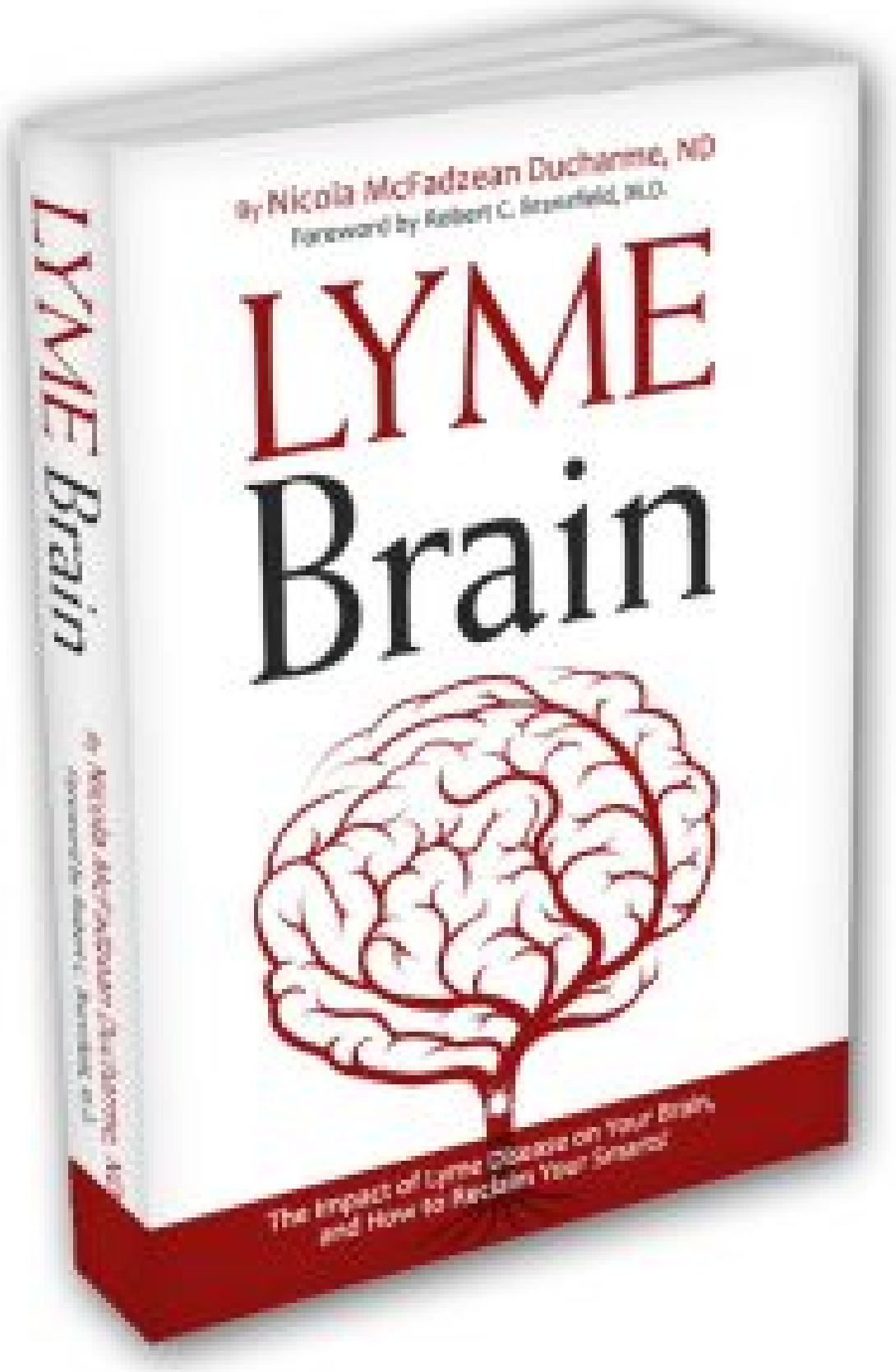
Book Excerpt: “The Impact of Lyme Disease on Your Brain and How to Reclaim Your Smarts”


LYME Brain
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LYME
Brain
The Impact of Lyme Disease on Your Brain,
and How to Reclaim Your Smarts!

B efore we discuss specific causes of Lyme Brain, let's get clear on two underlying premises. The first is that Lyme disease is a chronic infectious process, and that bacteria can and do persist in the body beyond the Infectious Diseases Society of America's "standard of care," which is a 14 to 21 day course of antibiotics. I'm not going to get into all the research supporting that general premise (for more detailed information, I refer you to my book The Beginner's Guide to Lyme Disease, which states the evidence clearly). The second premise is that the Borrelia spirochetes (and co-infections) can and do get into the brain itself. Therefore, a chronic infectious process can give rise to long-term exposure of brain tissue to spirochetes and other pathogens, which can have far-reaching consequences.

> If we can mediate the inflammatory response, then we can minimize cell damage and death.

Evidence of spirochetes in the brain is not new. It is well established that the spirochetal bacteria that is behind syphilis, Treponema pallidum, causes progressive dementia and brain atrophy in the late stages of that disease.[1] Although Treponema and Borrelia are different pathogens, both are spirochetes, so we can draw some conclusions about the activity of one and how that might relate to the other. As one of my patients once said to me, "Dr. Nicola, Lyme disease is the new syphilis."

Some of the research that indicated that Borrelia spirochetes could get into the brain was done on Alzheimer's patients. Researcher Alan MacDonald was one of the first to find spirochetes in the brains of Alzheimer's patients on autopsy.[2] Examination confirmed that the spirochetes were B. burgdorferi sensu stricto (one of the strains responsible for Lyme disease). In two cases, postmortem studies showed positive serology (on blood and cerebrospinal fluid) by Centers for Disease Control (CDC) standards. Neurofibrillary tangles were reactive with specific B. burgdorferi antibodies, and Borrelia antigens were found.

In another study, spirochetes of various kinds were found in the brains of 14 Alzheimer's patients; they were not found in 13 controls. Three of these cases were identified as Borrelia burgdorferi sensu stricto.[3] Yet another study detected Borrelia bacterial DNA by PCR in 5 of 16 Alzheimer's patients and only 1 of 16 controls.[4] Judith Miklossy, M.D., Ph.D. conducted a review of all available data concerning spirochetes and Alzheimer's disease. The cumulative

results showed that spirochetes of various kinds were found in the brains of more than 90% of Alzheimer's cases, and Borrelia burgdorferi was detected in 25.3% of cases.[5]

The correlation between Borrelia burgdorferi and Alzheimer's disease is intriguing. However, the purpose of presenting this research is to show that the Borrelia spirochetes can indeed penetrate the brain tissue. I also want to stress that there are many Alzheimer's patients who do not house Borrelia spirochetes in their brain, and not all Lyme patients are going to develop Alzheimer's disease. This is an important distinction to make. I don't want you all to read this and think that you're on the road to Alzheimer's disease – that is not the case at all. Yes, it's true that a subset of Lyme patients may develop Alzheimer's disease, but there are also other factors to consider such as genetic predisposition; perhaps they would have developed Alzheimer's disease even in the absence of Lyme disease.

Now that we have clearly established that Lyme disease infects the brain directly, let's look at the ways it can wreak havoc. We'll use the following points as a roadmap throughout the book to determine which treatments need to be used to stop these damaging processes.

DIRECT DAMAGE TO NERVE CELLS

We know that in the body, spirochetes can exist outside of cells or inside of cells. The intracellular invasion allows them some protection from host defenses, primarily our immune response. Bacteria in the brain are invasive, too, and can invade neurons (nerve cells that conduct electrical impulses) and glial cells (supporting cells of the nervous system that do not conduct impulses).[6,7] The invasion, and the following inflammatory cascade that results, can lead to death of the nerve cells.

Researchers back this up. "The presence of B. burgdorferi DNA in tissue samples from areas with inflammatory changes indicates that direct invasion of B. burgdorferi may be the pathogenetic mechanism for focal encephalitis in LNB (Lyme Neuro-Borreliosis)."[8]

Although this sounds dire—and not to make light of it, it can be—the neuronal death appears to be secondary to an inflammatory cascade triggered by the bacterial invasion. In other words, it appears to be the secondary inflammation rather than the pathogen itself that causes cell apoptosis.[9] There are ways to mediate such inflammation, which we'll discuss later. If we can mediate the inflammatory response, then we can minimize cell damage and death.

Borrelia may also cause demyelination of the white matter in the brain. The myelin sheath is

a protective sheath that surrounds the axon of the nerve cell (the branch that juts out from the nerve cell and transmits the impulse). Myelin serves primarily to increase the speed of nerve transmission, getting the message from one cell to the next in the quickest, most efficient manner. There are several neurological diseases that involve demyelination, but the best known, perhaps, is multiple sclerosis (MS). Given that a subset of Lyme patients have been diagnosed with MS, it does raise the question of whether their primary diagnosis is truly Lyme disease but the diagnosis of MS was made based on similar findings on MRI studies.

Unfortunately, there are no curative treatments for MS, and while Lyme treatment may not be quick or straightforward, I have seen Lyme patients who have also been diagnosed with MS improve with antibiotic treatment. This is often also evidenced by a reduction in white lesions on their brain MRI. So, determining whether MS is underlying Lyme disease can make all the difference in the world in a patient's prognosis.There are several studies that demonstrate demyelination in Lyme patients. Many of the studies are case reports, so it is unclear exactly how prevalent this is, but as with anything in Lyme disease, my suspicion is that it most likely occurs more frequently than the literature would imply.[10]

One researcher, Vesna Briner, did make this statement:
"The diagnosis of multiple sclerosis (MS), despite well-defined clinical criteria is not always simple. On many occasions it is difficult to differentiate MS from various non-MS idiopathic demyelinating disorders, specific and infectious inflammatory diseases or non-inflammatory demyelinating diseases. Clinicians should be aware of various clinical and MRI "red flags" that may point to the other diagnosis and demand further diagnostic evaluation. It is generally accepted that atypical clinical symptoms or atypical neuroimaging signs determine necessity for broad differential diagnostic work up. Of the infectious diseases that are most commonly mistaken for MS the clinician should take into account Whipple's disease, Lyme disease, Syphilis, HIV/AIDS, Brucellosis, HHV¬6 infection, Hepatitis C, Mycoplasma and Creutzfeld-Jacob disease, among others."[11]

Another quote from a study out of Croatia:
"Demyelinating diseases of the central nervous system include a wide spectrum of different disorders that may resemble multiple sclerosis (MS). The diagnosis of MS is based on typical clinical and paraclinical criteria…If some of these criteria are atypical, diagnostic *algorithm should be extended to some other procedures to exclude other diseases that can mimic MS not only in symptoms, signs or course of the disease but also in laboratory findings. In such a case, an alternative, better explanation for the clinical manifestations*

should be considered and performing *specific tests is helpful to exclude alternative diagnoses."*[12]

Certainly there are enough references and articles stating that infectious processes can be a cause of demyelination and that differential diagnosis must include those things. I wonder, then, why some doctors are still so reluctant to consider chronic infections such as Borreliosis in a patient presenting with MS?

THE INFLAMMATORY RESPONSE

As mentioned above, direct impact of the pathogens on the nerve cells, which either causes demyelination or nerve cell death, is one way that Borrelia and its co-infections cause brain problems. The second major mechanism is the inflammatory response. In fact, inflammation in the brain is perhaps the most significant cause of Lyme Brain.
Let's review some basic physiology. Inflammation can occur for a number of reasons, but notably in response to a pathogen in the body that the immune system is trying to fight. Even though it can seem like a bad thing, it's actually part of the body's protective response. Inflammation can involve not only white blood cells, but also blood vessels in the area and cells in the damaged tissue, too. It is only a bad thing when the immune system becomes too active or the inflammatory response is prolonged. When there is a pathogen such as Borrelia, the immune system activates to counter the threat and kill the pathogen. In doing so, the white blood cells of the immune system go to the affected area.

A whole cascade of events follows, the details of which are beyond the scope of this book. Suffice it to say that there are a few key features that are part of the inflammatory process.One of these features is the production of cytokines. Cytokines are small proteins that are released by various cells of the immune system and function to facilitate communication and signaling between various cells. They orchestrate the trafficking of immune cells, direct them to the sites of injury and influence immune cell function. They are released by a range of immune cells including B cells, T cells, macrophages and mast cells. In very simple terms, they are messengers and facilitators. Types of cytokines include chemokines, interleukins, interferons, lymphokines and tumor necrosis factors. Cytokines can also influence Th-1 and Th-2 balance within the immune system, which is significant in chronic infections such as Lyme disease.

Chemokines are chemicals that induce the movement of cells towards an area of damage or inflammation.

Chronic Lyme patients are found to have high levels of cytokines such as interferon-gamma, IL-10, TNF-alpha, interleukin-6, interleukin-1b, interleukin-8, interleukin-12 and C-reactive protein. Some cytokines are anti-inflammatory (IL-10 for example); however, the majority of cytokines found in Lyme patients are pro-inflammatory.[13,14,15]
Chemokines are chemicals that induce the movement of cells towards an area of damage or inflammation. Many chemokines have been found in Lyme patients: chemokine ligands CXCL12, CXCL13, CCL2, CCL3, CCL4 and CCL5.[16,17]

Nitric oxide (NO) is another inflammatory mediator. Nitric oxide is a reactive molecule that can cause oxidative stress and cell damage, giving rise to further inflammatory processes. Higher levels of nitric oxide have been found in Lyme patients as opposed to healthy subjects. Nitric oxide also controls blood vessel dilation and constriction, so nitric oxide levels may play a role in the blood flow and oxygenation of cerebral vascular tissue in Lyme patients.[18,19] One interesting characteristic of nitric oxide, however, is that it has been found to be toxic to the Lyme bacteria.[20,21]

In an article in the Townsend Letter (Feb/ Mar 2006)[22], Professor Robert W. Bradford and Henry W. Allen postulate that there might be a role for therapeutic agents that inhibit PDE-5, an enzyme that regulates c-GMP, which in turn influences nitric oxide. Medications that inhibit PDE-5 include sildenafil (Viagra), Cialis and Levitra. From a naturopathic standpoint, the amino acid arginine may have similar effects. Further research would be needed to determine whether this, indeed, is therapeutically significant and potentially

beneficial for Lyme patients.

Another byproduct of immune activation is changes in the vascular system and blood clotting mechanisms. Inflammation creates increased dilation of the blood vessels and increased permeability in the vessel walls. This allows more fluid to move into the tissue space, giving rise to stasis of the blood cells in the vessels. This serves a worthwhile purpose: it allows white blood cells to move along the vessel walls to the site of injury (think of all the traffic on a freeway as it pulls over and stops on the side of the road to allow an ambulance through. If the traffic were flowing as it usually does, the ambulance would have a hard time making its way to the problem location). However, it can also lead to negative effects such as reduced oxygenation of the tissues.

So, we see that inflammation causes blood coagulation, but coagulation itself also has the capacity to regulate immune response, again, largely through the activation of various signaling molecules.[23] Coagulation is balanced by the fibrinolytic system, which acts as an anticoagulant, preventing ongoing blood clotting. Anticoagulants also function to reduce cytokine production and protect the endothelial cells from the damage caused by inflammation.[24] So you can see that while inflammation is a necessary part of immune response, it is not without its negative effects on the body.

Think of it like a military invasion. If an intruder comes onto home soil, the military (immune system) are going to counter that threat. They will first go to the location of the invasion, spreading out to the extent that the bad guys have spread out. They will come in with guns blazing and missiles firing. The goal is to kill as many of the baddies as possible with the least impact on the home turf, but in the process of the invasion, some collateral damage may occur. Yes, the military might kill at least some (hopefully all) of the bad guys, but they may also take out a few local civilians, buildings might get blown up, and infrastructures may be destroyed. Some of this may be necessary to contain the original threat, but it's certainly not the goal of the military's defense strategy. Hopefully, once the invaders are neutralized, rebuilding of home base can occur to repair any collateral damage.

And so it is with inflammation in Lyme disease. When the immune system tries to protect the body from an invasion by pathogens, baddies will be eradicated, but inflammation will occur as a byproduct, which can damage tissues and create symptoms of its own. This is one of the necessary secondary effects, but it is also the mechanism for much of the collateral damage that we see. In chronic Lyme disease, collateral damage is often more extensive, due to the fact that the battle is ongoing over months and years, compared with shorter

battles that occur in acute infections.

NEUROTOXINS

One of the ways that Borrelia burgdorferi may act to cause Lyme Brain is by releasing toxins in the brain and central nervous system. Neurotoxins are substances that enter nerve cells through the nerve endings, disrupting the function of the cell along the way. There are many sources of neurotoxins, both infectious and non-infectious in nature. Other examples are heavy metals, molds and Candida, as well as the chemicals that we are exposed to by the industrialized products and services we consume in modern society.
While the concept of a specific neurotoxin produced by Borrelia has been a controversial one, there is at least some research supporting it. Researchers Cartwright, Martin and Donta presented an abstract at a conference in 1989, which identified DNA in the Borrelia bacterial genome that produces a neurotoxin. This was named BbTox1.[25]

This toxin is cited to be similar in structure to the botulinum toxin, belonging to a family of toxic proteins called zinc endoproteinases. Professors Bradford and Allen in their article in the Townsend Letter for Doctors and Patients (Feb/Mar 2006) claim that the Borrelia toxin works by disabling the neurotransmitter acetylcholine, which would then impact motor functions as well as psychoemotional states. In reality, there is fairly limited research in this area. A PubMed search of BbTox1 only revealed one match, a study from Poland citing the existence of BbTox1 but with no new information.[26]

Another possible mechanism of neurotoxicity secondary to Lyme disease may be increased levels of ammonia. David Jernigan, D.C., D.N.M., an integrative practitioner, founder of the Hansa Center for Optimal Health and developer of Jernigan Neutraceuticals, states that he discovered that the majority of Lyme patients have elevated levels of ammonia in their brain and potentially in other parts of their bodies, too, including the liver.

> Think of it like a military invasion. If an intruder comes onto home soil, the military (immune system) are going to counter that threat.

Here is an excerpt from Dr. Jernigan's blog:
"It would seem that Bb releases ammonia, which is converted to glutamine by way of the glutamine synthetase pathways, leading to localized swelling of astrocytes (brain cells). This ammonia-induced glutamine accumulation may cause dysfunction of astrocytes, which leads to impairment of vascular reactivity (other than through a decrease in arginine availability for nitrous oxide)

and increased production of nitric oxide…It has been reported that many neurological problems are caused by either congenital or acquired hyper-ammonemia."[27]

Dr. Dietrich Klinghardt, another well-known integrative doctor who works with many Lyme patients, also believes that ammonia in the brain may play a contributing role in Lyme Brain. He associates ammonia elevations with a condition called Kryptopyrroluria (KPU), also known as Hemopyrrollactamuria (HPU). This is a metabolic disorder that impacts one's ability to metabolize zinc, biotin, manganese, B6 and arachidonic acid.

Brain-related symptoms that may be associated with KPU include:
• Poor dream recall
• Nervousness/anxiety
• Pessimism
• Depression
• Paranoia/hallucinations
• Perpetual disorganization
• Mood swings/emotional lability
• Stress intolerance
• Poor short-term memory
• Substance abuse
• ADHD
• Autism
• Withdrawal
(List taken from reference below)

Dr. Klinghardt estimates the incidence of KPU in Lyme disease patients to be 80% or higher; in patients with heavy metal toxicity (lead, mercury, cadmium and others) over 75%; and in children with autism, over 80%.[28] He states that as KPU is treated, high levels of ammonia tend to normalize. Clearly, biotoxins and neurotoxins seem compelling and may well be a significant and under-acknowledged cause of Lyme Brain. Much more research is needed in this area. In the later sections, which address the treatment of Lyme Brain, we'll talk about the ways to minimize the effects of these neurotoxins.

NEUROTRANSMITTER IMBALANCE

Another contributing factor to Lyme Brain is neurotransmitter imbalance. This may be more of an effect than a cause; however, it is something that I frequently see in my patients and is prevalent enough to warrant a discussion here. Neurotransmitters are brain chemicals that

transmit impulses from one nerve cell to another. There are many different neurotransmitters and each has a different role and influence on brain function (so far, there are over 100 identified).[29] They play a central role in mood, cognition and emotional state.

Perhaps the best-known neurotransmitter is serotonin—so well known because many antidepressants function as selective serotonin reuptake inhibitors (SSRIs). They prevent serotonin from being discarded, and cause it to be recycled and reused in the brain. Why? Because low serotonin levels can cause depression (newer generation antidepressants work on a variety of pathways, but serotonin is still one of the more significant). Some neurotransmitters are stimulatory, while others are inhibitory. By definition, this means that some are likely to promote a nerve impulse while others will inhibit it. In terms of how they affect people, some are more "awakening" and some are more "calming." Epinephrine and norepinephrine are examples of more stimulating neurotransmitters, while serotonin and GABA are more calming. Dopamine is related to emotional states, pleasure centers and motivation. Dopamine and norepinephrine together influence working memory. Acetylcholine relates to motor system function but also plays a role in emotion, learning and short-term memory.

Glutamate is the most prevalent excitatory neurotransmitter in the brain. While it is inherently an excitatory neurotransmitter, excessive glutamate can cause overstimulation in the brain and excitotoxicity. This has been implicated in a range of different neurological issues including ALS, epilepsy, autism and Parkinson's disease. GABA is the most prevalent inhibitory neurotransmitter in the brain. GABA is often used clinically to treat anxiety and can be easily obtained in supplemental form. It has a very calming effect and a valuable role in Lyme treatment. GABA can also be used to balance excess glutamate. Neurotransmitter imbalances will be discussed in more detail in the treatment section, as we can use amino acids to fuel certain pathways and help balance altered neurotransmitters. This can help stabilize mood as well as assist with focus, concentration and memory recall.

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