neurodegenerative disorders such as Parkinson's disease. Given his failure to thrive and chronic iron deficiency and anemia, it's a high certainty that Donny had multiple vitamin and mineral insufficiencies, if not frank deficiencies. Labs revealed insufficient iron and vitamin D levels.

- **Microbiome:** As discussed, an unhealthy gut microbion promotes disease. Testing revealed gut dysbiosis and (inflammation in Donny. GI dysbiosis was evidenced by deficie levels of probiotic species; no growth of Bifidobacterium (lac of their anti-inflammatory benefit) or Enterococcus species. H also had lab high levels of pro-inflammatory, gram-negative IB associated Citrobacter freundii and lab high yeast overgrowth.

Donny's gut was on fire as evidenced by lab high stool levels of IBD markers—lactoferrin, calprotectin, and lysozyme. His lactoferrin level was 712 (abnormal is anything above 7.3), his calprotectin level was 452 (abnormal is anything above 50), and his lysozyme level was 1,750 (anything over 600 is abnormal).

Do you see the massive significance of using a person's history, medical records, examination, and laboratory testing as the clues to solve the case? If you do not use this framework to address cases, a patient will end up with a Seuss-like idiopathic diagnosis.

Donny's case is clearly not idiopathic. His medical record review and lab results reveal that his Crohn's disease involves autoinflammation, autoimmunity, gut dysbiosis, and systemic inflammation as probable causal and definite perpetuating factors. Because we were able to identify these major sticks in the spokes of his physiology, we had clinical targets to go after .

If you don't identify major causal, contributory, and perpetuating factors, how can you hope to create change? This is why conventional medicine says Crohn's is idiopathic and, even with their best pharmaceutical and surgical treatments, they say there

is no cure. You cannot cure something if you do not know what is causing it.

With the functional medicine framework, we determined the major clinical targets in Donny's case, and we addressed them using a drug-free, lifestyle, and supplementation-based individualized and specific functional medicine approach. Part of this approach is to follow patients using objective hard data, like labs and diagnostic tests, and with subjective quality of life questionnaires and reports. I want to establish objective and subjective baselines at the beginning of care, then reassess them midway through, and again at the end. This allows us to prove that we cannot only improve this person's quality of life and make them feel better but that we can also create objective change in their underlying physiology. When this is accomplished, positive change is created for everyone involved.

Donny's results

By day three of Donny's individualized and specific plan, his mom reported that he was no longer using the bathroom for hours a day. At six weeks, she reported a 75 percent reduction in Crohn's symptoms and a 50 percent improvement in Donny's sleep and attitude. She said his weight gain was a major reason for his improvement.

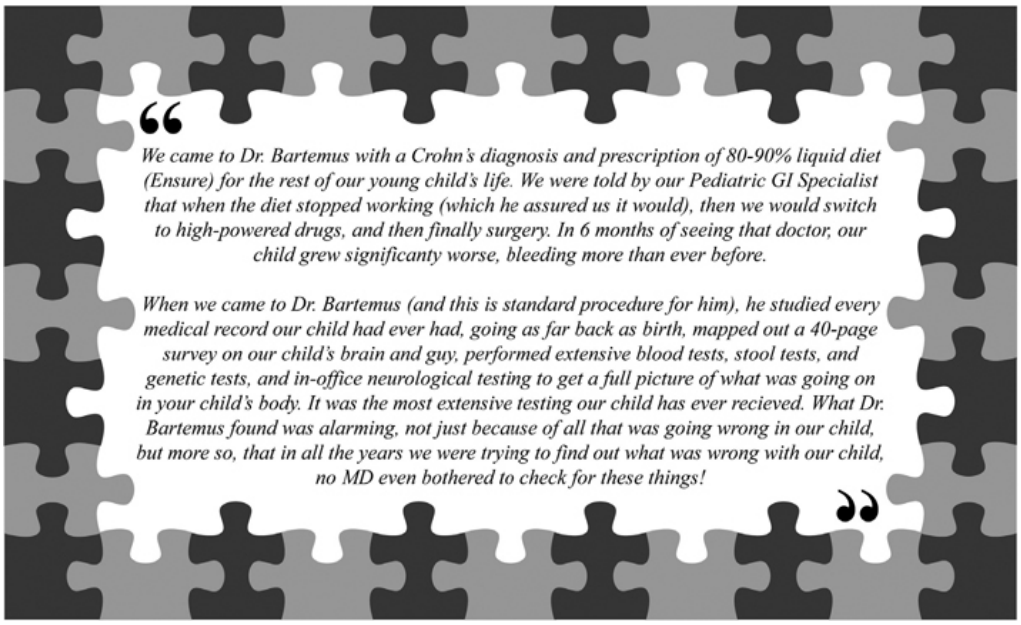
By the twelve-week mark, Donny had put on twenty pounds, and his lab tests revealed an elimination of his systemic inflammation. His previously high hsCRP, platelets, and uric acid were now normalized. The normalization of his uric acid meant that his inflammasome activation had been corrected, and his autoinflammatory driver had been optimized .

Donny's blood sugar was now optimal; the pre-diabetes trend had been reversed, and his insulin levels were now optimal. His iron and vitamin D levels were optimal, meaning his nutrient status was improved.

Regarding Donny's gut dysbiosis, his previously deficient Bifidobac-terium levels were now present and colonizing, and the pro-inflammatory pathologic species of Citrobacter and yeast had been eliminated. Remember those crazy high GI inflammatory markers—lactoferrin, calprotectin and lysozyme? They had all been reduced massively. His lactoferrin went from

712 down to 122, his calprotectin went from 452 down to 93, and his lysozyme dropped from 1750 to 1080.

While we can all see that Donny had quality of life and objective physiological improvements, it all culminated in his mother's testimonial, in which she wrote:



Reader action steps

To learn more about how Functional Medicine addresses Crohn's disease, dysbiosis, and SIBO, view my Gut video playlist at: https://www.FunctionalMedicineCharlotte.com/Gut

Consider implementing one or more of the following if you and your clinician suspect you need improved vagus nerve activation:

Aerobic exercise, meditation, acupuncture, relaxation, fish oil, hum, sing, gargle.

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CHAPTER 4

Inflammatory Disorders of the Brain

"Nerve cells become inflamed in response to any insult. This is called neuro-inflammation, and it promotes various neurologic and psychiatric disorders, such as pain and depression, respectively."

—Dr. Alex Vasquez [1]

Andy was nine when his parents traveled over seven hours to bring him to my office. By that time, he had been through the ringer with conventional medicine. After seven years of visits with pediatricians, neurologists, occupational therapists, and physical therapists, as well as MRIs, EEGs, and having his tonsils and adenoids removed without significant results, his parents were losing hope.

Andy's mom first realized that his focus, or lack thereof, was an issue around age two. He would often have a blank stare on his face. He struggled with learning, and he was very impulsive. By age four, Andy would frequently report that his "body feels silly."

After being examined by two separate doctors, he was diagnosed with ADHD and sensory processing disorder. Shortly after receiving those diagnoses, Andy suffered his first tonic-clonic seizure and was diagnosed with epilepsy. Two months later, he had his second major seizure. A month after that, Andy's preschool decided to discontinue his occupational therapy. His learning skills drastically declined throughout the rest of the school year.

When he was five, Andy was diagnosed with iron deficiency. He had a sleep study done and was diagnosed with insomnia. Andy also had anxiety that was triggered by loud noises, large crowds, and movies. When kindergarten started, his anxiety became overwhelming. Doctors had prescribed many medications for him over the years, including Adderall, Focalin, Strattera, and

Trileptal. By the time he came into my office, Andy was taking Neurontin and Klonopin at night and Concerta during the day.

His mother reported he would binge eat white bread and sweets if allowed, and he was averse to the textures of rice, oranges, fish, and cottage cheese. I also found that he had tested positive for gluten sensitivity at age six, yet he was still eating it.

With a thorough history and review of his medical records, I found out that Andy had never crawled as a toddler, had at least four positive group A strep cultures over the years, and had been on multiple courses of antibiotics. Infection early in life is associated with impairment of multiple aspects of childhood development. [2]

A neurologic examination revealed primitive reflexes that had not remediated. Specifically, Andy still had bilateral rooting reflexes and palmer reflexes present, which were an indication of neurodevelopmental delay. His eye exam revealed abnormal pursuits (the ability to follow the pen with your eyes) in all directions and hypometric saccades, which meant he could not accurately go from looking at one target to a different target. He also failed finger-to-nose testing bilaterally .

These findings suggested poor cerebellar function, leading to poor integration of vision with body movement, and were probably the reason he said his “body feels silly.” Past doctors had never checked for any of these findings. If they had, they were not noted in his medical records, and if they were found, it is typical that the doctor would have brushed them off with a statement such as, “Don’t worry. He’ll grow out of it.”

That statement is false. Primitive reflexes should disappear by eighteen months, at the latest. Different reflexes remediate at different ages. If they don’t, then that child will not reach proper milestones of neuro-development and will not develop normally until he or she reaches those milestones.

Dr. Robert Melillo is the author of five books on neurodevelopment and the founder of Brain Balance Centers. He has many years of experience helping people overcome learning disabilities, autism spectrum disorders, ADD, ADHD, OCD, Tourette’s, and more. He also trains doctors in how to achieve results with these disorders. At a training I personally attended

with him, he stated that 40 percent of patients that present to his practice have primitive reflexes present that need to be remediated.

Andy did not crawl. Crawling is a necessary milestone of neurodevelopment. Cross crawl movement integrates the right and left hemispheres of the brain through the corpus callosum and promotes optimal integration of various brain regions. Andy will not grow out of it—he will grow *over* it. This means his body will continue to grow and mature at a normal rate, but his neurology will not. This may lead to things such as learning disabilities, poor coordination or body awareness, mood or behavioral issues, et cetera. (I have had patients who were teenagers with learning disabilities that had a history of never crawling. The first thing I recommended was that they had to crawl around their house for fifteen minutes a day in order to go back and reach that milestone.)

The failure of the conventional medicine paradigm

Do you feel Andy's parents' pain? Their child could not focus or learn; he was anxious about everything and would not sleep. His insomnia meant that they were also sleep-deprived, which further added to their stress and hopelessness. Thankfully, they found me and the functional medicine framework.

Conventional medicine gave it their best, and they failed. Why? In a word—paradigm. Clearly, at least in the eyes of conventional medicine, the symptoms and diagnoses involved in Andy's case are neurological, and the paradigm that conventional medicine utilizes to approach neurologic disorders is the monoamine hypothesis. The monoamine hypothesis of depression is the framework that informs conventional medicine's treatment of neurologic disorders. "The monoamine hypothesis of depression predicts that the underlying pathophysiologic basis of depression is a depletion in the levels of serotonin, norepinephrine, and/or dopamine in the central nervous system." [3]

This thinking is behind the use of antidepressant, anti-anxiety, and anti-psychotic medications, and it was the thinking behind

the prescriptions given to Andy for his ADHD. Adderall, Focalin, and Concerta are all norepinephrine and dopamine reuptake-inhibiting drugs. Strattera is also a norepinephrine reuptake-inhibiting drug. If the monoamine hypothesis was the correct explanation for Andy's suffering, shouldn't the medications help, and not only help, but eliminate symptoms and restore his quality of life? If they all do the same thing, why would he need four different medications? The answer is obvious—the monoamine hypothesis is the wrong paradigm for achieving healing in Andy, but it's a great paradigm for selling drugs and creating repeat customers .

Research is piling up daily that reveals that the primary driver behind major depressive disorder is not a monoamine deficiency —it is neuroinflammation [4] , which occurs when microglial cells (the immune cells of the brain) become activated.

In his book *Pain Revolution for Migraine and Fibromyalgia* , Dr. Alex Vasquez[1] states, "Microglial activation occurs in response to peripheral inflammation from obesity, trauma, infection, or vaccination, and central within-the-nervous-system events such as trauma and stress."

In other words, the brain is on fire, and if you leave it on fire long enough, a monoamine deficiency may develop. However, that is not the primary perpetuator of the disease process. This helps explain why one-third of patients fail to respond to antidepressant medication. [5] There are other possible primary drivers of monoamine deficiency that, if present in a person and left unaddressed, will result in a failed response to medication. To learn more about other factors associated with dopamine, norepinephrine, and epinephrine, watch this video: https://www.FunctionalMedicineCharlotte.com/Dopamine

To learn more about other factors associated with serotonin, watch this video: https://www.FunctionalMedicineCharlotte.com/Serotonin

If recent research is correct and finding and addressing the cause of neuroinflammation is the Holy Grail in neurologic disorders, then we should see significant improvement in these cases by finding and eliminating neuroinflammation.

Do you know what one driver of neuroinflammation is?

Neuroautoimmunity. That's right—you can have brain autoimmunity. The most well-known example is multiple sclerosis, but there are many others.

If you haven't guessed by now, a neuroautoimmune process is what I discovered to be causing Andy's suffering, but Andy's other doctors never considered it, probably because his symptoms were "clearly" neurological.

This is why you don't want to assume you know what is going on based only on symptoms. Instead, put your detective hat on. Let's go back through Andy's history and put the pieces together. Step into my brain so you can see what I was seeing when working on this case.

Putting together the pieces of Andy's puzzle

The first thing that jumped out at me was Andy's four documented positive group A Streptococcus cultures, which meant he had strep throat. He had one positive culture each at the ages of two, four, six, and seven. Andy's parents reported that he had multiple other instances where they thought he had strep throat, but the culture was negative. A negative culture does not mean that you don't have strep throat. [6] Lack of symptoms also does not mean that you don't have strep throat. [7] Many studies show that false-negative throat swabs may occur due to a faulty technique or an infection that's sequestered deep into tonsillar tissue that can't be reached by the swab. [8]

Some people would say that you don't have a Streptococcus infection if you don't have high strep antibodies, but studies show that rising streptococcal antibodies frequently cannot be determined because symptoms have already been present for several weeks at the time of first evaluation.[8] This means you have an initial increase in antibody titers, but over time, they drop back down toward normal range, even though the infection may persist.

Negative titers are obtained in as many as 40 percent of group A strep infections. This means that it's possible that four out of ten kids with a current strep infection are told they don't have strep because the titers aren't showing it, so they go on infected and

untreated. A large fraction of new asymptomatic group A strep acquisitions and acute infections occur without a rise in antistreptolysin O (ASO) antibodies or anti-DNase B antibodies.[8]

The second thing from this case that I was intrigued by was the multiple courses of antibiotics he had taken in his young life. As we've discussed in previous chapters, antibiotics promote dysbiosis in the gastrointestinal tract, which makes your microbiome imbalanced. We've discussed multiple ways how that can lead to poor health outcomes.

Thirdly, Andy had positive anti-gliadin IgA antibodies at age six, indicating gluten sensitivity (see chapter 6 for more detail on gluten).

Fourth, he had iron deficiency anemia at the same time.

The fifth thing that stuck out to me—Andy had obsessive-compulsive tendencies surrounding his bedtime and also had separation anxiety.

Number six, he had multiple neurologic abnormalities (as we discussed above).

The seventh and final factor—on the day that Andy first presented in my office for his exam, he was not feeling well. His parents also reported he was "under the weather." When they were leaving my office, I was already suspecting neuroautoimmunity associated with chronic infection, so I asked them to get a throat culture for strep. It was positive, even though he had no sore throat. Bingo! That was a significant clue in helping solidify my suspicions.

You may ask why the strep piece of the puzzle was so significant. A group A Streptococcus infection is a known driver of pediatric autoimmune neuropsychiatric disorder associated with Streptococcal infections, aka PANDAS. [9] As you can see by the name, PANDAS is autoimmune, specifically *neuroautoimmune* . Being that it is a relatively new diagnosis, it is unlikely that any of his previous mainstream doctors would have picked up on it .

The PANDAS diagnosis is only about twenty years old and has since been updated to PANS—pediatric acute-onset

neuropsychiatric syndrome—because researchers and clinicians have found that other infections and environmental triggers besides Streptococcus can cause PANDAS symptomatology including gastrointestinal infections, dental infections, herpes simplex, Varicella, Epstein-Barr virus, enterovirus, and others, as well as Kawasaki disease and anaphylactoid purpura. [8] , [10]

In fact, after we received Andy's test results and the family went back and showed them to their pediatrician, he said, "I have never seen a case of this in my entire twenty-five year practice. I need to look at this." Props to that doctor for being open to learning more in order to help his patients, but do you really think he never had a case of PANDAS in his office in that entire time? Or do you think he did but didn't see it? How many cases of strep throat have walked into his office in the last 25 years? How about cases of repeated group A strep infection in the same child?

There's a high probability that at least a couple of the repeated group A strep-infected kids had or went on to develop PANDAS. Research shows that 92 percent of PANDAS cases had strep throat documented one to seven times before PANDAS' onset. The initial infection demonstrated definite throat redness, which was otherwise mild, with mild exudate and swollen lymph nodes, but usually no fever. [11]

What is the mechanism for group A strep infection producing neuroinflammation? A study in 2016 using mice revealed that repeated nasopharyngeal strep infections resulted in migration of group A strep-specific Th17 immune cells from the lymphoid tissue of the nose into the brain, leading to blood-brain barrier breakdown, microglial activation, and sterile inflammation, which means that the brain was inflamed without bacteria being detected. [1] [2]

Group A strep infection creates neuro-autoimmunity using a mechanism called molecular mimicry. Watch this video where I show you how this happens in PANDAS: https://www.FunctionalMedicineCharlotte.com/PANDAS

What is molecular mimicry?

Molecular mimicry is currently the prevailing hypothesis as to how pathogens initiate and perpetuate autoimmune responses that lead to specific tissue damage. In molecular mimicry, a foreign microbe shares an amino acid sequence (amino acids make up proteins) or a structural feature similar to an amino acid sequence or structure that makes up one of our human tissues. When a T cell or B cell recognizes the shared amino acid sequence or the shared structure, it promotes inflammation and the destruction of that target. [13]

Let's use the well-documented case of Group A Streptococcal ("Strep") infection and rheumatic fever as an example to better understand this. When a child develops a group A strep infection in their nasopharynx ("Strep Throat"), their immune system will create antibodies that recognize the M protein of the strep and seek to destroy it. That M protein (foreign) shares a similar amino acid sequence with the protein myosin (self) that makes up our heart valves. If the pro-inflammatory response your immune system mounts to kill the strep is too robust, goes on for too long, or is not properly extinguished, [14] your immune cells may look at that myosin as enemy and attack it, resulting in rheumatic fever (autoimmune disease of the heart triggered by molecular mimicry). [15]

As described by the 2016 study mentioned above[12] , mouse models reveal molecular mimicry to be a biologically plausible mechanism for neuro-autoimmune diseases like PANDAS .

The diagnostic criteria for PANDAS [16] is as follows:

- The presence of OCD and/or tics
- Onset of the disorder between age three and puberty
- Acute onset and relapsing-remitting course of the disease
- Association of group A Streptococcal infection
- Association with neurological abnormalities

PANDAS plays a part in Andy's neuroautoimmunity

As the detective, it was up to me to take the diagnosis from hypothetical to concrete, and the only way to do that was through testing. If I could prove that Andy had antibodies against brain tissues—specifically dopamine receptors—I could confidently say two things:

1. Andy has a neuroautoimmune process underlying his neurologic symptoms

2. There is strong evidence that the neuroautoimmune process is PANDAS.

Testing was positive on both accounts. Andy's results revealed lab high anti-dopamine receptor D1 antibodies, lab high anti-tubulin antibodies, and lab high calcium calmodulin protein kinase 2 (CaM kinase 2) antibodies. All three positives are sufficient for proof of neural autoimmunity.

The anti-dopamine receptor D1 antibodies make the strongest immunological case for PANDAS via molecular mimicry between strep and the D1 receptor. Anti-dopamine receptor D1 antibodies are associated with psychiatric issues, ranging from depression and anxiety to psychosis. The D1 antibodies are responsible for anxiety, mood instability, and sleep issues. Anti-tubulin antibodies exhibit the highest correlation with OCD. CaM kinase 2 antibodies were lab high at the same time as the D1 antibodies and indicated an acute infection and flare of the autoimmune process. [17] , [18]

The day after Andy's tests were drawn showing these results, he had a seizure and tested positive for group A strep culture at the hospital. This would suggest autoimmune epilepsy, which is the type one-third of people experiencing seizures are thought to have. [19] , [20]

If we address Andy from an immune perspective, and he responds by having decreased or complete elimination of seizures, it would support an autoimmune epilepsy diagnosis. [21] In that case, neuro-autoimmunity would be responsible for not just the PANDAS, but also the seizures.

Other findings of note in Andy's initial lab tests at my practice included suboptimal total immunoglobulin classes A, G, and M.

This suggests suboptimal immune surveillance of pathogens and suboptimal mucosal (gut, lung, sinus, bladder) immune defense. Testing also revealed low blood sugar. The brain needs fuel in the form of glucose and oxygen—a lack of these promotes neurologic symptoms such as brain fog, irritability, lightheadedness, anxiety, headaches, and more.

In terms of gut dysbiosis, Andy had low secretory IgA (sIgA), which is the first line of defense in the mucosal barriers. A landmark study in 2019 revealed that sIgA from the gut travels to the brain to decrease brain inflammation. [22] Therefore, deficient sIgA in Andy's gut was potentially promoting PANDAS and/or seizure flares (learn more about the Gut-Brain Axis in chapter 5). Andy was also positive for Helicobacter pylori infection, and he had deficient probiotic levels. Calprotectin was lab high, which indicates significant GI inflammation.

When we apply the functional medicine framework of exposome, epigenome, and microbiome to Andy's case, we get the following :

Exposome factors include stress and anxiety, sleep deprivation, diet, nutritional inputs such as sugar and gluten, infection, GI inflammation, suboptimal immune surveillance, and missed neuro-developmental milestones.

Epigenome factors include stress, sleep deprivation, and nutrition. [23]

Microbiome factors including lab high inflammation in the gut, deficient beneficial bacteria (probiotics), the presence of pathogens such as H. pylori, and deficient sIgA.

Healing Andy

All of these factors matter and may contribute to brain autoimmunity. As Dr. Samuel Yanuck states in his epic 2019 paper in *Frontiers in Psychology:* [24]

"…in a clinical setting, knowing how comorbidities that affect neuron-microglial signaling can influence patient biology may create the potential for clinical advantage in patients with neuropsychiatric disorders, through clinical attention to

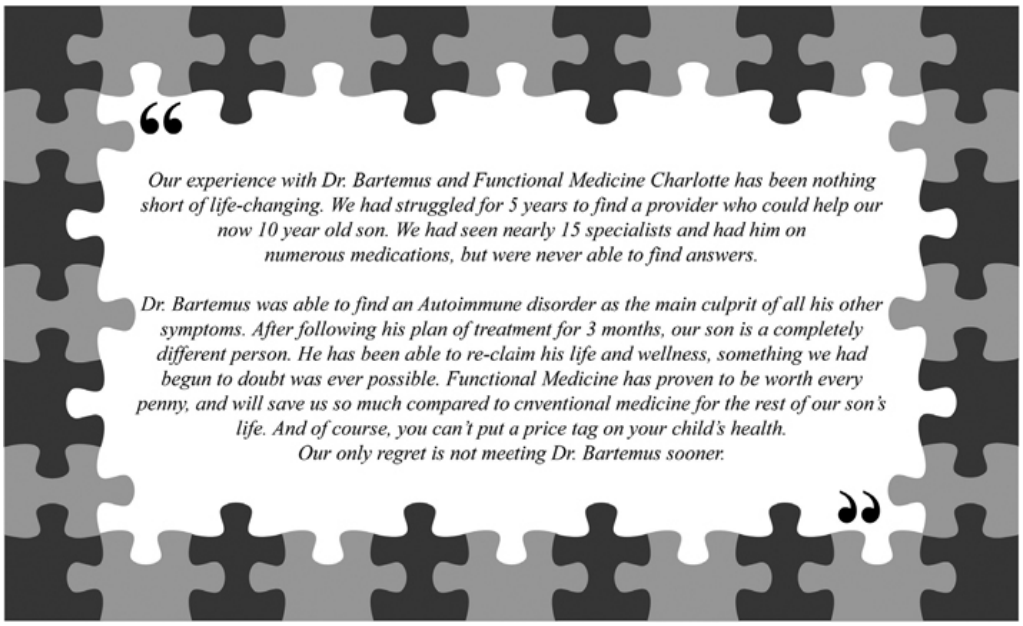
seemingly disparate factors like exercise, reducing inflammation, neurotransmitter support, stress reduction, and inhibition of autoimmune attack of self-tissue."

Based on all of this, I created an individualized and specific action plan for Andy. I'll share some of the key factors in the plan here, but please remember—this is individualized and specific to Andy only, not you. If you are dealing with something that seems similar to what he's dealt with, you must partner with someone who can do the work necessary to create an individualized and specific plan for you, based on your history, medical record review, exam, and test results.

From a nutritional perspective, we implemented a ketogenic diet for Andy that was supervised by his pediatric neurologist. From a sleep perspective, we utilized multiple strategies, including changing his device usage and timing, his pre-bedtime rituals, and utilizing specific nutrients to optimize sleep. The rest of the heavy lifting was focused on creating tolerance in his immune system in order to minimize the autoimmune attack against his brain, while at the same time, promoting optimal anti-infection defenses and surveillance.

Andy's twelve-week lab results revealed optimization of vitamin D status, elimination of H. pylori infection, and restoration of gut mucosal immunity (sIgA) from lab low to optimal. The progress report from his mother stated the following: "We are no longer using sleep medications after Andy has been on them for five years; Neurontin and Klonopin have been eliminated. Andy sleeps easily every night, all night long, and this has made all the difference. Beyond getting off the drugs, this area has been the most life-changing for the entire family, and Andy no longer has anxiety or panic attacks."

His mom rated a 75 percent reduction overall in his anxiety, a 75 percent improvement in his energy levels, and a 100 percent improvement in his digestive function, underscored by no longer suffering constipation. Andy's mother also said his brain fog had decreased 75 percent: "I can't tell you the number of people who have commented on how much more communicative he is," she reported. "It's easy to see that he can think through things better and is more present with the world around him."



Reader action steps:

To learn more about PANDAS, view my PANDAS video playlist at: https://www.FunctionalMedicineCharlotte.com/PANDAS

You may also enroll in my free PANDAS mini course at: http://functionalhealthacademy1.teachable.com

Begin a mindfulness practice such as meditation, diaphragmatic breathing, or Emotional Freedom Technique (EFT).

If meditation is your choice, download the Headspace App and complete a free meditation daily .

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CHAPTER 5

Gut-Brain/Brain-Gut Axis

"Growing evidence supports the possibility that both scenarios exist, with some patients presenting first with mood disorders without gut symptoms, and then later developing gut symptoms, brain driving gut. Whereas others first present with functional gastrointestinal diseases, and then emerged with psychological disturbance, gut driving brain. The intimate yet complex interactions between the gut, brain, immune system, and intestinal microbiota have far-reaching implications for health."

—Powell, Nick, Marjorie M. Walker, and Nicholas J. Talley. [1]

In 2005, Kenny suffered a mild traumatic brain injury (mTBI) in the form of a severe concussion while playing high school football. For the next twelve years, dizziness and migraines would incapacitate him. A four-year college degree took him seven years to complete due to poor mental processing created by the concussion. Once he graduated, he got a job and had to quit after one day because he was too dizzy to function.

In addition to the constant dizziness and migraines, Kenny had heartburn, muscle pain, insomnia, and weight gain due to the inability to function, let alone exercise or play his favorite sports, golf and disc golf. When Kenny presented to my office in early 2017, these were his main complaints. Upon further questioning, he also reported chronic GI complaints and a very restricted diet associated with many food sensitivities.

Kenny had never connected the dots that his gut complaints could be related to his head injury. Neither had his previous doctors. This chapter will connect those dots by building on the previous two chapters covering the GI tract and the brain. I will now connect them to form the brain-gut, gut-brain axis.[1]

In the U.S. alone, nearly 1.7 million Americans seek medical treatment for some form of brain trauma each year, with 2 percent of the American population, or about six million people, currently suffering from traumatic brain injury-related

disabilities. Traumatic brain injury, also known as TBI, is a particularly serious threat to health in newborns, children, the elderly, military service personnel, and athletes involved in contact sports. [2]

"Trauma to the brain can result in persistent and debilitating impairments in cognition, sensory function, mental health, and motor function. Furthermore, TBI-induced inflammation and pathology have been strongly linked to an increased risk of developing numerous neurological disorders including anxiety, depression, PTSD, Alzheimer's disease, chronic traumatic encephalopathy (CTE), Parkinson's disease, and ALS."[2]

The brain injury's role in immune activation in the brain

Whether it's called traumatic brain injury, mild traumatic brain injury, head injury, or concussion, its impact is likely to result in immune activation. "Closed head impact injuries, independent of concussive signs, can induce traumatic brain injury, as well as early pathologies and functional sequela associated with chronic traumatic encephalopathy." – *Brain,* 2018. [3]

In plain English, a mild concussion has the potential to activate an immune response in the brain that is greater than mild. Just because a person no longer feels dizzy or nauseous, can remember words and follow a pen with his eyes does not mean the immune and neuroinflammatory effects of the head trauma have resolved.

A 2016 study in *Frontiers in Immunology* [2] states, "Primary brain damage that occurs at the time of injury can be exacerbated and prolonged for months or even years by chronic inflammatory processes, which can ultimately lead to secondary cell death, neurodegeneration, and long lasting neurological impairment."

These prolonged effects are related to chronic immune activation —especially microglial activation—as well as blood-brain barrier disruption and associated upregulation of inflammatory mediators. This is why Kenny could sustain a concussion and still feel dizzy twelve years later.

What about the gut?

How does the head injury relate to the gut? The answer is the brain-gut axis. The consequences of head injury are not imprisoned in your skull—they are systemic.

Systemic physiological effects following head injury include autonomic dysfunction, systemic inflammation, and organ dysfunction. [4] Specifically, gastrointestinal dysfunction is frequently observed in traumatic brain injury patients, including motility abnormalities [5] and mucosal alterations that can lead to inflammation and increased gut permeability (leaky gut).

In fact, research has shown that within six hours of a head injury, leaky gut is present. Leaky gut, known in the research community as intestinal hyperpermeability, may allow bacteria and pro-inflammatory metabolites into the bloodstream, causing sepsis and eventually multisystem organ failure. [6]

How many athletes with concussions are checked for leaky gut? If your "gut" feeling is that the answer is zero, go with it. People who suffer from head injuries fall prey to the same issues we've been discussing with the conventional medical approach, namely symptom-based care and a specialist.

In this case, the "specialist" is typically not a specialist in head trauma, neurology, or physiology as a whole; he or she is usually the team's athletic trainer or the family physician. If that is the case, then the person is deemed healed from the head injury when the symptoms lessen or stop, and they can follow a pen with their eyes. Their GI tract is never even a consideration.

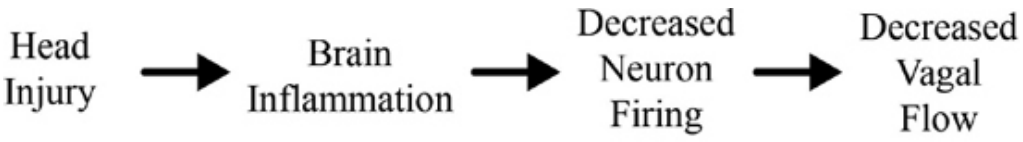
If, by chance, the head injury is bad enough or persistent enough that the person ends up in a neurologist's office, they may get further examination via imaging, but ultimately the treatments are symptom-based medication and watchful waiting. It has always baffled me that when I have patients ask a neurologist for help with GI complaints, the neurologists are confused as if to say, "I'm a neurologist, I deal with the nervous system. Why are you asking me for help with your gut?"

I also like to have people with inflammatory bowel diseases ask a gastroenterologist for help with their anxiety and depression. The same awkward moment of silence from the gastro occurs,

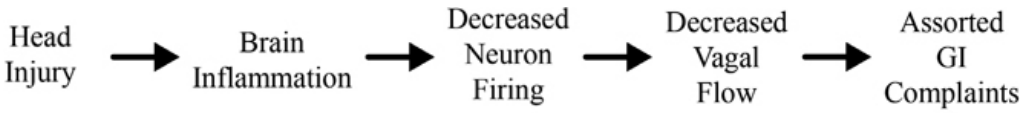
which says, “I deal with guts, not brain.” Hello! Our brain is connected to our gut, and our gut is connected to our brain. As we discussed in chapter three, the GI tract is under central nervous system control (brain) and enteric nervous system control (gut). *Two* nervous systems control the GI tract .

Research reveals the metabolites produced by the gut microbiome affect cognition and mood. [7] In my mind, that’s an excellent reason for a gastroenterologist to be concerned with the levels of anxiety and depression in his or her patient. Increasing or decreasing anxiety could be an indicator of worsening or improvement of the GI environment.

Another mechanism by which head injury contributes to gut symptoms is decreased vagal motor outflow [8] . A head injury creates neuroinflammation (aka, “brain on fire” [9]). An inflamed brain results in a decreased frequency of firing of brain neurons. This, in turn, results in decreased pontomedullary reticular formation (PMRF) activity and increased sympathetic nervous system activity, which combine to decrease vagal motor outflow.



As also discussed in chapter three, vagal motor outflow is integral for optimal GI function, as it promotes the creation of stomach acid and digestive enzymes, healthy peristalsis and motility, and an anti-inflammatory intestinal environment.[8] Now you can see the brain-gut axis mechanism by which head injury can lead to leaky gut, dysbiosis, constipation or diarrhea, GI inflammation, food sensitivities, nausea, and pain.



As explained above in the examples of the neurologists not checking guts, and the gastro not checking brains, if we are not thoroughly assessing the entire physiology of a person with a head injury, the case is more likely to become chronic. Why? Persistence of systemic symptoms after the person has

supposedly healed from the head injury. In other words, the GI symptoms are unaddressed, and they perpetuate the neurologic symptoms via gut-brain axis loops. I hypothesize that this is what is going on in many people diagnosed with post-concussion syndrome.

Let's use Kenny as an example. He sustained a concussion in a football game and had brain inflammation. Science suggests that within hours, he had a leaky gut, which promotes GI inflammation. Brain on fire plus gut on fire means both ends of the brain-gut axis are on fire. He then proceeds to suffer for twelve years.

Remember the concept of neuroplasticity we covered in chapter three? Neurons that fire together wire together. For twelve years, Kenny's central nervous system (his brain) and enteric nervous system (his gut) have developed plasticity. Deep ruts in the grass along the head injury-GI complaints pathway laid out above show his development of food sensitivities, chronic pain, and heartburn, in addition to dizziness and migraines. "The immune system integrates and modulates bidirectional signals between the brain and nervous system in the gut and, consequently, mechanistically links alterations in function in both brain and gut."[1]

Kenny went to a functional neurology clinic before I met him. (If you have not heard of functional neurology, it is awesome stuff, and you should check it out at www.iafnr.org .) Functional neurologists rehabilitate nervous system function in a much more nuanced and investigative way than conventional neurology does. It is a very deep field and requires a lot of study and practice. Because of this, many functional neurologists are not well versed in functional medicine. They address the patient mainly from a neurology perspective, which leaves out the gut, blood sugar, and global physiology. Dr. Brandon Brock and Dr. Datis Kharrazian are seeking to change this. They teach functional neurologists that leaving those things out may result in neuro-rehab not being as effective as it could be.

This is what happened to Kenny when he went to the functional neurology clinic. He was thoroughly examined and assessed from a functional neurology perspective. The doctors there created an amazing treatment plan for him focused on

rehabilitating his cerebellum and vestibular system with the goal of significantly reducing, if not eliminating, his dizziness and migraines.

Kenny was excited to get started. After one session of rehab, however, Kenny got very sick. He was cold and had diarrhea and stomach pain.

What happened? Why would this individualized and specific neurologic treatment create autonomic changes and exacerbation of GI complaints?

Because Kenny was still a mess metabolically, and this was not being addressed.

The brain requires fuel in the form of oxygen and healthy blood sugar regulation. At this point, Kenny had been suffering for ten years and had gained seventy pounds. The weight gain was due to physical inactivity as a result of dizziness, which promotes poor blood sugar regulation and insulin resistance. High insulin inhibits vagal motor outflow, which increases inflammation. Losing vagal motor outflow is especially bad when trying to heal from a head injury. Research has shown optimal vagal nerve function is neuroprotective and speeds healing by decreasing brain swelling. [10]

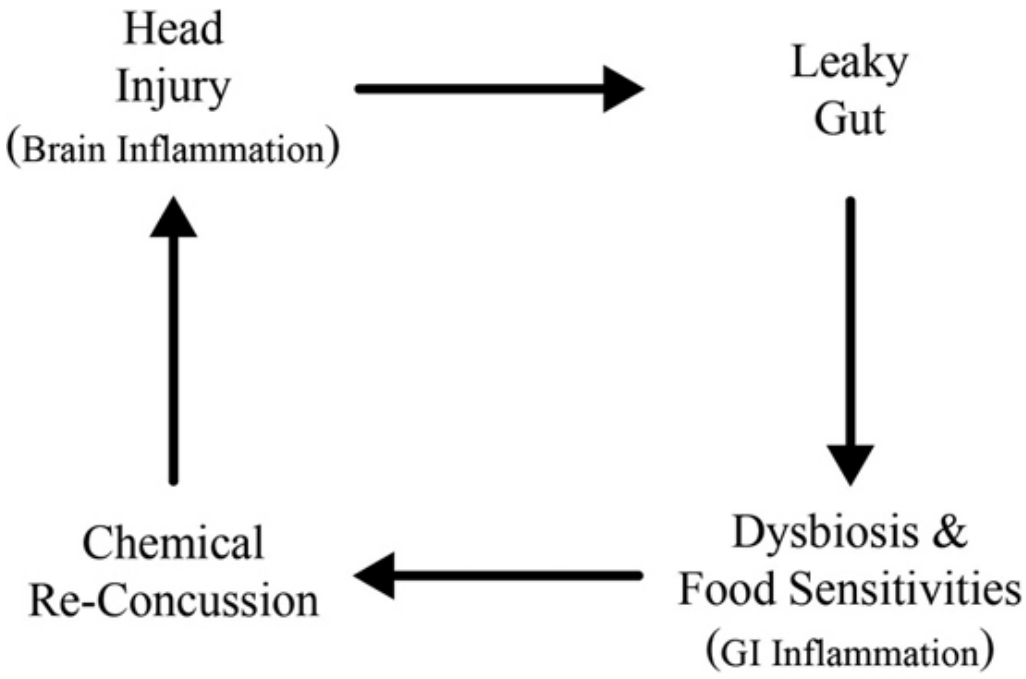
Kenny also had an iron insufficiency, which means he was not optimally carrying or delivering oxygen to the brain. Have you ever tried to exercise on an empty stomach at a high altitude after having not exercised in ten years? How do you think you would perform? That's how Kenny's brain felt, and that's why he responded so negatively to rehab.

In Kenny's case, before optimal results can be gained from an excellent neurologic rehab program, balance had to be restored to his global physiology and metabolic systems. Once accomplished, his brain would have optimal fuel supplies and be able to perform, recover, heal, and grow from the rehab.

This is an example of an initial head injury that led to GI issues, which perpetuated the neurologic symptoms. Let's perform a biologically plausible thought experiment showing another potential mechanism by which the gut could perpetuate brain symptoms via gut-brain axis.

Kenny had a head injury, which resulted in GI complaints, including food sensitivities. Food sensitivities are caused by loss of oral tolerance, which is the immune system's ability to tolerate food as friend rather than attack it as foe. This is commonly associated with dysbiosis. [11] In other words, food sensitivities are an immune response to food wherein it is looked at as an enemy (learn more in chapter 8). The immune system then reacts to enemies with inflammation and antibodies.

Eating food that you are sensitive to results in immune activation and inflammation. [12] Inflammation is initially in the GI, but in the context of systemic and neuroinflammation, adding inflammation anywhere can contribute to increased symptoms everywhere. In this way, even though Kenny didn't hit his head again after the first concussion, having the food sensitivities opened up the possibility that each time he ate food he was sensitive to, he was chemically re-concussed.



You see the vicious cycle? It started out as a *brain-gut axis* but became a *gut-brain axis* issue. It's a brain-gut, gut-brain loop. If you only close one end of the loop (for example) by only treating the brain, the other end of the loop that was not addressed, the GI issues, may eventually reopen the closed end. Thus, we must address the person presenting with a head injury

as a whole person, not an isolated head injury. This includes his whole physiology, whereas only addressing one site of injury leads to the ignorance of possible key perpetuating factors that cause the treatment to fail and leads to years of unnecessary suffering. Thorough detective work is the key to healing, as it reveals the key players in our functional medicine framework of exposome, epigenome, and microbiome.

What did detective work reveal as contributory factors in Kenny's case ?

Exposome factors

- **Functionally high homocysteine levels:** As discussed chapter one, homocysteine promotes migraines and brain fog v neuroinflammation.

- **Food sensitivities:** Kenny had positive food sensitivity reactio to 59 foods, including eggs, rice, wheat, black beans, chocolat chia, beats, artichoke, carrots, cauliflower, broccoli, garli onion, potato, sweet potato, tomato, avocado, blueberry, lemo lime, orange juice, lamb, and parsley.

Needless to say, there wasn't much he could eat. His diet consisted of chicken, beef, and bell peppers. There are obvious stress and frustration associated with such a restricted diet. Those stressors are conscious, mental, emotional, but also physiologic due to a lack of nutrients and raw materials needed to heal. Lastly, such a highly restrictive diet promotes blood sugar dysregulation.

- **Iron insufficiency:** Iron insufficiency promotes hypoxia or la of oxygen, which is a pro-inflammatory stimulus in the body. also leads to fatigue. Specific to the brain, oxygen is one of t two key fuel sources. Poor oxygenation results in poor cogniti function, poor short-term memory, and can increase brain fog.

- **Stress** [13] **:** Psychosocial stress is capable of causing immu imbalance and brain inflammation, which may develop in anxiety and depression. Among the brain regions that a involved in the neural circuitry of stress responses are t prefrontal cortex (which is where our executive function giv

us ability to focus, concentrate, and pay attention), tl hypothalamus (which is the thermostat for our body, sensing ar correcting hormone levels, body temperature, et cetera), tl amygdala (where our fear and anxiety centers are), and tl hippocampus (which is where short term memory lives).

Stress induces glucocorticoid insensitivity in immune cells. What this means is stress makes our immune system less responsive to cortisol. This insensitivity prevents the suppression of inflammation by reducing inhibition of NF-kappa B. Glucocorticoid insensitivity is pro-inflammatory.

Several studies have demonstrated that microglia are activated and increased neuroinflammatory signaling occurs after stress exposure. This stress-induced brain inflammation impairs hippocampus function, leading to short-term memory loss and cognitive and behavioral deficits.

- **Devices:** Devices made Kenny dizzy by making his ey converge when looking at the screen. This convergence activate the stress centers located in his midbrain. A device's blue lig stimulates midbrain sympathetic nervous system response further increasing stress physiology. [14]

- **Physical inactivity:** As discussed earlier, the brain requir glucose and oxygen as fuel. A third nutrient required by tl brain is stimulation, aka exercise. The dizziness prevente Kenny from exercising. Lack of exercise then cascades in metabolic consequences relating to insulin sensitivity and bloc sugar regulation.

- **Sleep deprivation:** Part of Kenny's neurological problem w autonomic dysfunction. Your autonomic nervous system is tl part of the nervous system that runs all the behind the scen functions that you don't think about such as heart rate, bloc pressure, blood vessel dilation and constriction,, et cetera. P simply, this is managed by balancing the fight or flight respon (the sympathetic nervous system) with the "rest and digest" vagus nerve response (the parasympathetic nervous system Kenny was sympathetic dominant or always in a state of fight

flight. This makes it easy to be wired, tired, and anxious, and is hard to calm down and fall asleep. Sleep deprivation caus systemic inflammation [15] which promotes brain inflammation.

Epigenome factors

Research on the specific epigenetic impact of traumatic brain injury in humans is in its early stages. One 2010 study in *The Journal of Neurotrauma* found that both TBI and mild TBI alter the levels of microRNA circulating in the blood and concluded that they represent a rich, new source of potential molecular biomarkers to aid in TBI patient classification and management. [16]

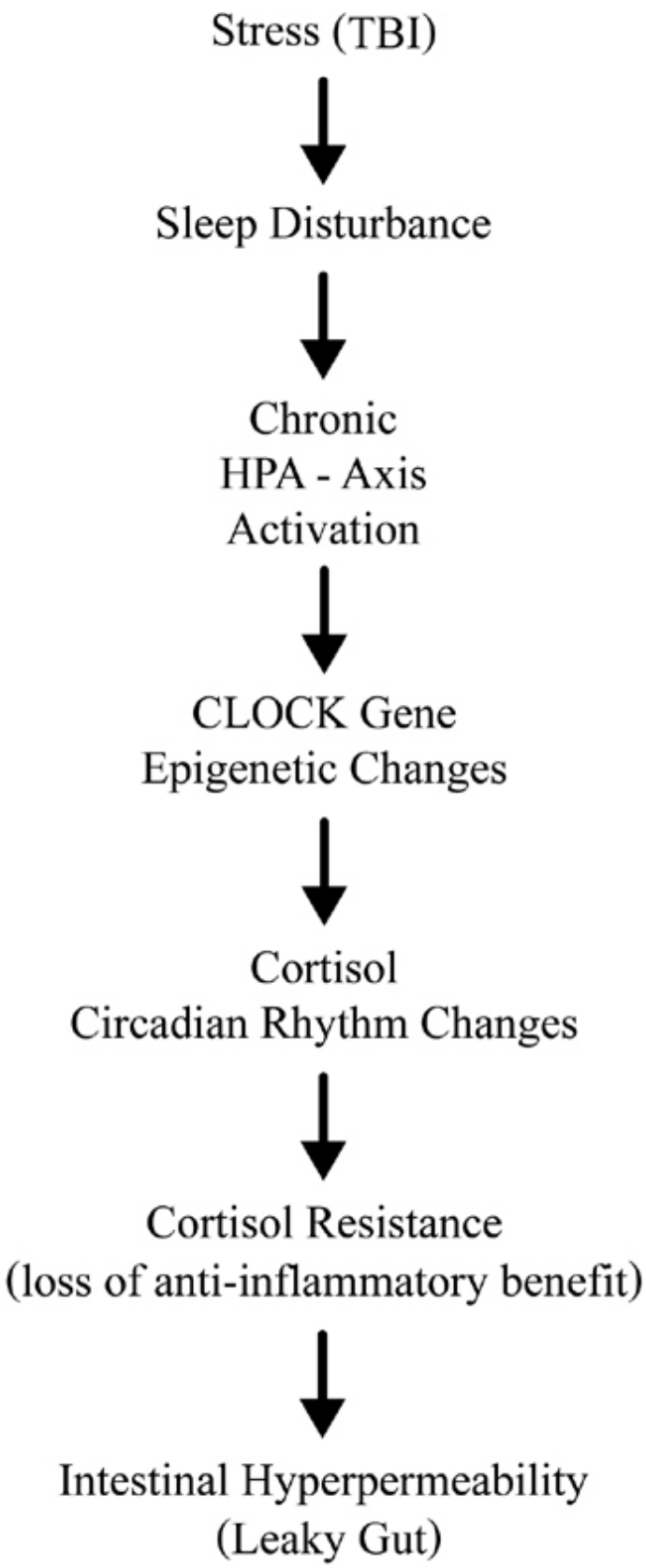
Although the research on the specific epigenetic impact of TBI is just beginning, there are stacks of studies on the impact of stress (TBI and mTBI are major stressors) and the glucocorticoid receptor on health. The glucocorticoid receptor is the major central nervous system determinant of metabolic rhythmicity in humans. Through the hypothalamic-pituitary-adrenal axis, or HPA-axis, it regulates peripheral glucocorticoids such as cortisol. Ten percent of all genes exhibit diurnal rhythmicity.

Cortisol binds to the glucocorticoid receptor in the cell and activates the NR3C1 gene. It is also responsible for driving circadian and ultradian bursts of transcriptional activity in the CLOCK genes. This rhythm is disrupted in major depressive disorder, bipolar disorder, and stress-related gastrointestinal and immune disorders. [17]

“Dysregulation of central and peripheral glucocorticoid receptors has potentially significant consequences for stress-related disorders affecting the brain-gut axis. Recent studies show that chronic exposure to cortisol in humans unmasks glucocorticoid receptor binding sites that are not evident with intermittent exposure to cortisol. This may help explain why chronic stress, which is accompanied by continuous cortisol secretion, acts to blunt healthy cortisol-mediated glucocorticoid receptor response later in life. In humans, this may be related to the disruption of circadian and ultradian rhythms and seasonal sleep habits associated with a variety of diseases.”[17]

“Diurnal rhythms in the HPA-axis and chronic intermittent stress have differential effects involving the brain-gut axis, including intestinal barrier function, peripheral pain signaling, and central nervous system modulation of pain perception. It appears that epigenetic regulation of NR3C1 expression plays a key role in these actions.”[17]

If we translate the above quotes into a word picture that is relevant to Kenny’s case, it looks like this:



Microbiome factors

Kenny's stool testing revealed lab high levels of Helicobacter pylori, which is a bacterium that is commonly associated with stomach ulcers and stomach cancer. [18] H. pylori damages the parietal cells of the stomach and creates a more hospitable environment for itself as it decreases stomach acid production by damaging these cells. In so doing, optimal protein digestion can suffer, resulting in a high protein meal feeling like a rock in your stomach. This maldigested protein then moves into the small intestine and becomes a fermentable substrate for bacteria resulting in protein malnutrition, gas, bloating, and/or small intestinal bacterial overgrowth (SIBO) in some people. [19]

Parietal cells and stomach acid are needed to produce intrinsic factor for the absorption of vitamin B12. [20] Vitamin B12 is required for many processes in the body, including energy production and the production of the myelin sheath used to cover our nerves. Poor vitamin B12 levels are associated with fatigue and poor cognitive function, sometimes called "brain fog."

Do you see how an H. pylori infection could play a large role in the gut-brain axis component of Kenny's case? To make matters worse for Kenny's parietal cells, testing revealed lab high parietal cell antibodies, which means he had an autoimmune process against his stomach. Research reveals cross-reactivity between H. pylori and parietal cells as a mechanism for creating this autoimmune process. [21]

Molecular mimicry is the mechanism by which that occurs. H. pylori wasn't the only evidence of infection in Kenny—his stool test also revealed lab high Citrobacter freundii. As with H. pylori, Citrobacter are gram-negative bacteria; meaning, they produce a metabolite called lipopolysaccharide (LPS). LPS is powerfully proinflammatory and is known to trigger microglial activation in the brain. [22]

The presence of Citrobacter is associated with inflammatory bowel disease in rodent models and is a known driver of diarrhea in humans. [23] In the bloodstream, it can be fatal. Kenny's secretory IgA (sIgA) was lab low, suggesting suboptimal mucosal immune response and tolerance. And as discussed in the last chapter, recent research suggests that the deficient sIgA levels are a key missing anti-inflammatory player

in Kenny's brain. [24] This deficient sIgA also contributes to food reactions. [25] Kenny was also deficient in healthy levels of the probiotic species Lactobacillus and Bifidobacterium.

Tying it all together

The graphic below from the A*sian Pacific Journal of Allergy and Immunology* [26] does a great job of tying together many of the components of the functional medicine framework into the context of the brain-gut, gut-brain axis. Many authors now call it the "microbiome-gut-brain axis" to give weight to the importance of the microbiome's involvement in the axis.

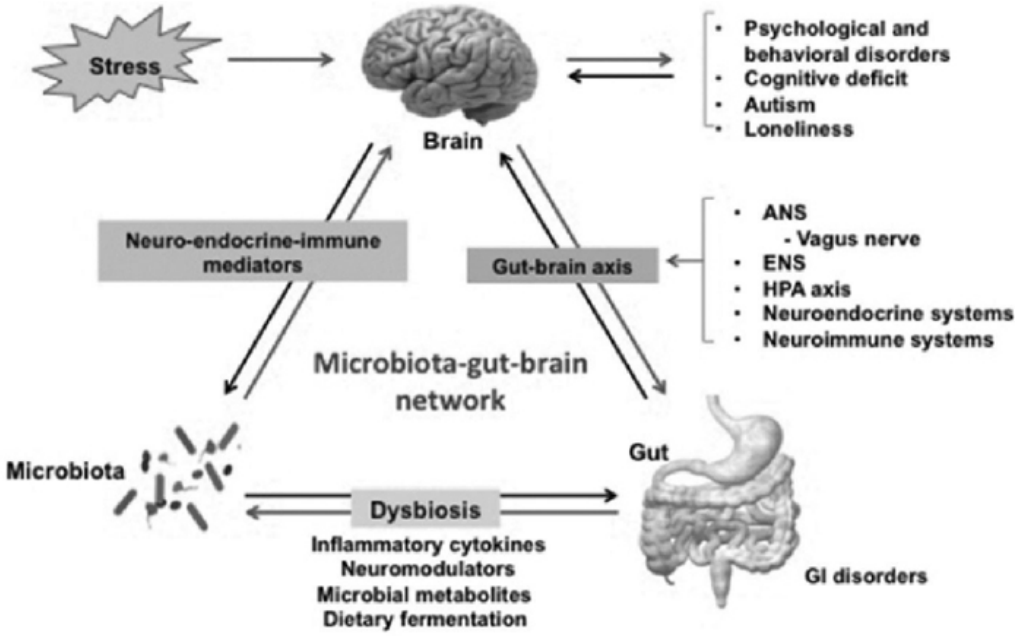


Figure compliments of the open access article from *Asian Pacific Journal of Allergy and Immunology* [2 6]

Addressing only the dizziness and migraine symptoms leaves any underlying contributions from the microbiome, GI tract, stress levels, and psycho-social context unaddressed. This creates a high probability that Kenny will fail his neurologic rehab, as he did at the first visit. In order to achieve the healing and restore the quality of life Kenny desired, we created a plan to address all the factors involved, not just the brain:

- A focus on optimizing blood sugar physiology by increasi fiber intake and changing when and what he ate. Focus optimizing probiotic levels and feeding them properly.

- Eliminating H. pylori and Citrobacter freundii using natur antimicrobials, restoring secretary IgA levels and oral tolerance
- Optimizing self-tolerance to decrease autoimmune attack c parietal cells, while also supporting stomach acid leve exogenously.
- Supporting optimal B vitamin levels and methylation to redu homocysteine and associated migraines and brain fog.
- Once oral tolerance was established, we re-introduced foods order to diversify nutrition for Kenny and his microbes.

Remember, Kenny suffered for twelve years from debilitating consequences of his head injury—change was not going to happen overnight. However, for Kenny, just knowing that there was a light at the end of the tunnel was enough to motivate him to work hard in the short term to get his life back. "Getting his life back" took six months.

Kenny's results

After six months of following an individualized and specific action plan based on objective testing, Kenny reported a seventy-pound weight loss, a significant decrease in pain, elimination of reflux, migraines and dizziness reduced in frequency, better sleep, and a 75 percent improvement in GI complaints. Kenny said, "I feel 90 percent better overall—I never thought 10 percent better was even possible." Kenny is now working a full-time job and playing golf and disc golf regularly. He is also eating a much more diverse and sustainable diet and loving life.

The brain-gut, gut-brain axis in anxiety, depression, and functional GI disorders

This chapter used Kenny's story and head injury as a context for teaching you the gut-brain, brain-gut axis. Head injury is only one example of how these loops can be started, but it is by no means the only way they are triggered. Plenty of research exists that has investigated and documented the reality of brain-gut, gut-brain loops and many diseases and disorders including

anxiety, depression, autism, neurodegeneration (such as Parkinson's and Alzheimer's), IBS, gastroesophageal reflux disease, and more. A simple PubMed search will reveal these studies to you.

A 2012 study in the UK journal *Gut* had 1775 people complete a validated questionnaire evaluating GI symptoms and symptoms of anxiety or depression. A follow-up survey was conducted twelve years later, and its key finding was that a clear population of patients with mood disorders, anxiety, or depression at the beginning of the study, who were initially free of functional gastrointestinal disorders, subsequently developed GI issues during that twelve years. [27]

On the flip side, individuals with functional GI issues that did not have anxiety and depression had a markedly increased chance of developing those twelve years later. The study concluded that the gut was probably the driver of psychological complaints in patients in whom GI symptoms predated mood disorder, and the brain was probably the driver of GI symptoms in patients in whom anxiety or depression manifested first.

In 2016, the same authors ran a follow-up study on 1900 people, which revealed that one-third of individuals had a mood disorder preceding their GI symptoms, whereas two thirds of people had GI symptoms that preceded their mood disorder. [28]

Brain-gut axis

As evidenced above, you do not have to sustain a head injury or any type of physical trauma to create abnormal brain-gut axis function; anxiety or depression is sufficient. The more traumatic the stress is physically, mentally, emotionally, chemically, or environmentally, the higher the likelihood that the brain-gut axis becomes dysfunctional.

Early life stressors, including a history of sexual, emotional, and physical abuse, are present in 44 percent of patients with functional GI disorders. [29] , [30] , [31] Abuse of any kind is a stressor, and as discussed earlier, psychosocial stress promotes neuroinflammation.

We have covered how neuroinflammation may result in GI symptoms. Brain inflammation and the associated

proinflammatory cytokines produced (IL-6, TNF-a, IL-1b) are implicated as the causal factor in major depressive disorder, as well as less serious versions of depression and anxiety. [32]

The depression and/or anxiety then result in HPA-axis activation with associated stress response and cortisol release. [33]

HPA-axis activation by psychosocial stress may result in gut symptoms via direct innervation of immune tissue in the gut from neurons of the paraventricular nucleus in the hypothalamus. These neurons release norepinephrine, which binds to large adrenergic receptors on immune cells in your gut and promotes a Th2 and/or a Th17 immune phenotype.

This process could be particularly relevant in functional GI disorders associated with Th2 immunity such as functional dyspepsia (GERD or acid reflux), IBS, and any eosinophilic or histamine-related GI issue.[1]

Research has shown that acute stress worsens GI function in IBD patients by increasing colon inflammation and intestinal hyperpermeability.[1] The stress of exposure to any one or a combination of factors promotes GI dysfunction, disorder, or disease by modulating visceral sensitivity, intestinal motility, secretory function, intestinal permeability, and vulnerability to intestinal inflammation. In short, stressors modulate those gut functions via the stress effect on vagal motor outflow, as discussed previously.

Gut-brain axis

According to the 2016 study[28] mentioned above, researchers found that two-thirds of the 1900 people with a mood disorder had a preceding gut disorder. It appears that the gut-brain half of the loop is more common, and based on my ten plus years of clinical experience, I believe this would probably hold true if we studied the U.S. population as a whole. Think about all exposome factors daily that can damage your gut and microbiome: glyphosate and other agricultural and industrial chemicals, processed food, gluten, alcohol, medications, antibiotics, vaccine ingredients, physical inactivity, mental, emotional, and relational stress, 5G and other EMFs, toxins and metals in our water supply, amalgam fillings, air quality,

deficient soils, declining nutrient density (even in organic foods), GMOs, sleep deprivation, financial and work stressors—the list goes on and on .

You may say, "Sure doc, that makes sense. But how do you explain the fact that while we are all exposed to many of the factors listed above on a daily basis, not everyone develops a gut-brain axis issue?"

Hallelujah! You are getting it. You are thinking like a detective now—great work! The answer to your profound question is because everyone is different in their physiologic integrity and capacity to deal with exposures. [34]

A key factor in determining a person's resilience from a gut-brain axis perspective is the state of their mucosal immune system. In chapter three, you learned that up to 70 percent of the immune system is in your GI tract. [35] You may remember that the reason for that is that most things that enter our bodies enter through the intestinal tract. The gut barrier that separates the outside world from our inside world is made up of a lining of epithelial cells that are one cell thick. Behind that one cell barrier sits our immune system.

Under healthy conditions, the immune cells in our GI tract exist in a state of physiological inflammation. "These cells are charged with the challenging task of remaining immunologically restrained in the face of trillions of commensal bacteria and, at the same time, poised to defend the vast surface areas of the GI tract from invading pathogens."[1]

Your GI immune cells must manage the identification of friend and foe while simultaneously communicating with the epithelial cells making up the gut barrier, the intestinal microbiota, and the enteric nervous system (ENS). If we add gut dysbiosis to the picture, such as a gram-negative E. coli or Klebsiella pneumoniae, the epithelial cells produce a genetic transcription factor called NF-kappa B that leads to the production of proinflammatory molecules such as IL-1b, TNF-a, IL-6. These molecules promote immune activation, which results in GI inflammation. Chronic GI inflammation can lead to systemic inflammation, which, in turn, can lead to brain inflammation.

This is how gut dysbiosis can result in anxiety, depression, migraine, brain fog, et cetera. [36]

We used gut infection (dysbiosis) as an example, but you could use any exposure known to promote intestinal epithelial damage as the example, such as gluten, glyphosate, antibiotics, or NSAIDs and have the same result in a susceptible person.

> "Although recognition of the directionality of this association might imply the existence of distinct mechanisms of disease, it is also possible that these different modes of presentation (that is, brain driving gut, or gut driving brain) might instead represent polar ends of the same disease process."[1]

In the next chapter, we'll discuss the role of gluten in autoimmunity of the brain, gut, skin, and various other tissues.

Reader action steps

To learn more about the brain-gut/gut-brain axis, view my Brain-Gut Axis video playlist here: https://www.FunctionalMedicineCharlotte.com/BrainGutAxis

Nutritional strategies to consider for healing the gut barrier and blood-brain barrier

L-glutamine, probiotics, SCFAs, baicalin, DGL, aloe vera, zinc carnosine, remove gluten (read next chapter), and any other food triggers (learn more about food reactions in chapter 8) .

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CHAPTER 6

Celiac Disease, Wheat Allergy, and Gluten Sensitivity

"Dietary cereal grains are the known environmental causative agent for at least two autoimmune diseases: celiac disease and dermatitis herpetiformis. Withdrawal of gluten-containing cereals from the diet ameliorates all symptoms of both diseases. Further, evidence implicates cereal grains in the etiology of other autoimmune diseases."

—Loren Cordain [1]

Timmy had always been underweight and undersized for his age, and for as long as he could remember, had experienced symptoms of a "nervous stomach." Gaining weight was always an issue, even when eating well and exercising hard.

It was so bad that during his college years, Timmy twice resorted to the "gallon a day milk challenge." As the name implies, he drank a gallon of milk a day for a couple of weeks (disclaimer: I do not recommend this). While on the milk binge, Timmy gained ten to fifteen pounds, but he also had increased stomach pain and developed anxiety. When he quit milk, the anxiety went away .

Four years later, after seeing a gastroenterologist and having endoscopy, colonoscopy, CT scan, ultrasound, and blood work done and finding nothing, Timmy was put on proton pump inhibitor medication for his stomach pain. A year later, a different gastroenterologist removed his gallbladder. The gallbladder was gone, but the stomach pain was still there. Timmy reported to me that his stomach pain got worse, his anxiety returned, and he lost thirteen pounds in one month.

Timmy presented to my office at twenty-seven with symptoms of white tongue (that was most pronounced after drinking beer), a lack of appetite, fatigue, stomach pain that was made worse by alcohol, anxiety about his stomach pain, brain fog, and frequent cold sores in his mouth. His goal was to eliminate his stomach

pain and anxiety and be able to eat and drink whatever he wanted.

Brittany was four when her mother brought her to my practice. Her major issue was chronic whole-body eczema with associated staph infections that began when she was two months old. When Brittany was three, she began having frequent stomach aches and multiple sinus infections. She was on daily hydroxyzine and Benadryl as systemic anti-histamine strategies, in addition to topically applying the steroid creams triamcinolone acetonide and Fluocinonide. Brittany's torso was covered in eczema, and her family referred to it as "elephant skin" because it was so rough and thick. Her mom's goal was to find and eliminate the cause of the eczema and achieve the clear skin that every mother wants for her daughter.

Jack was a senior Division 1 college football player who hadn't had a solid stool in six years and had been iron deficient twice in the same period. He had facial acne and reported that after eating, he often experienced a cloudy head and felt like the back of his eyeballs were burning. His diet was typical of a college athlete—it was made up of meals at the school cafeteria, plenty of pizza and fast food on weekends, with nary a vegetable. Other than seeing the campus medical clinic twice for fatigue (which led to the two iron deficiency diagnoses), Jack didn't have a medical record. His goal was to correct the underlying cause of his diarrhea and iron deficiency. If his skin cleared up, that would be a bonus.

Three cases, three different decades of life, three different disorders, one common culprit. Do you know what the culprit is? (Hint: the answer is in the chapter title.)

You nailed it! Gluten.

Gluten is the common major driver behind these three cases. Each of these people suffers from a different malady caused by gluten, but none share a common malady. "How does that work? Gluten is gluten and affects everyone the same, doesn't it?"

Well, not exactly.

"Taking into account all gluten-related disorders, it has been estimated that about 3 percent of the human population suffers from wheat intolerance. Today, almost half of the calories

consumed by the human population worldwide come from cereals, with wheat being the most popular grain in Europe and the Americas. Its use is so widespread that people suffering from gluten related disorders have difficulty in avoiding it." [2]

A 2014 U.S. *Consumer Reports* survey reported that 63 percent of responders felt that abstaining from bread and other gluten containing diets would enhance their physical and mental health. A 2015 Gallup poll reported that 21 percent of Americans disclosed they were trying to follow a gluten-free diet. [3]

The World Health Organization (WHO) lists twenty-eight wheat allergens, meaning it recognizes twenty-eight parts of wheat that have allergic potential in humans. [4] For the purposes of this book, we will divide gluten-related disorders into three diagnoses: wheat allergy, celiac disease, and non-celiac gluten sensitivity (NCGS, aka "gluten sensitivity"). Let us dive into the nuts and bolts of these three diagnoses and then return to our cases to determine who has which issue. Once we know who has what, we can create an individualized and specific action plan based on each person's unique puzzle of exposome, epigenome, and microbiome-related factors and pursue healing.

Wheat allergy

"A food allergy to wheat is characterized by T helper cell type 2 (Th2) activation, which can result in immunoglobulin E (IgE) and non-IgE mediated reactions. IgE mediated reactions are immediate and characterized by the presence of wheat-specific IgE antibodies. They can be life threatening. IgE mediated responses to wheat can be related to wheat ingestion (food allergy) or wheat inhalation (respiratory allergy). A food allergy to wheat is more common in children and can be associated with a severe reaction such as anaphylaxis and wheat-dependent exercise induced anaphylaxis. An inhalation induced IgE mediated wheat allergy can cause baker's asthma or rhinitis." [5]

"A food allergy to wheat manifests with a variety of symptoms that include hives, asthma, allergic rhinitis, abdominal pain, vomiting, acute exacerbation of eczema, and exercise induced asthma, all of which may start within two hours after the first exposure to wheat."[5]

“The diagnosis of an IgE mediated wheat allergy is based on an accurate history that documents symptoms specific of IgE mediated food allergy to wheat. When these symptoms occur within one to three hours of wheat exposure, the allergy to wheat needs to be confirmed by measuring IgE antibody specific to wheat by skin prick testing or in the blood. The presence of specific serum IgE to wheat without a clear history of symptoms after wheat exposure is not diagnostic, as many people can be sensitive to wheat but not have an anaphylactic reaction.” [5]

“In young children, gastrointestinal symptoms such as vomiting, diarrhea, or abdominal pain prevail. In about 40 percent of children, skin symptoms are observed in the form of hives, redness, itchiness, or worsening eczema. Older children suffer mostly from dermatitis, which is accompanied by respiratory disorders, and in the most severe cases, anaphylaxis. In teenagers and adults, the most severe forms of allergy prevail (such as anaphylaxis) in about 50 percent of people. Wheat allergy can be accompanied by allergies to other cereals, most often to rye or corn.”[2]

As stated earlier, the WHO recognizes twenty-eight allergens in wheat. If you experience symptoms when consuming wheat and ask your doctor to test you for a wheat allergy, he may run a skin prick test against wheat, gluten, or gliadin, and receive negative results. He may also test the same allergens through serum IgE and receive negative results. In this instance, he would tell you that you do not have a wheat allergy, and you may continue to consume wheat. But do you really not have a wheat allergy?

We cannot say for sure because there are twenty-five other allergens in wheat recognized by the WHO that were not tested. We do not have the ability to test for all twenty-five of those allergens, so the possibility remains that you may have a wheat allergy to one or more of those allergens in wheat. In this instance, you must take the symptoms from consuming wheat as a red flag from your body and STOP consuming wheat. Continuing to poke the bear does not end well.

The gold standard of a wheat allergy diagnosis remains the oral food challenge, also known as the elimination provocation test.[5] Eating wheat, experiencing a reaction, and suspecting an allergy is step one. Step two is strict elimination of wheat from the diet

for twelve weeks. Step three is to provoke the reaction by re-introducing the allergen. If you again experience a reaction, this suggests wheat allergy .

At the moment, management of IgE mediated wheat allergy is mainly based on avoidance of both food and inhaled wheat allergens.[5]

Celiac disease

“Celiac disease has traditionally been considered to be a pediatric gastrointestinal disease characterized by malabsorption and failure to thrive. However, this perspective has changed substantially in recent years. It is now considered a common autoimmune disease that can present at any age with both intestinal and extra-intestinal (outside the GI tract) manifestations.” [6]

“Celiac disease can be present in the absence of gastrointestinal symptoms. In fact, nearly half of the celiac disease patients diagnosed in adulthood do not have relevant GI complaints. In addition to the classic iron deficiency anemia, diarrhea, and osteoporosis, celiac disease is the cause of symptoms such as fatigue and chronic musculoskeletal pain, which accompany many systemic diseases and therefore implicates celiac disease as the great imposter.”[6]

“Celiac disease is known to be associated with other autoimmune diseases, most frequently autoimmune thyroid disease and Sjogren’s syndrome. The presence of autoimmune diseases associated with celiac disease is reason enough to consider performing blood testing for celiac disease in autoimmune patients with fatigue, anemia, and chronic pain.”[6]

“Celiac disease is considered to be an autoimmune enteropathy caused by exposure to gluten in genetically predisposed individuals. Those who are positive for HLA-DQ2 or DQ8 haplotypes may have an adaptive immune response to gluten with production of tissue transglutaminase and endomysium antibodies and infiltration of the intestinal barrier by intraepithelial lymphocytes; which, when severe, lead to the discovery of atrophy of the intestinal villi on their duodenal biopsy.” [6]

“Genetic factors greatly determine susceptibility to celiac disease. All celiac disease patients carry HLA-DQ2 and/or DQ8 haplotypes, but since the prevalence of HLA haplotypes in most populations is between 25 and 50 percent, only a minority with this necessary but insufficient genetic predisposition will ever develop celiac disease. This implies the involvement of additional non-genetic as well as environmental factors in celiac disease manifestation.” [7]

Historically a diagnosis of celiac disease is not final without a duodenal biopsy revealing villous atrophy. Recently though, multiple studies have suggested that celiac diagnosis can be made without biopsy on the strength of positive antibody levels alone. [8] , [9]

Celiac disease commonly leads to nutritional deficiencies in iron, folate, vitamins B12 and B6, copper, and zinc. Low bone mineral density may also be present secondary to malabsorption of vitamin D. Eighty-seven percent of celiac patients have deficiencies in at least one serum vitamin or mineral. [10]

Celiac disease is an autoimmune disease with systemic impact. The two main self-tissue targets in celiac disease are the enzyme tissue transglutaminase (tTG) and intestinal endomysium. Tissue transglutaminase enzymes are a family of enzymes with many physiological functions. For the purposes of this chapter, we will focus on three members of the human tTG family, tissue transglutaminase-2, -3, and -6 (tTG-2, tTG-3, tTG-6) [11] and microbial tissue transglutaminase (mTG). [12]

Tissue transglutaminase plays a significant role in diseases of inflammatory, degenerative, neurodegenerative, malignant, metabolic, hormonal, genetic, and autoimmune nature. A few examples to mention are type 1 diabetes, dermatitis herpetiformis, multiple sclerosis, lupus (SLE), Sjogren’s syndrome, and rheumatoid arthritis.[12]

Endogenous microbial transglutaminase is secreted by the gut microbiota, especially in a dysbiotic gut and is a potent driver of systemic autoimmunity. Massive use of microbial transglutaminase in the processed food industry and the increased use of probiotics with microbial transglutaminase activities may be additional contributors.[12] Microbial

transglutaminase is immunogenic in children with celiac disease and by complexing to gliadin its immunogenicity is enhanced. [13] Gliadin is an ideal substrate for endogenous tissue transglutaminase and exogenous microbial transglutaminase.

"Gluten is abundant in glutamine and lysine and thus is a very attractive substrate for post-translational modification of protein by both tissue transglutaminase and microbial transglutaminase. Both enzymes are able to deamidate or cross-link gluten peptides to numerous other peptides, thus turning naïve, self-proteins into immunogenic ones. Gut microbial transglutaminase derived from processed food or from the microbiome, or more specifically from a dysbiotic microbiome, is a major cause of modification of gliadin. Finally, it should be emphasized that gluten affects the microbiome, and the microbiome also affects gluten—it might even play a role in the breakdown in the immunogenicity of gluten."[12]

The result of intestinal hyperpermeability, nutrient malabsorption, GI dysbiosis, and chronic immune activation and inflammation is what leads to unique combinations of myriad symptoms in different individuals [14] and helps explain why celiac disease is nicknamed the "Great Imposter" or "Great Imitator."

Celiac disease and the skin [15]

Dermatitis herpetiformis (DH) is the skin manifestation of celiac disease. In 2002, epidermal transglutaminase was discovered as the main autoantigen tissue target in DH. Epidermal transglutaminase is also known as tissue transglutaminase-3 (tTG-3). People with DH have high levels of both tTG-2 and tTG-3 antibodies .

Dermatitis herpetiformis occurs in about 10 percent of people with celiac disease and is a chronic, extremely itchy skin rash made up of bumps and blisters. The disease is driven by a combination of genetic susceptibility (HLA-DQ2 or DQ8) and prolonged gluten exposure. Prolonged gluten exposure leads to immune stimulation that promotes tTG-3 based cross-linking of skin and autoantibody production, yielding DH.

Celiac disease and the brain

“Nowadays it is widely accepted that the typical disease represents a small portion of the so called ‘celiac disease iceberg’ because five to six fold more patients present with atypical or silent forms. Neurological manifestations may either precede or follow the disease or be present at its onset… Cerebellar ataxia, peripheral neuropathy, seizures, headache, cognitive impairment, and neuropsychiatric diseases are complications frequently reported…This presence of neurological symptoms in people who present with silent or atypical forms of CD is termed ‘celiac brain.’” [16]

As mentioned earlier, the human family of tissue transglutaminase enzymes includes tTG-6. Since its discovery in 2008, tTG-6 has been associated with neurologic symptoms such as gluten ataxia and gluten neuropathy.[15] In fact, nearly 60 percent of people with gluten ataxia are positive for tTG-6 antibodies.[11]

Similar to tTG-2, when tissue tTG-6 is exposed to gluten peptides, it can both deamidate and transamidate them. tTG-6 can also form the previously mentioned self protein-immune complexes with gluten, and it’s conceivable that in the event of blood-brain or blood-nerve barrier disruption, tissue tTG-6 may become exposed to gluten-derived antigens, activate the immune system, and lead to production of anti-tTG-6 antibodies.[15] In conventional medicine, if celiac disease is suspected, it is standard to run tTG-2 IgA and endomysial IgA antibodies along with performing a duodenal biopsy to investigate for villous atrophy .

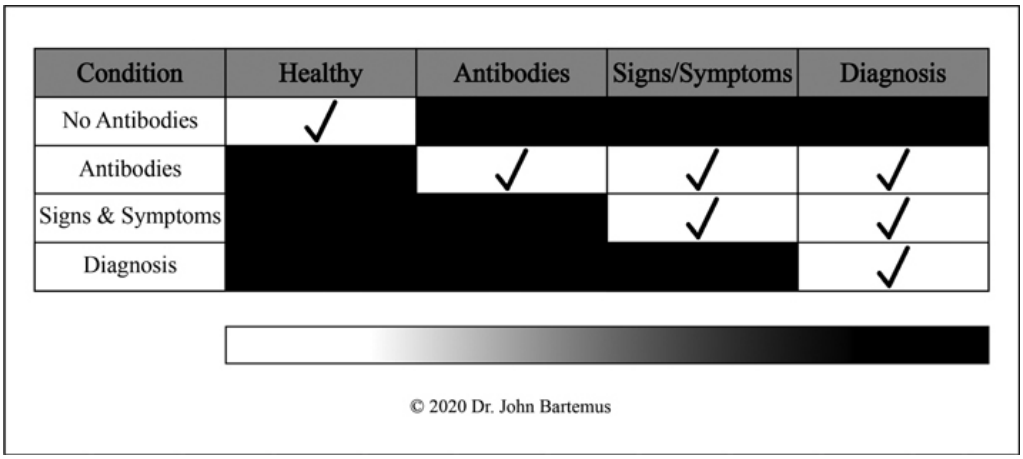
But what if you are one of the 50 percent of adults with celiac disease and zero GI symptoms? For example, what if you have symptoms of loss of balance, headaches, and anxiety that all seem to be worse after eating pizza? Do you think your doctor will suspect celiac brain? Unlikely. Most doctors are unaware of the existence of tTG-6 or tTG-3.

What if you have patches of extremely itchy skin with bumps and blisters made worse with beer consumption in the absence of GI complaints? Will your PCP have DH high up on their differential list? Probably not.

In both examples, it is highly likely that you would be a casualty of the "Great Imposter." You have a variant of celiac that looks a lot like more common diagnoses such as anxiety, psoriasis, etc. This could lead to you suffering for years and being put on many unnecessary prescriptions until, hopefully, you found a doctor that would do the detective work necessary to discover the correct diagnosis.

In the meantime, the chronic inflammation caused by your consumption of gluten and the resultant atypical celiac disease being left undiagnosed or misdiagnosed for too long has increased your risk of developing additional autoimmune diseases[3] such as autoimmune thyroid disease or type 1 diabetes[7], and it has increased your risk of death from all causes. [19]

Remember way back to the Introduction of this book, where we discussed the difference between an autoimmune process and an autoimmune disease? Do you remember the graphic I showed you helping you to understand that autoimmune diseases don't happen overnight?



They are first an autoimmune process that, at its earliest stages, is only recognizable as positive antibodies. As discussed, those antibodies are predictive of a possible future disease if changes are not made to your lifestyle and physiology. When those changes aren't made, the process continues and eventually signs and symptoms join the antibodies. At that point, you are suffering, but you do not yet meet diagnostic criteria for an autoimmune disease, so your doctors do not do anything to prevent the process from proceeding. Then, eventually, enough tissue damage (and suffering) has occurred for you to finally meet diagnostic criteria, and your doctor puts a name on it by

diagnosing you with an autoimmune disease. You and your doctor now feel relieved because you finally have a name for your suffering. Do not take solace in the diagnosis. Diagnosing the disease does nothing to stop, reverse, or heal it. You must TAKE ACTION to stop, reverse, and/or heal the disease. Otherwise, your health continues to decline while your all-cause mortality (risk of death from any and all causes) continues to climb.

Let's use celiac disease as an example. We are now going to build on our autoimmune process vs. autoimmune disease graphic in order to show you the danger of remaining undiagnosed or misdiagnosed. This new graphic will also show you the benefit of having a true detective clinician on your team.

But first, you must understand what a hazard ratio (HR) is. In plain English, a hazard ratio is a statistic used in research to compare the risk of death over time of a group of people with a given disease diagnosis compared to an age-and sex-matched group of people without the diagnosis. [20] For example, if the main outcome is all-cause mortality (ACM) or risk of death from all causes, what is the HR for people with celiac disease versus people without celiac disease?

An HR of 1 between the two groups would mean they have an equal risk of death. Said another way, an HR of 1 would mean that people with CD do not have an increased risk of death over time due to their CD diagnosis compared to people without a CD diagnosis.

An HR greater than one, for example 1.5, would mean that people with CD have a 50 percent increased risk of death from all causes over time compared to people without CD. Conversely, an HR less than one, for example 0.5, would mean that people with CD have a 50 percent decreased risk of death from all causes over time compared to people without CD. Got it? Good.

In 2009, a study in the *Journal of the American Medical Association* [19] examined the HR for all-cause mortality over an almost forty-year period in people with celiac disease based on small intestinal biopsy results. Biopsy results were graded based on Marsh Classification criteria.

Marsh Classification is ranking of the biopsy results from a stage 0 to a stage 3.

- Stage 0: Normal mucosa
- Stage 1-2: Inflammation and intraepithelial lymphocytos without villous atrophy
- Stage 3: Villous atroph y

What is really great about this study is that the authors didn't just investigate whether and how much the autoimmune *disease* (CD) increased risk of death, but they also studied (knowingly or unknowingly) whether the autoimmune *process* increased risk of death.

The autoimmune process is broken into two categories:

1. **Inflammation:** Defined by Marsh stage 1-2, which represents immune invasion of the small intestinal barrier (intraepithelial lymphocytosis)
2. **Latent celiac disease:** Defined by Marsh stage 0, which means the person had completely normal small intestinal mucosa on biopsy but was positive for IgG and/or IgA antibodies to gliadin, endomysium, and/or tTG-2.

Celiac disease was diagnosed using Marsh stage 3 criteria of villous atrophy of the small intestine. This study had 29,096 individuals with celiac disease, 13,306 with inflammation on Marsh stage 1-2, and 3,719 with latent celiac disease or Marsh stage 0. The authors found the following hazard ratios:

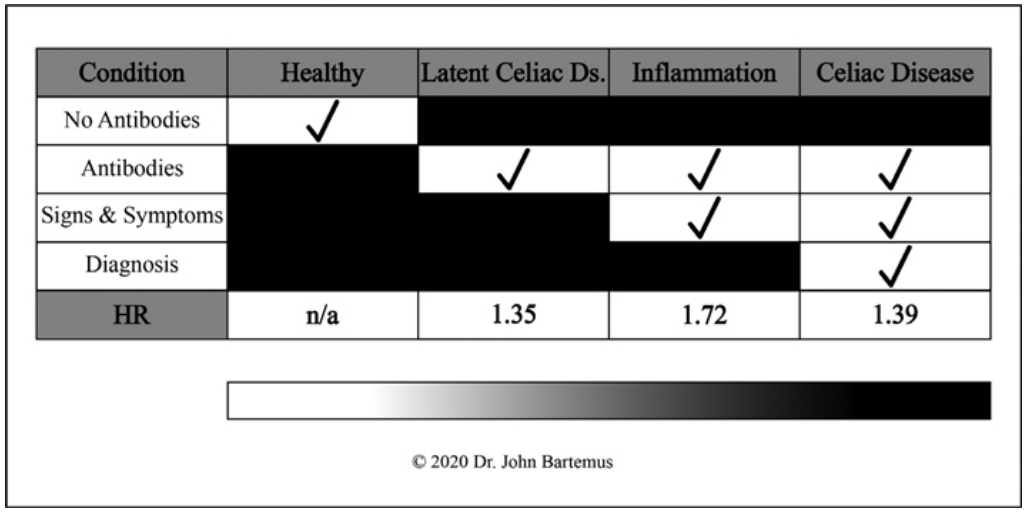
1. **Latent celiac disease = 1.35**
2. **Inflammation = 1.72**
2. **Celiac disease = 1.39**

Do you see that? The obvious result is that all Marsh stages increase the person's risk of death. Autoimmune process or autoimmune disease, doesn't matter—falling anywhere on the spectrum raises your risk of death.

Wow–let that soak in.

Now look closer. Do you see that fitting diagnostic criteria for CD or being early in the autoimmune process that may result in it (represented by positive antibodies) both increase your risk of death almost the same amount? And look at that inflammation number! Intestinal inflammation increases your risk of death from all causes by 72 percent!!!

Do you think GI inflammation is damaging?! How important is it to put that fire out ASAP? Do you see why you cannot trust symptoms? Feeling is not function! You may feel fine but have GI inflammation that is destroying your lifespan. If we add these findings to our graphic, here's what it will look like.



With all the information organized like this, I hope it is easier to see that positive findings for antibodies associated with celiac disease in the absence of signs or symptoms is not benign. In fact, this study suggests that it is as dangerous to your health and lifespan as having a CD diagnosis.

You should also see the extreme negative impact of chronic GI inflammation. Having positive antibodies and experiencing signs and symptoms of disease for years before you finally fit diagnostic criteria is very risky. In the case of the CD spectrum, it has the potential to be almost twice as deadly as having the diagnosis. This is one study on one autoimmune disease. My

suspicion is that similar findings would be discovered if other autoimmune processes to disease spectrums were studied.

Do NOT wait for a diagnosis! Take action today. Partner with a functional medicine detective, discover the key pieces to your puzzle, and put the fires out.

The astute reader is thinking, “Why is there a big decrease in risk of death from GI inflammation (Marsh stage 1-2) to celiac disease (Marsh stage 3)?”

Great, great question.

It is likely related to the fact that when you don’t know why you are suffering or what pieces of the puzzle are contributing to your suffering, you do not have concrete action steps to take to end the suffering. Therefore, you stay inflamed and, hopefully, keep searching for a detective that can give you answers. Whereas, the person with the celiac disease diagnosis now has concrete action steps to take to put the fire out and optimize immune function and overall health. In the case of CD, the first and most obvious action step is to immediately eliminate all wheat and other gluten-containing grains from your diet and life. As authors in a 2018 paper in the journal *Nutrients* [7] found: “While a gluten free diet does not reverse glandular autoimmunity, its early institution may delay or even prevent its manifestation.”

These authors found that avoiding gluten not only treats the celiac disease, but it also delays or prevents the manifestation of autoimmunity in glandular tissue, such as the thyroid and pancreas, in individuals with CD. By eliminating gluten exposure and then addressing the other relevant pieces to an individual’s puzzle, the person with CD is putting the fire out and decreasing her risk of thyroid autoimmunity, type 1 diabetes, and death at the same time .

Non-celiac gluten sensitivity

Non-celiac gluten sensitivity (NCGS) is an entity that has been documented clinically from as far back as 1978. For ease of communication, from here on out I will mostly refer to it as gluten sensitivity (GS) and consider the two terms synonymous. [21]

Gluten sensitivity is characterized by gluten-related intestinal and systemic symptoms in patients with negative celiac disease testing. Therefore, these people are not considered to be celiac patients. Gluten sensitivity is more prevalent than celiac disease and is estimated to affect around 5 percent of the population. There is no bulletproof diagnostic test for gluten sensitivity; there are a few blood tests that are useful when interpreted in context of the entire case. These include IgG antibodies to native gliadin, deamidated gliadin peptide, and anti-gliadin antibodies.[6]

As it stands to date, the diagnosis is based on the exclusion of celiac disease and wheat allergy in patients who have gluten-related symptoms.[6] There are many examples of patients who following strict criteria cannot be considered celiac, but whose profile overlap substantially with celiac disease.[6] The clearest examples are patients with gluten-sensitive gut inflammation without villous atrophy. In other words, people in the previous study that met Marsh stage 1-2 criteria.

In gluten sensitive GI inflammation, there may be no villous atrophy, only an increase in the number of intraepithelial lymphocytes. There are patients with celiac disease-like symptoms, negative tests for specific antibodies, and no villous atrophy, but they have HLA susceptibility and intraepithelial lymphocytosis on biopsy and respond positively to a gluten-free diet.[6]

As discussed in the celiac disease section, the people in this study would fall into Marsh stage 1-2 due to the intraepithelial lymphocytosis. In other words, these people would fall into the inflammation section of the Process to Disease graphic, putting them at the highest risk of death from all causes, even though they don't fit diagnostic criteria.

"Gluten sensitivity is distinguished by symptoms that typically take place soon after gluten ingestion, go away with gluten avoidance, and relapse following gluten challenge within hours to a day. The classical clinical picture of gluten sensitivity is a combination of IBS-like manifestations such as abdominal pain, bloating, diarrhea, or alterations in bowel habit…Systemic manifestations most commonly include brain fog, headache,

fatigue, joint and muscle pain, leg or arm numbness, eczema, skin rash, depression, or anemia." [22]

Historically, gluten sensitivity has not been considered an autoimmune disease, but recent research presents evidence that history has been wrong. Similarly to celiac disease, gluten sensitivity can be considered an immune system-related disease.[22]

A recent Italian study found that anti-nuclear antibody (ANA) positivity, a well-known marker of autoimmune risk, was present in 46 percent of gluten sensitive subjects compared to 2 percent of controls. The same authors found on retrospective analysis that 29 percent of gluten sensitive subjects went on to develop autoimmune diseases, with Hashimoto's thyroiditis being the most common. [23] Other studies have found association of gluten sensitivity with the autoimmune diseases systemic sclerosis, Raynaud's phenomenon, and Sjogren's syndrome.[22]

How does gluten sensitivity in the absence of celiac disease promote autoimmune development? A 2017 study in the journal *Nutrition Reviews* [12] says it this way: "Gluten affects the microbiome and increases intestinal permeability. It boosts oxidative stress and affects epigenetic behavior. It is also immunogenic, cytotoxic, and proinflammatory. Gluten intake increases apoptosis and decreases cell viability and differentiation." That is a mouthful, but that one quote reveals that ***gluten promotes autoimmunity by checking every box of our functional medicine framework*** —exposome, epigenome and microbiome.

As we have discussed at multiple points in this book, the Th17 cell line of the immune system is associated with promoting the tissue damage in autoimmunity. Researchers studying the influence of a gluten-containing diet on type 1 diabetes risk in mice found that gluten "substantially increased the Th17 cell population in pancreatic lymph nodes." [24] This means that feeding the mice gluten substantially increased the risk of immune-mediated pancreas destruction. Immune destruction of the pancreas is what causes the autoimmune disease known as type 1 diabetes. More importantly, these results were found in the absence of celiac disease. In other words, consuming gluten

increases damage to the pancreas in type 1 diabetes even if you do not have CD.

Gluten's role in diabetes is not limited to type 1 diabetes. A recent study found that mice consuming gluten in the context of a high-fat diet had higher hemoglobin A1c (Hba1c) levels and higher insulin resistance parameters. [25] This suggests that consuming gluten in the context of the Standard American Diet promotes type 2 diabetes.

Similar to the "celiac brain" described in people with CD, central nervous system pathology is frequently found in gluten-sensitive individuals. According to one study that followed its subjects for twenty years, the most common neurologic disorder in GS people is peripheral neuropathy followed by ataxia and encephalopathy. Interestingly, the authors found similar levels of tTG-6 antibodies in the CD group (67 percent positive) and the NCGS group (60 percent positive). The researchers concluded, "An important finding in this study is that patients with gluten sensitivity can present with neurological dysfunction in an identical manner to those patients with celiac disease, suggesting similar immunological processes being responsible at least for the neural damage. This is also supported by the similar prevalence of tTG-6 antibodies in the two groups." [2 6]

This means that gluten is not just toxic for you if you have CD. At minimum, the effect of gluten on your nervous system and the associated risk of developing peripheral neuropathy (such as numbness, tingling, and/or burning of the hands and/or feet), gluten ataxia (loss of balance), or gluten-induced brain inflammation (encephalopathy) is equivocal to the effect it has on a person with CD. Taken a step further, maybe you don't have frank neurological complaints such as neuropathy or ataxia. Maybe your complaint is "just" brain fog, headache, or something considered psychiatric such as anxiety or depression. These are all common symptoms found in GS people.

What if your anxiety or depression is being caused by gluten consumption, but instead of questioning you about your diet, your mental health doctor reflexively prescribed you an antidepressant medication? So you take the drug, but continue eating gluten and therefore get no better. Now the drug becomes 100 percent risk.

Don’t laugh; this is real. So real, in fact, that authors in the journal *Frontiers In Human Neuroscience* [27] challenged psychiatrists and psychologists in 2016, saying, “Perhaps because gastroenterology, immunology, toxicology, and the nutrition and agricultural sciences are outside of their competence and responsibility, psychologists and psychiatrists typically fail to appreciate the impact that food can have on their patient’s condition. Here, we attempt to help correct the situation by reviewing, in nontechnical plain English, how cereal grains, the world’s most abundant food source, can affect human behavior and mental health. We present the implications for the psychological sciences of the findings that, in all of us, bread 1.) makes the gut more permeable and can thus encourage the migration of food particles to sites where they’re not expected prompting the immune system to attack both of these particles and brain relevant substances that resemble them and 2.) releases opioid like compounds capable of causing mental derangement if they make it to the brain. ”

Perhaps first-line standard of care in mental health should be a period of strict gluten avoidance before any prescriptions are written.

Lastly, I will call your attention to the part of the authors’ quote above that says “in all of us.” You do not have to have CD or NCGS—IN ALL OF US gluten increases gut permeability, risk of autoimmunity via molecular mimicry, and risk of mental derangement.

Who had which disorder?

Let us now return to our three cases and determine who was suffering from the three gluten-related disorders covered in this chapter.

Our first case was Timmy, twenty-seven, who had lifelong complaints of “nervous stomach” and inability to gain weight. More recently, he had developed anxiety. I hope you noticed the gut-brain axis mechanism for his anxiety.

Timmy’s testing revealed lab high levels of tTG-2 IgA and anti-gliadin IgA antibodies. As you have learned in this chapter, this is serologic evidence of celiac disease. Some researchers believe

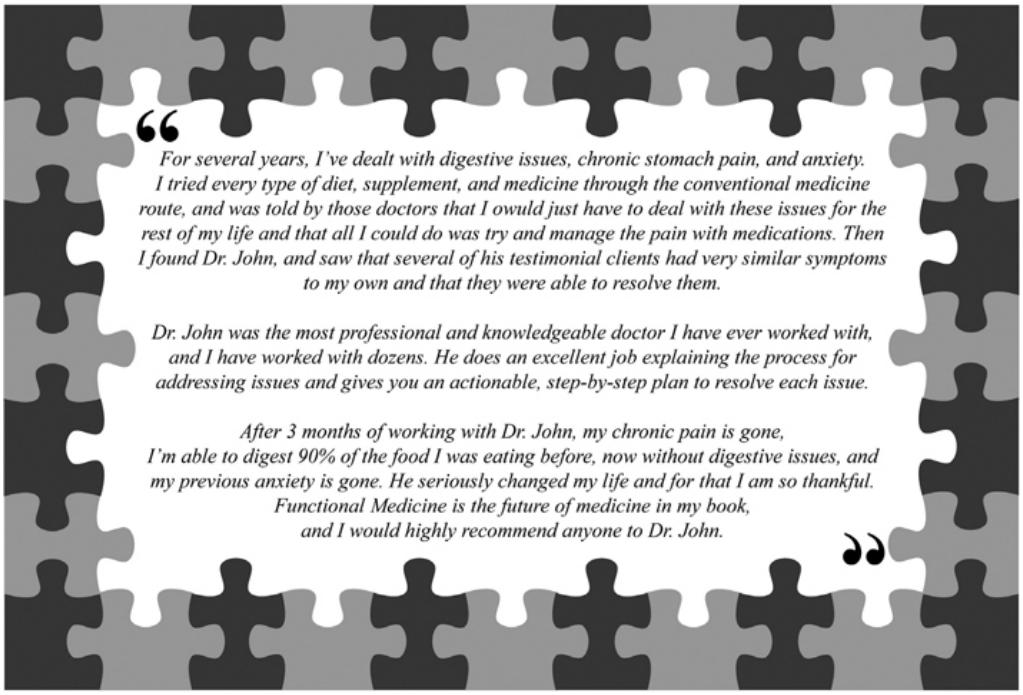
these findings combined with his clinical presentation are enough to diagnose it, but conventional medicine does not support this thinking. It wants to see a positive Marsh stage 3 small intestinal biopsy before it will give the diagnosis. This stubborn criteria by conventional standards is what has led to Timmy's lifelong suffering.

This evidence was enough to indicate, at minimum, latent celiac disease, and as you learned earlier, latent celiac disease increases risk of death from all causes on par with celiac disease.

In addition to these findings, and further supporting the celiac disease diagnosis, we found glandular autoimmunity in the form of positive thyroid peroxidase (TPO) antibodies and stomach autoimmunity evidenced by positive anti-parietal cell antibodies. It is plausible that the misdiagnosis or complete lack of diagnosis of a celiac process for so long in Timmy's case resulted in the development of polyautoimmunity (or multiple autoimmune processes). Lastly, stool testing revealed lab high levels of the pro-inflammatory parasite Blastocystis hominis as well as lab high levels of Candida in Timmy's gut. Add to these objective findings the fact that work stress and relationship stress were high, and it's no wonder Timmy was falling apart.

The first and most important actionable step Timmy had to take toward healing was elimination of all gluten from his diet and lifestyle. If he didn't do that, anything else we tried would be a waste of time and money because consuming gluten was pouring gas on the fire of the immune response vs. tTG-2 and gliadin.

Timmy was on board, and after three months of implementing a strict gluten-free diet and an individualized and specific action plan addressing his findings, Timmy was a different man. I'll let him tell you…



Brittany was the four-year-old with lifelong whole-body eczema and "elephant skin" that led to development of chronic skin and sinus infections. What was causing this Atopic March of symptoms?

What is an Atopic March? Researchers in the journal *Nature Reviews Immunology* [28] stated, "The atopic diseases tend to occur in a progression termed the Atopic March in which the initial manifestation of atopic disease in infancy or early childhood is often atopic dermatitis [also known as eczema], followed by the development of food allergy, allergic rhinitis, and allergic asthma." These atopic diseases are the result of an immune system that has become dominant along a Th2 phenotype. The Th2 phenotype is responsible for allergic reactions.

Brittany's testing revealed lab high levels of eosinophils, which is suggestive of a Th2 dominance. She also had lab high platelet levels, lab high IgE levels, and tested positive for IgE responses to wheat. Brittany had a wheat allergy. Stool testing revealed deficiency in the probiotic species Lactobacillus and lab high levels of the pro-inflammatory bacterium Enterobacter cloacae.

Again, in Brittany's case, the linchpin was eliminating wheat. If she did not do that, she would continue to promote the allergic inflammation and Atopic March. Eliminating wheat, combined with an individualized and specific action plan focused on

balancing her immune phenotype and creating a balanced gut microbiome, was our strategy for healing.

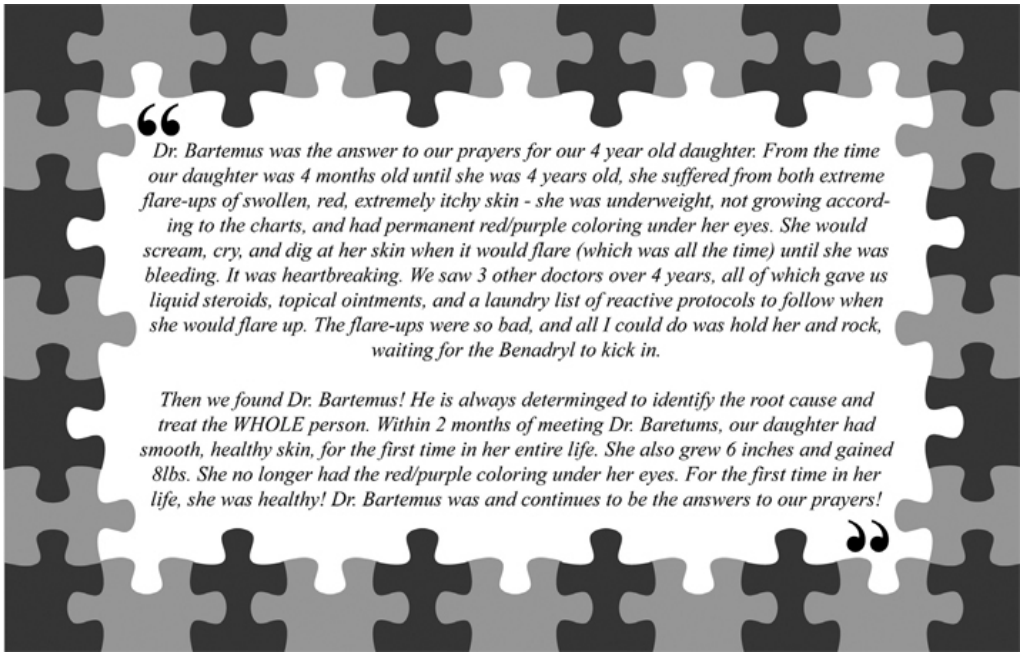
How did it go? Here are her mom's words: "Within three weeks of cutting wheat, dairy, and egg out of Brittany's diet, and taking her supplements according to the plan provided, the feel of her skin was smooth to the touch for the first time in almost four years. The first couple of days seemed to be rough, with more inflammation; however, we knew that this was possible when going through the detox process. It appeared as though her skin began clearing up from the torso and then moved to her extremities. Her hands and feet were the last to clear up.

After being on the dietary and supplement regimen for just over three weeks, we went to a fall festival where there was a demonstration of antique farm equipment, one shucking corn stalks and the other bailing hay. The bailer was being fed wheat, which we discovered after it was all in the air and falling all over us. Within fifteen minutes, Brittany's skin completely inflamed and was swollen. She was screaming and crying that she was 'so itchy.' She was digging into her legs so badly that she began bleeding on her legs. We rushed her home and gave her Benadryl."

Within three weeks Brittany had complete clearance of her skin, suggesting significant balancing of her immune system. Does balance mean she is healed? No. The IgE antibodies were still present and waiting for stimulation by wheat exposure. That exposure came in the form of inhaled wheat from the air, and then BOOM, allergic reaction.

I share this with you, dear reader, because I do not want you to be lulled into thinking Brittany is (or you are) healed just because her/your skin clears up in three weeks. It takes more time and consistency to rebuild immune tolerance, and the allergic reaction can be triggered by forms of wheat other than food. Inhaled wheat can do it as evidenced here. Topical exposure can do it as well.

Ultimately, we overcame this exposure, and Brittany was able to achieve healing. Five weeks after that flare, Brittany had smooth skin and had gained eight healthy pounds. Here is the testimonial from her mother:



Jack was the college athlete with acne, iron deficiency anemia, chronic diarrhea, brain fog, and burning eyes associated with eating. Testing on Jack was negative for tTG-2 and gliadin antibodies. These results suggested no celiac disease and on the surface suggest absence of gluten sensitivity. We must remember, however, that up to 50 percent of people with gluten sensitivity test negative for gliadin antibodies. [29] Jack's stool testing revealed lab high Helicobacter pylori, Giardia (parasite associated with traveler's diarrhea), and deficient digestive enzyme production.

I had Jack keep a food journal and track when he felt the eye burning and brain fog symptoms and associate them with the foods he had eaten. We discovered that the symptoms were associated with pizza, pasta, and other gluten-containing foods. Given the multiple symptoms associated with gluten sensitivity and the fact that Jack associated consumption of gluten-containing foods with his neurological symptoms, I suspected gluten sensitivity .

We embarked on an individualized and specific action plan to eliminate Jack's gut pathogens, improve his pancreas' ability to produce digestive enzymes, and eliminate gluten. In just six weeks, Jack reported that diarrhea had disappeared and been replaced by well-formed stools. He also reported that he hadn't had eye burning or brain fog since cutting out gluten. Lastly, his energy levels had improved. Energy improvement was likely

associated with the improved nutrient content of his diet and improved digestion and absorption of those nutrients.

Do you experience symptoms associated with gluten consumption? Have you mentioned it to your doctor and been laughed at or chastised? Were you told gluten is a fad, and there is no evidence behind it? I hope this chapter has busted those myths for you and shown you that reactivity to gluten-containing grains is a real issue and a real danger to your health.

Do not ignore those symptoms—they may be quietly promoting autoimmunity and increasing your risk of death from all causes. Take action today by cutting out all gluten-containing grains from your diet and lifestyle, and seek out a clinician who will partner with you to perform the detective work necessary to figure out your puzzle and create optimal health and function.

"Give us this day our daily bread… but deliver us from evil."

– Matthew 6:11 and 13[27]

Reader action steps

Cut gluten-containing grains out of your diet for a minimum of twelve weeks and observe for reduction in symptoms and improved quality of life.

Learn more at my Wheat/Gluten video playlist:
https://www.FunctionalMedicineCharlotte.com/Gluten

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CHAPTER 7

Thyroid Autoimmunity

"Hypothyroidism may be present despite laboratory tests suggesting it is not."

—Dr. Broda Otto Barnes

Candace, thirty-seven, was a competitive CrossFit athlete and elementary school teacher when she presented to my practice with complaints of fatigue, brain fog, and crippling anxiety that was so bad that she was socially isolating herself. When friends would ask if she wanted to hang out, she would make up an excuse that she couldn't because she had to go do something for one of her children.

She was on thyroid hormone replacement medication for hypothyroidism caused by removal of her thyroid gland eleven years prior. She had been diagnosed with Graves' disease at age fifteen, which was not well controlled by medication and was offered radioactive iodine treatment later in life but declined because she was newly married at that time and wanted to have children. Therefore, she had her thyroid removed, which caused medically induced hypothyroidism.

Candace's question when she came to me was, "I've been taking a thyroid hormone replacement medication for eleven years and have seen five endocrinologists who cannot find anything wrong with me. Why do I feel so terrible? "

At fifty, Brandon was falling apart. He reported that he hadn't felt good for a couple of years. The main issues robbing him of his quality of life were low energy, weight gain, heartburn, sleep apnea, and joint pain. His sleep apnea was accompanied by snoring that was so bad that his wife would wake him five to six times a night. Neither of them was getting any rest. Brandon's joint pain was in his elbows. He had suffered with it for two years, despite the fact that he'd received months of physical therapy.

The only recommendations offered by Brandon's medical doctor were a sleep study, which would likely end up in a CPAP

machine, and a proton pump inhibiting drug for his heartburn. Brandon did not want either of those; he wanted to find the causes of his suffering and eliminate them. He wanted a doctor that would do the detective work necessary to heal him.

What is the thyroid? [1]

The thyroid gland is a butterfly-shaped gland in your neck that is responsible for the metabolic rate of almost every cell in your body. Ninety-three percent of thyroid hormone produced by the thyroid gland is in the form of thyroxine (T4). The other 7 percent is triiodothyronine (T3). Most of the T3 in your body is produced by converting T4 to T3 in the body tissues and inside cells outside of the thyroid.

Once inside your cells, 90 percent of the thyroid hormone that binds receptors is T3. When T3 binds its receptor inside your cells, the net result is a generalized increase in functional activity throughout the body. A sampling of the effects of thyroid hormone on specific body functions include:

1. **Stimulation of carbohydrate metabolism** , which leads to increased glucose uptake.

2. **Stimulation of fat metabolism** , which decreases fat storage in the body.

3. Increased thyroid hormone **decreases levels of total cholesterol** , phospholipids, and triglycerides, while increasing free fatty acids. Decreased thyroid hormone does the opposite. (This is important to know because if you have hypothyroidism or low thyroid hormone production and high cholesterol, the answer is not to lower cholesterol with a statin drug. The answer is to normalize thyroid hormone production.)

4. **Increased requirement for vitamins.** The proteins produced as an effect of thyroid hormone include a number of enzymes, many of which require vitamins as essential cofactors in order to function. When thyroid hormone increases, so does enzyme production, and therefore, so does the need for the vitamins those enzymes use. Key vitamins and nutrients needed for

enzymatic production include vitamin A, vitamin B12, vitamin B6, CoQ10, iron, selenium, and many more.

5. **Decreased body weight.** Significantly increased thyroid hormone levels lead to weight loss.

6. **Increased number and activity of mitochondria.** These powerhouses of our cells produce adenosine triphosphate (ATP), which is the energy currency used by our cells to function. A classic symptom of low thyroid function (hypothyroidism) is fatigue. This is one mechanism of hypothyroid-induced fatigue.

Again, this is just a sampling of how the thyroid impacts body function. Since almost every cell has thyroid hormone receptors, the potential symptoms associated with too much (hyperthyroidism) or too little (hypothyroidism) thyroid hormone are broad. This means that each individual with hyper- or hypothyroidism may present with a different set of symptoms, and the clinician must be thorough in their history, exam, and diagnostics in order to determine what is going on. People are not textbooks—they will not always present with the classic symptoms of a given disorder or disease and may have multiple issues going on at once .

Thyroid autoimmunity

Thyroid autoimmunity is the most common autoimmune disease in the U.S. and worldwide. [2] , [3] , [4] It is estimated to affect 5 percent of Caucasians with diagnosis occurring five to ten times more often in women than men. Dysfunction of the thyroid gland is found clinically in up to 2 percent of the population, while subclinical Hashimoto's disease is estimated to occur in up to 15 percent of the population. [5] For the purposes of this chapter, we will limit thyroid autoimmunity to two diseases—Graves' and Hashimoto's.

- **Graves' disease** causes the immune system to produ thyrotropin receptor antibodies, which induce overproduction thyroid hormone. These elevated hormone levels result hyperthyroid symptoms such as weight loss, fatigue, he intolerance, tremor, anxiety, and palpitations (atrial fibrillatic

may be caused by hyperthyroidism in up to 10 percent patients age 60 and older).

Clinical signs of Graves' disease include a thyroid goiter, bulging eyes with lid retraction, plaque skin lesions, and clubbing of the fingers. The most common and serious systemic manifestation of hyperthyroidism is damage to the eyes, including corneal breakdown (optic neuropathy) in up to 5 percent of patients. [6]

The manifestation of Graves' disease depends on the age of the patient at the onset of hyperthyroidism, as well as the severity and duration of hyperthyroidism. Graves' has both genetic and epigenetic determinants. You may have a genetic susceptibility, which is then triggered by environmental epigenetic factors.

"Environmental factors such as dietary iodine, exposure to tobacco smoke, infections, and emotional stress are frequently cited in Graves' disease. Therapy with alemtuzumab, a CD52- targeting monoclonal antibody medication, can also induce it."[6] Alemtuzumab is known by the trade names Campath and Lemtrada and is used to treat chronic lymphocytic leukemia (CLL) and multiple sclerosis (MS). Infection with Epstein-Barr virus (EBV), the virus that causes "mono," is also an associated risk factor for Graves' disease. [7]

The diagnosis of Graves' is based on characteristic clinical features and biochemical abnormalities, and treatment is based on the patient's preference between radioactive iodine, thyroid removal, or anti-thyroid medication in uncomplicated cases. Smoking cessation is an absolute must. In up to 20 percent of hyperthyroidism cases, autoimmune hypothyroidism develops.[6]

- **Hashimoto's disease** is the most common cause of autoimmu hypothyroidism. Thyroid autoimmunity is the cause of 9 percent of hypothyroidism cases. [8], [9] The clinical manifestatio of Hashimoto's vary and include euthyroidism (normal thyro hormone level), subclinical hypothyroidism, and clinic hypothyroidism (meeting diagnostic criteria).

Hashimoto's is associated with the production of thyroid peroxidase (TPO) antibodies and thyroglobulin (Tg) antibodies. As with Graves' disease, Hashimoto's is believed to require both genetic susceptibility and environmental triggers for manifestation. Common environmental triggers that increase risk are alcohol, stress, [10] pregnancy (three to eight months postpartum, hypothyroidism occurs in 2 to 4 percent of the population but is transient 90 percent of the time)[8] , too much iodine, and drugs such as interferon alpha and immunomodulatory agents.[10] Many infectious microbes have been associated with Hashimoto's disease including Epstein-Barr virus (EBV) [11] , parvovirus B19, hepatitis C, human T-cell leukemia virus type 1, Yersinia enterocolitica [12] , human herpesvirus 6 [13] , and Helicobacter pylori [14] .

As discussed in the previous chapter, Hashimoto's disease is associated with the coexistence of other autoimmune diseases such as celiac disease. Additional associations include vitiligo, type 1 diabetes, autoimmune liver disease, alopecia areata, rheumatoid arthritis, lupus, and Sjogren's syndrome.[10] Recent research has found that the presence of TPO antibodies in people with normal thyroid hormone levels (aka, euthyroid) is correlated with a worse health-related quality of life and high levels of anxiety and depression. [15]

Did you catch that? *There are TPO antibodies present in those with normal thyroid hormone levels.* That qualifies as an autoimmune process and not an autoimmune disease, as we will discuss in the next section. By the way, "normal" thyroid hormone levels on lab work do not mean your thyroid is normal.

A diagnosis of hypothyroidism is based on a lab high thyroid-stimulating hormone (TSH) level in the blood. Typical treatment of hypothyroidism is T4 replacement with the drug levothyroxine. Unfortunately, conventional medicine often stops there. It does not investigate further to see if Hashimoto's is the cause of the person's

hypothyroidism for reasons I cannot explain, other than the fact that finding it would not change the recommended treatment. They do not have a drug to address TPO or Tg antibodies, so why bother?

According to the American Thyroid Association, "The diagnosis of Hashimoto's thyroiditis may be made when patients present with symptoms of hypothyroidism, often accompanied by a goiter (an enlarged thyroid gland) on physical examination, and laboratory testing of hypothyroidism, which is an elevated TSH with or without a low thyroid hormone (free thyroxine—free T4) level. TPO antibody, when measured, is usually elevated.

Occasionally, the disease may be diagnosed early, especially in people with a strong family history of thyroid disease. TPO antibody may be positive, but thyroid hormone levels may be normal, or there may only be isolated mild elevation of serum TSH. Symptoms of hypothyroidism may be absent." [16] As you are about to learn, hypothyroidism is more complicated than a lab high TSH. Normal thyroid labs do not mean your thyroid is normal, and conventional medicine's standard of care for thyroid issues is quite substandard.

Thyroid labs

A thorough and complete lab workup of the thyroid in the blood consists of nine markers. Those markers are TSH, total T4, free T4, total T3, free T3, reverse T3, thyroglobulin, thyroglobulin antibodies, and thyroid peroxidase antibodies. The standard of care in conventional medicine is to run one marker: TSH.

If this were math class and we were using fractions to represent the blood work we are running, a full thyroid panel would yield 9/9, or 100 percent of the information we are looking for. "Standard of care" testing would yield 1/9, or 11 percent of the information we are looking for.

I am no rocket scientist but you tell me, dear reader, which test is going to give us the most information and best help us crack your case? Which test will allow us to say with absolute confidence that your thyroid is or is not "normal"?

The test that provides us the most information !

This is why so many people (and especially women) are frustrated and suffering, because conventional medicine runs a "thyroid test" that consists of 11 percent of the possible information and then makes a definitive statement about that person's thyroid function. I hope you see the disconnect.

The TSH tells us nothing about whether or not there are thyroid antibodies present, representing an autoimmune process against the thyroid. The TSH tells us nothing about whether reverse T3 is lab high and preventing ideal free T3 binding of cellular receptors.

The TSH can definitely tell us something by itself in only one situation. When it is lab high for the first time in a person with symptoms of hypothyroidism, it fits the diagnostic criteria for hypothyroidism. For conventional medicine, that is enough; they don't care about anything else.

The flaw in that thinking is stated above in the quote from the American Thyroid Association: "TPO antibody may be positive, but thyroid hormone levels may be normal or there may only be isolated mild elevation of serum TSH."

YOU CAN HAVE POSITIVE ANTIBODIES AND NORMAL TSH. If this is you, you are in the gray area. You have an autoimmune process against your thyroid. It may be associated with your thyroid complaints but you will be told you are normal until your TSH is lab high. Then the doctors will admit you have something wrong, but still DO NOTHING TO ADDRESS THE IMMUNE SYSTEM.

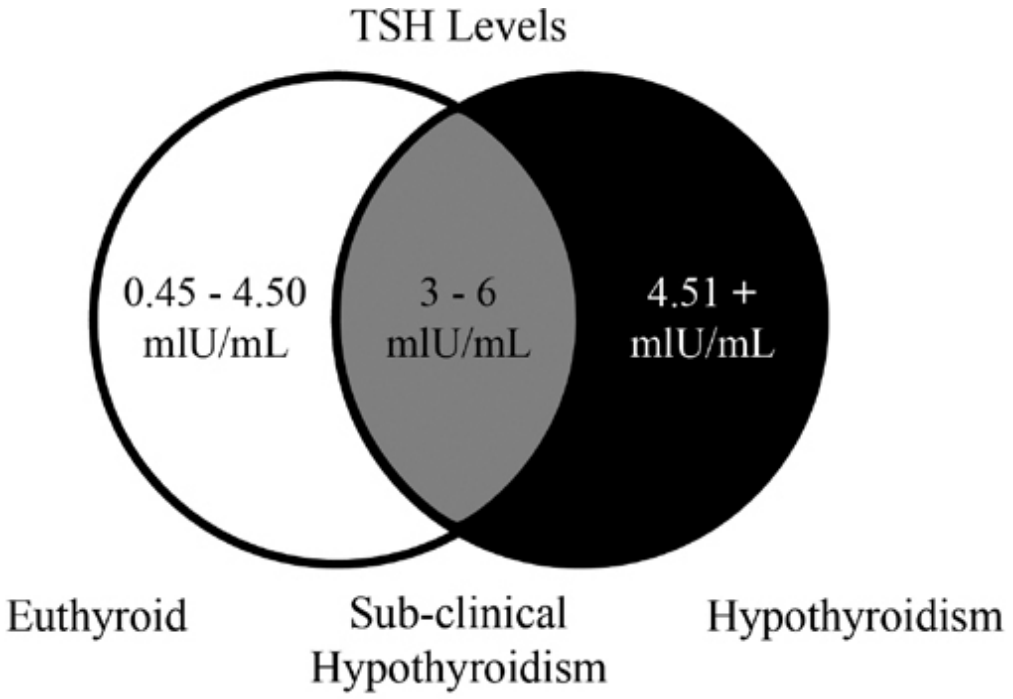
As you've learned, in order to truly find the causes of a person's chronic health issues, thorough detective work must be done. Ordering one-ninth or two-ninths of a thyroid panel is not thorough. In fact, this helps explain why so many people suffer from thyroid symptoms, yet are told by their medical doctor that their thyroid is normal .

Thyroid autoimmunity is the cause of 90 percent of hypothyroidism cases.[8], [9] You may feel hypothyroid before you clinically meet diagnostic criteria for hypothyroidism. Autoimmune thyroid disease can be present in all cases, whether

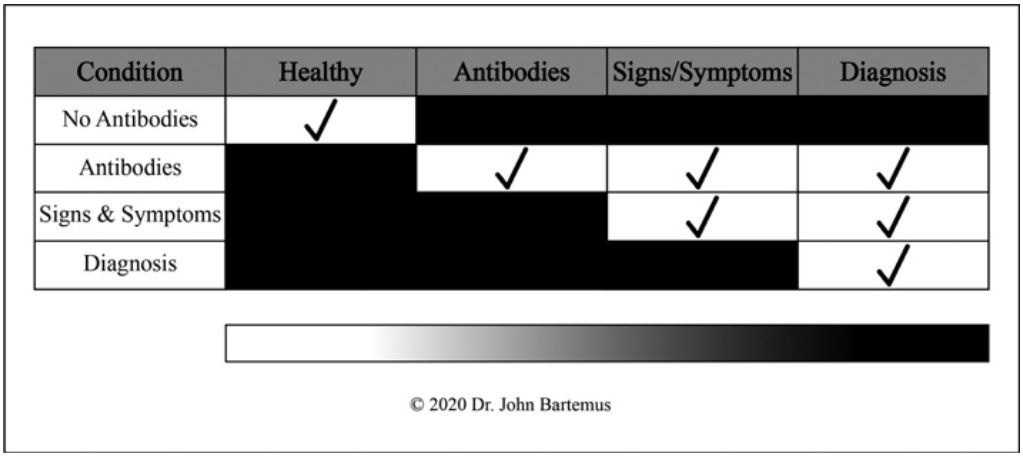
the person has normal thyroid levels (euthyroid), subclinical hypothyroidism, or clinical hypothyroidism.[10]

Subclinical hypothyroidism is defined as a mild thyroid failure with a slight TSH level increase between approximately three and six micro IU per milliliter. [17] As of February 2020, the normal range for TSH, according to national laboratories Quest Diagnostics and LabCorp, are 0.4 to 4.5 and 0.45 to 4.5, respectively.

Multiple studies argue against prescribing levothyroxine or T4 hormone replacement in people with a TSH less than ten micro IUs per milliliter. [18] , [19] If subclinical hypothyroidism is defined as a TSH of three to six micro IU per milliliter, and lab high is defined as 4.51 micro IU per milliliter or greater, but recommendations are not to prescribe thyroid hormone replacement until greater than ten, there is a lot of gray area for people to suffer before being treated.



Why does this happen? Let's return to our autoimmune process versus autoimmune disease graphic.



If 90 percent of hypothyroidism cases are due to thyroid autoimmunity, it stands to reason that 90 percent of subclinical hypothyroidism cases are too. Depending on the primary care provider or endocrinologist you see, with a TSH of 5.0 you may or may not receive a hypothyroidism diagnosis, which would put you in the diagnosis category. If your doctor subscribes to the thinking that a TSH less than ten should not be medicated, then you will be left in limbo as a subclinical hypothyroidism case that puts you somewhere on the spectrum between positive antibodies only and antibodies with signs and symptoms. [20]

Therein lies the disconnect between patients reporting poor quality of life caused by symptoms associated with thyroid disease and doctors claiming that the thyroid is “normal”. The disconnect is in the diagnostic criteria.

It is not standard of care in conventional medicine to run thyroid antibodies or a full thyroid panel. Given that the research has repeatedly shown that 90 percent of hypothyroidism cases are caused by thyroid autoimmunity, [8] , [9] antibodies may show up in autoimmune thyroid disease up to seven years before the disease manifests (i.e. fits diagnostic criteria) [21] , and the presence of TPO antibodies in people with normal thyroid hormone levels is correlated with worse health-related quality of life and high levels of anxiety and depression[15] , it seems conventional medicine is not practicing what it preaches; namely, “evidence-based medicine.” The evidence here makes a pretty bulletproof case that high-quality care should include a full thyroid panel, which itself includes thyroid antibodies.

Making a full thyroid panel standard would allow us to catch people with preclinical or subclinical thyroid autoimmunity up

to seven years sooner. As the research states, "early intervention at preclinical stages may lead to prevention of overt disease development and even cure of the autoimmune disorder."[20]

I ask you, dear reader, who is practicing evidence-based medicine—the conventional healthcare system that is failing daily to help people with chronic illness due to its focus on the patient fitting diagnostic criteria so that a drug that has no chance of ever healing the person may be prescribed, or the clinicians reading the research and implementing it into their practices in the form of "above standard" or "medically unnecessary" testing (aka, a full thyroid panel), in order to find and address the cause of the person's chronic illness?

I believe the answer is clear.

You may ask, "Why isn't true evidence-based practice the standard in conventional medicine?" The answer is a five-letter word: money. Healthy people don't make money for the conventional medical system and the pharmaceutical companies that run the show. Their goal is not to catch autoimmunity when it is a preclinical or subclinical autoimmune process. Discovering it in the early stages and taking action would mean that the process would likely never progress into a full-blown diagnostic- criteria-meeting disease. That means the person would likely not enter the "healthcare hamster wheel" of lifelong worsening of the disease and increasing levels of medications and chronic issues, which translate into chronic repeat business for the system. [22] Health is not the goal in that model—money for the shareholders is. Considered from this perspective, who are the real quacks, charlatans, and snake-oil salesmen?

Cracking Candace's case

Candace had a history of Graves' disease that resulted in surgical removal of her thyroid gland and medically induced hypothyroidism. She asked, "I've been taking a thyroid hormone replacement medication for eleven years and have seen five endocrinologists who cannot find anything wrong with me. Why do I feel so terrible?"

By this point, I hope you can yell out the answer: "Because standard of care is failing you, Candace."

Candace still felt terrible because each of her endocrinologists was following standard of care, which is to run a TSH and a free T4 once a year to make sure her thyroid medication level is appropriate. They did that and, though Candace would tell them she felt terrible on the appropriate dose of medication, they did not dive any deeper. I did by running what should be standard of care, a full thyroid panel. This allowed us to find the reason she felt terrible.

Candace had lab low T3 levels. Remember that T3 is what binds 90 percent of the thyroid receptors inside your cells. If you do not have enough T3, you do not have enough thyroid hormone binding intracellularly, and you do not receive the metabolic effects of thyroid hormone. Therefore, you feel hypothyroid even though your blood levels of T4 are normal. The ironic finding in Candace's case was that her free T4 levels were actually lab high and she still felt hypothyroid, further supporting the importance of T3 levels. Her doctors never once ran a full thyroid panel, so they never once checked her T3 levels.

Test results also revealed Candace had lab low vitamin D levels and gut dysbiosis evidenced by lab high overgrowth of yeast, Enterobacter cloacae, and E. coli, and deficient levels of the probiotic species Bifidobacterium and Enterococcus. Low vitamin D has been correlated with thyroid autoimmunity in multiple studies.[10] Gut dysbiosis and the associated imbalanced microbiome affect T4 to T3 conversion and therefore peripheral thyroid homeostasis. Dysfunction in the gut and liver impact thyroid function and may promote subclinical hypothyroid symptoms via inefficient T4 to T3 conversion. [4], [23]

By finding and addressing these issues, Candace was able to get her life back. Her anxiety was eliminated, which allowed her to stop isolating herself socially and accept her friends' invitations to hang out. Her microbiome was balanced, and her vitamin D levels were restored.

These changes allowed for optimal T4 to T3 conversion. Matter has limitations, and in Candace's case, her body's optimal level of T4 to T3 conversion was not enough to help her function to the highest level she desired. A low level of T3 hormone replacement with the drug Cytomel was necessary. Without the

thorough detective work using the functional medicine framework, which included a full thyroid panel, Candace would still be feeling terrible.

Solving Brandon's puzzle

Brandon was falling apart from sleep apnea, joint pain, weight gain, heartburn, and fatigue. He did not want a CPAP machine and multiple prescriptions. He wanted to find the cause and address it. His testing revealed the following: lab high total cholesterol, LDL, and triglycerides, the presence of Epstein-Barr virus infection, lab low vitamin D, completely normal thyroid hormones, but lab high TPO (greater than 900 IU/mL), and thyroglobulin (571 IU/mL) antibodies, indicating euthyroid Hashimoto's.

Stool testing revealed lab high presence of parasites and worms, deficient mucosal immunity, and lab high fat in his stool, suggesting fat malabsorption. As discussed above, gut dysbiosis and deficient vitamin D promote thyroid autoimmunity, as does Epstein-Barr infection. The lab high lipids may also be driven by thyroid dysfunction. Symptomatically, we know that weight gain and fatigue are thyroid symptoms.

After creating an individualized and specific action plan for Brandon based on his findings, the following results were created: his vitamin D level was optimized, his lipids were significantly reduced, and his Epstein-Barr virus infection, the parasite, the worm, and fat in his stool were all eliminated. Brandon reported that he had quit snoring by day three of his plan. His sleep apnea had been eliminated and so was the potential need for a CPAP machine. His heartburn was also gone; he could even eat hot sauce again without issue. The two years of joint pain that could not be solved with physical therapy had finally disappeared as well.

Lastly, Brandon had lost ten pounds. He was full of energy, and his wife was very happy that she was once again getting a full night's sleep. Another win for the functional medicine framework of finding and addressing issues in the exposome, epigenome, and microbiome.

Evidence-Based Nutritional Considerations for Hashimoto's Disease

As you now know, there is no one-size-fits-all solution for any condition, including Hashimoto's disease. Every person is different and requires thorough detective work that assesses their entire physiology in order to determine the unique contributing factors in each case. However, scientific research has found that, in the case of Hashimoto's disease, there are various nutrients to include or exclude that may be very helpful in optimizing physiology.

The list[10] includes:

1. Selenium (include)
2. Vitamin D (include)
3. Vitamin A (include)
4. Iodine (exclude)
5. Gluten (exclude)

Selenium [10]

Selenium is an essential micronutrient with many effects, including functioning as an antioxidant and anti-inflammatory and increasing active thyroid hormone production.[10] In fact, a 2019 study [24] found that selenium not only dampens inflammation but initiates resolution of the inflammatory process. There are over 30 selenium dependent enzymes in the body and 20% of them play a unique role in thyroid function and thyroid hormone homeostasis. Two enzymes (iodothyronine deiodinases – D1 and D2) are integral in conversion of T4 to T3; therefore, people with insufficient or deficient levels of selenium are more susceptible to thyroid hormone conversion issues.

Since it is not standard for conventional doctors to run a full thyroid panel, which would allow them to see T3 levels, insufficient selenium levels increase susceptibility of having

thyroid complaints but being told by your doctor that "everything is normal. "

Foods rich in selenium include brazil nuts, oysters, tuna, sunflower seeds, most meats, and mushrooms. If supplementing with selenium, research[24] has found that the selenomethionine form is the best absorbed.

Multiple studies [25] , [26] , [27] have confirmed that selenium effectively suppresses serum levels of TPO and Tg antibodies in Hashimoto's patients.

What dose of selenium is shown to be beneficial? A 2016 study in the journal *Thyroid* [25] found that 200 micrograms per day was effective. As stated throughout the book, everyone is an individual; therefore, the effective dose is unique for each person. 200 micrograms might work brilliantly for one person and not work at all for the next. One of many possible factors contributing to variable results between people is their iodine status.

It is possible to take too much selenium. Science has shown that consumption of 330+ micrograms per day could be toxic and lead to problems with thyroid hormone synthesis as well as metabolism of growth hormones and insulin-like growth factor 1 (IGF-1). [28]

Vitamin D

Low vitamin D3 status is associated with many autoimmune diseases[10] , including Hashimoto's disease. Vitamin D3 (cholecalciferol) supplementation has been shown to effectively reduce TPO antibodies in people with Hashimoto's disease and vitamin D deficiency. [28] It has also been shown to effectively reduce TPO antibodies in women with Hashimoto's and normal vitamin D levels. [30] The suppression of thyroid antibody levels occurs via the ability of vitamin D to inhibit Th1 cell physiology and promote immune tolerance. [31]

How much vitamin D is enough? If you have invested any time trying to answer this question, you know how many differences of opinion there are on the topic. I recommend you read the seminal work(s) of Dr. Alex Vasquez. He has "written the book"

on vitamin D. According to Dr. Vasquez, “Optimal vitamin D status correlates with serum 25-Hydroxyvitamin D3 levels of 50-100 ng/ml”. [32]

You might say that 50-100 is a broad range for optimal. I agree. This should reinforce the point that optimal is different for everyone because everyone’s puzzle is made up of different pieces. Detective work must be done to determine what your optimal level is.

Vitamin A

As discussed earlier in the chapter, when thyroid hormones bind the thyroid hormone receptors inside your cells there is genetic upregulation of protein production. This occurs when the thyroid hormone binds the thyroid hormone receptor which is attached to the DNA strands inside the nucleus of your cell. The thyroid hormone receptor forms a heterodimer with the retinoid X receptor (RXR) at specific thyroid hormone response elements on the DNA.[1]

The retinoid X receptor is vitamin A (retinoic acid) dependent. Without optimal vitamin A levels, the optimal cellular response to thyroid hormone does not occur. This may result in thyroid symptoms. Therefore, optimal vitamin A status is important for optimal thyroid function in everyone.

What about people with Hashimoto’s, what is the specific benefit of vitamin A for them?

Vitamin A has recently been shown to inhibit antibody production in people with Hashimoto’s disease. [33] Vitamin A has also been shown to inhibit the pathogenic Th17 cell lineage associated with autoimmune disease. [3 4]

Iodine

Authors of a 2017 study in the *Hellenic Journal of Nuclear Medicine* stated, “High iodine supplementation in Hashimoto’s Thyroiditis should be discouraged, as not beneficial and possibly harmful”.[10]

The authors referenced multiple studies that indicated mild to moderate excess iodine intake is associated with more frequent

occurrence of hypothyroidism. Excess iodine was defined as median urinary iodine greater than 220 micrograms per 24 hours (your doctor can test this for you).

One mechanism by which excess iodine could be harmful to a person with Hashimoto's is by increasing the numbers of thyroid infiltrating Th17 cells. [35] Remember that Th17 cells at inappropriate levels promote the tissue damage in autoimmunity. Excess iodine was also shown to inhibit T-regulatory cells. T-regulatory cells help prevent autoimmune disease.

These findings suggest an immune double negative effect of excess iodine:

1. Increased autoimmune promoting Th17 cells
2. Decreased autoimmune preventing T-regulatory cells

Key point: Iodine is a necessary nutrient for optimal thyroid function. Beware of *excess* iodine intake, that is when the bad things can happen.

Gluten

Hopefully chapter 6 provided enough explanation for why you should avoid gluten. Just in case it didn't, here is some information as to why gluten should be specifically avoided by people with autoimmune thyroid disease.

According to a recent meta-analysis [36] , all people with autoimmune thyroid disease should be screened for celiac disease. The authors make this recommendation based on the increased prevalence of the coexistence of thyroid autoimmunity and celiac disease (which was mentioned in the last chapter). If the person with autoimmune thyroid disease (such as Hashimoto's) tests positive for tissue transglutaminase-2 antibodies, investigation of small intestine villous integrity should be a consideration.

Regardless of whether or not a person with Hashimoto's disease tests positive for evidence of a celiac process, research has shown that gluten avoidance slows the rate of disease progression and decreases the risk of complications. [37]

Reader action steps

If you are suffering from what you believe are thyroid symptoms, you must partner with a clinician who will run a full thyroid panel as well as do the detective work on your global physiology to find and address the causes of your suffering.

Make sure they run a complete thyroid panel, which includes:

TSH, total T4, free T4, total T3, free T3, reverse T3, thyroglobulin, thyroid peroxidase (TPO) antibody, thyroglobulin (Tg) antibody

If Grave's disease is suspected, then TSI antibody and TRH antibody should be added.

Based on the information above on the importance of vitamins A and D and selenium, as well as avoiding excess iodine, testing for levels of these nutrients is prudent.

For more information, view my Thyroid video playlist at:
https://www.FunctionalMedicineCharlotte.com/Thyroid

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CHAPTER 8

Food Allergy, Food Sensitivity, and Food Intolerance

"An estimated one-fifth (20%) of the population believe that they have adverse reactions to food."

—Turnbull, et, al. [1]

"Exposure to these candidate food antigens caused immediate breaks within five minutes in the gut epithelia."

—Katrina Ray [2]

Ed couldn't breathe. He had been diagnosed with exercise-induced asthma in college but this was different; he hadn't been exercising. Ed was dealing with repetitive bouts of wheezing and shortness of breath that left him dizzy, which were getting more frequent and intense. When I asked if he was able to pinpoint any specific triggers to these episodes, Ed listed food, weather, dust, heat, and cardio at the gym. That didn't narrow things down much.

At twenty-nine, Ed had a medical history with significant evidence of a Th2 immune phenotype. He reported lifelong symptoms of IBS, and his medical records revealed mild esophagitis, patches of stomach inflammation, and a hiatal hernia. Stomach pain was a daily occurrence. Ed worked a sales job that was commission-based, which added daily stress to his life. All of these factors led us to investigate Ed's immune function and allergy risk more thoroughly. His goal was to eliminate the breathing issues and stomach pain.

When Dawn came to my office, she reported having diarrhea for thirty-eight years. At fifty-eight, she hadn't had a normal stool in her adult life. Everything Dawn did during the day had to be planned with a mind toward knowing where the nearest bathroom was. She also reported chronic fatigue, sinus infections, and urinary tract infections.

Her medical records revealed that she had a significant allergy to environmental molds, and she had her gallbladder removed

thirty-seven years before. Dawn had recently retired from an occupation that required her to work twelve-hour overnight shifts—she had not had a normal sleep schedule in years. Her goal was to decrease the diarrhea and improve her energy so that she could enjoy retirement.

Food reactions

In 2019, the U.S. population was estimated to be 330 million people. [3] If that estimation is correct, quick math tells us that 66 million people in the U.S. experience adverse reactions to food. According to the American Autoimmune Related Diseases Association (AARDA), [4] there are 50 million (and growing each year) Americans with autoimmune disease. In 2019, that represented 15 percent of the U.S. population.

Taken together, these estimates suggest a strong association between adverse food reactions and autoimmune disease. Mechanistically, the research also supports this association. As we discussed in chapter three, up to 70 percent of the immune system resides in the GI tract and its role is to play gatekeeper, allowing nutrients in and keeping enemies out. [5] This process is called immune tolerance. We touched briefly on immune tolerance in chapter five. Let's go more in depth on the subject now with the goal of better understanding why food reactions occur.

In immunology, anything that the immune system sees and must choose whether to kill or tolerate is given the general name of antigen. Broccoli is an antigen. Flu virus is an antigen. Your thyroid tissue is an antigen. A cancer cell is an antigen. Get it? Antigen doesn't mean good or bad, the immune system decides if an antigen is good or bad and responds appropriately.

When you consume whole food, the healthy immune system should see those food proteins as non-threatening antigens and respond with a state of local and systemic non-responsiveness. This state of non-reaction versus food antigens is called oral tolerance. According to the *Journal of Allergy and Clinical Immunology* in 2016: "Oral tolerance to food proteins is likely to be intimately linked to mechanisms that are responsible for gastrointestinal tolerance to large numbers of commensal

microbes…perturbations in these mechanisms may promote the loss of oral tolerance and development of food allergies." [6]

In order to maintain immune tolerance, the immune system must be able to clearly discern self from non-self, while also distinguishing between friendly non-self (such as commensal or probiotic microbes) and dangerous non-self (such as pathogenic E. coli).

The GI tract is where most of this tolerance speed dating occurs. In order for immune tolerance to be maintained in a healthy state, many complex interactions between immune cells, non-immune cells, and the microbiota must occur.

As the authors state: "These cells must act in concert to limit inflammatory responses to resident bacteria and food proteins that could lead to tissue injury, keep microbes confined to the gut, and recognize and respond to pathogens that can cause tissue injury or disease. Failure to achieve an appropriate balance in these roles can lead to loss of tolerance, resulting in inflammatory diseases such as inflammatory bowel disease or responses to innocuous food antigens, such as those occurring in celiac disease and IgE-mediated food allergies."[6]

What causes a loss of oral tolerance?

There are many possible factors that could lead to a loss of oral tolerance resulting in food reactions. We will discuss five common factors below, but this is by no means an all-inclusive list:

- **Poor protein digestion:** When you swallow protein, it trave down your esophagus into your stomach. A major role of tl stomach is to produce hydrochloric acid. The majority of prote digestion occurs in the stomach via hydrochloric acid ar protein enzymes called proteases. Appropriate protein digestic in the stomach substantially decreases the potential of foc proteins to bind IgE antibodies and promote food allerg Insufficient protein digestion leading to increased allergy ri has been demonstrated in studies of acid suppressi medications. [7] Stomach acid decreases protein antigenicity (threat) by breaking it down into small pieces.[6]

Properly digested protein in the stomach is broken down into small peptide fragments that then move into the small intestine and are easily broken down further into amino acids by pancreatic and brush border enzymes. The amino acids are then absorbed into the body.

If the protein is incompletely digested in the stomach, it moves into the small intestine in a form that is too big for the pancreatic and brush border enzymes to digest. This may leave you feeling like you have a rock in your stomach. This protein rock could become fermentative substrate for small intestinal bacteria and lead to gas and bloating and possibly constipation or diarrhea, depending on the gasses the bacteria are producing. This could result in small intestinal bacterial overgrowth, also known as SIBO. Even if SIBO does not occur, large proteins and peptides that survive the digestion process intact can pass through the intestinal epithelial barrier and promote a pro-allergy, pro-histamine Th2 immune response.

- **Insufficient or deficient vitamin A:** "Mucosal tolerance is necessity for us to survive; without it we would not live a sing day. The cells along the vast mucosal surfaces of the body a constantly in contact with foods, microbes, and toxins. As tl gut makes innumerable immunological decisions, it rela information from the innate to adaptive immune system. Vitam A is the key to the gut making the right decisions." [8]

A deficiency in vitamin A skews the body toward the Th17 immune phenotype, which is responsible for driving the tissue damage seen in autoimmune disease. "Since Th17 cells reside mainly in the mucosa of the gut, it is an elegant serendipity that our food (nutrient) choice should have such a potentially powerful effect on our local and systemic immune response."[8] In other words, a deficiency in vitamin A may be the causal factor in some people connecting the immune dysfunction resulting in food reactions and autoimmune disease.

Optimal levels of vitamin A play a preventative role in food reactions and autoimmune development. In the intestine, immune cells convert dietary vitamin A into

retinoic acid. Retinoic acid promotes the induction of T-regulatory cells, which produce the anti-inflammatory, tolerance promoting chemical messengers interleukin-10 (IL-10) and transforming growth factor beta (TGF-b). [9]

Vitamin A cannot be made by the human body. Therefore, it must be obtained from the diet and/or supplements. One very important piece of information you must know is that beta-carotene is not vitamin A. Beta-carotene must be converted to vitamin A in your body. The media gives the impression that this conversion is easy and efficient for our bodies to perform. However, research reveals otherwise. A 2009 study found that 50 percent of women were unable to efficiently convert beta-carotene into vitamin A, and therefore, may be retinoic acid deficient. [10]

Remember the AARDA estimate that said 50 million Americans have autoimmune disease? The AARDA also states that 75 percent (or 35 million) of those 50 million people are women.[2] If half of those 35 million women are retinoic acid deficient, perhaps vitamin A would be a very inexpensive and very powerful clinical strategy as a piece of their puzzle for healing.

- **Poor fiber intake and/or gut dysbiosis:** Microbial diversi and abundance promotes tolerance in the gut. Gut microb ferment fiber to produce short chain fatty acids (SCFAs) such butyrate. When healthy microbes are making healthy levels SCFAs from fiber, multiple positive effects occur[6] :

  - SCFAs produce IL-18 which promotes a healthy epithelial barrier and prevents leaky gut

  - SCFAs promote production of T-regulatory cells, which are anti-inflammatory and promote tolerance

  - SCFAs contribute to production of antimicrobial peptides in mucus in the gut barrier to prevent infection

In a person that does not consume enough fiber and/or has gut dysbiosis, changes in the microbial abundance or

diversity (because of this or antibiotic exposure, consumption of alcohol, or other reasons) results in a reduction of SCFAs and the benefits listed above. Lack of these benefits leads to compromised epithelial integrity or leaky gut, which facilitates passage of microbes and food antigens leading to activation of Th2 cell-associated immune responses and allergic sensitization.[6]

- **Food coloring and other additives:** "Whether it's throug licking lollipops repeatedly, eating ice cream, using medicatio or applying cosmetics, shaving cream, or skin treatments, significant amount of food coloring and food additives manag to enter the bloodstream through the GI tract" [11] on a daily basi These food-coloring agents form strong bonds (called covale bonds) with proteins. Food coloring agents are non-specific terms of the proteins that they bind with—they readily bind foo proteins and have also been shown to bind human proteins ar induce immune reactivity and allergy. [12]

"Artificial food dyes are made from petroleum…During the past fifty years, the amount of synthetic dye used in foods has increased by 500 percent. Simultaneously, an alarming rise has occurred in behavioral problems in children such as aggression, ADD, and ADHD…The consumption of synthetic food colors and the ability to bind with body proteins can have significant consequences including induction of leaky gut, cross reactivity, autoimmunity and even neurobehavioral disorders." [13] In other words, one mechanism for the induction of food allergy by food coloring is that binding of the colorant to the protein decreases its digestibility. This leads to large protein fragments reaching the intestinal epithelium and passing into the body to stimulate immune activation as discussed above in the section on protein digestion .

Artificial sweeteners (such as saccharin and other food additives) commonly used by the processed food industry have also been found to increase risk of food reactions, particularly in the young. They do this by inhibiting development of oral tolerance early in life. [14]

- **Developing oral tolerance:** The mucosal epithelial barrier ar immune system are poorly developed in newborns. The perinat period is critical with regard to the induction of food allerg This is where innate and adaptive immunity are beir coordinated by immune cells and orchestrated by microbi products from probiotics in the gut. Nutrients key to the processes include vitamin A and omega-3 fatty acids. The factors may, in various ways, exert beneficial effects on tl immune phenotype of the infant, and the same is true for brea milk. Breast milk provides immune inducing factors lil secretory IgA, which reinforces gut barrier integrity in a infant.[9]

These findings underscore the importance of breastfeeding and epigenetics in the development of optimal immune tolerance mechanisms in infants. Breastfeeding is key; infants are born with a leaky gut and immature GI physiology. [15] Infants are designed by nature to consume breast milk only for the first few months of life—introducing anything else too early may result in eczema, allergy, and/or other components of the Atopic March discussed in chapter six.

Intestinal barrier integrity and a healthy gut microbiome in infants are developed during key moments of pregnancy, the birthing process, and early life. Research [16] has elucidated the following mechanisms for how the mother seeds the infant's microbiome in order to start healthy development of oral tolerance:

- **Direct seeding in utero**

- **Passage through the birth canal and picking up vaginal flora.** Babies born by C-section have been shown to have altered microbiomes compared to babies born vaginally. The C-section babies are colonized by higher numbers of potential pathogens that frequent the hospital environment, increasing risk of immune and metabolic disorders. [17] Scientists have found that swabbing mom's vaginal fluids and exposing the C-section baby to them partially restores a normal microbiome. [18]

- **Breastfeeding** via breast milk and skin-to-skin contact
- **Caregiving** via oral transfer from kissing or topically from skin-to-skin contact[14]

Even with these evolutionary strategies in place, babies are still born with an immunoglobulin A (IgA) deficiency. IgA in the GI tract is called secretory IgA (sIgA) and is present in the mucus layers of the intestinal epithelium (or gut barrier). Secretory IgA provides important immune protection in the mucus by binding antigens and preventing them from entering the body, as well as regulating the immune response to dietary antigens.[15] Secretory IgA is the predominant immunoglobulin class found in human maternal milk, and maternal milk IgA compensates for the IgA deficiency in newborns.

In order for breastfeeding to be as effective as possible, the mother must have optimal levels of vitamin A, omega-3 fatty acids, and probiotics. Once food is being introduced to the child, care should be given to ensure that food coloring, additives, and artificial sweeteners are avoided. Stick to vegetables and fruits that are non-GMO, local, and organic. Both probiotics and prebiotics taken by mothers during pregnancy and breastfeeding have been shown to decrease risk of allergy and eczema in the infant during the first two years of life. [19], [20], [21]

- **Intestinal inflammation:** Intestinal inflammation, no matter tl cause, can prevent oral tolerance from developing in the infa or lead to loss of oral tolerance in the adult. Factors that cou cause intestinal inflammation include: lack of breastfeedin poor nutrition, nutrient deficiencies (such as lack of vitamin A lack of omega-3s, lack of probiotics), antigens (whether it's foc antigens, infection, toxins, etc.), and dysbiosis (due insufficient probiotics or overgrowth of pathogens and leaky g for any reason).[9]

As you have learned, the presence of one or more of these factors can lead to intestinal inflammation, which promotes loss of oral tolerance. As oral tolerance is lost,

food reactivity occurs. Food reactions quickly promote a vicious cycle of intestinal inflammation and the further loss of tolerance in five minutes or less.

A 2014 study in the journal *Gastroenterology* reported that exposure to food antigens in people with food reactions led to immediate breaks and increased spacing between the epithelial cells making up the gut barrier and increased intraepithelial lymphocytes in the intestinal mucosa. [22] This is scientific proof that food reactions promote leaky gut moments after exposure. The results of this study also suggest that continuing to eat foods that you react to may increase risk of death from all causes. How?

Our hazard ratio table from chapter six tells us that the highest hazard ratio for all-cause mortality was associated with increased levels of intraepithelial lymphocytes. If this is true, then you definitely don't want to eat the foods you react to—not even "just one bite."

If this food-induced destruction only takes five minutes to happen, how long does it take to heal? The authors in the *Gastroenterology* study found that "Upon implementation of a diet that eliminated the triggering foods, symptom scores improved by over 50 percent after four weeks of elimination, with improvements increasing 74 percent after six months of elimination."[22]

The allergy and sensitivity spectrum

By reading this far, you have learned that physiology is not black and white; it is a spectrum made up of white, then many shades of grey, and then black. You do not go to bed tonight with a healthy colon (white) and wake up tomorrow with colon cancer (black). Colon cancer takes months to years (many shades of grey), to grow large enough and destructive enough to be detectable and diagnosable (black).

As you have learned, autoimmune diseases follow the same path. First you are healthy (white), then you have an autoimmune process (shades of grey), consisting of antibodies and eventually signs and symptoms, then you finally fit

diagnostic criteria and have an autoimmune disease (black). This process can occur quickly or take years, depending on the individual and all the factors (exposome, epigenome, microbiome) involved.

It should be no surprise to you that food reactivity presents in the same way. You may have even figured it out yourself by experiencing it. With some foods, you won't have issues (white). With some, you may experience symptoms that range from minor to extreme (shades of grey). And with others, you may need an Epipen (black).

You have experienced a spectrum of responses to food, yet your MD says you don't have a food allergy because you haven't experienced lip swelling, throat swelling, or anaphylactic shock. Is your doctor correct? Is it really that black and white?

Research says no. Scientific study reveals that allergic reactions to food come in a spectrum from white to grey to black. The following table reveals one example of the spectrum of possible allergic responses to food published in the journal *Alimentary Pharmacology & Therapeutics* [1] in 2015.

		Likelihood of allergy from specific IgE (kU/L)		
		LOW (eg. nut <0.35)	**INTERMEDIATE** (eg. nut 0.35 - <15)	**HIGH** (eg. nut >15)
Likelihood of allergy from history	**HIGH** eg. urticaria & wheeze on 2 exposures	Possible allergy	Probable allergy	Allergy
	INTERMEDIATE eg. urticaria on single exposure	Possible allergy	Possible allergy	Probable allergy
	LOW eg. non-IgE symptoms	No allergy	Possible allergy	Possible allergy

On the left side of the table is the likelihood that a person has a food allergy based on history alone. It is intuitive that the worse the person's symptoms are when they eat a specific food, the higher the likelihood that they are allergic to it.

Across the top of the table is the likelihood that a person has a food allergy based exclusively on testing the blood for specific IgE antibodies to a specific food. Again, it is intuitive that the higher the antibody response (immune response) to the food, the higher the likelihood that the person is allergic to that food.

When you combine the two spectrums (symptoms only plus lab response only), you get the white to grey to black spectrum. You can see the box in the lower left hand corner is white and says "no allergy." Heading in an upward diagonal line toward the upper right corner, we next reach the center box—this box is light grey and says "possible allergy" and is flanked by darker grey boxes that say "probable allergy." Lastly, in the upper right hand corner, the darkest box (which should be black) reads "allergy." You finally fit diagnostic criteria in that box. The problem is, you've had symptoms since way back in the lower left hand box that read "no allergy." Why wait until an Epipen moment to take action?

How sharp a detective are you? Did you notice that I said you've had symptoms since the "no allergy" box? Did that cause a bit of anxiety in you? Were you thinking, "That is the 'no allergy' box, I don't have any symptoms!"

Not correct—look at the graphic again. The symptom description associated with that square is "Low (e.g., Non-IgE symptoms)"—it doesn't say "no symptoms." Non-IgE symptoms are any symptoms associated with eating that food that are not being caused by an IgE antibody response. This could be a non-immune-based food reaction such as food intolerance, but it is likely an immune-based food reaction such as food sensitivity. Food sensitivities are non-IgE immune-based food reactions that occur due to IgG or IgA reactivity (some studies term IgG food reactions food intolerance, which can cause confusion because non-immune-based food reactions are called food intolerance as well. In order to prevent confusion, in this book food sensitivity is what we will call immune-based IgG food reactions, and food intolerance is what we will call non-immune-based food reactions). Food sensitivities are believed to affect up to 20 percent of the population.[1]

Whereas IgE reactions are classified as acute hypersensitivity (potentially life-threatening) reactions, IgG and IgA reactions are classified as delayed hypersensitivity (not life-threatening but can be destructive to quality of life) reactions. Because food sensitivities are not typically acute or life-threatening, they are not recognized in conventional medicine as being an issue. In fact, many allergists will say that food sensitivities do not exist. Therefore, if you are a person suffering from food reactions but

your skin prick test, RAST test, and/or your IgE specific food testing with your allergist are negative, you will fall through the cracks and suffer unnecessarily.

These people fall in the white "no allergy" box in the graphic above. Are they faking it? Is it all in their heads? Do they need psychiatric medications? No—again, the research has answers for us. A study from 2016 says, "Patients clinically presenting with allergic symptoms are usually investigated for the presence of specific IgE antibodies that may not be present among the subgroup of patients presenting with allergic symptoms due to food sensitivity. These symptoms however, take time to manifest, since the formation of IgG takes days to months. As a result, this group of patients may not only remain undiagnosed, but also continue to suffer from significant preventable morbidity associated with the considerable financial burden on both patients and healthcare resources." [23]

This study wanted to investigate what is causing allergic symptoms in people who test negative for IgE evidence for allergy in the blood. They took seventy-one people with hives, which is an allergic symptom, who tested negative for IgE-specific positivity to any food. This means that from a lab perspective there was no allergy. The researchers then tested these people for IgG-specific antibodies against 223 different foods. The seven most common food sensitivities were found against cola nut, yeast, wheat, red kidney bean, pea, corn, and egg whites.[23]

In looking at that list, you can see three staples of the Standard American Diet (SAD); namely, wheat, corn, and egg white. Cola nut has historically been used in brown colored sodas, and pea is all the rage in the health community lately in the form of pea protein powders. Could your "allergic" symptoms be due to IgG food sensitivity?

Research says the possibility is real. It is not in your head and you are not faking, regardless of what your MD says. Get this—the study also said that IgG food reactivity was significantly more prominent in women. IgG food reactions have been implicated in irritable bowel syndrome (IBS) [24] , hives [25] and asthma [26] , migraines [27] , and autoimmune diseases. In fact, an observational study comparing patients with diagnosed

autoimmune disease to a control group with no autoimmunity found that the group with autoimmune disease had significantly higher IgG antibody responses to food than people with no autoimmunity. In this study, the most reactive food epitopes were casein protein, cow's milk, wheat, gliadin, egg white, and rice. The study concluded, "In general, these products should be forbidden to people with or at risk of autoimmune disease." [28] You and I know it would be better to determine on an individualized and specific basis what foods should be eliminated and what can be kept in the diet.

Food sensitivities occur due to many possible contributing factors. Therefore, the answer will be different for each individual. Two factors that play a huge role are a loss of oral tolerance and intestinal hyperpermeability ("leaky gut").

As discussed earlier in the chapter, some of us may have been dealing with this since birth. Others of us have developed issues over time due to various factors. No matter what the cause or combination of causes for your food sensitivity, the long-term solution is not to eliminate those foods forever—that is just putting a band-aid over the symptom. It will likely provide short-term relief, but if you do not use the time that buys you to find and address the cause(s), you have wasted it, and you will likely find that you are sensitive to more and more foods, which leads you to an ever increasingly restrictive diet without improvement in health or quality of life. You'll be left with a diet consisting of three things that you don't yet react to and a miserable existence.

Find the cause(s) so that you may address them and return to as diverse a diet as possible .

Non-immune-based food reactions

Not all food reactions are immune-based. When the mechanism behind a person's food reactions does not involve the immune system as the primary culprit, it is termed food intolerance or food malabsorption. For the purposes of this book, we will use the term food intolerance (FI).

"Food Intolerance is associated with poor nutritional status and/or impaired liver biotransformation (detoxification). Food

intolerance causes gastrointestinal nonspecific and extra intestinal symptoms when a particular nutrient or a combination of certain nutrients cannot be absorbed and digested properly." [29] Examples of common food intolerances are fructose intolerance and lactose intolerance.

- **Fructose intolerance** : Caused by inadequate absorption of fructose by glucose transporters in the small intestine
- **Lactose intolerance** : Caused by a deficiency in the enzyme lactase, which means lactose does not get digested.

In patients with intolerance, these carbohydrates (fructose or lactose) reach the large intestine and are metabolized by intestinal bacteria, resulting in fermentation and hydrogen production.[29] Studies reported combined lactose and fructose intolerance in patients with functional gastrointestinal disorders (FGID). [30]

Do you see the pieces coming together? We discussed FGID such as IBS and GERD in chapter three—could food intolerance be the driver of your FGID? Other examples of food intolerance include MSG (monosodium glutamate) sensitivity, lectin toxicity, tyramine intolerance, and histamine intolerance.

- **MSG sensitivity:** Associated with a deficiency in vitamin B6 and/or magnesium. These deficiencies may result in defects in liver function and/or symptoms of neuro-excitotoxicity such as pain, depression, anxiety, migraine, seizure, neurodegeneration. [31]
- **Lectins:** Carbohydrate-binding proteins of non-immune origin found in plants that cause agglutination or clumping together of cells. [32] Legumes represent the largest family of lectins. Common sources of lectins in the diet include beans, peas, lentils, soybeans, wheat, and peanuts. [33] Red kidney beans are the highest food source of phytohemagglutinin (PHA), which is highly pro-inflammatory due to its ability to potently activate the nuclear transcription factor for inflammation, nuclear factor kappa B (NFkB). [34]

The amount of lectins present in food depends on plant genetics and environmental factors. Lectins are not efficiently broken down by digestive enzymes, have anti-nutrient properties, and have been documented to cause gastroenteritis, nausea, and diarrhea.[33] The GI inflammation caused by lectins is due to their ability to potently inhibit repair of cell membranes. By preventing cell repair, lectins are toxic to wounded cells and promote cell death. [35]

Given this information, do you see how foods that contain lectins could cause symptoms or exacerbate disease in people with ulcers, Crohn's disease, ulcerative colitis, or any other situation where the GI epithelial barrier is damaged? The damage that lectins may cause to a person's health is not limited to the GI tract—they have been documented to bind to various cell and tissue targets body wide. [36]

- **Tyramine intolerance:** May result in high blood pressure ar headaches. Common foods high in tyramines include strong aged cheeses like cheddar or bleu cheese, cured or smok meats like sausage or salami, beer on tap or home-brewed, ar certain beans. [37]

- **Histamine intolerance:** Has many possible symptoms includi but not limited to hives, shortness of breath, and GI complaint It is hypothesized to be due to a deficiency in the histami degrading enzyme diamine oxidase (DAO). DAO is made b healthy intestinal cells. Any mucosal damage (infectio autoimmunity, surgery, various medications) in the sma intestine has the potential to reduce DAO activity and promo histamine intolerance. Single nucleotide polymorphisms (SNP in the DAO allele are not uncommon, so genetic variants al contribute to histamine intolerance.[29]

Putting the pieces together

Do not overlook the fact that you may have multiple food intolerances occurring at once, or a food intolerance that is the result of a combination of two antigens. For example, research

has shown that tyramine and histamine exhibit synergistic toxicity to intestinal cells in culture. This means that if you react to both, consuming both will exacerbate damage compared to the damage caused by consuming one of them alone. The possibility also exists that a person does not react to tyramine or histamine at all when consumed individually, but would react if he or she were to consume them in tandem due to their synergistic toxicity. [38]

There are also cases where immune-based food reactions are present in an individual at the same time as non-immune-based reactions. In other words, a person may have a food allergy or sensitivity and food intolerance at the same time—for example, gluten sensitivity overlapping with lectin consumption or lactose intolerance overlapping with milk allergy or IBD[15] . When we consider treatments, we have to be aware that both mechanisms may coexist and exacerbate symptoms in a patient suffering from food reactions.

The puzzle can be, and often is, very complicated. This is why cookie-cutter diets and treatment plans have not helped you. As the authors of a 2018 study in the journal *Inflammation Research* have stated, "Food intolerance requires personalized treatment in an individual dietary intervention for sustained relief of symptoms. After a detailed diagnostic workup for all possible etiological factors in each patient, a targeted dietary intervention for a single or possibly combined malabsorption might be more helpful than an untargeted diet low in FODMAPs or the widespread uncritical use of gluten free diets."[29]

In other words, if you tell your doctor you are experiencing food reactions and they offer a cookie-cutter response such as "adopt a low FODMAP diet or a gluten-free diet" without performing a detailed diagnostic workup (aka, detective work), they are failing you. We will discuss this more in the next chapter.

Ed's testing and results

How does all of this information help Ed? Could any of this be involved in his inability to breathe? That's what we investigated.

Ed's environmental allergy testing was negative. His food allergy testing revealed lab high IgE-specific antibodies to milk

and egg whites. His immune phenotype testing revealed lab high transforming growth factor beta (TGF-b) and white cells involved in the pro-allergy, pro-histamine Th2 immune response. This combination promotes a Th9 immune phenotype, which you could envision as a more intense allergic (Th2) response .

Ed also had lab high anti-Saccharomyces cerevisiae antibodies (ASCA), which are associated with Crohn's disease. Ed did not have signs or symptoms of Crohn's or fit diagnostic criteria, so the presence of these antibodies puts him early in the autoimmune process that could one day result in Crohn's if he let his health deteriorate. It is conceivable that these antibodies were playing a role in his lBS.

Stool testing revealed lab low digestive enzyme production by the pancreas and lab high levels of E. coli and the parasite Blastocystis hominis. Ed's probiotic levels were sufficient.

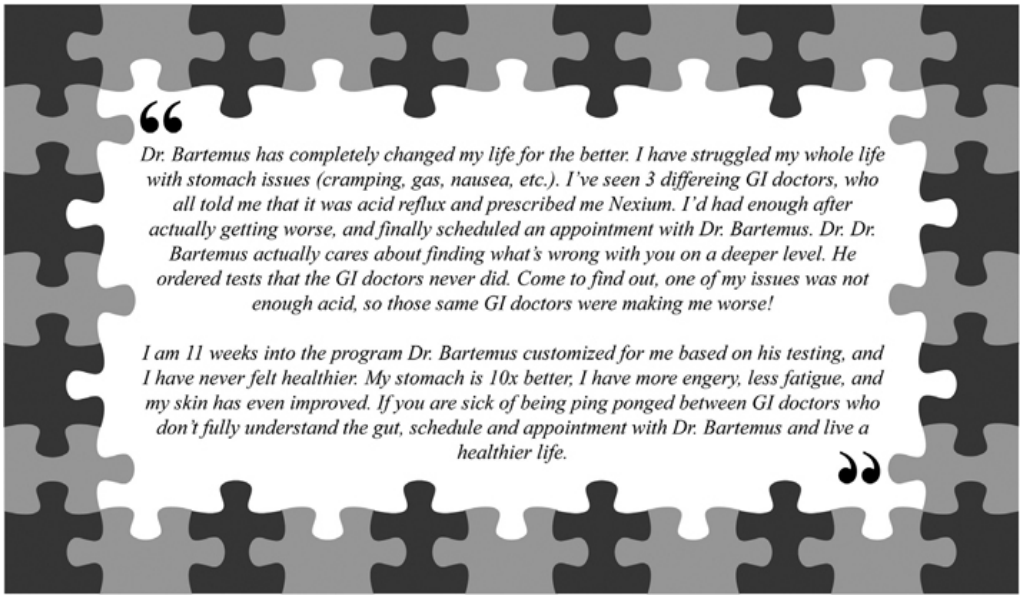
If you are following along at home, Ed's history and test results reveal the following functional medicine framework puzzle pieces:

- **Exposome:** Stressful job, poor diet, alcohol, and hypoxia fro breathing issues.
- **Epigenome:** Stress, poor nutrition, alcohol, hypoxia, ar dysbiosis all have potential for epigenetic affects.
- **Microbiome:** Deficient enzyme production, dysbiosis due overgrowth of E. coli and Blastocystis.

Using this information, an individualized and specific action plan was created for Ed, which included strict elimination of all dairy and eggs. We also included immune support with the goal of balancing immune phenotype and restoring oral tolerance. In order to do that, we had to address all factors that promote intestinal inflammation and interfere with optimal digestion. Specific to Ed, that meant we had to decrease his stress, increase his digestive enzyme production, and eliminate the E. coli and the parasite.

Ed reported almost immediate elimination of breathing issues once dairy and eggs were removed from his diet. By the eleventh week, Ed reported his stomach was ten times better, yielding

quality of life results in the form of eliminated stomach pain, increased energy, and healthier skin.



Dawn's results

Food reactivity played a massive role in Dawn's case. Our detective work revealed that Dawn had her gallbladder removed thirty-seven years before coming into my office, and she came in reporting thirty-eight years of daily diarrhea. My investigative mind connected the two; it is not uncommon for gluten sensitivity to cause symptoms associated with the gallbladder. Because many MDs are not aware of this, they commonly recommend the patient have their gallbladder removed. Often, patients have their gallbladder removed and don't feel any better afterward—this was Dawn's experience.

If gluten sensitivity is the cause of the symptoms associated with the gallbladder, then it is no surprise that removing the gallbladder doesn't help. The gallbladder-like symptoms are not actually being caused by the gallbladder, so removing the gallbladder but leaving the gluten means the symptoms stay too.

Beyond suspected gluten sensitivity, Dawn's history and medical records included many factors that promoted a loss of oral tolerance:

- Overnight shift work that promotes circadian rhyth dysfunction and sleep deprivation. [39]

- Chronic diarrhea and chronic mucosal infection

Testing revealed hard data on these puzzle pieces. Dawn's total cortisol production was lab low and cortisol-awakening response was deficient. Years of shift work had led to circadian rhythm dysfunction. At the time of testing, Dawn had a Klebsiella pneumoniae urinary tract infection. She also had lab high liver enzymes, lab high TGF-b, deficient probiotics, and the presence of a parasite.

Dawn's individualized and specific plan included completely eliminating gluten, optimizing liver function, and improving mucosal immunity. Within two weeks, her diarrhea had been eliminated after thirty-eight consecutive years. At six weeks, Dawn also reported 50 percent improvement in energy levels, 75 percent reduction in anxiety, 75 percent improvement in digestive function and 50 percent improvement in sleep. Lastly, Dawn reported that her attitude and outlook on life had improved by 75 percent, and she was excited that she could now function with a higher quality of life in her retirement and enjoy the life she had envisioned.

Reader action steps

If you are suffering from food reactions, reach out to a detective clinician who can help you get to the underlying cause(s) of your reactivity. It is not enough to just eliminate the foods you react to. You must also address the "why" behind the food reactions. Are you lacking stomach acid? Digestive enzymes? Oral tolerance? Are you over stressed? There are many potential causes. You must have your framework assessed.

Remember, food reactions due to loss of oral tolerance can be a HUGE factor that is often overlooked. As stated in a 2020 paper by Aristo Vojdani [40] :

"The failure of oral tolerance triggers immune reactivity against dietary antigens, which may initiate or exacerbate autoimmune disease when the food antigen shares homology with human tissue antigens."

Learn more by viewing my Food Reactions video playlist:
https://www.FunctionalMedicineCharlotte.com/FoodReaction s

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CHAPTER 9

There Is No Perfect Diet

"Nutrients play an important role in the development and functionality of the immune system and any deficiency, either single or multiple, is often the cause of a compromised immunity."

—Zapatera, Belén, et al. [1]

"Our poor dietary choices are encoded into our gut, our genes, and are passed to our offspring. While today's modern diet may provide beneficial protection from micro- and macronutrient deficiencies, our overabundance of calories in the macronutrients that compose our diet may all lead to increased inflammation, reduced control of infection, increased rates of cancer, and increased risk for allergic and auto-inflammatory disease."

—Ian A. Myles [2]

Kendra sat in front of me and cried. Between tears, she said, "My husband and I have just done three months of a strict ketogenic diet. He lost twenty-five pounds on it, and he cheated. I followed it to the letter, and I did a bootcamp four days a week, and I haven't lost a pound." Kendra is almost sixty, 5'8" and 226 pounds. Besides the inability to lose weight, she reported chronic diarrhea and sleep deprivation .

What is the perfect diet?

There is no perfect diet for the U.S. population as a whole. There's no perfect diet for a specific gender, race, or body type. There is no perfect diet for your family. There's only a perfect diet for you, and even that will change. The diet that is perfect for you today is likely to be different than the diet that is perfect for you two years from now.

If you've read enough diet and nutrition books, you've realized that most of them are promoting the same diet with a tweak here or there that gives the reader (and the author) a false perception that something new has been created.

It hasn't.

What will make the perfect diet for you two years from now different than the perfect diet for you today is that your physiology is dynamic and always changing. That can be a good thing or bad thing.

It is advantageous if you are using discoveries in epigenetics, nutrigenomics, and microbiome research to promote optimal physiology. Dynamic physiology is disadvantageous when a person is not aware of the exposome, epigenome, and microbiome, and consumes a diet that promotes dysfunction in those areas.

Exhibit A: The Standard American Diet

The Standard American Diet (SAD) has been shown in human research [3] to induce endotoxemia (high levels of circulating bacterial toxins) in less than 3 days. This led to a 35% decrease in insulin sensitivity, which promotes high blood sugar and increases the risk of diabetes.

To paraphrase the authors discussing dietary prescription in a 2018 paper published in *Inflammation Research* , [4] after a detailed diagnostic workup for all possible causal factors in each patient, an individualized and patient-specific nutrition plan should be created. This type of plan is likely to help more than non-specific dietary recommendations given without any critical thinking, aka detective work.

In addition to the completely non-specific, population-based dietary recommendations made by the US government, the authors give two examples of the use of "untargeted and uncritical dietary recommendations" in the context of gluten sensitivity: a low FODMAP diet and a gluten-free diet.

Do not misinterpret this. I am not implying, and neither are the paper's authors, that a low FODMAP or gluten-free diet is

useless for gluten- sensitive people. What we are saying is that it is bad healthcare and clinically lazy to hear a person's complaints and reflexively recommend the diet without doing any detective work.

As an example, the paper discusses how the symptoms of gluten sensitivity overlap with the symptoms of histamine intolerance, and therefore a doctor cannot know if one or both are involved in the patient without doing the work. Once a thorough investigation has been done, then and only then can the doctor know what factors are driving the person's symptoms and which nutritional strategies are best for that person at that time.

The concept of individualized nutrition is not a fringe concept. The September 2019 issue of the *Journal of the American Medical Association* (JAMA) [5] published an editorial that stated:

"The application of advanced biomarker discovery…and knowledge of genetic and gut microbiota differences in response to diet offer promising new strategies toward optimizing nutrition…These methods seek to address causality and understand mechanisms that bridge the influence of diet on health across the lifespan…These methods also encourage enthus iasm for personalized or precision nutrition in contrast with the current population-based model that provides nonspecific health eating advice."

The conversation was continued in a 2019 editorial published in the *American Journal of Clinical Nutrition* [6] stating:

"Given the importance of non-genetic factors (lifestyle, environment, demographics, etc.) in many health concerns… precision medicine that focuses solely on people's genome is doomed to fail. Inaccurate 'genotype-specific' recommendations may be misleading and have potentially negative consequences. It is clear that to predict disease accurately, or to personalize treatment, an integrated approach that accounts for people's unique genetic and non-genetic characteristics is needed."

Do not think that the population-based nutritional recommendations versus individualized and specific nutritional recommendations debate is limited to scientific journals. It is being tested in real-time on the biggest of mainstream medical stages at the Cleveland Clinic.

In October 2019, *JAMA Network Open* [7] published the results of the first of its kind study that compared patients who received conventional family medicine treatment at the Cleveland Clinic with patients who received Functional Medicine care at the Cleveland Clinic Center for Functional Medicine. The primary outcome measure was the patient-reported health-related quality of life after 6 months of care. Results revealed that the patients who received Functional Medicine exhibited significantly larger improvements in health-related quality of life.

This study is important for two reasons:

1. It shows that Functional Medicine is being recognized as a health care approach that must be taken seriously and investigated as the possible solution for the chronic disease pandemic in America.

2. Functional Medicine beating conventional medicine in patient-reported quality of life suggests that further studies comparing the two models should be done following more objective outcome measures such as improvements in lab biomarkers, body composition, etc.

The goal

The goal of this chapter is not to teach you the ins and outs of every diet out there. If you want to know the nitty-gritty about a specific diet, I promise you there are too many books written on each of them. Find the book written by that diet's guru and read it. My goal is to get you to understand that none of those diets are perfect, but all of them have the potential to be perfect for someone at some time.

The problem with diet books is they have to be written to the population. That is tough because a population-wide avatar

does not walk into my office. When someone comes into my office, they are one in seven billion. They are unique, a puzzle made up of a combination of pieces that no one else has.

Where most dietary authors find grace is that the U.S. population as a whole is eating the worst diet possible, the Standard American Diet, so writing a book to the population will still be a win. If the population adopted what that book is promoting, the majority of people would be helped by that diet compared to the SAD. However, some people would be hurt by it. It doesn't matter if you are writing about paleo or keto or vegetarian—giving the wrong diet to the wrong person will hurt them.

My goal is to help you understand considerations you should be making when deciding what to eat, whether you are designing the diet yourself, or you are given a recommendation by a healthcare professional. Since this is a book about autoimmunity, I will focus mostly on the impact that food has on immune function .

We have touched on it throughout the book, with chapters six and eight covering the most ground to this point. Let us now dig into the topic known in the research as immunonutrition.[1] Immunonutrition encompasses the whole person. It includes nutrition, immunity, infection, inflammation, and injury. The handy way to remember this, coined by one author, is "Nutrition and the 4 I's." All of the interconnectedness of the endocrine, hormonal, nervous, and the immune systems, as well as the gut microbiome, is within Nutrition and the 4 I's.

Immunonutrition involves the entire physiology. Therefore, it is subject to a wide range of variables, including genes, lifestyle, and idiosyncratic features unique to each individual. For these reasons, a person's state of immunonutrition is dynamic. As changes occur in their diet, physiology, and/or confounding variables, so will their immune tolerance and risk of autoimmunity, infection, and cancer.[1]

The immune system is exquisitely sensitive to environmental changes. Diet constitutes one of the major environmental

factors exerting a profound effect on immune system development and function. [8]

“Nutrigenomics is an emerging discipline examining the role of dietary influences on gene expression. There’s increasing evidence that the epigenetic mechanisms that regulate genetic expression during immune differentiation are directly affected by diet or indirectly through modifications in the gut microbiome induced by diet.”[8]

Many nutritional factors influence the immune system epigenetically in a positive or negative way. Those that positively influence the immune system through epigenetic mechanisms include folate, choline, and betaine (these three nutrients function in the methylation cycle), vitamin E, carnitine, dietary fibers (result in SCFA production by your gut microbiome), fat consumption, proteins, and hormones. Nutritional factors that could negatively impact the immune system through epigenetic mechanisms include fat consumption, protein, hormones, alcohol, and carbohydrates.[8]

High glucose increases inflammatory factors, which leads to immune dysfunction.

Vitamins also influence immune function via non-epigenetic mechanisms. For example, sufficient levels of folate, niacin, vitamin A, and vitamin D are required to promote differentiation of naive T cells into T-regulatory cells. T-regulatory cells are anti-inflammatory and are the major tolerance-promoting cells of the immune system. [9] Deficiency in one or multiple of these vitamins may result in suboptimal T-regulatory cell differentiation, which could result in a pro-inflammatory immune phenotype and loss of tolerance. As discussed in the previous chapter, this could result in Atopic March, food reactions, and/or autoimmunity.

Protein malnutrition can lead to a compromised immune system due to associated micronutrient insufficiencies, namely vitamin A, iron, zinc, and copper. Several nutrients play key roles in modulating the intensity of inflammatory responses of the immune system. Examples include vitamin E, vitamin A,

zinc, and essential fatty acids, which include the properly balanced ratio of omega-6 to omega-3 fats.[1]

As an example, let us use omega-3 fatty acids. The two primary omega-3 fatty acids that are relevant to this discussion are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The label "essential fatty acid" means that we, as humans, cannot make them. We must consume them in our diet, primarily through fish, as fish oil supplements, or alpha linolenic acid (ALA). [10]

If we consume ALA, we must then convert it to EPA and DHA.[10] EPA and DHA are precursors of lipid mediators called resolvins and protectins. EPA is metabolized into the E-series resolvins, and DHA is metabolized into the D-series resolvins and protectin D1 (PD1). Both E series and D series resolvins promote resolution of inflammation (healing). [11]

When appropriate, this is a good thing because if your inflammation doesn't resolve, you have chronic inflammation, which promotes chronic disease, including autoimmunity. The protectin D1 that comes from DHA quiets brain inflammation and has been shown to be protective against Alzheimer's disease.[11]

Nutrition and cancer

This is not a book on cancer, but since we are discussing the effect of nutrition on the immune system, it is worthwhile to invest a paragraph or two. Plus, we have discussed inflammation and autoimmunity at length, and both are considered risk factors for cancer. "Inflammation has been considered a predisposing condition for tumor development since 1863, and nowadays at least 20 percent of all cancers are considered to be a direct consequence of a chronic inflammatory process." [12]

Chronic inflammation persistently promotes a pro-tumor microenvironment in the body, which is rich in inflammatory chemicals. These inflammatory substances are the primary players and regulators of the crosstalk between cancer cells and surrounding tissue cells. Chronic inflammatory intestinal

disorders such as IBD, Crohn's disease, and ulcerative colitis are considered to be risk factors for colon cancer.[12]

The World Cancer Research Foundation and the American Institute for Cancer Research consider diet to be one of the most important factors in colon cancer development. A 2019 study in the *World Journal of Gastroenterology* [12] looked at how dietary inputs can directly or indirectly act to promote colon cancer prevention or colon cancer initiation and progression. The authors found that food choices directly promote cancer prevention by protecting cells from DNA damage. Food choices could indirectly prevent cancer by positively impacting the gut microbiome.

The same findings could also be seen from the opposite angle. Food choices directly promoted cancer by promoting DNA damage, activating genes that promote cancer growth, and causing systemic inflammation. Cancer was promoted indirectly by the induction of obesity through poor dietary choices and the negative effects on the gut microbiome.

Direct and indirect effects of food choices impact immune function and immune surveillance. Positive food choices promoted better immune surveillance and decreased risk of cancer. Negative food choices did the opposite. Positive food choices included higher fiber, foods rich in minerals, antioxidants, and nutrients such as zinc, selenium, flavonoids, carotenoids, probiotics, and prebiotics. Foods that promoted cancer included proinflammatory processed fast foods, overcooked meats, foods containing hormones and other chemicals, and high sugar foods.[12]

Food choices can impact the gut microbiome in prevention or promotion of colon cancer. Gut bacteria can promote colon cancer by metabolizing pro-cancer dietary/digestive components such as meats and bile acids into metabolites such as secondary bile acids and hydrogen sulfide. [13]

Conversely, gut bacteria can protect against colon cancer by metabolizing beneficial dietary inputs such as plant-based polyphenols and fiber into tumor-suppressive metabolites such as the short-chain fatty acid butyrate.[13]

Bacteria can have direct effects on normal and cancer cells in the colon through these mechanisms. The main point to remember is that whether you are concerned about developing autoimmunity, cancer, or any other chronic disease, the daily nutritional choices you make at each meal matter, every one of them .

Constructing the perfect diet for you

How do I, as an author, give you the nutritional recommendations that constitute the perfect diet for you? I cannot—I don't know you unless you come into my office. In truth, no one can unless they meet you, take a thorough history, and perform further detective work using examination and diagnostic tools. This is why you have not been able to Google yourself well. It is probably the reason you're reading this book—if your Google searches had worked, you probably wouldn't have bothered.

Alas, the field is littered with the bodies of people failed by Dr. Google. It's time you invest in yourself. You must partner with the detective who has the know-how to work your case and construct an individualized and specific action plan that includes the perfect diet for you. Doing it any other way will result in frustration.

Remember, as a person dealing with autoimmunity, proper immunonutrition is a key piece to your puzzle and involves more than avoiding nightshades. Immunonutrition involves the entire physiology, therefore it is subject to a wide range of variables including genes, lifestyle, and the idiosyncratic features unique to each individual. This means that your genes and environment, nutrition, physical activity level, sleep quality and quantity, toxic load, stress levels, and mental health all matter. Each person's puzzle consists of pieces from all of these areas and more.

Avoiding nightshades will not address all of those pieces; it could play a significant role in one person and have no effect in another. The difference is the puzzle. This may seem like a sales pitch or a cop out, but it is not. Just take a look at the various cases in this book. Each person required different

nutritional strategies as part of their overall action plan, and their care consisted of many pieces. Nutritional recommendations were only one part.

Let's take a look at the various cases we covered :

In chapter one, the key piece to Wanda's nutritional puzzle to positively impact her Parkinson's disease and insulin resistance was intermittent fasting. Intermittent fasting has been shown in the research to create a reduction of body fat and body mass, which supports a healthy cardiovascular system. It has also been shown to improve stress tolerance, increase stores of alternate energy sources such as ketones, enhance sensitivity to insulin, and elevate factors that promote healthy memory and cognition such as brain-derived neurotrophic factor. [14]

Intermittent fasting has also been shown to increase vagus nerve function, reduce brain inflammation, improve mitochondrial health, and enhance autophagy. [15] Wanda is a living example that intermittent fasting was the perfect diet for her to follow as part of an individualized and specific action plan created to address her unique puzzle.

In chapter two, a key piece to Abby's nutritional puzzle to positively impact her psoriasis was the paleo diet, with additional avoidance of nightshades (aka, the autoimmune paleo diet or AIP) and focus on optimizing her vitamin A and vitamin D status.

A national survey [16] of over 1200 people with psoriasis found that 69 percent of respondents experienced skin improvement following a paleo diet. Over 50 percent of respondents reported skin improvement after cutting out alcohol, gluten, and nightshades. Cutting out alcohol and gluten is required by the paleo diet, but cutting out nightshades as well makes it the AIP diet.

Lastly, over 40 percent of respondents reported skin improvements with the addition of omega-3 fish oil, more vegetables, and vitamin D, all of which are increased by following a paleo diet.

Abby is a living example of how AIP was the perfect diet for her to follow as part of an individualized and specific action plan created to address her unique puzzle .

In chapter three, a key piece to Donny's nutritional puzzle to positively impact his Crohn's disease was the specific carbohydrate diet (SCD). Research states, "the SCD is not an approach suited for every inflammatory bowel disease patient." [17] In other words, detective work must be done to determine if this is the right diet recommendation for a given individual. Several studies have been published suggesting the effectiveness of SCD in pediatric Crohn's disease and revealed reductions in inflammatory markers such as C-reactive protein and calprotectin, as well as improvements in symptom scores and quality of life.[17] Donny is a living example of how SCD was the perfect diet for him to follow as part of an individualized and specific action plan created to address his unique puzzle.

In chapter four, a key piece to Andy's nutritional puzzle to positively impact his PANDAS and associated autoimmune epilepsy was a medically supervised ketogenic diet. The ketogenic diet was originally developed in 1921 for children with epilepsy (aka seizures). The classic ketogenic diet is tightly controlled and specifically calculated for each person as a high fat, low carbohydrate, and adequate protein diet. [18]

Keto has been shown in recent research to be an effective treatment strategy in autism [19] and cancer. [20] Andy is a living example of how the classic ketogenic diet was perfect for him to follow as part of an individualized and specific action plan created to address his unique puzzle.

In chapter five, a key piece to Kenny's nutritional puzzle to positively impact his concussion-induced brain-gut/gut-brain axis dysfunction was specific testing for and avoidance of food sensitivities, which are caused by a loss of oral tolerance. [21]

As discussed in that chapter, oral tolerance is lost when intestinal inflammation is present. Intestinal inflammation is increased when intestinal hyperpermeability, or leaky gut, is present. Within six hours of a head injury, a leaky gut

develops, [22] and the loss of oral tolerance is not far behind if leaky gut persists.

Kenny is a living example of how discovering and avoiding food sensitivities was the perfect dietary approach for him to follow as part of an individualized and specific action plan created to address his unique puzzle.

In chapter six, a key piece to the individual puzzles of Timmy, Brittany, and Jack was the complete avoidance of wheat or gluten. Timmy, Brittany, and Jack are living examples of how this was the perfect dietary approach for them to follow as part of an individualized and specific action plan created to address their unique puzzles of the celiac process, wheat allergy, and gluten sensitivity, respectively.

In chapter seven, a key piece to the individual puzzles of thyroid autoimmunity that Candace and Brandon were suffering from was optimization of their blood sugar regulation. Candace had Hashimoto's disease and high anxiety. Brandon had joint pain, poor sleep, and couldn't lose weight. I discovered the Hashimoto's process in him as well.

Autoimmunity is promoted by the leaky gut and gut infections caused by high blood sugar. [23] Insulin resistance causes high blood sugar. Brandon's inability to control his blood sugar wasn't only promoting weight gain, systemic inflammation, and resultant joint pain and sleeping issues, but also autoimmunity.

Case reports reveal a link between hypoglycemia, low blood sugar symptoms, and generalized anxiety disorder. [24]

Although thyroid dysfunction is a known driver of anxiety, so is low blood sugar. Candace was suffering from an anxiety double whammy. The key nutritional strategy in both cases was proper nutrient timing. You've probably pondered what the best way to eat is—three meals per day with no snacks or six small meals per day? The answer depends on the person and their unique puzzle. Candace needed to start out at six small meals per day in order to keep her blood sugar stable. Over time, we progressed her so that she could go longer and longer between meals without anxiety symptoms.

Brandon was the opposite. Due to his insulin resistance tendency, he needed to eat three meals a day with no snacks. This way, his insulin levels would drop between meals and promote improved insulin sensitivity (aka reverse insulin resistance).

Candace and Brandon are living examples of how nutrient timing was the perfect dietary approach for them to follow as part of an individualized and specific action plan created to address their unique puzzles of thyroid autoimmunity paired with hypoglycemia and insulin resistance, respectively.

In chapter eight, the key pieces to the individual puzzles of food reactivity that Ed and Dawn dealt with were different. In Ed's case, he was suffering from food allergy. In Dawn's case, gluten was the cause of her thirty-eight years of chronic diarrhea. The key nutritional strategies for Ed were to completely avoid the foods he tested positive for allergy against and follow a low histamine diet. Ed is a living example of how discovering and avoiding food allergies and a low histamine diet was the perfect dietary approach for him to follow as part of an individualized and specific action plan created to address this unique puzzle.

The key nutritional strategy in Dawn's case was to eliminate gluten. That immediately ended her thirty-eight year run of diarrhea (pun intended). I also had her eliminate dairy due to her history of chronic mucosal infections in the sinuses and urinary tract. Dawn is a living example of how discovering and avoiding food sensitivities was the perfect dietary approach as part of an individualized and specific action plan created to address her unique puzzle .

I hope these real case examples have opened your eyes to the fact that there is no perfect diet for the population. There's only a perfect diet for you at this time, and it cannot be found in a book or on a search engine. It can only be created for you when you partner with a detective clinician that can put the clues together and solve your case. Only then will the doctor know you and your case well enough to create an individualized and specific action plan that includes the perfect diet for you as a part of it.

Kendra's detective work and subsequent plan

I had Kendra track her metabolic rate and caloric intake versus expenditure for me for seven consecutive days—I needed to know how much she was consuming versus how much she was burning. Over those days, she burned an average of 2,100 calories total per day, with about 700 of those calories being burned during exercise. She ate an average of 1,400 calories a day.

Kendra was at a caloric deficit. Shouldn't she be losing weight? Caloric deficit can be a stressor that promotes cortisol release. [25] If her deficit was promoting cortisol release, eating less to lose weight may have been working against her. Chronically elevated cortisol promotes weight gain in the waist and hips.

After three months of strict ketogenic diet, initial testing with me revealed that Kendra's thyroid panel was perfect. (I'm talking about a complete thyroid panel with nine markers, not the typical incomplete two-marker panel done at your MD's office.)

It was important to perform thorough thyroid testing because the thyroid sets your metabolic rate, as discussed in chapter seven. Diet and exercise are the low hanging fruit. If someone is dieting perfectly and exercising perfectly like Kendra was and not losing weight, then it is important to look higher up the tree metabolically. Common metabolic fruits found higher up in the tree include thyroid dysfunction, sex hormone dysfunction, systemic inflammation, gut dysbiosis, HPA-axis maladaptation, et cetera.

Thyroid was not an issue for Kendra, but her vitamin D was suboptimal, her total salivary cortisol levels were lab high, and her cortisol awakening response was overactive. These findings indicate hypothalamic-pituitary-adrenal axis (HPA-axis) maladaptation (high stress), which contributes to weight gain, immune suppression, sex hormone dysfunction, and

sleep issues. [26] It appeared that her caloric restriction was not helping her cortisol levels or weight loss.

A second roadblock keeping Kendra from losing weight was decreased cell sensitivity to insulin; a shift toward insulin resistance. This loss of insulin sensitivity was likely a result of the chronic stress associated with her caloric deficit, overtraining relative to her caloric intake, and mental anguish over her inability to lose weight.

All of this promotes accumulation of visceral fat and central obesity (fat around the midsection). [27] Stool testing revealed lab high calprotectin levels, which indicated significant gut inflammation. Her levels were in the range where clinicians must consider inflammatory bowel disease such as Crohn's and ulcerative colitis. Her gut inflammation and chronic diarrhea suggested IBS-D at a minimum. Dysbiosis was indicated by overgrowth of Citrobacter species and the presence of two parasites.

My focus with Kendra's individualized and specific action plan was to create optimal balance in her gut microbiome, cortisol physiology (aka, balance her stress response), and blood sugar regulation. Like all my plans, I adjusted many factors in her lifestyle and used supplements where appropriate to speed our results.

Kendra's specific plan required a combination of multiple strategies. First of all, we knew that the ketogenic diet was not the right diet for her, so I moved her to a paleo diet. It was important to bring carbohydrates back to her system in appropriate amounts. Paleo is not low carb or no carb—it is the right carbs in the right amount. Next, I had her continue to track her daily energy equation. (Calories burned plus calories consumed = caloric deficit/surplus) and aim for a three-hundred calorie surplus per day.

We had to teach the body that it was no longer starving. Living at a caloric deficit is a stressor and an environmental signal to the body that there is an environment of lack outside. This makes the body want to hold tighter to its energy reserves because it thinks you are starving or at risk of starving. From a

basic biochemistry perspective, one gram of fat is made up of nine calories, while one gram of protein or carbohydrate is made up of four calories.

Fat provides more than double the energy of protein or carbohydrate—no wonder Kendra's body was holding so tightly to it. My goal of having her eat a slight surplus daily was to reeducate the body with an environmental signal that said there were plenty of energy sources available to Kendra daily. *You can let go now. She is not going to starve. Let the fat go* .

Lastly, I wanted to reverse the insulin resistance trend and increase cell sensitivity to insulin by allowing its levels to drop between meals. We utilized the same strategy here that I used with Brandon. Three meals per day and zero snacking allowed.

At six weeks, Kendra reported that her diarrhea was 100 percent eliminated, and her sleep was 75 percent better.

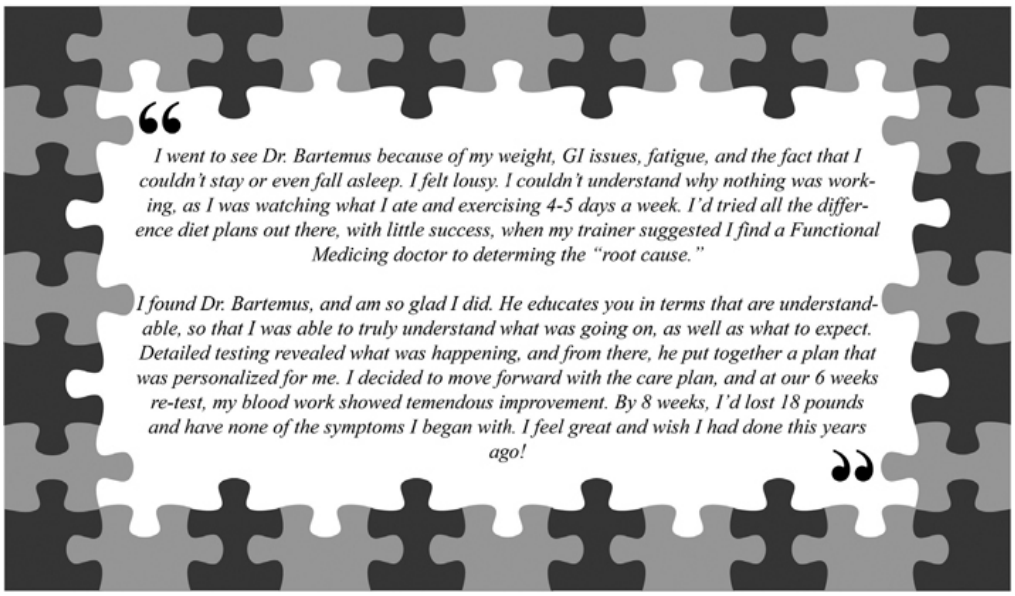
Three months of individualized and specific care, including the proper nutrition, yielded the following results :

Calprotectin decreased from lab high IBD levels to normal range, indicating a significantly important reduction in gut inflammation, from pathologic levels to homeostatic levels.

Her total salivary cortisol and cortisol awakening response levels were now normal, indicating a significant reduction in stress from all causes.

This also indicated that she was no longer promoting fat deposition around her hips and waist and no longer promoting insulin resistance. Her vitamin D levels were now optimal.

Most importantly to Kendra, she had lost twenty pounds and reported a 100 percent improvement in energy, gut function, and sleep. She reported happily, "I feel great, and although in the beginning this was one of the hardest things I've done, it's been totally worth it."



Reader action steps

Partner with a clinician detective who can design the perfect diet for you in your current state, and if you have been consuming the Standard American Diet for most of your life, then the following tests will help you and your detective understand your current state of immunonutrition: Omega-6 to omega-3 fatty acid ratio, vitamin A, vitamin D, iron panel, zinc (serum and red blood cell), copper status (serum copper and ceruloplasmin), folate, methylmalonic acid, stool testing, complete blood count and a complete metabolic panel.

This is in no way an all-inclusive list, but it is far more in-depth than anything I've ever seen a medical doctor do in the hundreds of thousands of pages of records that I've reviewed over the years.

Learn more by viewing my Diet video playlist:
https://www.FunctionalMedicineCharlotte.com/Diet

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CHAPTER 10

You Cannot Google Yourself Well

"Don't you know that they're coming 'round to get you?
Standing right behind you their eyes are fixed on me, too
Can't you feel all dirt from their money?
The leather from their briefcase?
The chill from their cold, cold heart?"

—"Coming 'Round To Get You", Farewell Milwaukee

I recently received the following email from a man named Sam who had met with me for an initial visit five months earlier but decided at that time that he would try solving his issues on his own:

"I'll give your office a call this week and move forward with testing. It's become obvious that I am not able to piece together what's going on with me. I recently added soil-based probiotics to my diet, and my symptoms flared up—I am feeling bloated with a random, rapid heart rate, moments of brain fog, and fatigue. Hopefully, you can help me find and address the root cause."

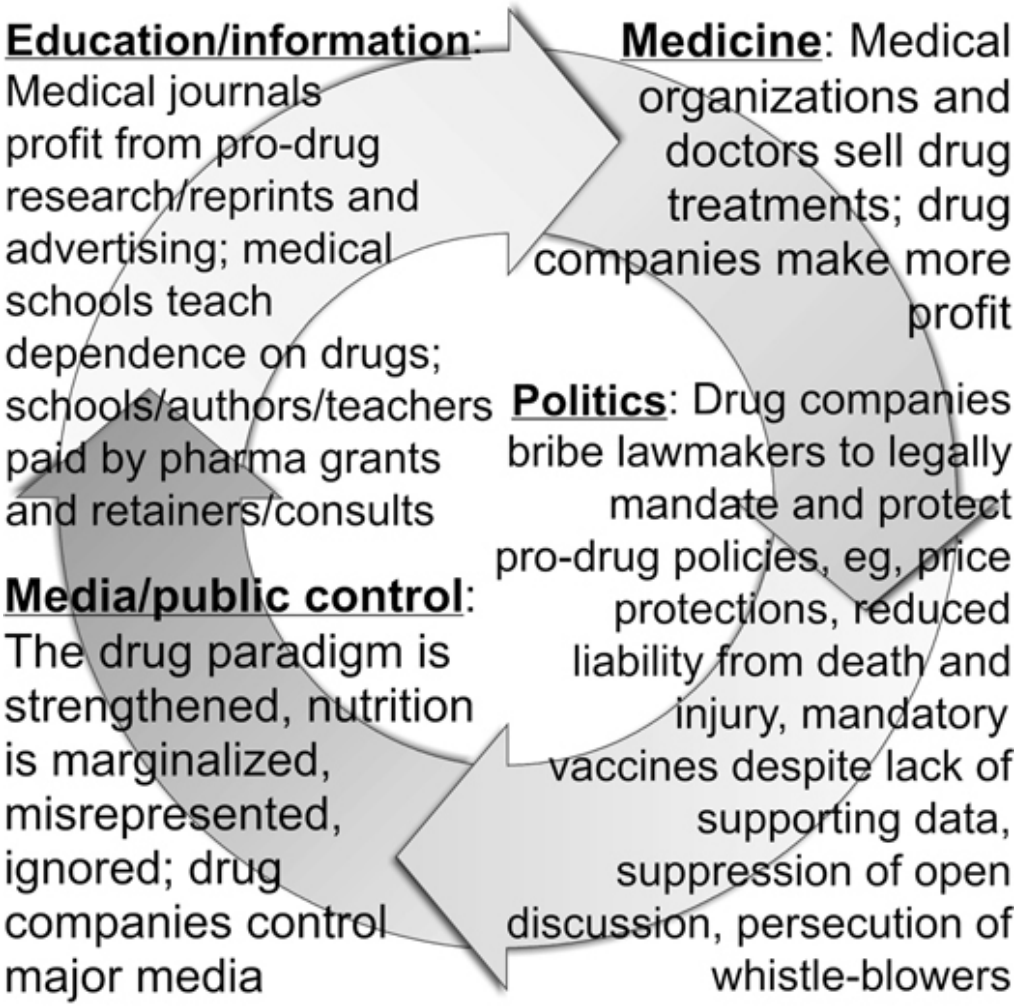
Doctor Google will not save you

You cannot Google yourself well. If it were ever possible (it wasn't), there is now no chance. In fact, Google does not want you well. If they did, they would lead you to information that could move you closer to that goal. As it turns out, Google is doing the opposite .

Google has been censoring health information since August 2019. Specifically, it is censoring non-mainstream health websites by driving such sites far down the search results. In place of non-biased, non-pharmaceutical company funded truth, Google is showing top results from "institutional health websites." Institutional health websites are sites founded by hospitals and government institutions. Examples are WebMD, Healthline, Mayo Clinic, Cleveland Clinic, CDC, FDA, etc. all

with clear connections and financial support from the pharmaceutical industry. [1]

The fact that Google (as well as YouTube and Facebook) is censoring non-pharma health information further proves Dr. Alex Vasquez's concept of the Pharma Echo Chamber and Power Vortex [2] viewed graphically below.



Vasquez and Pizzorno, Concerns About the Integrity of the Scientific Research Process. *Integrative Medicine* 2019 academia.edu/39907759 and **ncbi.nlm.nih.gov/pmc/articles/PMC6601430**
Pharma Echo Chamber, Sociopolitical Matrix, and Power Vortex. *IJHNFM* academia.edu/38476348
Vitamins Against Viruses: Implausible Pro-Vaccine Publications Contrasted Against Ignored Public Health Campaigns and Double-Blind Placebo-Controlled Clinical Trials. *Journal of Orthomolecular Medicine* 2019 academia.edu/39406350 and https://isom.ca/article/vitamins-against-viruses/

Google receives more than one billion health questions every day. That is 70,000 health questions a minute! [3]

By burying natural health websites Google is preventing you from finding scientifically validated health information that may help you get healthy without the use of pharmaceuticals. In so doing, they are partnering with Big Pharma and their

government puppets in funneling you toward the promotion of drugs, surgery, vaccines, toxicity, deficiency, chronic disease, hopelessness, and early death—all for money.

The goal of the pharmaceutical industry-controlled conventional health care system is to make money, not get you well. If you are well, you are not in the system making money for pharmaceutical and insurance company shareholders. Their goal is not to make you well; their goal is to make money for shareholders. Don't take my word for it—that was the headline quote of one pharmaceutical company CEO in 2016.

J. Michael Pearson, the CEO of Valeant Pharmaceuticals was quoted in an interview with MSNBC [4] saying, "My company's responsibility is to its shareholders, not the customers who rely on drugs to live."

If you are placing your faith in a Google-curated health topic search, this is what you are up against—cherry picked information that will funnel you toward a system whose goal it is to extract as much money from you as possible. Healing be damned.

How attempting to Dr. Google yourself can make you worse

It's bad enough that Google is hiding the health information that has the highest probability of helping you heal, but the damage to your ability to heal does not stop there. Just the act of searching Google in an attempt to heal yourself is likely to make you worse .

Let's use Sam, the writer of the email above, as an example. Sam chose to try and heal himself by going the Dr. Google route. He has been dealing with chronic stomach pain, acid reflux, dizziness, heart palpitations, brain fog, and migraines for over four years. Sam is a salesman with a high stress, commission-based job. He commented to me during his initial visit that he makes a lot of money, but his wife spends it as fast as he makes it. That was one reason why he chose to go the Google route instead of moving forward with the testing I recommended.

Sam chose to be his own Internet detective. As you already learned, one problem with that is Google is not going to make it easy for him to find the information he is looking for. A second problem is his job—Sam must focus on work and performance there so he can make the money he needs to fund his life (and wife). That means he cannot be conducting health searches during the day, or if he does it is likely to hurt his performance at work (I will tell you how shortly.)

Sam must work all day, then come home and be the husband and father he needs to be. Therefore, he does not have time to do his Google sleuthing until after the kids are in bed. His first click is unlikely to happen until 9pm, at the earliest.

This turns Sam into a night owl, spending far too much time on the Internet when he should be sleeping. This habit of spending late nights on a smartphone, computer, tablet, or any other device going down a Google rabbit hole hurts Sam's health in multiple ways. The following is a list of just a few:

1. Interference with cortisol circadian rhythm and sleep physiology

2. Reduction of cognitive bandwidth

3. Increase in attention residue and decrease in performanc e

Interference with circadian rhythm and sleep physiology

The screens used on devices such as flat screen TVs, computer monitors, tablets, and smartphones emit blue light. This blue light affects the human circadian rhythm by suppressing melatonin levels. The act of using these devices at night is known in the research as artificial light at night (ALAN). [5]

"Circadian homeostasis is essential for the maintenance of body function and health. When circadian rhythms are disrupted, for instance through sleep deprivation, shift work, or blue light from screens, negative health consequences can appear."[5]

The negative impact of ALAN is not limited to blue light from screens. Any artificial light at night could compromise your circadian rhythm and associated hormone functions (i.e., melatonin, estrogen, testosterone, thyroid, and cortisol). In fact, studies reveal that the fluorescent lighting found in hospital intensive care units (ICU) directly promotes inflammation in ICU patients and directly negatively impacts the patient's outcome. [6]

Think about it. The lights in the ICU never go out. Patients in the ICU and neonatal intensive care unit (NICU), as well as nurses and employees that work overnight shifts, develop circadian rhythm dysfunction. This leads to worse inflammation and worse outcomes in the patients.

In the nurses and anyone working third shift (overnight), ALAN is implicated in the development of multiple diseases including metabolic syndrome, obesity, depression, and cancer. Chronic artificial light exposure decreases immune function and elevates cortisol levels.[5]

Studies have also found that artificial light can have a significant negative effect on thyroid function. Studies on humans living in polar regions have highlighted the risk of the so-called "polar T3 syndrome," a hallmark of which is chronically low levels of blood T3. As you remember from chapter seven, T3 is the most metabolically active form of thyroid hormone. Such syndromes are usually associated with psychological disorders such as depression and increased aggression. [7]

The negative effects of artificial light in general and blue light from devices specifically are not limited to your health. A 2017 study in the *Journal of Psychiatric Research* [8] found that, in addition to significantly decreasing sleepiness and delayed melatonin release, blue light also significantly increases commission errors.

The Cambridge dictionary defines errors of commission as "a mistake that consists of doing something wrong, such as including a wrong amount," or subtracting when you should be adding.

In other words, even if staying up late and using Google to try and solve your puzzle doesn't cause a life-changing disease like depression or cancer, it could result in you making mistakes at work that cost you a commission check (a literal commission error) or perhaps your job.

Reduction of cognitive bandwidth

The blue light exposure during Sam's late-night Google searches is not the only reason his work performance will suffer. With every day that Sam does not find the answer to his health puzzle, he is losing time and losing health. These become more and more scarce with each passing day.

According to Princeton University professor of psychology Eldar Shafir and Harvard economist Sendhil Mullainathan, this scarcity in any key resource such as time or health causes a lack of cognitive bandwidth. In other words, we get tunnel vision and can only focus on the present problem which causes us to then neglect, forget about, or perform poorly in our other tasks and responsibilities. Like a computer trying to download too many files at once, a person who has lost cognitive bandwidth can only do one thing at a time—and even that is not at top-level performance. [9]

As Sam spends more and more time on Google searching for help, his lack of health becomes his major life focus, and he develops tunnel vision around the idea of healing himself. That in and of itself is not necessarily a bad thing, but when the obsession means he is accelerating his loss of health due to blue light exposure and the associated negative effects on hormone levels, sleep quantity and quality, and cognitive performance, it becomes a serious problem, which could negatively impact he and his family from a medical expense and an income perspective. If that happens and financial scarcity is added to his list, you can see how his cognitive bandwidth and ability to finish tasks would continue to decrease.

Increase in attention residue and decreased mental performance

The downward spiral gets worse. In 2009, business professor Sophie Leroy published a paper explaining why multitasking leads to decreased performance. As she revealed in two experiments, "People need to stop thinking about one task in order to fully transition their attention and perform well on another." If they don't, their performance on the new task will suffer due to Attention Residue associated with the previous task. [10]

For example, say Sam had a productive Google session last night that made him feel like he was really onto something. That excitement led him to wake up early this morning to continue his search before he goes to work, and he gets excited about what he is finding. Ultimately, however, he must halt his discovery until later because he has to go to work.

Sam goes to work, but all day while performing his sales tasks, he's thinking about what he read on Google last night and this morning. That is Attention Residue, and it is preventing him from fully focusing and performing his work responsibilities.

As Professor Leroy says, "When people experience Attention Residue, part of their attention is focused on a prior task, and, as a result, their attentional focus and mental presence are likely to be reduced."[10]

Can you see how attention residue could lead to poor performance, mistakes, and potential loss of finances? Our multitasking culture is fertile with Attention Residue. Perhaps another name for ADD should be ARD, Attention Residue Disorder.

The Google triple whammy

Do you see the vicious cycle? Here it is laid out in steps:

1. A person has a health issue and wants to solve it on their own using Google searches for natural health solutions

2. Google hides natural health information by burying it in search results

3. The person spends many hours after dark exposed to blue light from devices they are searching on and artificial light from the room they are performing searches in

4. This may lead to any or all of the following: worsening of current health issues and/or new health issues, decreased cognitive bandwidth, and increased Attention Residue

5. This leads to further loss of quality of life, performance in home and work tasks and responsibilities, and potentially finances

6. Which leads to more scarcity and increased urgency to find the answer on Google

7. Rinse and repea t

For some people, this vicious cycle continues without end; some give up hope and unfortunately, accept the lie that there is no help for them, while others stumble across functional medicine, take action, and are helped. Still others like Sam stumble across functional medicine, choose not to do it for any number of reasons, and go back to Google. Some of these people, like Sam, eventually realize they are caught in a vicious cycle on the Google train, get off, and partner with a detective trained in solving complicated puzzles.

How will your search end?

As you can imply from Sam's email at the beginning of this chapter, Sam is done with Google. He wants an honest, individualized, and specific solution to his issues. He restarted the process with me and we will see what the testing reveals.

Will you let Google censor you into the Pharma Echo Chamber and cause you to continue to suffer poor health and poor quality of life?

What is your next step? Who will you partner with to solve your puzzle?

Reader action steps

As the saying goes, "you cannot track what you do not measure."

- Work to minimize your use of devices and exposure to blue light, especially after dark.
- How much time, cognitive bandwidth, and productivity are you losing on devices? Probably more than you think. Use apps such as Moment on iPhone or Quality Time on Android to track the time you are losing to devices that could be used more productively to promote health and quality of life.
- Consider purchasing a pair of blue light blocking glasses and wearing them in the evening after dark until you go to bed.
- You can minimize Attention Residue by following these three steps:

Focus on one project at a time (as much as you can)

Break down projects in short, clear tasks.

Take short deliberate breaks between tasks.

Learn more viewing my Sleep video playlist: https://www.FunctionalMedicineCharlotte.com/Sleep

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Conclusion

"Learn how to see. Realize that everything connects to everything."

—Leonardo da Vinci

"Functional Medicine is a disruptive technology that will overthrow the tyranny of the diagnosis."

—Jeffrey Bland, Ph.D.

We have come full circle. I started the book with the above quote from Leonardo da Vinci, and I now return to it. One of the major purposes of this book is to teach you how to see your health, or lack thereof, from a new perspective.

That perspective is Functional Medicine, which honors the truth espoused by Da Vinci—*everything connects to everything* . I hope that I've been successful in helping you to see why conventional medicine has not been able to help you. When it comes to complex, multifaceted, chronic disease they don't know how to see; they don't even try to. Yes, they will give lip service to the fact that everything is connected, but when it's time for clinical application, the interconnectedness is left behind in favor of a focus on their specific specialty in one small part of the whole, and you go on suffering.

Through the real life cases that I've presented in this book as examples of the functional medicine framework in action, it is my hope that you see how it is indeed 21st -century healthcare. It's the upstart that will overthrow the tyranny of the diagnosis.

After all, receiving a diagnosis doesn't bring you any closer to health. All it does is satisfy the doctor who gave it by making him or her think that by giving your complaints a name and a prescription, you have been served well. As you have learned, what conventional medicine has really done is delayed your healing and promoted further decay of your health.

A diagnosis is a label given to a pathological process (every one of which is preceded by changes in biology). Labeling it and suppressing its symptoms with medication does nothing to

correct its cause. In order to return to health, all causes and contributing factors must be addressed. That is done using the functional medicine framework of exposome, epigenome, and microbiome.

Functional Medicine is the science of creating health. Each chapter in this book shows you how it shines in regard to specific autoimmune diseases.

In chapter one, you were taught that a Parkinson's disease diagnosis does not have to ruin your life. You learned that by finding and addressing the physiologic imbalances in a given individual using the functional medicine framework of exposome, epigenome, and microbiome, you could restore normal health and function. Furthermore, you discovered that the key areas to investigate in Parkinson's disease are gut infections and homocysteine levels.

In chapter two, we covered psoriasis. You learned that a psoriasis diagnosis does not mean you can never wear a bathing suit again—you can indeed have clear skin once the cause is found. Remember, the research found that many people with psoriasis demonstrated immunoreactivity to gluten.

In chapter three, we covered gut function and Crohn's disease. You learned that up to 70 percent of the immune system is in the GI tract. This fact is the reason that every blog out there says the cause of everything is the gut—that is not true, but the gut is often involved. You found that the gut has two nervous systems and that the microbiome is a huge factor in the state of health or disease. Lastly, you've learned that healthy vagus nerve function is key to a healthy gut. Don't forget to exercise it by gargling, humming, and singing.

In chapter four, we covered neuroinflammation and brain autoimmunity using PANDAS as the case study. One key point to remember is that it is not normal to miss neurodevelopmental milestones and you will not "grow out of it." Another key point is that depression is not caused by a deficiency of tryptophan; it is caused by brain inflammation. You must find and eliminate the cause of brain inflammation to eliminate the depression. Lastly, you've learned that

repetitive strep throat infections could lead to autoimmune disease in the brain. Do not take them lightly—ask yourself why your child's immune system is not effectively running surveillance on and clearing the infection.

I combined what you learned from chapters three and four on the gut-brain/brain-gut axis using the case involving Kenny in chapter five. You were taught that a head injury can cause gut issues and brain inflammation. Remember, research shows that within six hours of a head injury, an increased risk of leaky gut develops. Just because a person can pass the "concussion protocol" does not mean that their brain is healthy enough to resume normal activity. Chemical re-concussion due to food reactivity must be considered.

In chapter six, we discussed wheat/gluten reactivity from celiac disease to gluten sensitivity to wheat allergy. There were two key take home points here. First, gluten is a promoter of autoimmune disease via multiple mechanisms and second, even if you don't have obvious symptoms of gluten reactivity, it is promoting degradation of your health. It must be avoided if optimal health is your goal, especially if autoimmunity is part of your puzzle .

In chapter seven, we covered thyroid autoimmunity. You learned that conventional medicine is woefully ineffective at both determining what is causing your thyroid issues and addressing those causes. You discovered that many nutrients are key for optimal thyroid health, but too little or too much could cause thyroid dysfunction. These included vitamins A and D, selenium, iodine, and gluten. Reread the chapter to know which to include and which to avoid. Lastly, do not forget that when your conventional doctor tells you that your thyroid is "normal," you shouldn't believe him, especially if you continue to have thyroid symptoms. Partner with a detective who will perform a complete investigation.

Chapter eight covered oral tolerance—food allergy versus food sensitivity and food intolerance. It taught you how to give your newborn the best shot at a healthy gut microbiome and immune system, and the differences between allergy and sensitivity. You found that not all food reactions are immune-

based. The key point to remember is the research that showed consuming trigger foods created leaky gut within five minutes of consumption.

In chapter nine, I taught you why there is no perfect diet, and what you consider the perfect diet today may not be the same two years from now. You learned that your diet has a huge impact on your immune system and gut microbiome and discovered their effects on your risk of autoimmune disease and cancer. Immunonutrition is the field you want to study further.

Chapter 10 taught you that Google is not going to save you; you cannot Google your way to health. There are various reasons for this, not the least of which is that Google is actively hiding the natural health information you are seeking. Remember that each moment after dark spent obsessively searching is promoting circadian rhythm dysfunction, a decrease in cognitive bandwidth, and increased Attention Residue. Each of these individually promotes a decrease in mental performance and an increase in cortisol production .

The key to your future

Congratulations on reading this book. You are dedicated and resolute in your desire to solve your own personal puzzle. Your future is now in your hands. The choices you make from here on out will determine whether you continue to suffer with the issues that led you to read this book, or you heal from those issues and live an optimal life. There are three keys to creating a #LifeAtOptimal:

1. **Choose to be proactive.** Take off the antiquated and obsolete pair of glasses that society gave you. Those glasses show you a world of lack, fear, genetics, drugs, and disease. Put on a pair that shows you the world in its true form—a world of unlimited possibilities, hope, and choice. Being proactive allows you to achieve and live the quality of life you desire.

2. **Partner with a doctor who practices Functional Medicine —a clinician detective.** You cannot be proactive in a reactive system, which is what conventional medicine is. Their idea of

prevention is to expose people to harmful screening tests that have not been shown to decrease death from the specific disease in question. For example, mammography (mammograms) takes breast tissue that is highly sensitive to damage from radiation and blasts it in radiation yearly under the premise of breast cancer prevention. Yet the Cochrane Review of mammography found, "Today with over 600,000 women studied, there's no clear evidence of a reduction in overall mortality (death) in mammography screening." [1] In 2015, *The Journal of the American Medical Association* found that "the public has an inflated sense of the benefits and discounted sense of the harms of mammography screening, the cervical smear test (pap smear), and PSA (prostate screening)." [2] Authors of the 2016 study in the *British Medical Journal* concluded, "We encourage healthcare providers to be frank about the limitations of screening. The harms of screening are certain but the benefits in overall mortality are not. Declining screening may be a reasonable and prudent choice for many people." [3]

The key to prevention is not to look for something once a year or once every five years after a certain age, it is to choose health every minute, every meal, every relationship. The key is to be proactive so that it never happens. A doctor trained and versed in Functional Medicine will be able to determine areas in your puzzle that need to be addressed by specific strategies, including making better and proactive choices.

3. **Understand that there is no pill that will heal you.** The pharmaceutical industry has been looking for magic bullet drugs since its inception. It has failed and will continue to fail. The only magic bullet is consistency—consistent application of a functional medicine mindset and the associated proactive choices. Do not be fooled by the term precision medicine—it is the pharmaceutical industry's latest attempt at marketing the perception that they are closer to finding the magic bullet, but what they're really talking about is pharmacogenomics, which is the study of how a person's genetic makeup affects his or her response to a medication.

Their thinking is they can determine the best drug or drug cocktail for a specific person based on his or her genetics. Do you see how this is a failure before it starts? Drugs are not the answer. There is no magic bullet. Even if you tailor a drug to a person's genes, you still are not addressing all the parts of their puzzles that are creating the disease in the first place. *Consistency is the only magic bullet* . Consistent application of a healthy lifestyle, which includes healthy lifestyle choices in regards to nutrition, physical activity, toxic exposure, internal dialogue, relationships, social network, profession, location, technology, and philosophy, to name a few. Remember, the exposome includes all external and internal exposures. Choose healthy exposures as much as possible because in our world there are always unhealthy exposures such as EMF pollution, ubiquitous toxins, et cetera. Change is hard, but worth it.

I've been where you are

My story includes gluten and dairy sensitivities. Like most people, I grew up eating the Standard American Diet, with its staples of wheat and dairy. I did not realize until I was in chiropractic school that the reason for my lifelong loose stools, consistent acne, and brain fog was my immune reaction to these foods. I discovered these sensitivities when I first learned about and implemented the paleo diet, which eliminates all grains and dairy.

After nine days on the diet, I had lost ten pounds and my skin started to clear. When I decided to celebrate my success by eating pizza, I immediately felt terrible. Behind my eyes started to burn and a brain fog descended over me. I also had diarrhea. What I realized then was that I had never known what feeling good felt like. It wasn't until I had cut out grains and dairy that I realized good can feel so much better. The problem was that in order to truly feel good and get healthy, I would have to eliminate my favorite foods—pizza, lasagna, spaghetti, and ice cream. That was sad, but I chose to feel good. I told a classmate of mine what I was going to do, and he joined me.

Adrian and I were the guys who would travel around restaurants in St. Louis that had the food challenges and seek to conquer them. A restaurant called Cheeburger Cheeburger had a two-pound burger challenge. Of course, we both successfully finished our two-pound burgers. Another restaurant, Pointer's Pizza, had a 28-inch Pointersaurus pizza challenge, with a pizza weighing over ten pounds! (On that one, we were unsuccessful). Based on our shared love of mass quantities of food—you can understand that it wasn't an easy decision to cut out our favorite foods cold turkey .

Nevertheless, having an accountability partner increased the probability of our success. We had been accountable to each other in our gluttony, and we would now be accountable to each other in health creation.

By successfully and consistently eliminating dairy and grains from my diet, my stool quality improved and I no longer experienced brain fog after eating. I realized that the dairy was the trigger of my gut symptoms, and gluten was the trigger of my burning eyes and brain fog. Today, I still avoid both.

As I continued through school, graduated, and began my postgraduate work in Functional Medicine, I have sought out colleagues and mentors who will function as accountability partners and detectives, respectively. Throughout the years, detective work revealed the pieces of my puzzle that needed addressing. Included were high homocysteine levels, a Helicobacter pylori infection, low vitamin D, and insufficient pancreatic production of digestive enzymes. I have corrected all of these issues using natural strategies. Not once was a medication involved.

Being your own detective

What are you struggling with? What does your puzzle look like? Regardless of the answer to those questions, there's hope. The science of epigenetics proves that you can optimize your health by finding the causes and taking action to eliminate them. The cause is the cure—when you eliminate the cause, you optimize your health. Seek out a clinician detective, a Functional Medicine provider, who can solve your puzzle and

be the accountability partner you need to help you achieve optimal health. Health is a journey, not a destination. If I chose to eat gluten today, I would have burning eyes and brain fog. I must continue to choose health daily—consistent choice is a journey.

As Lao Tzu says, "The journey of a thousand miles begins with one step." No matter how ravaged your body is with autoimmune disease, you can choose to get healthier right now. Take that first step by choosing. Then take the second step, by contacting your detective clinician and continuing on your journey with them. I promise, you'll be glad you did. Please let me know all the changes you create.

Thank you for reading this book. I'm privileged to have the opportunity to positively impact your knowledge of health and healing. If you found it worthwhile, please share a copy with your closest friend.

Good luck on your journey toward optimal health!

Reader action steps

Find your detective clinician - The following sites have searchable lists of doctors certified in Functional Medicine near you:

www.IFM.org

www.FunctionalMedicineDoctors.com

Use the search engine DuckDuckGo.com and search "Functional Medicine (Your Town)"

Contacting Dr. Bartemus

Dr. Bartemus speaks to businesses, organizations, and groups of people of all sizes. If you would like him to speak at your business or event, reach out to him via:

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Instagram: @FunctionalMedicineCharlotte

www.FunctionalMedicineCharlotte.co m

More from Dr. Bartemus

Dr. Bartemus has over 600 videos on his YouTube Channel covering a broad range of health topics from a Functional Medicine perspective. You can find testimonials and/or more information on a given topic by searching his channel at:

www.YouTube.com/c/DrJohnBartemus

At the end of each chapter in this book, Dr. Bartemus has provided a topic-specific curated playlist from his YouTube channel. Here is the list of channel links again all in one place:

Chapter 1 – Parkinson's: https://www.FunctionalMedicineCharlotte.com/Parkinsons

Chapter 2 – Psoriasis: https://www.FunctionalMedicineCharlotte.com/Psoriasis

Chapter 3 – Gut: https://www.FunctionalMedicineCharlotte.com/Gut

Chapter 4 – PANDAS: https://www.FunctionalMedicineCharlotte.com/PANDAS

Chapter 5 – Brain-Gut/Gut-Brain Axis: https://www.FunctionalMedicineCharlotte.com/BrainGutAxis

Chapter 6 – Celiac, Wheat, Gluten:
https://www.FunctionalMedicineCharlotte.com/Gluten

Chapter 7 – Thyroid:
https://www.FunctionalMedicineCharlotte.com/Thyroid

Chapter 8 – Food Reactions:
https://www.FunctionalMedicineCharlotte.com/FoodReactions

Chapter 9 – Diet:
https://www.FunctionalMedicineCharlotte.com/Diet

Chapter 10 – Sleep:
https://www.FunctionalMedicineCharlotte.com/Sleep

Bonus Testimonials:
https://www.FunctionalMedicineCharlotte.com/Testimonials

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