

## Health Condition: Autoimmune Disorders

“I love the story of the blind man trying to figure out what an elephant is by just feeling one little part. From the traditional [medical] perspective, I don't think you get a 10,000-foot view of what autoimmune disease is. But from a functional medicine point of view, you can. We make the assumption that autoimmune disease is a systemic and multifactorial disease. From the functional medicine point of view, we look at chronic disease differently. We look at it from the perspective of what the predisposing factors are, and what things the patient brings from his or her past that create susceptibility to a certain disease. We look at the triggers and mediators going on that keep the disease going. For example, some of these people will have three other people in their family that have had viral infections, yet that patient might be the only one in the group who never got better. They'll tell you that since they expressed that ‘something,’ they've never been the same. They appear to have some type of susceptibility that singles them out to become susceptible to autoimmune disease.”

—Jacob Kornberg, MD  
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### The Concept of “Autoimmune Disease”

According to Dorland's Illustrated Medical Dictionary, autoimmune disease is defined as “A condition characterized by a specific humoral or cell-mediated immune response against constituents of the body's own tissues (self).” The question one might ask is, what is ‘self’? As defined by Brickman and Shoenfeld (2001), it can refer to the native self, or double-stranded, native DNA; complexes of self such as beta-2-glycoprotein I bound cardiolipin; and even to altered self through post-translational modification of our cellular material. One might raise the more philosophical question of whether we are protecting ourselves against ourselves, or whether this innate strategy of attack is truly self-protective. Another perspective posed by Dr. Nevo in 2003 is that autoimmune disease is: “Tolerance to self is not a lack of response to self, but the ability to tolerate an active defense response to self without developing an autoimmune disease.”

From a more metaphorical sense, why are conditions of inner attack through immune dysregulation some of the greatest known conditions on our planet right now? Are there issues that we are not paying attention to that require our attention? Is the outer environment too much for our inner reserves? Let's explore the etiological reasons for this intriguing modern-day cluster of diseases.

### Who Has Autoimmune Disease?

In the book *How Doctors Think*, author Jerome Groopman, MD, a Harvard University professor of medicine, starts by going through a case history—a medical detective story that goes on for many pages—about a woman who has many symptoms, and many problems, and multiple surgeries. The conclusion of Dr. Groopman's story is that this woman's many years of health challenges were caused by celiac disease, one more than 80 conditions that fall into the medical category known as autoimmune disease.

Almost 90 percent of autoimmune disease disorders of the most common forms—rheumatoid arthritis and systemic lupus erythematosus (SLE)—are found in females. According to the American Autoimmune Related Diseases Association, “...autoimmune diseases strike women three times more than men. Some

diseases have an even higher incidence in women. In fact, of the 50 million Americans living with autoimmunity, 30 million people are women, some estimates say. Autoimmune diseases have been cited in the top ten leading causes of all deaths among U.S. women age 65 and younger. Moreover, these diseases represent the fourth largest cause of disability among women in the United States."

Furthermore, there appears to be a hormonal component involved in the etiology of autoimmune disease, which might explain why there can be changes in symptoms before, during and after pregnancy. For example, increase of cortisol, progesterone, estradiol and testosterone during the third trimester of pregnancy leads to Th2 cytokine polarization and suppression of Th1 immune response. Cutolo et al. (2005) reports that "Epidemiologic evidence indicates that during the fertile period women are affected by rheumatic diseases, particularly autoimmune diseases, more often than men..." "Several studies and reviews showed that there are reduced serum concentrations of DHEA-S, T, and progesterone in male and female patients who have RA or SLE. These data strongly support an accelerated peripheral metabolic conversion of androgen precursors to E2."

In March 2005, a report published by the U.S. Department of Health & Human Services through the National Institutes of Health (NIH), titled "Progress in Autoimmune Disease Research."<sup>1</sup> It is the summary of a report to Congress on the progress on autoimmune disease, and it contains some remarkable statistics.

Autoimmune disease is much more prevalent today than previously recognized because historically it has been broken up into 80 or more clinical conditions. For reasons we are still trying to understand, approximately 23.5 million people in this country have autoimmune disease, and the number is rising. In fact, the number of people affected rivals that of other major disease indicators, including dyslipidemia, insulin resistance, and hypertension. However, even these conditions, along with cardiovascular disease, in general, may have links to autoimmunity and inflammation. Recent research is pointing in the direction that individuals with autoimmune disease may also have premature formation of atherosclerosis. Clearly, the autoimmune family of disorders is a significant problem worldwide, and may even be the largest cause of death on the globe if we were to take cardiovascular disease implications into account.

Also pointed out in this 2005 report is that although these conditions have been segmented as independent diseases under respective diagnostic categories, they are now being found to be associated with changes in various immunological mechanisms. Our concept of this disease category is that the individual diseases are distinctly different from each other. For example, we try to completely segregate myasthenia gravis from systemic lupus erythematosus, multiple sclerosis, and ulcerated colitis. This concept of differentiation is starting to change; we are starting to look at similar mechanisms of immunological imbalance and dysregulation of the thymus dependent 1(Th1) and thymus dependent 2 (Th2) lymphocyte system to help us better understand the etiology and the potential origin of these diseases.

## **The Role of the Gastrointestinal System in Autoimmune Disease**

The immune system of the digestive tract is often referred to the gut-associated lymphoid tissue (GALT). Lymphoid tissue found in various sites of the body, including the gastrointestinal tract as well as the thyroid, breasts, lungs, salivary glands, eyes, and skin is known as the mucosal-associated lymphoid tissue (MALT). There are extraordinary messages sent out through the GALT and the MALT that are received systemically as well as regionally. They influence, at a distant site, how a tissue or organ responds to its environment and can potentiate or modulate inflammatory response.

The GALT is responsible for secreting about three-quarters of the body's antibodies through the B cells. It is also involved with the secretion of various types of lymphokines and cytokines. It is actively involved in phagocytosis mucous secretion, and secretory IgA, the immunoglobulin that coats the interior lining of the gastrointestinal (GI) mucosa. The GALT plays an active role in translating friend to foe, or foe to friend at the GI barrier level. One might think of the GI mucosal cells as being loaded with antennae or membrane receptors on their external membranes which pick up messages from the internal milieu of the GI tract. These are messenger molecules that come from the digestion of food, biological organisms, contaminants, and xenobiotics. These messages are picked up by the GI mucosal information system and translated through the immune system into regulatory modulators such as cytokines, lymphokines, leukotrienes, and prostanooids. Downstream, these messages ultimately influence the Kupffer cells in the liver (the embedded white blood cells), the circulating white cells, and even the embedded white cells in the brain called the microglia, all of which receive some of their messages from the process that was initiated at the gut level.

The gut mucosal tissue represents over 50 percent of the overall immune tissue of the body clustered around the gut. Over the course of life, a person eats at least about 60 tons of food. Because those foods are partly composed of molecules foreign to the body, they need to be translated into friendly molecules. That is partially accomplished by digestion, during which these molecules are changed into small nondescript nutrients like amino acids, monosaccharides, and free fatty acids. There are also some residual information molecules present in the diet that have to be further identified as friends or foes, and this is done through the agency of the gut immune system. There are antigen-presenting cells, dendritic cell activity, mucus secretion, and IgAs present in the gut to defend the body from foreign information coming from the diet. Some people have food allergies due to a breakdown in the translation process of what is food/friend and what is a foe/toxin. Classic examples of food constituents that produce adverse immunological responses are peanuts and wheat, each of which can produce fairly severe anaphylactic or life-threatening responses based upon activation of the immune system during an alarm reaction.

Not only is the gut/immune system inhabited by many interesting immune cells, but almost a kilogram of foreign cells resides in the colons of most people. These organisms are called the commensal bacteria. We hope they are commensal and symbiotic, and not parasitic. On a simple arithmetic basis, in any gram of stool, there are hundreds of species of bacteria. The gut is a highly populated area, and the GI bacteria turn over very rapidly. Rather than turning over in a matter of weeks, months, or years, they turn over in a matter of hours. The composition of the gut microflora (its "personality") can change based upon what it is fed and the environment that is provided for the bacteria found within it.

Relative to flora and digested food, how do the contents trigger a gut/immune response? Individuals with hypersensitive or highly sensitive upregulated inflammatory systems experience a loss of tolerance by alteration in both the thymus-dependent 1 (Th1) and thymus-dependent 2 (Th2) components of the gut immune system, resulting in increased IgG formation, increased formation of tumor necrosis factor alpha (TNF- $\alpha$ ), IL-1, and interferon gamma (IFN $\gamma$ ). As a consequence, there is much greater inflammatory potential that occurs at the interface between the luminal adjuvants, the leaky mucosal barrier, and the brush border cells.

When the luminal contents of Crohn's disease patients are examined, different types of bacteria are found. We might ask whether the altered flora is a consequence of the disease, or does the flora cause the disease? It is the old push/pull, cause-and-effect argument.

A paper appeared in *Gastroenterology* that talks about fluorescent probes detecting increased mucosal-associated bacteria in an IBD biopsy.<sup>2</sup> Some good genotyping has been done relating to polymorphisms in people who are more susceptible to these types of interactions, with an upregulation of gut/immune function producing an NF $\kappa$ B-mediated process that activates nearly 100 genes associated with inflammation of the gut. There is immune-dysregulation with antigen-presenting cells at the gut mucosal level that is triggered through the personality of specific types of bacteria.

In experimental colitis and enteritis, a series of different antibiotics has been studied—metronidazole, Cipro, and various types of tetracyclines—to see if they have different influences on different bacteria in animal models relative to the outcome of irritable bowel syndrome (IBS). The implications of this research are that a combination or broad-spectrum of antibiotics is needed to manage what would be considered the animal model of Crohn's disease and ulcerative colitis. We do not yet know what selective antibiotics might work on specific biota to eliminate or alleviate the inflammatory-initiated process. Antibiotics can work, but we still do not know everything we need to know. If we look at various things that have been used clinically, like metronidazole, there does not appear to be any real difference in treatment versus placebo in conditions such as Crohn's disease. Possibly altering the GI environment would be equal to, or even more successful than, antibiotic therapy in patients with chronic IBD. Those cases lead us into looking at different kinds of bacteria and modifying the gut mucosal environment to try to rebalance Th1 and Th2 immune function, and to decrease chronic conditions leading to acute inflammation associated with IBD, its progression, and its serious interrelationship with colon cancer risk.

If we look at the luminal microbe biological environment trying to find the right balance, the injurious organisms associated with proinflammatory effects that could lead to IBD include the *Bacteroides* species, *Enterococcus faecalis*, and the enteroadherent/invasive forms of *E. coli*. Those are the injurious proinflammatory organisms, or what we call invasive or aggressive commensals. On the other side, protective probiotics are emerging, such as specific species of *Lactobacillus*, *Bifidobacterium* and non-pathogenic *E. coli*. That opens the door for an intervention for IBD, one that would change the GI environment to a less proinflammatory state by modifying the function of enteric bacteria, and trying to reduce the activity of the aggressive commensals, while increasing the activity of the symbiotic bacteria.

We are starting to understand that there is a dynamic interrelationship between commensal bacteria in the gut, their metabolic activity, and how that influences the GALT, which subsequently influences the immunological system of the host at large and sets up a balance or imbalance of regulatory mediators. This is an important part of the overall story of how the dynamic interplay occurs between the body's external environment and internal immunological signaling, as translated through the GALT.

## Rheumatoid Arthritis

How might systemic inflammatory conditions such as rheumatoid arthritis (RA) be connected to localized gut-immune activation and enhanced immune activities of the GALT and MALT? Looking at RA as an autoimmune disease, there could be cross reactivity from epitopes (the part of an antigen that is recognized by the immune system) on environmental stimuli leading to superantigens (a class of antigens which cause non-specific activation of T-cells resulting and massive cytokine release). What environmental factors lead to those cross-reacting epitopes? One family of organisms to consider are those that have urinary tract infection correlation, like *Proteus* organisms.

A paper appeared in *Clinical and Developmental Immunology* that looks at the relationship between rheumatoid arthritis and *Proteus mirabilis* infection of the urogenital tract.<sup>3</sup> The authors propose that a subclinical *Proteus* urinary tract infection could be a main triggering factor related to this molecular mimicry and cross reactivity between bacteria and RA-targeted tissue antigens that perpetuate disease through the production of cytopathic autoantibodies.

This is a complex world in which we live. There are literally thousands of microorganisms that have their own molecular personalities. On their surfaces sit all sorts of different potential hapten or antigenic components, which may then react with receptor sites on host immune tissue in genetically unique individuals to activate those cells into a heightened stance of inflammatory expression. The urinary tract may seem like a long way away from the joints, but we are all connected together through our immune system.

In this particular paper, the authors talk about how this connection may explain why vegetarian diets (diets higher in water and juices that are acidic and contain certain phytochemicals, like cranberry juice) have been useful in certain studies with patients not only with urinary tract infections, but also those who have conjoint arthritis. These patients find that as their diets change and their urinary tract infections improve, their joint pain improves, too, because there is this connection through the immune system between the reaction of receptor sites to antigens (these cross reactive materials-this mimicry, so to speak, between a bacterial antigen and a self antigen).

Is there any demonstrable connection between the foods in our diet and their chemical personalities (as it relates to their immunological activity) and cross reactivity with antibodies that are associated with rheumatoid arthritis? That is a question that has been discussed for several decades. As we get better immunological assessment tools, this association becomes more recognized.

In 2006, a paper was published in the journal *Gut* titled "The Gut-Joint Axis: Cross Reactive Food Antibodies in Rheumatoid Arthritis."<sup>4</sup> This study was aimed at patients with rheumatoid arthritis who have differing severity of their condition that seems to track against different dietary persuasions or different foods that they might eat. The authors of the paper wanted to investigate a putative immunological link between gut immunity, rheumatoid arthritis, food antibodies, and general quality of the diet of these individuals who have this food exacerbation.

The investigators looked at IgG, IgM, and IgA antibodies to dietary antigens to measure the potential for food allergy in the study participants. The antigens they evaluated were from cow's milk (a-lactalbumin, b-lactoglobulin, casein: the three most reactive proteins in cow's milk), cereals containing gluten, ovalbumin (hen's egg), codfish, and pork meat. In the intestinal fluid of many of the rheumatoid arthritis patients, all three immunoglobulin classes showed increased food-specific activities. Except for IgM activity against b-lactoglobulin, all other IgM activities were significantly increased, irrespective of the total IgM level (so you have to look at the individual class of IgM). The rheumatoid-associated serum IgM antibody responses were relatively much less pronounced. And compared with IgM, the intestinal IgA activities were less consistently raised, with no significant increase against gliadin and casein.

Considerable cross reactivity of IgM and IgA antibodies was documented by looking at absorption tests. Although intestinal IgG activity to food was quite low, it was nevertheless significantly increased against many antigens in the rheumatoid arthritis patients. Three of the five rheumatoid arthritis patients treated with sulfasalazine for 16 weeks had initially raised levels of intestinal food antibodies. These became normalized after treatment.

Rheumatoid arthritis is a heterogeneous condition with many different contributing variables. We can't say one rule covers all patients, but certainly the diet connection to antibody exacerbation of these autoantibodies is worth consideration. Food may have an additive effect to other contributing factors to the etiology of immune imbalance that is associated with rheumatoid arthritis.

## **Multiple Sclerosis**

Multiple sclerosis (MS) is an autoimmune disease that affects the brain and spinal cord (central nervous system). MS is caused by damage to the myelin sheath, the protective covering that surrounds nerve cells. When this nerve covering is damaged, nerve signals slow down or stop. Symptoms of MS can be muscular, such as loss of balance, spasms, or tingling, and can also be related to GI complaints, such as constipation. A person with MS may experience eye symptoms, such as double vision or uncontrollable rapid eye movements. Fatigue is common and often progressive in MS patients. MS affects more women than men.

There are parts of the world where MS appears to be more common. Research has been done on this for decades, and in recent years a theory has emerged linking geographic phenomenon to the body's availability of vitamin D. In August 2004, Dr. Jeffrey Bland interviewed Colleen Hayes, PhD, a noted expert in the field of vitamin D research, and she explained this new research in greater detail. First, an

expanded description of “vitamin” D from Dr. Hayes, which in fact is not a vitamin, but rather a hormone:

“This is a so-called vitamin that isn’t really a vitamin at all. It’s a compound that derives from 7-dehydrocholesterol in the skin when ultraviolet B radiation penetrates the epidermal layer. The photons cleave to one of the bonds in 7-dehydrocholesterol and form previtamin D3, which then isomerizes to vitamin D3. It is transported on a vitamin D-binding protein out of the skin to the liver, where a 25-hydroxyl group is put on that compound. Now, we have the circulating form—25-hydroxyvitamin D3, the form that a clinician should measure to determine a patient’s vitamin D status. It is not the biologically active form, however. The final activation step occurs in the kidney, but also in many other tissues. One  $\alpha$ -hydroxyl group is placed on the molecule to generate 1 $\alpha$ ,25-dihydroxyvitamin D3. Another name for that is calcitriol, a hormone in the steroid hormone family. Although we call it a vitamin for historic reasons, it really is a hormone.”

With the understanding that vitamin D is a hormone and that it is natively present in the body via UVB exposure of the skin, Dr. Hayes explains the research linking this molecule to multiple sclerosis:

“The story begins with a very old observation that was made by an astute World War I Army physician in the United States. He noticed, in examining recruits, that those who had symptoms of MS came from the northern states, such as Maine, Vermont, New Hampshire, Michigan, Wisconsin, Minnesota, and Oregon. He never saw a recruit from the southern states, such as Florida, New Mexico, or Georgia, with symptoms of MS, so he began to collect data and wrote up a description of a latitude gradient in the incidence of this disease. That triggered four decades of epidemiological research around the world, attempting to find out if the latitude gradient that had been described in the United States was also a feature of other places. In fact, it was a very robust finding. MS does show a gradient of prevalence with latitude. The disease is almost unknown at the equator; it is very, very rare at the equatorial part of the world. As you move away from the equator, either to the north or to the south, the disease becomes increasingly prevalent. It reaches its peak of prevalence in northern Scotland and northern Canada, as you might expect. The same gradient applies in the Southern hemisphere, although there are not as many data about that.

The next piece of the puzzle came in 1960. A man named Donald Acheson was trying to sort out all the variables that might be associated with latitude and determine which one of the many variables might best explain the prevalence of MS. After a long and intense study, he determined that winter sunlight showed the best correlation. It was an inverse correlation. The more the winter sunlight, the lower the disease prevalence; the less the winter sunlight, the higher the disease prevalence. The chairman of my department, Dr. Hector DeLuca, discovered the active hormone 1,25-dihydroxyvitamin D3 when he was a graduate student. He has researched that hormone ever since. We are steeped in the biology of vitamin D here and I knew, as did Hector, that sunlight catalyzes the first step in vitamin D biosynthesis. He and I were also interested in why the vitamin D receptor was in lymphocytes. We had been talking for some time about trying to figure out why lymphocytes had a receptor for this hormone, which was known at the time for its skeletal maintenance function. We put 2 and 2 together and formed a hypothesis that sunlight might protect people from getting MS because it might be catalyzing vitamin D synthesis, and the vitamin D might be essential for lymphocytes for some functions that would protect a person from MS. We went about testing that idea in an animal model of the disease called experimental autoimmune encephalomyelitis. In that mouse model, we can induce a disease that looks very much like MS if we force a mouse to make an immune response against myelin basic protein, which is a component of the axonal sheath allowing axons to transmit an electrical pulse. We treated some mice with the hormone 1,25-dihydroxyvitamin D3, and other mice were given a placebo. I should also mention that Dr. Marguerita Cantorna worked with us on this

project and was a key person in doing experiments. Then, we attempted to induce the disease and, to our astonishment, we found that when mice were given the hormone, we could not induce it. Furthermore, if we first induced the disease and then treated the mice with the hormone 1,25-dihydroxyvitamin D<sub>3</sub>, the disease symptoms went into remission and didn't come back. We were very excited. That was back in 1996. We thought we had some evidence that it was, in fact, correct that sunlight protects against MS through the activity of sunlight generating vitamin D, and that was a starting point for my last decade of work, trying to figure out why that's the case."

The work of Dr. Hayes and her colleagues falls into the field called translational medicine, also called interventional epidemiology. We are now seeing translational medicine start to accelerate the process of moving discoveries made in laboratories into clinical practice. In 2006, an article was published in the *Journal of the American Medical Association* titled "Serum 25-Hydroxyvitamin D Levels and Risk of Multiple Sclerosis."<sup>5</sup> This was the first prospective study addressing the hypothesis that vitamin D and multiple sclerosis may be linked. This study involved more than 7 million US military personnel who have serum samples stored in the Department of Defense Serum Repository. The results of this study suggest that high circulating levels of vitamin D are associated with a lower risk of multiple sclerosis, and so the research continues to move forward.

### **Gluten Sensitivity and Celiac Disease**

With the gastrointestinal immune system, the epithelial layer really provides the first barrier to the environment. This is really a unique lymphoid organ because it is exposed to a vast array of exogenous antigens from food and commensals that line the intestinal tract. It is really important that the epithelial cells and these intestinal dendritic cells (which also can kind of extend their dendrites out into the lumen) have cross-talk and maintain a nice homeostatic level of inflammation and a healthy gut. Upon insult by either an invading pathogen or tissue damage, these dendritic cells, or monocytes that come in from the peripheral blood, actually can sense various pattern molecules. When they detect these danger signals, they will then become activated and secrete numerous types of chemicals that are called cytokines and chemokines that direct the downstream events (i.e. the adaptive immune response).

Celiac disease is a condition that damages the lining of the small intestine and prevents it from absorbing parts of food that are important for staying healthy. The damage is due to a reaction to eating gluten, which is found in wheat, barley, rye, and possibly oats through cross-contamination with the other grains. Gluten is a term that applies to a family of different proteins that have similar electrophoretic mobility and similar kinds of personalities as it relates to their primary amino acid sequence. But there may be differences in specific composition within the members of the family as it pertains to post-translational glycosylation reactions, and so they may have different degrees of glycosylated residues that change their epitopic personalities slightly, one member to another. So we might say "gluten" as the general generic family, but we really should be talking about the specific members within the gluten family that are the antigenic determinants that really create autoimmune-type responses in genetically susceptible individuals.

There are many people that have chronically activated gut-immune system inflammatory response just by the nature of eating a high fat/high sugar diet; they put the immune system of their gut on notice continuously. Do you know the old Pasteur saying "Chance favors the prepared mind"? If the immune



system of the gut is already activated then it is more readily sensitized to other triggers, like these antigenic determinants/epitopic determinants in gluten, which can put the straw on the camel's back and push this over into an acute inflammatory response.

In 2009, Dr. Jeffrey Bland interviewed two women with amazingly similar lifelong mystery stories involving debilitating symptoms that eventually tracked to gluten sensitivity and celiac disease. One, Alice Bast, has established a nonprofit organization called the National Foundation for Celiac Awareness (NFCA) and is devoting her life to educating both clinicians and the public about the need for better diagnosis of celiac disease, as well as the need for continued funding for research programs to alleviate the suffering of millions of people worldwide who suffer from this condition. The other, Christine Doherty, is a naturopathic physician who now specializes in helping patients—one person at a time—manage and recover from the symptoms of this autoimmune condition that went undiagnosed in her own life for so many years. These are their stories.

Alice Bast, National Foundation for Celiac Awareness:

“In order to have celiac disease, you have a genetic predisposition; thirty percent of the population has that. I had traveled to Mexico and had giardia. I got very sick in Mexico. At that point in time, I had a lot of stomach discomfort and diarrhea, so I had an insult to my body. I never got better. I kept going from doctor to doctor to doctor, and no matter what was happening to my body, they would just say, ‘Here, you need Kaopectate.’ I was given something to remedy the symptom at the time.

I got pregnant. Midway through my pregnancy, I started feeling very uncomfortable, like something was going wrong. It started with diarrhea again. I went to the doctor and they said, ‘It's okay. Everything's okay. It's probably just that you've eaten something.’ Again, they were giving me something for the symptom. Unfortunately, they were wrong. I had a full-term stillborn child, and I can still think about how, at the end of my pregnancy, I could feel the movement decreasing. I knew something was wrong; intuitively, I knew there was a problem. I remember saying to my husband, ‘Honey, this movement has really decreased.’ I was walking around, tasting foods, and the movement just wasn't there. I was correct. He put his head on my belly, he listened, and there was nothing. We called the doctor and they saw me on an emergency basis, and I had a full-term child. We named her Emily. She was seven pounds, and it was labeled as ‘intrauterine growth retardation.’

For years and years I kept struggling, from one doctor, to the next, to the next, to the next, and they still couldn't find out what was wrong with me. I had migraine headaches. My hair was falling out. My teeth were starting to break. I just had every symptom that somebody with celiac disease has if you look at the symptom checklist. I had terrible (what we call) hard-to-flush stools, I had fatigue, I had joint pain, I was missing my periods, all kinds of things were happening to my body. At one point in time I was 105 pounds.

I got pregnant again, and this time, midway through my pregnancy, the same things started to happen—terrible terrible diarrhea, I was not feeling well—and the doctors put me on bed rest. I was on bed rest for almost three months, and then I had an emergency C-section and I had a two-pound baby daughter. Her name is Beatrice Linea. I'm happy to say that she is 5'8" and well, but that was the scariest time of my life. I almost lost daughter #2; thank goodness I didn't. After she was born she kept getting healthier and healthier, and I kept getting sicker and sicker and sicker. I was wasting away to nothing. They thought I had post-partum depression. They thought I had anorexia.

Finally, a friend of mine who is a veterinarian said, 'Maybe it's the grains you are eating. Maybe the grains that you are eating are causing your problems.' And then my dentist looked at my teeth and my mouth and said, 'Alice, something is systemically wrong with you. You need to find out what. I think there's something really wrong with you. Don't listen to the doctors; you've got to find the solution.' Doctor #23 said, 'Okay, I'll run this blood test for you. It's a rare disease of childhood. Very few people have it. I'll run this panel; it's called celiac disease.' Sure enough he ran the blood test, and my serology came out positive. They did an endoscopy, and it turned out the villi in my intestines were totally flat, which meant I was absorbing none of my nutrients. I was malnourished—my entire body was malnourished—and my system was 100 percent off.

Within weeks of going on a gluten-free diet, I started to feel better. I started to restore my health and reclaim my life, and I couldn't believe it. I was so happy that they figured out what was wrong with me. When the doctor diagnosed me, he said, 'I have good news and bad news. The good news is we know what's wrong with you; you have celiac disease. The bad news is you have to follow this lifelong diet. Good luck. Join a support group. You're not going to be able to eat in restaurants and you're going to have to order your food from Canada.' Well, I didn't want to accept that. I thought, 'We can make life better. I can deal with this. I don't have cancer. I'm not dying.'

Getting diagnosed with celiac disease is just the beginning because your whole immune system is out of alignment; you're out of balance...I said, 'Instead of being upset, change it, Alice. What can you do to be a change agent and work with other people that are the best and the brightest in their field to get them to understand that this is an important disease, and that through celiac disease we can learn a lot about autoimmunity. We can learn a lot about how people who have lupus, and MS, and other autoimmune problems that people don't have the ability to just go on a gluten-free diet and change their nutrients to feel better-what is it that our body is doing? What goes on with this autoimmune cascade?' I know it's kind of a tall order, but I thought I could plant that seed and create a garden.

Alice's garden is blooming as the prevalence of gluten sensitivity continues to rise. For complete information about the NFCA and to access tools that can help determine your risk or manage your diagnosis, visit the organization's website at [www.celiaccentral.org](http://www.celiaccentral.org).

Look for the parallels in the story of Christine Doherty, ND, who has a private medical practice in New Hampshire:

"I made it all the way through naturopathic school and I still didn't really know what was wrong with me. I still didn't feel like I had the answer I was seeking. To give you more background on my medical history, when I was young, even as a child I remember having joint pain, bone pain, abdominal pain, irritable bowel syndrome. It got to the point where I just stopped telling doctors about what symptoms I was having because I knew they couldn't really make sense of it. As I got to my teen years, I started getting really heavy periods and weight gain. The bone pain got even worse, and I remember telling my dentist that whenever I drank beer my gums would bleed uncontrollably. He said, 'There is absolutely no connection between beer drinking and gum bleeding. You just need to floss your teeth.' I remember thinking, 'If I floss my teeth I'm going to bleed to death.' It was definitely a connection in my mind.

When I was about 13, I developed a really itchy, vesicular rash on my lower back, which would travel around over the next 25 years. I spent one summer in France, living on baguettes, and by the end of that summer I had this rash all over me. When I got back to Canada and went back to my regular diet, the rash went back down to one or two spots. In retrospect, I now know it was the dermatitis herpetiformis.

As I mentioned, I experimented with a lot of different dietary pathways. By the time I got to Bastyr, I started getting even sicker. My liver became inflamed (my liver enzymes were elevated). I was always anemic; my iron levels (my ferritins) would be around 6 or 7 on average. I had a lot of infections. I was definitely irritable, moody, and fatigued a lot.

It all started getting much more serious after I got married. I married an acupuncturist right after we graduated and we started trying to get pregnant. Two years later I still wasn't pregnant, so that was when we started to think, 'Okay, I'm definitely medically infertile at this point.' My husband and I undertook a really intensive program. We took gluten out of our diet (we both did it). We did yoga every day. Lo' and behold, I got pregnant the first month. In retrospect, that was the major piece of the puzzle. I wish I had known that gluten was really the cornerstone of everything, because I went right back to eating gluten as soon as I was pregnant. I had a very complicated pregnancy. It was unbelievable, really. I developed hypertension. I got gestational diabetes. Something bizarre happened to my thyroid; it was both hyper and hypo. I even wound up at an endocrinologist's office and they couldn't make heads or tails of it.

I went into premature labor at 27 weeks. With the acupuncture every day I managed to keep the baby to term (I went on bed rest). The delivery was complicated. I developed septicemia, so I was very ill. I had the baby and that all went fine, thank goodness. About four days later I developed severe abdominal pain; I mean, just mind-boggling pain. I wound up going back to the doctor and he said, 'Oh well, you've just got a urinary tract infection.' I had done an abdominal exam on myself and I found a huge abdominal mass. It turns out it was a fibroid (a necrotic fibroid), but they thought it was a sarcoma, which basically—I knew—would have meant that I probably only had a year to live. Initially they thought it was a hematoma, so they watched it.

Eight weeks later (bear in mind I have a newborn through all of this), I had a radical cancer surgery, and they basically took out half of my small intestine, ten lymph nodes, two-thirds of my large intestine, and it was quite a rough recovery. And then I basically went into immune failure for the next two years. I got the Norwalk virus. I got trigeminal neuritis. I got four bouts of bacterial pneumonia.

Eighteen months later, I was back in for more surgery from obstructions from adhesions and they removed my gall bladder. I definitely felt like I was dying. I knew there was something wrong with me, and I just couldn't figure out what it was. No matter how much iron I took my iron levels wouldn't come up. I was getting pretty desperate to find the answer. A low point was when I developed severe nystagmus. I was vomiting uncontrollably at a play date at the local park and had to be carried out by ambulance. I had severe bouts of vertigo for about another year-and-a-half after that happened, so I was definitely having neurological problems. I haven't even emphasized the gut piece, but I was having constant gut pain.

One day I was sitting in my clinic waiting room and I was reading the magazines on the coffee table. I think *Eat Well* was the magazine, and it had a headline that said 'Could Wheat Be the Problem?' (or gluten—I can't remember the exact title). 'Do have constant anemia? Do you have infertility?' It kind of listed through a lot of my symptoms, and it was the epiphany that I had been waiting for. I tested myself, and sure enough it came up positive. I went gluten-free, and I was really lucky that I responded. The rash went away (finally!). All my gut symptoms healed up. My immune system is much, much better. I occasionally get a cold—once a year, maybe (my doctors had told me they had surgically immune-compromised me because they had removed so much of my gut). I have no doubt the gluten-free diet saved my life. I feel really blessed, and I guess evangelical, since it was my past that led me to this point.

Dr. Doherty is in the unique position of being able to provide clinical insight as well as personal perspective:

“In terms of the clinical approach to patients, it's going to sound almost embarrassingly simple. What I have found, over the years, is that you have to start with the nutrition. When I was at the NIH Consensus Conference there was a moment that was another epiphany for me and has really guided my work. A woman, Cynthia Cooper, who is the head of the Gluten Intolerance Group of North America, said the statistic that 10 years after diagnosis 50 percent of celiacs still have multiple nutritional deficiencies. I have definitely seen that in practice. People have been gluten-free for years, but they are still not feeling well. They are tired, they are irritable, they are depressed, they are not sleeping well, they have brain fog, and they may still have gut symptoms.

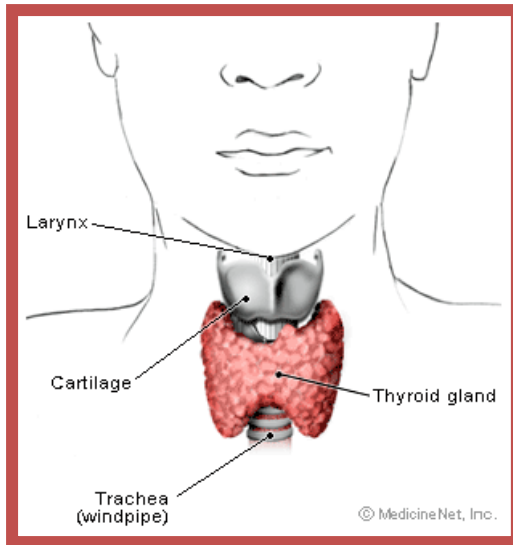
This is where I really see starting with the basics of nutritional supplementation. I often see patients who have been to other doctors (including holistic doctors) and they have been given more specific things (for the liver, for example), but often nobody has just looked at the basics, like whether they have an essential fatty acid deficiency. They often have issues with fat soluble vitamin absorption, so it is a really good idea to give them the active forms of all of them, and I give them the fat soluble versions of vitamin A, not just beta carotene, because I find they don't convert the beta carotene very well.

The other sneaky thing about this population is they have been suffering a long time. Just as I got to the point where I didn't bother mentioning so many of my symptoms, I find you have to ask specific questions about things like night vision and how are they sleeping. They'll try to boil it down, but if you start asking about things like chronic canker sores (which is another symptom I definitely had for years), that is when they start seeing they've got all these symptoms of deficiencies, but they're not putting it together with their celiac (and neither are their doctors, in many cases). A lot of those are just symptoms of deficiency. Getting the B vitamins in there, the calcium, the magnesium, all the minerals, the essential fatty acids will often do wonders.”

And finally, Dr. Doherty can also provide some optimism for the future:

“I read a statistic yesterday that said more people in America have celiac disease than ulcerative colitis, Crohn's disease, and cystic fibrosis combined.<sup>6</sup> I thought that kind of drove the point home. What I'm hoping—and I think everybody who is advocating for celiac is hoping—is that really the big thing is to get people diagnosed. There's a ton of great dietary resources out there. There are a ton of restaurants that now have gluten-free menus, lots of national chains. It's a huge, exploding market in terms of the options; it has never been as easy to be gluten-free as it is now and I'm sure it's just going to get easier. I'm optimistic. I've seen a huge change just in the five years that I've been gluten-free. When I lecture to doctors, it's still about, ‘Here are the celiacs; recognize them, screen them, and then get them on the road to wellness.’ But once they are gluten-free and their deficiencies are fixed, they are just like everybody else. Their mortality rate is just like everybody else. We can be fine.”

## Thyroid-Related Autoimmune Conditions



Hashimoto's Disease and Graves' Disease are thyroid-related conditions that have an autoimmune component. Additionally, there are some reported associations with relationship to gluten sensitivity, changes in enteric bacteria, altered estrogen metabolism, xenobiotic exposure, and even nutrient insufficiencies such as selenium, zinc, iodide and vitamin E.

Specifically, Hashimoto's thyroiditis is an autoimmune thyroid disease in which the immune system makes antibodies to the enzyme TPO and thyroglobulin and destroys the thyroid gland. Additionally, Hashimoto's thyroiditis is marked by infiltration of immune cells into the thyroid along with the presence of autoantibodies directed at thyroglobulin and thyroid peroxidase. It is the

most common thyroid disease in the U.S. and is associated with other autoimmune diseases. As with most autoimmune conditions, it is more prevalent in women compared with men (five times more common in women than men in the U.S. with a prevalence of approximately 1 in 182 or 0.55% or 1.5 million people in the U.S.).

Graves' disease is a more rare autoimmune disease and is the most common form of hyperthyroidism. In this condition, an auto-antibody is formed against the Thyroid Stimulating Hormone (TSH) receptor, resulting in stimulation of the gland. Similar to other autoimmune conditions, Graves' disease is 4 to 8 times more common in women and usually begins after age 20.

## Genes vs. Environment: The Potential for Personalized Lifestyle Intervention

In the NIH report, it is stated that although approximately one-third of the risk of developing an autoimmune disease can be attributed to heritable factors, the remainder of risk is thought to be associated with non-inherited events such as issues like mercury in the environment, and other toxic heavy metals now being seen as potential immune-activating substances in sensitive individuals. It also includes exposure to certain chemicals and xenobiotics, such as halogenated hydrocarbons, polynuclear aromatic hydrocarbons, and polychlorinated biphenyls. All of these have potential xenobiotic risk to the neuroendocrine and immunological systems in susceptible individuals.

Infectious agents are the most often-cited environmental factors implicated as triggers of autoimmune disease. We know about the classic example: the Group A beta-hemolytic streptococcus in the development of rheumatic heart disease. Acute Guillain-Barré syndrome has been associated with a number of bacterial and viral infections. Even reactive arthritis has been linked to a variety of intestinal infections. We begin to see focal infections, which could be a root canal, dysbiosis of the gut, or sinusitis, any of which may result in continued leakage of bacterial and viral products that initiate immune

imbalance.

Lifestyle and dietary factors are now being seen as much more important issues in autoimmune disease. Diets very high in total calories and fat calories induce injury to DNA and produce "funny", or foreign, DNA. The immune system may recognize these as "foreigners" and begin to form antibodies against DNA called "anti-DNA autoantibodies." It is actually the action against a foreign DNA that has resulted as a consequence of oxidative injury to native DNA.

Diet is beginning to be seen as a potential additional modifying factor in the expression of autoimmune disease. We know that food allergy and food sensitivity may modify function via the immunological changes that occur. Gluten sensitivity stands out in conditions such as thyroiditis, UC, and Crohn's disease. Dr Kenneth Fine, MD, reported 62% of patients he tested with autoimmune disease were gluten sensitive. We are beginning to understand how the food of one may be the poison of another, as it relates to the immune system.

Estrogen is another factor in autoimmunity. It used to be thought that 17-beta-estradiol was strongly correlated with autoimmune disease. Now, there is more and more evidence indicating that estrogen metabolites, possibly the 16-hydroxyestrogens, and perhaps the 4-hydroxylated estrogens, may be precipitating metabolites for immunological imbalance, inducing immunological activation of inflammation. The prevalence of autoimmune disease in females as compared to males may relate to androgen/estrogen balance and estrogen metabolism. Some therapies for arthritis have to do with increasing androgen, such as administering DHEA at high levels with patients with SLE, or giving an aromatase inhibitor, which has shown to be of some benefit. Taking women off birth control pills to lower estrogen exposure, or giving Tamoxifen to block estrogen signaling have been found to decrease some of the signs and symptoms observed in autoimmune disease.

Stress also plays a large role in autoimmunity. Patients develop an "autoimmune personality" with their family histories, evidence of an inflammatory lifestyle, and increasing auto-antibodies years before they are diagnosed with an autoimmune disease. It is interesting to observe that autoantibodies (or these antibodies produced against self material) start to appear seven to fourteen years out from the formal diagnosis of an autoimmune condition, suggesting that the immune system is under severe stress for years before it manifests a full-fledged disease. In a paper published in *The Journal of Neuroscience* in 2005, researchers describe maternal programming of stress responses, and how activation of the hypothalamus/pituitary/adrenal axis can initiate various types of messenger molecule changes, including inflammatory cytokines and other cell regulating substances that have to do with growth hormone and gene expression patterns. This interaction can create a feed-forward cycle that can facilitate and activate stress responses that we see as inflammation, and encourage and feed into the inflammatory pathway.<sup>7</sup>

Int J Immunopathol Pharmacol. 2011 Jan-Mar;24(1 Suppl):51S-54S.

### **Work stress and innate immune response.**

Boscolo P, Di Gioacchino M, Reale M, Muraro R, Di Giampaolo L.

Source

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Abstract

Several reports highlight the relationship between blood NK cytotoxic activity and life style. Easy life style, including physical activity, healthy dietary habits as well as good mental health are characterized by an efficient immune response. Life style is related to the type of occupational activity since work has a central part in life either as source of income or contributing to represent the social identity. Not only occupational stress, but also job loss or insecurity are thus considered serious stressful situations, inducing emotional disorders which may affect both neuroendocrine and immune systems; reduced reactivity to mitogens and/or decreased blood NK cytotoxic activity was reported in unemployed workers or in those with a high perception of job insecurity and/or job stress. Although genetic factors have a key role in the pathogenesis of autoimmune disorders, occupational stress (as in night shifts) was reported associated to an increased incidence of autoimmune disorders. Monitoring blood NK response may thus be included in the health programs as an indirect index of stressful job and/or poor lifestyle.

Int J Sports Med. 1997 Mar;18 Suppl 1:S91-100.

### **Exercise immunology: practical applications.**

Nieman DC.

Source

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Abstract

During the last 95 years, 629 papers (60% in the 1990s) dealing specifically with exercise and immunology have been published. Major findings of practical importance in terms of public health and athletic endeavor include: (a) In response to acute exercise (the most frequently studied area of exercise immunology), a rapid interchange of immune cells between peripheral lymphoid tissues and the circulation occurs. The response depends on many factors, including the intensity, duration, and mode of exercise, concentrations of hormones and cytokines, change in body temperature, blood flow, hydration status, and body position. Of all immune cells, natural killer (NK) cells, neutrophils, and macrophages (of the innate immune system) appear to be most responsive to the effects of acute exercise, both in terms of numbers and function. In general, acute exercise bouts of moderate duration (< 60 min) and intensity (< 60% VO<sub>2</sub>max) are associated with fewer perturbations and less stress to the immune system than are prolonged, high-intensity sessions. (b) In response to long-term exercise training, the only finding to date reported with some congruity between investigators is a significant elevation in NK cell activity. Changes in the function of neutrophils, macrophages, and T and B cells in response to training have been reported inconsistently, but there is some indication that neutrophil function is suppressed during periods of heavy training. (c) Limited data suggest that unusually heavy acute or chronic exercise may increase the risk of upper respiratory tract infection (URTI), while regular moderate physical activity may reduce URTI symptomatology. (d) Work performance tends to diminish

with most systemic infectious, and clinical case studies and animal data suggest that infection severity, relapse, and myocarditis may result when patients exercise vigorously. (e) Although regular exercise has many benefits for HIV-infected individuals, helper T cell counts and other immune measures are not enhanced significantly. (f) Data suggest that the incidence and mortality rates for certain types of cancer are lower among active subjects. The role of the immune system may be limited, however, depending on the sensitivity of the specific tumor to cytolysis, the stage of cancer, the type of exercise program, and many other complex factors. (g) As individuals age, they experience a decline in most cell-mediated and humoral immune responses. Two human studies suggest that immune function is superior in highly conditioned versus sedentary elderly subjects. (h) Mental stress, undernourishment, quick weight loss, and improper hygiene have each been associated with impaired immunity. Athletes who are undergoing heavy training regimens should realize that each of these factors has the potential to compound the effect that exercise stress is having on their immune systems.

Nutrition. 2012 Nov-Dec;28(11-12):1109-14. doi: 10.1016/j.nut.2012.02.009.

### **Nutritional status in relation to adipokines and oxidative stress is associated with disease activity in patients with rheumatoid arthritis.**

Hayashi H, Satoi K, Sato-Mito N, Kaburagi T, Yoshino H, Higaki M, Nishimoto K, Sato K.

Source

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Abstract

**OBJECTIVE:** We assessed whether disease activity was associated with dietary habits, nutritional status, adipokines, and oxidative stress in patients with rheumatoid arthritis. **METHODS:** The subjects were 37 patients with RA. The assessment of the nutritional status included anthropometric and biochemical parameters. A food-frequency questionnaire and a 3-d diet record to assess dietary intake were used. The serum levels of adipokines and oxidative stress markers in sera and saliva were measured. The disease activity was determined using the 28 Disease Activity Score (DAS28). We divided the subjects into high (DAS28  $\geq$ 3.2) and low (DAS28  $<$ 3.2) disease activity groups. **RESULTS:** The serum leptin and albumin levels were significantly lower, whereas the inflammatory markers were increased, in the high disease activity group. The dietary intake assessment showed a lower intake of fish oil and a lower ratio of monounsaturated fatty acid intake in the high disease activity group. There was a negative correlation between the DAS28 and the dietary intake of the ratio of monounsaturated fatty acid to total fatty acid intake. The serum oxidative stress marker (reactive oxygen metabolites) showed a positive correlation to the DAS28. The salivary reactive oxygen metabolites also correlated with C-reactive protein and serum reactive oxygen metabolites. **CONCLUSION:** Altered serum adipokine levels with decreased albumin may reflect the deterioration that is associated with rheumatoid arthritis. An increased oxidative stress was observed in sera and saliva. Intakes of  $\omega$ -3 polyunsaturated fatty acids, fish oil, and monounsaturated fatty acid seem to affect disease activity and may have beneficial effects by decreasing inflammation.

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