

www.DavidSBell.com

Read past issues of the Lyndonville News

Join the mailing list

*Download Dr. Bell's book Faces of CFS (Free!)
and more!*

Lyndonville News

Volume 3, Number 1; September 2006

Information and Support for the ME/CFS/FM Community
David S. Bell MD, FAAP, Editor

THE ROLE OF INFECTION IN INITIATING ME/CFS

Introduction: It has been over a year and a half since the last Lyndonville News, and I would apologize. Writing for me has always had a mood requirement, and I am very fortunate that I do not support myself by writing as I would be getting quite hungry by now. I do not like to write about ME/CFS if it is just making words. But I do like to write if I feel an enthusiasm about a topic, or there is something exciting happening. As far as the Lyndonville News, I feel like a grizzly bear coming out of a cave in early spring, ready to get to work. We'll see.

I would also apologize to those who have sent e-mails to the web site. I do not seem to be able to respond to them as I once did, and in general, it is better not to write. I want to thank Fireside Design Studio and Carrie's patience during this past dry spell. She does a lot of work and has never charged a penny for it.

I am cautiously considering writing another book. Of course, I am just coming out of winter's lethargy and projects seem much more appealing than when I am mired down in the middle. But it has been over 15 years since The Disease of a Thousand Names and 12 since The Doctor's Guide. Lots of new thinking and new studies published. I am considering naming it a Disease of Two Thousand Names, because the most progress has been in creating new names for the illness.

Anyway, the book would have three parts. Part I would be clinical descriptions, not much different now from fifteen years ago. Part II would be Mechanisms of Disease, and here is the first chapter of this part, dealing with the relationship of infection to the illness, and later on, how the infection sets off

the abnormal vascular and energy production problems that cause the symptoms. By the time I get this finished (if I get it finished) it will be quite different so you will have to buy the book at that time. Remember you are only getting a first draft so don't bug me about the little stuff—spelling, grammar, biochemistry and science.

Chapter II-1: The Role of Infection in Initiating ME/CFS

Part II: Mechanism of Disease in ME/CFS

While the question of what causes ME/CFS is logically the first question on people's mind, it is almost an inappropriate question. It has occupied many years of research on the illness, and has caused enormous confusion, yet now fades to the background because it is becoming apparent that it is almost irrelevant. And the difficulty in finding "a cause" has been one of the prime reasons that people have doubted the reality of this illness. What has become apparent is that there are many "causes", and what is important is not so much the initiating event or infection, but the mechanism of what perpetuates the illness. In other words, it is not the actual onset that matters, but why the symptoms do not resolve after the onset.

The confusion relates to the fact that the initiating factors for ME/CFS are commonplace. Every day patients come into my office with something that can begin the nightmare of ME/CFS. Fortunately, the vast majority of persons resolves their problem and never comes to know of the nightmare that could have been.

I would estimate that there may be more than ten causes of the process we are calling ME/CFS. But for the sake of simplicity, let us restrict ourselves to just a few. The first in this list would be infection. It is the classic presentation of a previously healthy person who develops a commonplace sinus infection or bronchitis and then never gets better. That seventy five percent of all persons with ME/CFS begin this way is a reasonable guess. The remaining will initiate their illness with head injury, other types of neurologic injury, toxic exposures, or some type of stress. For some, the illness comes on gradually without a clear initiating event.

Assessing the cause is much more difficult than it would seem. It is human nature to seek explanations, and sometimes we will come up with an explanation even if it is wrong. It has been my experience that when I ask a patient how the illness began, they will say, "with a fever, on January 18th." On further questioning, however, they had been tired and run down for weeks before, and had recently developed migraine headaches and irritable bowel. Perhaps the episode of fever merely pointed out a process well underway already.

Infection is the first of the causes we will examine here. The infection may be due to a virus (hence the older term "post-viral fatigue"), or it may be due to a parasite, bacteria, rickettsia, or other type of infectious organism. It can be difficult to identify the initiating infection, because by the time you diagnose ME/CFS at six months of illness, it is nearly impossible to find by the standard tests because too much time has elapsed. For a standard infection, for example, it is necessary to measure the antibodies at the beginning, before the body has made an immune response, and again at six weeks

when the immune response is cranking out antibodies. This is never done in ME/CFS because during the initiating infection it is assumed that it will be just another trivial virus that is going to go away by itself. As one of my patients said in disgust, “just another damn virus.” Soon a technology called PCR will be available to look for viral load, to measure the actual virus load of the body, and not the body’s response to it. More on that later.

There is a second issue that looms and has caused an enormous amount of confusion. Does the infection that starts ME/CFS go away after initiating a process, a “hit and run” onset, or is the illness due to a persisting infection? This is the critical question because if it is a “hit and run” illness, the damage caused by the infection cannot be treated with antibiotics or antivirals because it is too late; if ME/CFS is a persistent or ongoing infection, then the antibiotic or antiviral, (if you choose the right one) will do the trick and cure the illness. Figure II-1:1 illustrates this difference.

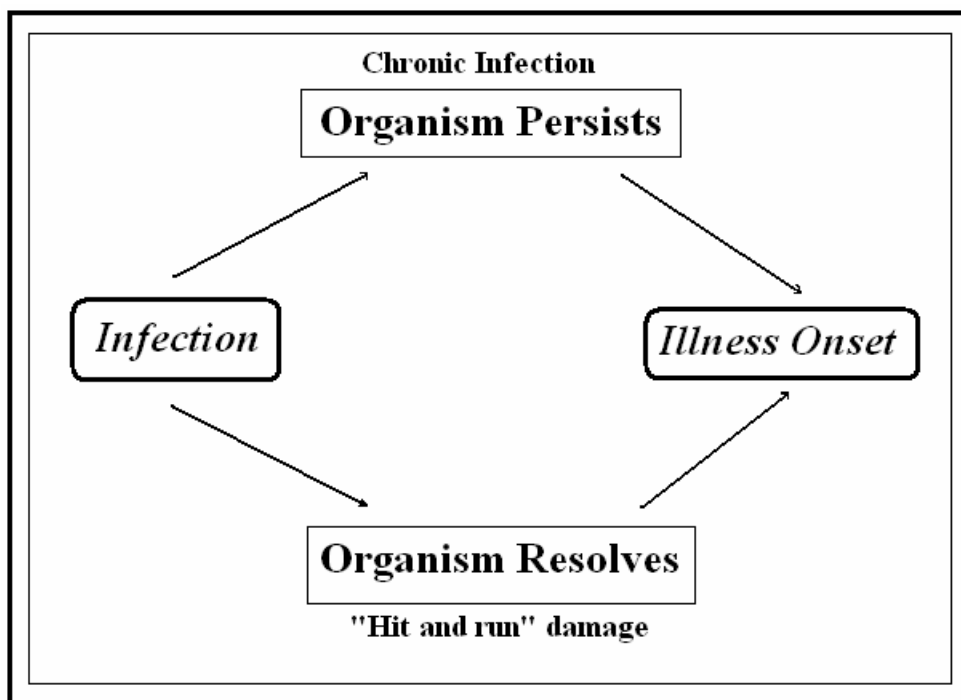


Figure II-1:1

An example of both mechanisms is illustrated by the strep germ. An initial infection causes a strep throat, which may go away by itself, even without antibiotics. Sometimes there is persistent infection, an abscess in the tonsils, and this can be treated and cured by penicillin. Other times, the strep germ resolves normally but has started the process of rheumatic fever, and at a certain point giving the penicillin is not going to cure the problem because it is not simply a persistent infection. In rheumatic fever, the strep germ began an illness that takes on a life of its own.

Let us look at some of the infectious agents that have been implicated in ME/CFS, with specific reference to the question of whether evidence points to either “hit and run” phenomenon or persistent infection.

a) Epstein-Barr virus

Long ago, what we now call ME/CFS was called chronic mononucleosis. Oddly enough, fifty years later it turns out that this name was more accurate than anything we now have. We became confused when we could not identify the virus of mononucleosis (Epstein-Barr virus or EBV) causing an ongoing infection. But clinicians knew that some persons who got mono just did not recover properly. A study in Dubbo, Australia, has helped to clarify this.

In this study, researchers identified patients who came down with mononucleosis and two other infections, and followed them to see what happened. The majority had an unpleasant time for a few weeks and then started to improve with complete recovery within a month or so. However, of the 101 persons with Epstein-Barr virus mononucleosis, six percent developed ME/CFS one year later. The most important predictor of developing the illness was the severity of initiating infection, and neither emotions nor history of psychiatric problems was a factor at all. (Jones, J. Dubbo Infections Outcome Study. Presented at the 2004 AACFS meetings Madison, WI.) For these persons, it can be said that mononucleosis, or rather the Epstein-Barr virus, was the cause of ME/CFS.

The next part of this study is the more important part. The investigators looked at the differences that existed between those people who had a regular course of mononucleosis, and those who developed ME/CFS. While all the answers are far from in, there appears to be a series of events that takes place that causes the persistence of illness in some persons. Understanding this process is critical to interrupting it, and we will be discussing this process in the other chapters.

In past years the attempts to treat ME/CFS have revolved around attempts to kill the virus or organism which has caused the illness. For example, if Epstein-Barr virus were to cause or start ME/CFS, then why not treat the person with antiviral drugs to eradicate the virus? There are several good anti-viral drugs effective against Epstein-Barr virus, but they have not worked in treating ME/CFS. This is because while EBV may have set off the illness, the Epstein-Barr virus has resolved by the time we attempt to treat it. It is like a hiker on the top of a mountain who kicks a rock off the edge and then walks away. The rock tumbles down the hillside, picking up speed and other rocks and starts a landslide. The hiker walks back to his car and hears about the landslide on the evening news.

b) Poliomyelitis

EBV is one infectious agent that has been associated with ME/CFS, but there are many others. Historically the enterovirus family of viruses has been connected to the development of ME/CFS and has been the center of interest in the UK ever since the Royal Free Hospital outbreak in 1950. Poliovirus belongs to this family and is well known to cause post-infectious fatigue, called the post-polio syndrome.

There are two separate difficulties that come from infection with the poliovirus. First is damage to the spinal cord which results in acute paralysis; it is this which the infection is noted for and which caused the widespread panic in the 1950's. Second is the "post-polio syndrome" characterized by exhaustion, progressive muscle weakness, pain, and other symptoms. It is likely that the post polio syndrome is due to damage to the midbrain that does not become fully apparent for some time. However, it appears that the poliovirus itself is cleared by the immune system whether or not damage is done. The later problems are unlikely to be due to a persistent infection.

Other enteroviruses, and there are many, have been implicated in ME/CFS for over twenty years. During the period that this was being studied most intensely, an understanding of the immune response or cascade initiated by the infection was in its infancy, and emphasis was placed on looking for remnants of the virus in muscle tissue of patients with ME/CFS. Interestingly, there is evidence of increased presence or persistence of enterovirus in muscle tissue.

c) Parvovirus

Parvovirus is an exceptionally interesting candidate to cause both ME/CFS and FM, and the evidence is in conflict as to whether this “cause” is from the initiation of a cytokine cascade or from persistent infection. This is an important candidate to study in that parvovirus B19 infection may cause no symptoms at all, a minor infection, or prolonged complications, including ME/CFS, fibromyalgia, anemia, arthritis, heart muscle infection, and other problems. How this virus can do this is critical to know. Jonathon Kerr and co-workers have noted that 10 to 15% of parvovirus B19 patients developed ME/CFS, and up to 60% developed fibromyalgia. On standard testing, these patients appeared as if they had cleared the initiating infection effectively despite having persistent symptoms. Importantly, one patient with ME/CFS developing from parvovirus B19 infection had no antibodies at all against it one year after developing ME/CFS. This means that it is unreliable to look for parvovirus once the ME/CFS has developed. However, persistent fatigue was associated with the presence of gamma interferon and tumor necrosis factor alpha. This would imply that symptom persistence would be related to the immune activation and the presence of cytokines.

However they also did a couple of other things. They looked at the pro-inflammatory cytokines, and attempted to see if there was an abnormality in the genetic makeup of an individual who had persistence of symptoms after infection. They found that one gene in particular (Ku80 gene) was abnormal. This gene happens to be a B19 co-receptor. Therefore, this would give a potential mechanism for virus persistence and ongoing infection. In addition, they published three cases of persistent chronic fatigue treated with intravenous gamma globulin which resolved persistent B19 in the blood, the cytokine dysregulation, as well as the symptoms of ME/CFS.

There are several take home messages from their studies. First, this virus may “cause” both ME/CFS and fibromyalgia, strengthening the link between these two conditions. Secondly, if you can find parvovirus as an initiating infection and if you find persistence of this virus in the blood stream, there may be an effective treatment available, but this requires aggressive clinical management starting from the first week of severe fatigue. Thirdly, both immune system mediators and persistent infection may play a role in ME/CFS. And fourthly, if no investigations had been carried out during the first two years of illness, it may be impossible to detect parvovirus B19 even if it had initiated the illness.

d) Q fever

Q fever happens to be one of my personal favorites in the study of infections which initiate CFS for strictly personal reasons. I had the good fortune to visit Professor Barry Marmion in 1987 in Australia and see a few of his “Post Q fever” patients who looked exactly like my patients in Lyndonville. My patients had been exposed to unpasteurized milk but did not have Q fever. Dr Marmion’s patients had classical Q fever and had been treated properly right from the beginning.

Q fever is an infection caused by *Coxiella burnetii* which is not a virus but a rickettsia, and is an occupational hazard for abattoir workers in Australia. The infection is carried in sheep and after processing lamb for market, some persons get Q fever. It has been well recognized and well treated in Australia for years.

At first, when cases did not seem to resolve normally despite appropriate antibiotic treatment, the government felt they were “faking it” in order to collect unemployment. (Sound familiar?) However, two managers developed the “post Q fever debility syndrome” and they were not eligible for unemployment benefits. The government then became interested and began a series of studies with Dr. Marmion. It is now clear that more than 5% of persons with Q fever who were treated well at the onset of their infection go on to develop ME/CFS.

e) Lyme disease

Lyme disease has its controversial side, and it is not surprising that it fits in this discussion of ME/CFS. As an acute illness, Lyme is known for its neurologic and rheumatologic symptoms, and a percentage of persons who get Lyme disease do not recover. It is caused by a spirochete, *Borrelia burgdorferi*, and, unlike viruses, it is an organism that can be cured with antibiotics. The crucial question that plagues the subject of chronic Lyme disease is whether the illness is due to persistence of the organism, or is it a “hit and run” illness. If it is entirely due to persisting infection, it should be treatable with high dose antibiotics.

At present there are anecdotal reports that long term antibiotics have been successful in the treatment of ME/CFS, but it should be remembered that a substantial number of persons with the illness get better by themselves in the first few years of the illness. That means that if someone is quite ill at two years of illness and begins either antibiotics or vitamins or any other treatment, they have nearly an 80% chance of getting better over the next two years regardless of the treatment. However if someone is still ill at five years, it is unlikely that they will improve spontaneously. We will discuss this in greater length in the prognosis section.

Personally, I have not had success with long term antibiotics in my patients.

f) Others

There are many other infections implicated in starting ME/CFS, and each of them has its own supporters. In the past, studies have shown that each of them is not “the cause”, meaning that there is not a large enough block of one initiating infection to make a statistical dent if looked at a whole population.

In Lyndonville, for instance, in 1985 there was an outbreak, and I was certain that it was one specific virus or virus-like organism that set it off. I feel this way because the appearance of the first few weeks was nearly the same from person to person. This is different from the patients I see now from different areas in the country who have had their ME/CFS initiated in a variety of different ways.

Other legitimate contenders for ME/CFS cause include *Brucella*, Ross River virus, Hepatitis C, mycoplasma, Inoue-Melnick virus, and Borna virus. I have one patient whose illness began after

documented Histoplasmosis and another after psittacosis. There is likely a huge range of infectious agents that have the potential to cause ME/CFS. We need to establish what these particular infections have in common which can set off ME/CFS in susceptible persons.

Conclusions

Infection is likely to be the most common way that ME/CFS begins. It is likely that for people who are to get the illness, they have an infection like other members of their family. However their immune system does not resolve the infection properly and continues to produce chemicals called cytokines which cause the person to feel ill even though the initiating infection may go away. Alternatively, there may be persistence of the infection in the patient, although at a level that is difficult to detect. In Chapter II-4 we will examine this link between infection and cytokines.

My conclusions on this subject are that both mechanisms occur simultaneously: both contribute to the persistence of symptoms, sometimes for the rest of a person's life. If this is true, the implications of this are straightforward. First, it is necessary to know which infection began the illness, and this means early recognition of ME/CFS. Testing for specific initiating infections should occur if someone has a particularly severe first three weeks of illness, or is still ill at one month after an infection. It is not appropriate to waste this time by saying that a person not recovering at three weeks may have had a childhood trauma that has turned him or her into a whiner.

Secondly, treatment should be aggressive and directed toward the initiating infection early in the course of the illness, perhaps beginning by three weeks into the illness. And thirdly, medications which can disrupt the cascade of cytokines should be sought, but this must be done carefully because of potential immunologic complications.

As we will discuss in the next chapter, infection is not the only cause of ME/CFS. But I suspect that there is a common mechanism past the immune dysregulation that leads to the persistence of exhaustion and pain that is similar to the symptoms initiated by an infection. What is frustrating for any experienced clinician is this: we now know, through experience, that patients with debilitating fatigue and exhaustion because of a possible "virus" that is not really mono is not going to get better. But it is still accepted medical practice to say that there is really no problem, everything is fine, and maybe we should get you to a psychiatrist if things don't shape up over the next three weeks. The role of infection initiating what we are now calling ME/CFS is becoming very clear scientifically. I can only hope that this information will be communicated to medical providers in the future.

References

Cairns V, Godwin J. Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. *Int J Epidemiol.*2005;34:1340-1345.

Chia JK. The role of enterovirus in chronic fatigue syndrome. *J Clin Pathol.* 2005;58:1126-1132.

Kerr J, Cunniffe V, Kelleher P, Bernstein R, Bruce I. Successful intravenous immunoglobulin therapy in 3 cases of parvovirus B19-associated chronic fatigue syndrome. *Clin Inf Dis* 2003;36:e100-e106

Kerr JR, Cunniffe VS, Kelleher P, Coats AJ, Matthey DL. Circulating cytokines and chemokines in acute symptomatic parvovirus B19 infection: negative association between levels of pro-inflammatory cytokines and development of B-19 associated arthritis. *J Med Virol* 2004; 74 (1):147-155.

Kerr JR. Pathogenesis of parvovirus B19 infection: host gene variability, and possible means and effects of virus persistence. *J Vet Med B Infect Dis Vet Public Health*. 2005; 52(7-8):335-339.

Kerr JR, Barah F, Matthey DL, Laing I, Hopkins SJ, Hutchinson IV, Tyrrell DAJ. Circulating tumor necrosis factor- α and interferon- γ are detectable during acute and convalescent parvovirus B19 infection and are associated with prolonged and chronic fatigue.

White P, Thomas J, Sullivan R, Buchwald D. The nosology of sub-acute and chronic fatigue syndromes that follow infectious mononucleosis. *Psychol. Med.* 2004;34:499-507.

White P, Thomas J, Amess J, al. Incidence risk and prognosis of acute and chronic fatigue syndromes and psychiatric disorders after glandular fever. *Br. J. Psychiatry* 1998;173:475-481

Question and Answer

I have several questions that have plagued me for years; I'm hoping that you can provide the answer.

1. I have always been amazed at the similarities between CFS and BSE and Scrapie. I am curious to know if you have ever found a person with CFS among the vegan/vegetarian population?

I have never systematically looked for lifetime vegans with ME/CFS. Your question is really about the possibility that the illness may be a prion disease. To my knowledge no one has looked at this in any detail. I would be interested to hear from any reader who has any information about this. The known prion diseases are neurologic illnesses that are fatal. It may be that there are variations not yet understood that are not fatal.

2. Have you ever found CFS to exist in people or their children who are monogamous and have had only one sexual partner?

The question is whether ME/CFS can be transmitted sexually. The question cannot be answered because we do not know the specific agent that has initiated ME/CFS in a specific individual. It is likely that some known sexually transmitted illnesses can initiate ME/CFS. (Remember, the illness is more often a post-infectious phenomenon rather than due to a specific infection) However ME/CFS clearly may occur in persons who have never had sexual exposure. One "outbreak" many years ago occurred in a convent.

To Subscribe: If you wish to subscribe to the Lyndonville News, go to www.DavidSBell.com/DSBJoin.htm and follow the instructions. The e-mail subscription is free, while the hard copy sent by mail costs \$20 per year. To unsubscribe, send an email to Admin@DavidSBell.com or click the unsubscribe link at the bottom of this email.

Disclaimer: Any medical advice that is presented in the Lyndonville News is generic and for general informational purposes only. ME/CFS/FM is an extremely complex illness and specific advice may not be appropriate for an individual with this illness. Therefore, should you be interested or wish to pursue any of the ideas presented here, please discuss them with your personal physician.