

Lyndonville News

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Information and Support for the ME/CFS/FM Community
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Introduction

Welcome to the Lyndonville News. In the issue today I would like to present a chapter in a new book about cellular hypoxia in ME/CFS about the immune cascade. I have been hoping to finish this book about these mechanisms and perhaps soon it will be ready. I do not know what to call it. Cellular hypoxia in ME/CFS? A little awkward. Neuro-Immune Fatigue? What about “The mechanisms of mitochondrial encephalopathy and cellular hypoxia in neuro-immune fatigue.” A little wordy and no one will know what the hell the book is about. Feel free to let me have your opinion at lynnews@davidsbell.com.

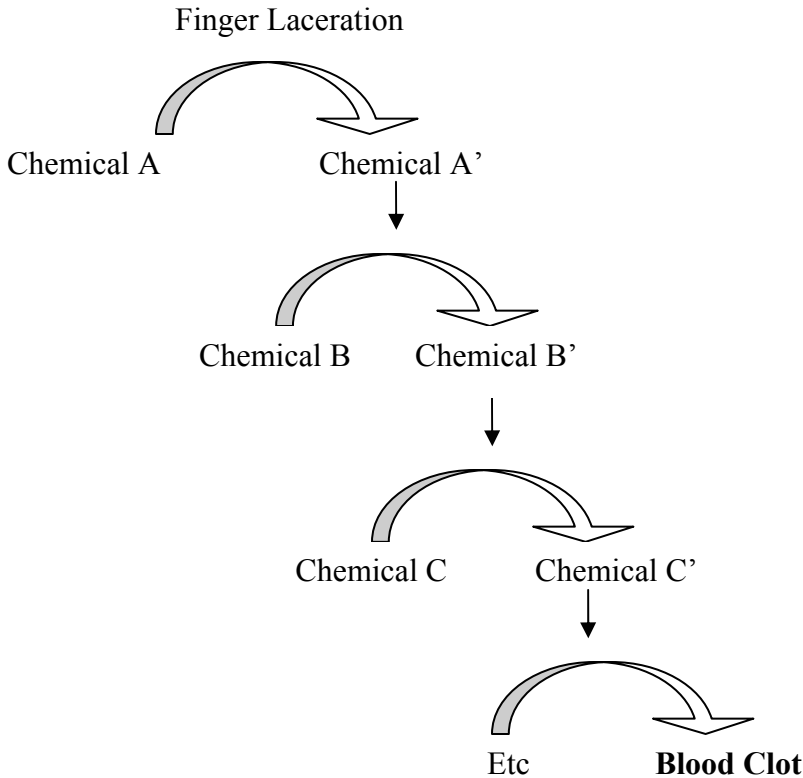
At any rate, I am working toward retirement and plan to cut down soon. I would like to write like mad and get all this out of my system. And spend more time with my feet up on the back porch of the farm. I would like to do more newsletters. I would like to give more talks about the mechanisms of the illness. Hopes and dreams. I do hope the chapter makes some sense.

New Book

*ME / CFS,
Neuro-immune Fatigue
And
Cellular Hypoxia*

Chapter 6: The Immune Cytokine Cascade in ME/CFS

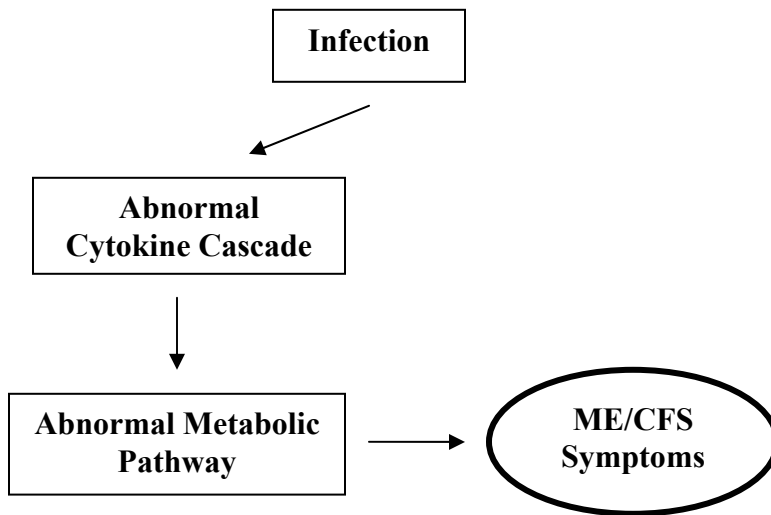
Many, many years ago I was in medical school and one of the hardest pieces to study was the blood clotting cascade in hematology.



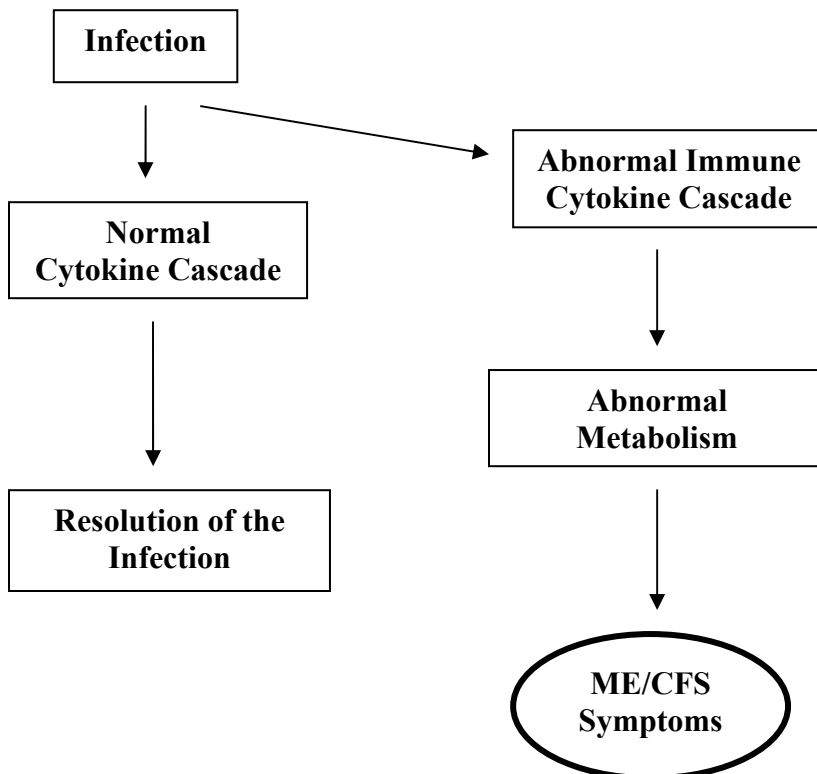
The cascade looked like a series of water fountains. The one at the very top (Chemical A becomes A') causes a change in chemical B to make it B'; that causes chemical C to become C', and so on for twenty-five or thirty steps. Each step had its own rules and enzymes and was influenced by different factors. It was impossible to memorize, particularly so because not all the steps were known at that time.

Unfortunately for me, the body seems to love cascades. Moreover, we do not understand the specific waterfall steps of the immune system cascade perfectly. Add to that, each step can go in different directions – the immune system talks to the nervous system, and the nervous system regulates the endocrine system, and so on. But the cascade creates a redundancy or safety net which makes it less disastrous if something goes wrong.

And of course, with every step something can go wrong. In the blood clotting cascade, if one enzyme or protein is missing the result is hemophilia A. With another error it is delta granule storage disease; another is Von Willebrand's disease. They may look similar from the symptoms – a cut does not stop bleeding – but the mechanism that has gone wrong in the cascade is different in each illness. In ME/CFS there is a problem, or there are problems, with the immune activation cascade. The end result of this problem or these problems is the symptom complex of ME/CFS.



In the first chapter of this section we discussed the evidence pointing to certain infections causing ME/CFS. The next question is how do these infections cause the prolonged symptoms, and for some, the flu that never ends. The answer to this question involves the immune mechanism set off by the infection, and specifically the abnormal immune mechanism that allows for persistence of symptoms even after the obvious infection has gone away.



In the second chapter we discussed the non-infectious causes of ME/CFS, and that there is a variation in these pathways from the cascade initiated by a standard infection. Yet many of the same cytokines are involved, and ultimately that all these cascades (which result in ME/CFS) come to a common point.

The confusion regarding ME/CFS and the one thousand or so other illnesses loosely contained under this umbrella term is that both sides are correct. ME/CFS is caused by an infection, and is caused by neurological insults other than direct or obvious infection. Perhaps in the future we will be able to classify all one thousand subtypes more accurately, but for now ME/CFS will have to do. It appears that this common point where the cascades merge is in the area of cellular metabolism, more specifically the inability of converting oxygen into energy, or cellular hypoxia. In this chapter we will be looking primarily at the immune mechanism (or abnormal immune mechanism) following an infectious insult; we will be ignoring the ME/CFS caused by toxic exposure, brain injury, heavy metal poisoning, cigatura poisoning, and the like as it is likely that the cascade will be different.

In the early days of ME/CFS research in the US, emphasis rested upon looking at the Epstein-Barr virus as the cause to the immune activation that seemed to be the hallmark of the illness. The name Chronic Fatigue Immune Dysfunction Syndrome (CFIDS) dates from this time and remains accurate as a name for some types of this illness. However, most patients assumed that this meant that patients with ME/CFS had an “under-active” immune illness response, an immune deficiency. The dominant aspect is just the opposite, an over-active immune state. ME/CFS is a condition where the immune system is spinning its tires in the sand, getting really tired and going nowhere.

There are some immune deficiencies in ME/CFS, which some scientist/clinicians like Dr. Nancy Klimas and Dr. Roberto Petarca have been studying for years. The natural killer cells are off both in number and function, and some cellular immune responses are delayed. The arguments raging in the literature about the usefulness of these studies relate to which particular subgroups are being studied. The immune deficiencies may be the critical issue if they turn out to cause persistent infection and the resulting immune over-reaction. For now, let us turn our attention to the cytokine cascade activated by the initiating infection.

Definitions

For the rookies among the readers, there are a few basic definitions that must be mastered before proceeding. Cytokines are chemicals made by the cell which act to carry out essential functions. While there are many subgroups (perhaps thousands) of these messaging chemicals, I will oversimplify by referring to them collectively as cytokines. The ones I will be discussing are related primarily to immune function and communication between the brain and the immune systems. The group of cytokines that seems to play the biggest role are the “pro-inflammatory” cytokines.

One cytokine that we will be referring to extensively in the next chapters is interferon, and there are three major types established so far: α , β , and γ (alpha, beta, and gamma). This is one of the first cytokines discovered, and as I recall from the history, it was named because when someone had a viral infection, a chemical was produced by the immune system that “interfered” and prevented another virus from causing an infection at the same time. The good news is that you only get one virus at a time; the bad news is that interferon makes you feel really sick. It has been studied extensively and has been used to treat illnesses such as cancer, hepatitis and multiple sclerosis.

Another cytokine is TNF (tumor necrosis factor), and it also comes in various Greek subgroups. It is used to treat rheumatoid arthritis, psoriasis, and other illnesses. The interleukins are cytokines that act as communicators in an unbelievably complex cellular system. There are thousands of tasks to do within the cell and every task requires a specific mechanism to carry it out.

Getting the Flu

With an infection, the body jumps into action to defend itself, but usually not for several days. For example, if you are in the checkout lane at the grocery store and the person next to you coughs on you, you breathe in the flu virus. The virus particle lodges in your airway and begins to multiply; yet you feel just fine. In fact you feel fine for three days or so (the incubation period) even though the virus is growing like mad. Then, Saturday afternoon, at exactly three PM, you come down with the flu: fever, headache, aches and pains, exhaustion, sore throat, nausea... What actually happened on Saturday was that your body recognized the attack by the flu virus and began making cytokines to begin the counter-attack. And the cytokines make you feel sick.

You stay in bed for a few days while the battle rages. The battle is carried out on several fronts and after the immune system makes antibodies the infection is brought under control. When that happens the production of cytokines slows down, stops, and you feel better. A few more days and you are back to normal, if everything goes right.

The production of these cytokines, (specifically interferon, IL-1, IL-6, and TNF) is known to cause the symptoms of illness, often called “acute sickness behavior.” This term does not imply that there is anything artificial or psychological about the behavior, it is as real as limping behavior in a person with a broken leg. These effects of cytokines were discovered during trials where the cytokines were given to healthy volunteers who then developed fever and other symptoms.

In ME/CFS something goes wrong. The infection may be an ordinary “garden variety” virus, an enterovirus, or the Epstein-Barr virus of mononucleosis. But in a person with the genetic vulnerability the process does not shut down and the flu-like sensation persists for months, years, sometimes for the rest of his or her life. It is this abnormal mechanism that is the center of attention in ME/CFS.

The symptoms caused by cytokines differ from “end organ” symptoms. For example, weakness is a common symptom in ME/CFS, but muscle testing with electrodes does not indicate muscle fiber disease. Characteristically, the sensation of profound weakness is experienced by those persons given cytokine injections despite normal muscles. Confusion and problems with memory and attention are symptoms caused by cytokines and in experimental subjects, when the cytokine wears off these cognitive symptoms resolve without damage to brain cells (presumably). It is precisely because these symptoms are not caused by diseases of muscle or joint that medical providers have ignored them. If you go to the doctor with a cough caused by the flu you are patted on the head and ignored, unless you cough up gobs of lung tissue. Then it is taken a little more seriously.

Examples of the Cytokine Cascade or Cytokine Storm

Among the many frustrations of seeing the reality and the importance of ME/CFS questioned over the past twenty years is that there are well known examples of cytokines causing serious illness.

One interesting study looked at the relationship between pro-inflammatory cytokines and the degree of fatigue in patients with multiple sclerosis (MS). Those MS patients without significant fatigue had much lower levels of pro-inflammatory cytokines. This study is of value as there is known to be a substantial variation in the degree in fatigue in patients with MS (Heesen 2006)

A published example of a cytokine storm occurred in healthy volunteers given an experimental drug (Sunthralingam, 2006). The drug was an antibody whose function was to stimulate T cells, which, it turns out, it did too well. The subjects were healthy volunteers and the drug caused a cytokine cascade involving many different cytokines, including tumor necrosis factor alpha, gamma interferon and several interleukins. The healthy volunteers all became very ill and had to be admitted to an intensive care unit. The importance of this disastrous trial was to show the progression of a cytokine storm precipitated by a specific monoclonal antibody in previously healthy persons. In medical school I used to volunteer for these kinds of trials because I was broke.

There are many different cytokine cascades. Variations in ME/CFS may relate to variations in individual cascades, which are just now beginning to be studied. But the essential point has been established. Cytokine cascades cause symptoms and illness. Sometimes the illnesses caused are very severe, even fatal. It remains to be seen what will be the exact profile or profiles that comprise what we have been up to now calling ME/CFS.

Cytokine Production in ME/CFS

Over the past ten years there has been a concerted attempt to measure the cytokine response in ME/CFS. Unfortunately it is not a simple process. The blood stream, where the medical tests get

done, is far away from the cellular mechanisms. It is generally agreed that an abnormal response exists, with the normal balance between pro-inflammatory cytokines and the cellular responses being disrupted. In the studies mentioned earlier by Dr. Kerr and associates, TNF- α and IFN- γ are present for long periods of time when parvovirus initiates ME/CFS. They were even able to demonstrate an abnormal TNF- α gene which could affect the development of persistent fatigue.

In one interesting study, the cytokine IL-6 was injected into patients and healthy controls as it is known to cause a pattern of symptoms very similar to ME/CFS. As expected the cytokine caused an increase in fatigue, headache, muscle and joint pain. Other studies have looked at cytokines in the spinal fluid and during stress responses.

One question that has not been resolved is whether the cytokine cascade of ME/CFS is due to ongoing infection, or if it is abnormal and there is no measurable infection present. It is a chicken and the egg question, and at present, there is no clear answer. It is likely that when the research answers are in, it will be both. There will be an element of ongoing infection due to an abnormal cytokine cascade.

2'-5' A Synthetase and Rnase L

This is the next step in the process that was started by Suhadolnik and his group around 1995 and continues actively at the present time. An enzyme called 2'-5' A Synthetase is normally stimulated by the cytokine interferon to make Rnase L, an enzyme that can "chew up" viral RNA. Therefore it is part of the normal anti-viral defense system. In ME/CFS there is a glitch present with an abnormal protein present (the 37kDa fragment) in those most severely affected by the illness.

There are three ways that an abnormality in this system may cause problems in ME/CFS. First it allows for the continuous stimulation and production of interferon which, as we will see, could be a major player in the symptoms of the illness. Secondly, it may permit the persistence of the initiating infection. And thirdly, an excess of Rnase L can cause other difficulties down the road, because its actions are not limited to viral RNA. It may be chewing up good RNA as well. In a follow-up study it was noted that 72% of patients had an excess of the abnormal protein in ME/CFS while only 1% of the normal population had it.

Hepatitis C Study

In 2004 a remarkable study was presented at the AACFS scientific meetings that began to draw together this information. So far we have seen that the immune system is overactive or "upregulated" in ME/CFS, and we know that people feel lousy, but are the two facts connected? Does the presence of these cytokines actually cause the persistence of symptoms?

Interferon is a cytokine used as an anti-viral treatment in certain illnesses such as Hepatitis C. In a study conducted by Dr. Charles Raison, patients with known Hepatitis C were given interferon. Prior to treatment 22% of the patients had significant chronic fatigue and 3% would fit criteria for ME/CFS. After treatment with interferon 70% of the subjects had chronic fatigue and 30% met criteria. What this means is that administration of the cytokine interferon transformed some persons with a known persistent virus (Hepatitis C) but without chronic fatigue into having ME/CFS along with their hepatitis C. The importance of this study should not be overlooked. We finally have a model for the progression of the illness that can be studied, and, with any good luck, treatment interventions can be tested.

Autoimmunity

Many persons with ME/CFS have some autoimmunity. It has never been clear whether this autoimmunity is another spin off (or epiphenomenon) of the abnormal over-active immune response, or whether it is important to the generation of symptoms. Up to 25% of ME/CFS patients have an abnormal ANA, a test that can suggest the disease lupus erythematosus. The more you look for autoantibodies, the more of them can be found, but it is unlikely that these autoantibodies are doing much harm.

Because the immune system is “revved-up”, it is looking for something to attack. When this happens it can sometimes attack normal tissue, autoimmunity. This is similar to allergies where the immune response is directed toward otherwise harmless pollen or cat dander.

In true autoimmune disease demonstrable tissue damage can be found, as in rheumatoid arthritis. An interesting concept is the possibility that multiple sclerosis is ME/CFS with overlying brain tissue autoimmunity due to an injury of the blood-brain barrier. To a carpenter everything looks like a nail.

Finally, a word about medications that increase serotonin, commonly known as “antidepressants.” It is known that blockade of at least one serotonin receptor will reduce several cytokines including tumor necrosis factor, and some of the interleukins. Reduction in pain for some persons with ME/CFS may be a side effect of these medications, and not due to the “antidepressant” effects.

In a standard infection like the flu, we can see that the viral infection and the stimulated cytokines cause symptoms, but we never paid any attention because in a few days the cytokine cascade shuts down and the symptoms go away. Who cares why the cytokines cause exhaustion, headache, muscle and joint pain? But with ME/CFS the process does not stop, so the next step becomes critical: how does this cytokine cascade cause symptoms? If we can understand the answer to this question we will be able to understand how to intervene and stop the symptoms.

Conclusions

There are several conclusions from the studies concerning the immune response in ME/CFS.

- 1) Persons with ME/CFS have persistent immune activation as if there were a persistent infection going on. More technically, there is an abnormal shift of the immune response to Th2 instead of the normal balance between Th1 and Th2.
- 2) There is a persistence of cytokine secretion that is likely responsible for the persistence of ME/CFS symptoms.
- 3) The symptoms of ME/CFS can be temporarily reproduced by injections of cytokines such as interferon and interleukins.
- 4) ME/CFS can be caused by treating a patient with Hepatitis C with interferon.

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Question and Answer

Question: *It was Volume 2, Number 3: July 2005, The Presence of Cerebral Atrophy in CFS, Cognitive Symptoms of CFS, Abnormal Cerebral Perfusion in CFS.*

I have CFS/FMS/MPS. I am very sick, with no good medical care... But what is really hurting tonight is that article. My tests are showing diffuse brain shrinkage and I have gotten sicker and sicker the past 3 years. I first got FMS in 1994. Anyway that article has me feeling hopeless, because my brain isn't working anymore and I'm getting worse and worse and have no \$ to get good help. I feel really hopeless after reading that article. I am alone, family not close - alone and scared. Is there any hope?

Attempted Answer: The periods of despair that persons with this illness experience are beyond description. I apologize for the article of cerebral atrophy and progressive cognitive difficulties, but unfortunately they are true findings for some with the illness. I apologize for rubbing salt into the wounds. When will the medical providers begin to approach this illness with compassion? I

don't know. Is there any hope? Absolutely yes. And it is not a false hope. I remain convinced that the problems with this illness are reversible, and someday we will find them.

Question: Dear Dr. Bell, This is the first time I've ever heard about the origins of CFIDS. My question, to me, is simple. How does a debilitating medical condition appear from nowhere? I consider myself a reasonable person. I am 59 years young and have been suffering from Fibromyalgia for the last 10 years...diagnosed in the last year. If something is that time specific and geographic specific then logically it must be causal.

Answer: Good question and I have no idea of the answer. It seems to strike out of nowhere. I have a number of professional athletes as patients and they were in the peak of health when they got sick. But where does a strep throat come from? Before we understood about germs we considered "evil humors" as the cause. Someday we will understand exactly the genetic predispositions, the triggering factors and the reasons the illness is sustained. Now we are stuck with the "evil humors" equivalent.

Question: Hi Dr. Bell, If the new study at Stanford confirms the first one, will you be ready to prescribe it? This seems to be the best news on ME/CFS I've ever heard. Do you agree?

Answer: A very exciting development, and the group at Stanford is working as hard and as fast as they can. Until we get some answers from their next round of studies we have to sit and wait. But I agree it is the best news I have heard in many years.

Thanks for the questions.

Clinical Notes – Frustration

The other day I saw a patient in the office who was in desperate circumstances because of ME/CFS. She was alone as her husband decided there was more fun elsewhere. The social security appeal has been pending for a couple of years after the initial denial. A neighbor will buy a few groceries every once in a while. The simple activities of daily living are not simple at all: a shower is a difficult task, requiring a chair. She has no primary care.

Meanwhile in the office I get notes from specialists saying that some counseling might be of value, and that she should start an exercise program with daily walking. A consultant recently said to me, "After all, exercise is the only known cure for chronic fatigue syndrome." Persons with ME/CFS are known to have abnormal MRI scans of the brain, and because of the sometimes severe cognitive symptoms an MRI is an important test. But to get an MRI, the medical provider must go through the pre-authorization process: discussion with a low level employee to justify the test. The employee probably gets an incentive to deny the tests. We live in an era of health care rationing by nuisance. Because the hurdles are such a nuisance for the

provider they say “to hell with it.” As for the patient with ME/CFS, the insurance companies say, “To hell with them.” If they only knew...

But before we get so depressed we all go and jump off a bridge, there is a bright side. Sometimes the fight against all odds makes a person stronger. It can do something to the soul, whatever that is.

Fifteen years ago I had a patient just like the one mentioned above. She was sick and scared, and alone, and depressed. But over ten years she became a different person. She decided that life was better without her worthless husband. She lived on peanut butter for a couple of years but eventually got social security so that her most basic needs were met – she had a roof over her head and food on the table. She learned to accept the limitations of her illness, and, most importantly, that the illness was not her fault. She learned to manage her time so that within each day she had one to two hours of activity where she could get something done. And she became grateful for those two hours. She lived patience for the remainder of the day. She even learned meditation and yoga to clear her cluttered mind. Anger and resentment melted away. She recently said to me the only people who understand the story of Job in the Bible are those persons who have lived it.

It has been fifteen years and I would not wish her illness on anyone, not even the medical skeptics who ridicule persons with this illness. But, despite the odds, this person has become happy in a way that I have not seen happen to my able bodied patients. There are truths hidden in the religious teachings of the world, but she is one of the few who has come to learn them.

Lyndonville Research Group Report

Recently we had the good fortune to send out samples to researchers for some different studies. One group of samples went to study genomics in the lab of Dr. Jonathon Kerr in London. I am very excited that his work, and that of Drs. Gow, Vernon, and others will eventually uncover the genes that predispose to the illness, become turned on or turned off because of the illness, and help unravel the mechanisms. Brave new world.

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