by Bonnie Gorman RN

The Massachusetts CFIDS/ME & FM Association Fall 2002 *UPDATE*

Dr Sam Donta presented a comprehensive, compassionate, cutting-edge lecture to Massachusetts CFIDS/ME & FM Association members on November 3rd. His topic was "The Interface of Lyme Disease with CFS and FM: Diagnostic and Treatment Issues." Dr. Donta is a nationally recognized expert on Lyme disease. He is the Director of the Lyme Disease Unit at Boston Medical Center and a Professor of Medicine at BU Medical School. He is a bacteriologist and an infectious disease specialist, who views the Chronic Fatigue Syndrome/Chronic Fatigue and Immune Dysfunction Syndrome/Myalgic Encephalopathy (CFS/CFIDS/ME) and fibromyalgia (FM) from that vantage point. He is also a consultant to the National Institutes of Health (NIH), and presented at NIH's scientific meetings on CFS research.

What does Lyme disease have to do with CFS/CFIDS/ME and FM you might be asking? Some people believe that Lyme disease may be one of the causative factors in both CFS/CFIDS/ME and FM. Others believe that some CFS/CFIDS/ME and FM patients are really misdiagnosed chronic Lyme disease patients and vice versa. Some believe that there is no such thing as chronic Lyme disease, instead these patients actually have CFS/CFIDS/ME or FM. We asked Dr. Donta to help sort all this out.

Parallel Symptom Patterns

Dr. Donta presented the symptom lists for chronic Lyme disease, chronic fatigue syndrome (CFS), fibromyalgia (FM), and Gulf War Illness (GWI). He pointed out the similarities between them, and found there were few differences. He has treated hundreds of patients with these illnesses. He found that CFS and GWI have identical symptoms, and FM is only distinguished by a positive tender point exam, that is often positive in CFS and GWI as well. Clinically it is almost impossible to distinguish or differentiate these illnesses.

He has concluded that chronic Lyme disease is remarkably similar to CFS, FM, and GWI. These multi-symptom disorders have similar symptom patterns consisting of fatigue and neurocognitive dysfunction, along with numerous other symptoms that probably relate to altered neurological function. Musculoskeletal symptoms may be more frequent in FM and in some

patients with chronic Lyme than in CFS, but the definition of CFS and GWI also includes muscle aches (myalgias) and joint aches (arthralgias).

Lyme Disease Symptoms

Flu-like illness, fever, malaise, fatigue, headache, muscle aches (myalgia), and joint aches (arthralgia), intermittent swelling and pain of one or a few joints, "bull's-eye" rash, early neurologic manifestations include cognitive disorders, sleep disturbance, pain, paresthesias (including numbness, tingling, crawling and itching sensations), as well as cognitive difficulties and mood changes.

The only symptom difference in Lyme disease is the expanding circular rash with a clearing area and center resembling a "bull's eye." He pointed out that Lyme has multiple types of rashes and half of the rashes are not typical, they may not even include the "bull's eye" rash. They can appear from two days after the bite, then go on for a week or so. Patients who are infected may not develop or see the rash, and may not develop any future symptoms. In studies, only one third of the patients were actually aware of their tick bites.

30-50% of acute Lyme disease patients went on to develop chronic Lyme disease. Additionally, some previously asymptomatic patients may reactivate their infection following various stressors such as trauma, surgery, pregnancy, coexisting illness, antibiotics treatment, or severe psychological stress. The Lyme vaccine can also reactivate their infection. Similar triggers such as trauma, surgery etc. are known to precipitate CFS, FM and GWI as well. This is not a new phenomenon with infectious diseases. We know infectious diseases (i.e. TB) will reactivate after illnesses or surgery—any stressor.

Dr. Donta reported on the effects of gender on host susceptibility in Lyme disease, CFS, FM and other multi-symptom diseases. In all these disorders, women appear to be more affected than men, usually at about 2:1 ratios. He noted that neural cells contain estrogen and progesterone receptors, and that herpes viruses can utilize estrogen receptors to gain access to the reservoir in the cell nucleus. Treatment of chronic Lyme disease also seems to be gender-dependent to some degree, with men generally having more speedy and complete recoveries compared to women. He concluded that gender relationships are known for a number of infectious diseases, so it would not be surprising that such a relationship exists for chronic Lyme disease, CFS, FM and other multi-symptom disorders.

Etiology

Lyme Disease:—A distinct difference between Lyme disease, CFS and FM is that the origin of Lyme is clear. Lyme disease is caused by spirochetal bacteria transmitted by the bite of an infected deer tick. This bacteria is the *Borrelia burgdorferi* bacteria. It was identified in the late 1900s in Europe. The US was late to recognize what Europe had described. Lyme disease was not formally identified by the CDC until 1977 when arthritis was observed in a cluster of children in and around Lyme, CT. Since that time Lyme disease has been identified in many states. The CDC reports that it causes more than 16,000 infections per year in the US. Some researchers feel that the prevalence is higher than that.

CFS and FM—Dr. Donta feels that Lyme disease is an important cause of CFS and FM. In addition to Lyme, there are a number of other possible causes. The evidence is still circumstantial though. Epstein-Barr virus (EBV), the major cause of infectious mononucleosis, continues to be debated as a cause of CFS. It is uncertain whether EBV can cause symptoms other than fatigue, such as myalgias and arthralgias that are not seen during acute or reactivated EBV infection in patients who are being immunosuppressed, but it remains possible that EBV could cause one type of chronic fatigue disorder. There are also other herpes viruses i.e. HHV-6 that are being evaluated as potential culprits.

Dr. Donta reported that recently recognized species of Mycoplasma (*Mycoplasma fermentans, Mycoplasma genitalium*) have been implicated in CFS, FM and GWI. These same bacteria have also been implicated as causative agents of rheumatoid arthritis, based on PCR-DNA evidence in patients with these disorders in which 50 percent are found to have the DNA of the Mycoplasma in circulating white blood cells, compared to 5-10 percent of a normal population. Whether the presence of this DNA represents past exposure or ongoing infection remains to be resolved. No long-term studies have yet been performed in patients with CFS and FM to determine whether the finding of Mycoplasma DNA persists over months or years or whether such patients have any evidence of other infection such as Lyme disease or infection with Chlamydia species.

Central Nervous System Involvement

Dr. Donta reported that in Lyme disease, the nervous system seems to be the primary target for the bacteria causing the disease. Patients with Lyme disease express many neurologic symptoms such as pain, paresthesias including numbness, tingling, crawling and itching sensations, as well as cognitive difficulties and mood changes. Even the joint pains and occasional arthritis appear to be neuropathic in origin, as anti-inflammatory agents such as ibuprofen and other nonsteroidal anti-inflammatory drugs (NSAIDS) have little if any effect on the pain. Experimental evidence from animal models also affirm the localization of *B. burgdorferi* DNA to the nervous system. Dr. Donta postulates that the disease mechanisms could involve inflammatory responses, autoimmune responses or toxin-associated disruption of neural function. Any inflammatory responses appear to be weak, and there is no compelling evidence that Lyme disease is a result of immunopathologic mechanisms.

Commenting on his research, Dr. Donta speculated that if they are correct, and Lyme bacteria is a nerve toxin that interferes with the transmission of the nerve impulse, then that is all you need to impede the normal flow of information. There is a lot of cross-talk in the nervous system. This toxin will decrease that cross-talk causing delayed responses resulting in cognitive problems—the brain fog so commonly described in all these multi-symptom disorders.

Although the disease pathways for other possible causes of CFS and FM have not been defined, Dr. Donta postulates that the central nervous system would appear to be a logical target for other pathogens or other disease processes. These illnesses clearly affect the brain and are bound to cause many neurological manifestations. Any changes in immunologic function would not appear to be sufficient to explain the various symptoms, and are likely to be secondary to other disease processes.

He feels we have been thinking too simplistically about finding whole organisms replicating in chronic diseases. It is highly likely that there is no single cause for these illnesses. It's more likely that there are multiple causes—different organisms causing the same final set of symptoms. Researchers need a better algorithm to study these fatiguing illnesses. We need to be more inclusive, rather than trying to separate the illnesses. Sometimes in medicine, if an illness is too complex to study, research interest dwindles. We have the technology to do the research, but there hasn't been the will and the momentum to get it done.

Clinical Diagnosis

Dr. Donta reiterated that the diagnosis of Lyme disease is primarily based on clinical grounds, just as with CFS and FM. Once other disorders are ruled out, the combination of symptoms over months is sufficient to make a presumptive clinical diagnosis. The diagnosis of Lyme is made easier if a typical rash is present during the early phase of infection. After that, it is difficult to distinguish the flu-like illness that can occur a few weeks later, or can recur over a number of months.

Dr. Donta reported that some patients develop severe headaches and an aseptic (infection free) meningitis, which frequently is diagnosed instead as viral meningitis. If a Bell's palsy occurs (drooping of one side of the face), the possibility of Lyme disease is likely. If an unprovoked arthritis occurs, causing swelling of a single joint, especially the knee, but sometimes more than one joint, then the possibility of Lyme disease should also be given high consideration.

He emphasized that it is the chronic phase of the disease that causes most problems for physicians and patients, because of the lack of objective signs and the presence of so many symptoms that it causes some doctors to attribute psychological reasons for the patients' symptoms. Many patients then receive a diagnosis of CFS or FM, when they may have underlying chronic Lyme disease as the cause of their symptoms.

Diagnostic Tests

Tests for Lyme disease, like tests for other infectious diseases, are often confusing and circumstantial, and their analysis and interpretation has often been flawed. In infectious diseases you do a Western blot test to see if you have a specific reaction. *Western blot* separates out proteins antigens of an organism you are looking for. It tells you if a person has been exposed.
It is not a direct measurement of the organism
. It is a measurement of whether the person has antibodies to it. Antibody tests are useful in the early stages of illness as with other acute infectious illnesses. Once the illness is in a chronic phase, antibody tests are not useful.

Just as viruses change from year to year, we know the Lyme bacteria mutates. There are a number of organisms that can shift their surface protein in a matter of hours and that is how they evade detection and patients test negative. These organisms attach themselves to proteins and conceal themselves—creating a cloaking mechanism that defies detection. This allows them to get where they want to go—*the nervous system*. Once they are inside a cell, the immune system can't see them.

That said, Dr. Donta explained that lab tests have been helpful is some patients with Lyme disease, especially those with arthritis, in whom there are stronger antibody responses than in those with the chronic, multi-symptom form of Lyme. The criteria for the laboratory diagnosis has been patterned after the arthritic form of the disease, and not the chronic form; as a result, there are many physicians who are misinformed about the test's lack of value in chronic Lyme disease. The Lyme Western Blot is helpful when it shows reactions against specific proteins of *B. burgdorferi*
, but can be negative in 25-30 percent of patients who otherwise have chronic Lyme disease.

PCR-DNA tests for Lyme in blood, urine and spinal fluid are rarely positive, most likely because the bacteria and their DNA are not present in those body fluids, but inside nerve cells. Additionally, PCR-DNA studies are very easy to contaminate.

In chronic Lyme disease, the *MRI exam* of the brain is positive in about 10-20 % of patients. It can show some white spots (unidentified bright objects—UBO) in various areas, similar to those seen in multiple sclerosis (MS), a neurologic disease of unknown cause that has some overlapping symptoms with Lyme disease, CFS and FM, such as the numbness and tingling or paresthesias. (There are also positive MRI findings in CFS and FM patients as well.)

Dr. Donta reported that the *brain SPECT scan* shows some changes in blood flow to various parts of the brain, primarily the temporal (cognitive processing) and frontal (mood) lobes in about 75 percent of patients with chronic Lyme disease. Patients with CFS have also been reported to have some brain SPECT scan changes, frequently involving the occipital lobe. No comparative studies have been made among patients with chronic Lyme disease, CFS and FM. The mechanisms underlying these changes remain to be defined, but may be due to a mild vasculitis (inflammation of blood vessels) or to a signaling problem within the nerve network of the brain in those specific areas. It is promising that these changes are reversible in most patients treated with antibiotics that appear to be effective in treating the chronic Lyme disease. These MRI changes are often slow and may take a year to reverse themselves.

These are covert organisms we are dealing with. We need more direct detection methods for blood, spinal fluid and other body fluids. How do you detect organisms in spinal nerve roots or brain? Right now we can't. Nobody is going to biopsy patients. We need an illness registry so we can do direct detection studies, particularly of the brain, after death.

Treatment: Persistence Pays Off

Dr. Donta reported that there are lots of drugs that are active against the Lyme bacteria in the *te st tube*
, but the big question is whether the drug can get to the bacteria? Lyme bacteria lives in the cells of the nervous system, perhaps other cells. Dr. Donta has experimented with various intracellular-type antibiotics. He reviewed his journey through various antibiotics. After listening to his patients he decided that some antibiotics were better than others. He then looked at clarithromycin (Biaxin) and azithromycin (Zithromax) which he found had powerful activity against Lyme bacteria in a test tube.

But the antibiotics, by themselves, did not seem to do any good. He found that you need to change the cellular pH (the degree of acidity or alkalinity), making it more or less acidic, to maximize the effectiveness of the antibiotic. This allows the antibiotic to work better i.e. doxycycline seemed to work better when the pH was higher. Dr. Donta has experimented with

various agents to adjust pH—i.e. amantadine (used to treat flu) and plaquenil (used to treat malaria). He just submitted proposals to NIH to study various agents to determine which is most effective.

Dr. Donta emphasized that the most important aspect of treatment is that it must be *long-term*—12-18 months, sometimes 24-36 months. This length is not unusual in the treatment of infectious diseases i.e. TB. In the first few months of treatment patients can expect an adverse reaction—symptoms will increase and you'll feel worse. You need to be able to hang in through this period, and allow 3-6 months of a treatment trial to determine if it is working. The earlier in the disease process that you start on treatment, the more successful it is. The more chronic the condition the less successful it is, and you'll need to treat over a longer period of time. This treatment resulted in substantial improvement and cures in 80-90% of patients with chronic Lyme disease. There are 10-20% who do not respond— generally those with a strongly positive Lyme test.

Dr. Donta reported that similar results have been found in some patients with CFS and FM of unknown cause, supporting the hypothesis that some patients with CFS and FM have an underlying infection responsive to those antibiotics. Antibiotic trials in CFS and FM have been limited to one month, a duration that is inadequate to properly evaluate the potential of certain antibiotics to have a positive effect on the disease. Additional studies, examining both potential etiologic agents of CFS and FM as well as treatment trials should lead to a better understanding of both the cause and treatment of patients with CFS and FM.

Q&A

Q: If the Lyme lab tests are inadequate and the symptoms are the same as CFS and FM, why not just treat all CFS and FM patients with the Lyme protocol?

A: You want to be conservative with your medicines. I think we have enough info now to tell CFS and FM patients to consider going on a 3-6 month trial of antibiotics and see if you're better. Consider all the other meds you are already taking that just treat symptoms and not the cause of your illness. They all have side-effects that can be hazardous. Is it worth it to you to consider a primary treatment aimed at a cause? There will be resistance from some MDs. They need to be educated. Your primary MD will need to consult an LD specialist re the treatment protocol.

Q: Do patients with Lyme disease also have bowel and bladder problems like interstitial cystitis

(IS) and irritable bowel syndrome (IBS)? How are they affected by treatment?

A: Yes, many patients with Lyme have IS and IBS. He was surprised how much the bowel disorders affected treatment. Tetracycline generally helps the IBS. Plaquenil can sometimes irritate the bowel.

Q: I have received different results for the Western blot Lyme test. Why?

A: Lyme test results are not reproducible from one lab to the next. You will get different findings from different labs. The Western blot is not a great test for Lyme since the responses to Lyme bacteria are already very small responses.

Q: I've been sick for 15 years with CFS and my Lyme test was negative. Is there any value in treating now?

A: If the test was negative but you have the complex of symptoms and there is no other obvious answer, why not give antibiotics a try?

Q: I had the Lyme vaccine then got Lyme symptoms. Why?

A: Lyme vaccine was pulled from the market because it was causing reactions and reactivating a slow onset of Lyme disease.

Q: What are the ocular problems in Lyme?

A: He sees optic neuritis, similar to that seen in atypical MS patients.

Q: Is there any Lyme connection to cutaneous lymphoma?

A: He has looked closely for any cancer/Lyme associations, but has not seen many.

Q: Is there a connection with thyroid problems?

A: Thyroid problems are a very common co-existing condition with Lyme, as they are with CFS.

Q: How do I differentiate itching from allergic reactions?

A: The same sensory nerve fiber pathways that carry pain carry itching, numbness, tingling etc. Rash is common symptom. Rashes could be caused by medications, especially if they are body-wide. Is it an allergic reaction or hypersensitivity reaction? Get a complete blood count (CBC) with differential. Eosinophils will be elevated if allergic reaction. If not, then it's a hypersensitivity reaction. Treatments are similar.

Q: How do we get funding for research to advance these illnesses?

A: He stressed how important it is to combine advocacy and research efforts. Ultimately it will be a political solution. Get active legislatively in DC. The CFS Coordinating Committee is a very good forum. Lyme does not have anything like that. Groups need to work together, not fight with each other. There should be a coalition of all these groups. We also need to show insurance companies the benefits of primary treatment to patients, as well as to insurer's bottom line.