Lyme Disease: What We Know and What We Don't Know

An Editorial by Tom Grier, Lyme Writer

In 1975 the term "Lyme Arthritis" first entered the vocabulary of the physicians in America. Since that time Lyme disease and Lyme-like diseases have become recognized worldwide. But in the 28 years since "Lyme Arthritis" was first described: What do we actually know? And what do we yet need to learn about this illness?

Why is it that in the three decades since Lyme disease was first described that it still perplexes us and vexes us with controversy and puzzlement?

In a nutshell it comes down to the inescapable fact that victims of Lyme disease all too often have lingering symptoms that remain or return even after aggressive and multiple antibiotic treatments. They remember wellness, but with each passing year the fog that fills their brain, the palpitations that shake their hearts, and the fatigue that plagues their bodies becomes the ever present reminder that they were stricken with a poorly understood and often underestimated pathogen.

Here are some things we know: The pathogen that causes Lyme disease is Borrelia burgdorferi and it is a highly motile spirochete that belongs to a genus of bacteria that are notorious for giving rise to variant strains. Borrelia are bacteria that are associated with dozens of tick and louse-borne Relapsing Fevers that are found throughout the world. These related illnesses range in symptoms from cases of mild fevers to rapidly fatal encephalitis'. The hallmark attribute that most Borrelia bacteria have in common is their ability to adapt, change and infect host animals that in turn infect many species of ticks and lice.

We know for example that if you rank all the known Borrelia pathogens in a phylogenetic tree based on related genetics, you will find many disease causing pathogens that cause similar symptoms will often end up close together in related groups on the phylogenetic family-tree.

In other words Borrelia burgdorferi, Borrelia afzellii and Borrelia garinii that cause Lyme disease in America and Europe are all genetically similar to each other and have similar tick vectors. It is believed that they are closely related and variations occurred as separate tick populations over thousands of years migrated with animal populations and the bacteria became isolated populations. At one time all Borrelia had a common ancestor.

Exactly how long ago we don't know, but the evidence of common ancestry is in their related and similar genes. This year when the genomic sequence of Borrelia burgdorferi was determined, it came as quite a shock that most of the genes in this large bacterium had no known counterparts or similarities to other known bacterial genes. This means the function of the majority of the genes in the Borrelia species has yet to be determined.

What we don't know: The Lyme bacteria Borrelia burgdorferi likes to preferentially express certain genes and suppress others. This allows the bacteria to adapt to new environments. But what does it take for Borrelia burgdorferi to express one of the suppressed genes of an ancient pathogen cousin? Borrelia burgdorferi like all Borrelias have genes that are latent but intact. If a gene is expressed or triggered by the environment as it is suggested by research done of Relapsing Fever strains, then could a latent but deadly gene be triggered in one individual with unique genetic markers and not expressed in another patient? Could pathogen-host interactions

based on patient genetic markers explain why some Lyme patients have persisting symptoms?

What we know: Dr. Andrew Pachner infected mice with Borrelia burgdorferi and later extracted the bacteria from the blood and from the brains of the infected mice. What he found was basically that the Bacteria in the brain changed: they now expressed a new set of genes. The result was bacteria so different from what he started with, that the antibodies from the peripheral blood could no longer detect the bacteria isolated from the brain.

This is bad news as the CNS is isolated from the rest of the body. If the Lyme spirochete can adapt to the human brain and circumvent the immune system, it is less likely to be inhibited by our natural immune defenses. Further studies by Pachner in primates using PCR suggested persistent infection post-antibiotic treatment. This is more bad news as this suggests that the CNS of primates is an isolated and protective incubator for Borrelia bacteria.

What other gene expressions of these bacteria do we need to understand better?

What we need to find out: Occasionally patients infected with Relapsing Fever will report a Bull's-Eye rash identical to Lyme disease, and experience symptoms similar to Lyme without a recurring febrile states (Recurring fevers). If Relapsing Fevers can behave like Lyme disease, does this mean Lyme could suddenly cause an aggressive encephalitis in a patient similar to East African Relapsing Fever? Since we don't know or understand the reasons for patient variation in symptoms, it is something we need to investigate and learn. We know for instance from early work done by Dr. Patricia Coyle M.D. PhD that the Lyme bacteria can get into the CNS of a lyme patient very early , but only a small fraction of these patients develop serious mennigo-encephalopathies.

Understanding the recently sequenced genomic sequence of Borrelia burgdorferi and gene _expression is essential to understanding both chronic and acute Lyme disease. In patients with HLA-DR4 tissue type, are there markers in the joints responsible for chronic Lyme arthritis ? We need to study the role of genetics, and receptor sites in both humans and within the Lyme spirochete. How the bacteria interacts with one person may be radically different than how it acts in another patient.

What we don't know: One of the most frequent complaints from Lyme patients is the loss of cognitive abilities. Their minds are fuzzy, foggy and they complain of short term memory loss and poor word retrieval. Their fear is: How permanent is this memory impairment? And will it progress? We don't know why so few bacteria can cause such a profound affect on conscious thought, but unlike Syphilis a related and similar spirochetal infection, the Lyme bacteria is found in the human body in extremely low numbers?

Why are there so few bacteria in a Lyme infection? Are their other forms (sphereoplasts or cell-wall deficient forms) of the bacteria in greater numbers that we just aren't recognizing? How can so few bacteria cause such horrible symptoms like cardiomyopathy, encephalitis, hepato-spleenamegaly, heart arrhythmias, rheumatoid-like arthritis, optical neuritis, Bell's Palsy, muscle spasms, fibromyalgia, and multiple sclerosis-like presentations. Can it be that a small number of bacteria initiate cascade responses of inflammation and autoimmunity in the human body? If autoimmunity is playing a role, how does it affect the various tissues?.

What we know: Since 1911 dozens of papers have associated spirochetes with Multiple Sclerosis. The most dramatic and convincing of these papers were all published prior to 1954 which was decades before the numerous controversies of Lyme disease would appear. Recently in experiments using a rat-brain model, one researcher showed that Borrelia burgdorferi was directly neuro-toxic to neurons and caused the death of brain cells on contact. This happened rapidly and consistently. This means there is an evolved mechanism within the Borrelia bacteria when in contact with the CNS to not only change it's antigenic identity but to paralyze and destroy neurons and glial cells.

In recent years the incidence of Alzheimer's disease has risen sharply. Even more recent research has shown that the incubation of Borrelia burgdorferi in mouse brain cultures for eight weeks resulted in creating many of the laboratory markers for Alzheimer's disease. We see the synthesis of amyloid precursor protein and the rapid conversion to amyloid and beta sheet amyloid. We see the hyperphosphoralation of Tau protein, we see similar fibrillary tangles and fibrin deposits. In other words we can essentially create a laboratory model of Alzheimer's in-vitro simply by virtue of adding Borrelia to living brain cells. An animal model of Alzheimer's was something researchers dreamed of for decades, and now that it is within our technical abilities almost no one is exploring this model of Alzheimer's pathology.

What we need to know: What receptors are on the Borrelia membrane that triggers neuron destruction? What causes the cascade of Amyloid synthesis in brain-cell cultures? If we knew these things we could develop potential new treatments to prevent amyloid production in Alzheimer's patients, and perhaps a way to stop neurological damage in Lyme patients.

What we need to do? If even a few percent of the cases of M.S. and Alzheimer's disease were caused by spirochetes, we could save countless people from the morbidity and disability of these diseases, and millions in health care dollars. But we need much more money and research to explore a link between Borreliosis and dementia in humans. Clearly if it turns out that spirochetal infections are playing a role in some dementias, we need to find out Who to treat? and How to treat?

The first is advanced and thorough research to establish whether a link between M.S. and Lyme disease does or does not exist. Even a 1 % incidence would be an important finding. But before we can give M.S. and Alzheimer's patients that 1 in 100 chance of an effective treatment, we need to do the basic research, and frankly while monies are currently being spent on more Deer studies, almost nothing with respect to Lyme disease is being spent on Dementia research .

We need millions of dedicated research dollars to study a link between Lyme-related-spirochetes and Alzheimer's disease and M.S. To do these studies we need more than just money. We need human brain tissue from dementia patients and M.S. patients. To obtain these samples we would need to pre-enroll affected patients into a nationwide autopsy study and create a tissue bank for the tissues, and then make them available to researchers to specifically look for spirochetes and the markers of Borrelia. Prior to this however we need to train pathologists in techniques to detect spirochetes. Unfortunately if you don't know how to detect them, the spirochetes are virtually invisible on a normal autopsy.

With a national annual budget of a mere seven million dollars to study Lyme disease and to educate the public, we are about 100 million dollars short of an effective Lyme disease research program in America.

What we know: We know that many Lyme patients with established disease can test negative on serology tests. Seronegative Lyme has been reported in the medical literature and has been confirmed in patients with Erythema Migrans rashes, it has been confirmed by PCR, it has been confirmed by culture, and even by biopsy and staining of surgically removed tissue. So we know antibodies do not always manifest in all Lyme patients and cannot be the sole determinant of diagnosis. We also know by all the same methods of confirmation that some patients remain actively infected with the live bacteria even despite antibiotic treatment. Treatment failures have been reported in all treatment studies that required a follow-up of patients.

What we don't know? Why do some patient's not express adequate antibodies against this bacteria? If a patient is infected and has low or no detectable antibodies are they more sick than patients with a high natural immunity? Why do some patients maintain an active infection when they receive the identical treatment as patients who recover? Why do symptoms remain in so many Lyme patients despite aggressive therapy?

What we need to do: To answer these questions we need research that includes a budget for extensive pathology and histology. We need studies that look at the modes of action of the various antibiotics against spirochetes. We need more pharmacological studies and newer and better antibiotics. We need studies that investigate adjunct therapies that address patients lingering symptomatic sequela post treatment. If nothing else we need better delivery systems for the medicines we already have.

In the 1950s it was recognized that penicillin did not consistently get into the brains of Tertiary Syphilis patients. Only when the CNS was extremely inflamed or if the drug was given in gigantic single doses did penicillin enter the brain in therapeutic levels. So some clinicians in desperation tried to inject penicillin directly into the brain only to discover that this induced seizures. Now fifty years later we are faced with a very similar dilemma.

How do we get amoxicillin and other inexpensive and readily available drugs into the CNS? One potential answer is more research in better delivery systems to deliver the drug into the CNS. Another option is to add fat soluble carrier molecules or to use micronized antibiotics encapsulated in lipids. Of course there is no guarantee of success with these and other methods, but drug companies do not pursue this area of research, the market is perceived as being too limited. But if you expand these delivery systems beyond Lyme for such diseases as fungal infections of the brain, then the market is much larger! Once again the World Health Organization may be a source to stimulate this kind of research.

Conclusion: To do these studies that have never been done, we need to put a stop to the impediments hindering good research. Until the studies are done no one has the answers. And we won't find the answers if we don't invest more money into more and better designed studies. What Lyme disease has lacked in the past twenty five years has been research dollars that focus on the pathological disease process.

TOM Grier

“What Lyme Disease Research Needs To Be Done And Why”

By Tom Grier

Lyme disease is a perplexing illness. Early in 1970s in Old Lyme Connecticut, Lyme disease was first described as a rheumatological syndrome called “Lyme Arthritis”. The symptoms of “ Lyme Arthritis” mimicked Juvenile Rheumatoid Arthritis (JRA) and many kids with Lyme disease were misdiagnosed as having JRA.

It was only a matter of a few years before “Lyme Arthritis” was associated not only with arthritis but also with causing a host of serious neurological symptoms. Further investigation soon showed that the characteristic bull’s-eye rash was associated with the bite of a new species of tick named the Ixodes dammini tick. (The I. dammini tick turned out to be the same species as the I. scapularis deer tick.)

In 1981 when the culprit of the illness was isolated both from the suspect tick and from human Lyme rashes, it was all but decided by the medical community that while Lyme disease was a real concern, it was easily treated. This assumption was based on the fact that “Lyme Arthritis” was caused by a bacterium: and with few exceptions bacterial pathogens are all successfully treated with just a few weeks of antibiotics.

While in the test tube the Lyme bacteria Borrelia burgdorferi responded to many common antibiotics including erythromycin, tetracycline, doxycycline, penicillin and amoxicillin, the truth was that in the early days of treatment, in every human trial of antibiotic drug treatment, some patients either did not respond at all, or their symptoms quickly relapsed.

The unfortunate fact of Lyme disease is that more than twenty years later medical science has not developed any significant breakthroughs in either diagnosis of or the treatment of this disease. Despite all of what we have learned about Borrelia burgdorferi , our diagnostic tests are still poor, and our treatment regimens are for the most part unchanged for the last two decades.

The early Lyme tests that were developed made heavy assumptions that a patient’s level of antibody was a consistent marker of exposure and active infection. More distressing is that most early treatment studies considered a drop in antibody levels during antibiotic treatment as a quantitative marker for indicating a cure. Researchers inappropriately accepted a negative antibody titer as an absence of active infection. It was not considered that the bacteria was surviving beyond the reaches of the bloodstream’s immune system.

Despite the overwhelming evidence that seronegative Lyme is common and that infection can persist despite treatment, today’s researchers and manufacturers of these tests still squabble over patents and royalties and spend more time thinking up clever ways of making their indirect tests more competitive in the drug market rather than creating better direct tests.

An example of this was when a new PCR test by the U of MN was compared not to other PCR tests but to culturing Lyme rashes. Assuming only a 4 % success rate of culturing rashes the press

release for the new test was complete with cost for the test and boldly stated that this test was 4 times more accurate than culturing. To the lay person this sounds good but it really meant the new PCR test was accurate only in 1 out of every 5 patients with a bull's eye rash. This kind of research is not in the best interest of the patient.

So what research needs to be done that isn't being done?

In the last twenty years the goal of medical research has become so economically competitive that so much of the work being done is secretive and proprietary, many institutions won't even pursue research that doesn't look economically rewarding. In today's bottom line medical system, most institutions will not do work in an area that might duplicate the work of a competitor who may already own patents on the end product. Yet work on endless "me-too" versions of existing tests continues simply because manufacturers see more money in patient testing and vaccines than in treatment.

I have said it many times before and still believe that Lyme patients would be better off if no test had ever been developed, and Lyme treatments were based entirely on symptom response to therapy. I don't have a quick solution to the problem of the current patent-or-parish mentality of universities, but I do think more time needs to be spent on some old technologies such as blood smears and tissue stains before we listen to any more press releases from universities and drug companies telling us how their new test is better than that of their competitors.

In truth I have little hope in ever developing a quick easy reliable blood test for Lyme and feel we are better off without the ones currently being demanded by insurance companies and HMOs.

My first suggestion for research is to spend less money developing tests for the living, and spend more money investigating the disease process in the dying. Understanding the pathology of this disease is paramount to making any significant advances in the treatment of this illness.

We have seen in animal models going back to the 1980s that the blood brain barrier of mammals is quickly breached by this bacterium. (4) What role does early invasion of the Lyme spirochete into the human brain mean to patients? Is there long-term sequela to CNS invasion? These are questions are left wholly unanswered and require a deeper commitment to research than what has been allocated to Lyme disease!

In the 1990s we learned that the Lyme spirochete has a predilection for and attaches to the lining of blood vassals. When this occurs the endothelial cells break down and creates blood vessel holes. No one has suggested or pursued any receptor site research. Perhaps one form of treatment might be finding a way to block these attachment sites?

Drug Therapy: While we have in the past twenty years explored the use of dozens of antibiotics and combinations of antibiotics, we have not made any real advancement in antibiotic therapy. The quick and easy answer is to say we should develop newer and

better antibiotics. While this is obviously true it still falls far short of what else can be done.

One of the problems of treating Lyme disease is that the bacteria is known to penetrate difficult to reach and difficult to treat areas of the body. While the argument still persists on whether Lyme disease is an intracellular disease, there is no argument that the bacteria can get inside the joint, connective tissue and the brain which are tissues difficult to treat. In most cases you must overdose the rest of the body in order to penetrate these tissues.

A solution not currently being pursued is better drug delivery systems. In 1991 I proposed to the company I worked for at the time, Wyeth labs, that research be done on better CNS delivery systems for amoxicillin.

With the advent of diseases like AIDS and Lyme it seemed that we needed a better way to get drugs safely into the brain in higher concentrations where they were needed. While old drugs like amoxicillin can no longer be patented, the drug delivery systems can be patented for more than a decade. This could give new life to many old drugs. Better delivery systems make dozens of drugs available rather than just concentrating on a singly new drug option.

Devises that optimize direct infusion of antibiotics into joint and brain is one method of accomplishing this, and the use of fat soluble carrier molecules conjugated to or surrounding the drugs is another method (lipo-spheres, DMSO etc). The response to a 28 page proposal that I drafted in 1991 to my employer, was a single sentence in a short letter. “ Dear Mr. Grier: At this time there is no interest or economic feasibility in developing new treatments for Lyme disease ...there are not enough new cases of Lyme annually to warrant development of clinical treatments. ”

Since economic interests seem to be the main concern in researchers developing better tests for diagnosis and better drugs for the treatment of Lyme disease, it appears that Lyme disease research may be left in the hands of foundations still willing to fund research directed by need and not economics. The bonus is that almost any new treatments will be economically viable because of use in Lyme and other emerging infectious diseases.

Here is a list of areas of research that have not been aggressively pursued and that I believe have potential in producing useful breakthroughs in diagnosis and treatment.

First we need to devote less monies to tick studies and urban exposure studies and more monies to basic pathology and microbiology studies. In a world filled with people traveling via SUVs and airplanes, Lyme disease can occur to anyone who travels through Lyme endemic areas. We need to put research money into science and not into the politics of boundaries.

I care less about which counties have Lyme, and more about what long term untreated Lyme is doing to our medical system? If Lyme patients have been misdiagnosed as having M.S. how many Lyme patients have in the last 50 years been draining insurance companies

out of money for long term care of patients with M.S-like disorders caused by Lyme. We don't know the answer and we will only find out by doing autopsies on enough dementia patients to establish an accurate percentage. Even if just a few percent of dementia patients are found to have spirochetes in the brain at the time of death, this translates to billions of health care dollars wasted on caring for sick patients when it would take just a fraction of that money to treat patients caught earlier.

A very simple study that has never been done but would be quite revealing about tick-borne illnesses is a quality of retirement-life study that looks at the differences between the quality of health of retirees in professions that are at high risk for tick-borne illness compared to lifestyles with professions at a low risk of contracting tick-borne illnesses. Previous studies have shown a higher incidence of M.S. among agricultural workers, owners of large dogs, and in Europe M.S. is highest in areas of high rodent infestations. Perhaps a large-scale quality of life study would tell us if outdoor living is really a healthy lifestyle? Is there a greater risk for forestry workers to get M.S. than say a secretary? A survey of this type would be simple and cheap to do.

Pathology: I am sorry to say it but the only way to get a definitive answer to the question of whether Lyme can still be an active infection post treatment, is to do autopsies and recover and test biopsies done on chronic Lyme patients that die of any other cause (cancer, heart attack etc) and do labor intensive searches for the bacteria using immuno-fluorescent tissue stains and silver stains of selected tissues. If we find it in the brain after treatment then all the arguments for not treating patients who respond to antibiotics becomes moot! Borrelia burgdorferi has been found in so many tissues that it makes sense that any autopsy study that is undertaken should investigate many tissues to determine what tissues are target tissues and are most resilient to successful antibiotic therapy.

Receptor site research : It appears that the Lyme spirochete has an affinity for certain tissues. It seeks out connective tissue and may use N-Acetyl Glucasamine as a food source. Borrelia burgdorferi also attaches to specific cells in animal models of Lyme disease including endothelial cells, B-cells, fibroblasts, peripheral nerves, and specific brain cells. It may be that the bacteria has receptor sites that can be blocked by new and specialized therapies? If so this may be both an effective treatment and a preventative.

To do this we need more and better animal models including mammalian brain models that investigate the pathologic mechanisms of Borrelia.

In Switzerland a Neuropathologist Judith Miklossy showed that when she looked for spirochetes in the brains of Alzheimer patients that she found them in an alarming percentage of Alzheimer's patient's brains. Since this is a bacteria that is invisible in human tissue unless you look for it and stain for it post-mortem, we need to do more dementia based autopsies to determine the role and frequency of spirochetes in debilitating neurological, and neuromuscular diseases. Part of Miklossy's work showed an association of the location of the spirochetes in the patient's brain

with amyloid plaques. What role can this bacteria or other bacterial pathogens play in producing amyloid in mammalian brains? Better animal models of brain cell metabolism and infection are needed to find out.

In summary we are still essentially diagnosing and treating patients in the same manner as we did in the 1980s and the bulk of Lyme disease research seems to be oriented around everything except pathology, and treatment. I believe to make significant strides in patient treatment we need to devote more time and money to pathology, better drug treatments and better drug delivery systems. I also believe privately funded foundations are the best hope of directing and funding these kinds of projects.

Tom Grier

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Abstract #D646 - 1995 Rheumatology Symposia Texas chaired by Alan Steere P.K. Coyle, et al, Multiple Sclerosis vs. Lyme disease a diagnostic dilemma. Forty-seven patients were identified as possible MS patients. Many had brain lesions on their MRIs, consistent with MS 61%. CSF was constant with MS in 46 % of the patients. The final breakdown of the 47 patients was: 21 MS, 15 LD, 7 had findings constant with both LD and MS. Thirteen patients responded to antibiotics but only those who had CSF findings consistent with LD.

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