

*by Ken Casanova*

June 27, 1999

*On June 27, 1999, Dr. Nancy Klimas, an internationally respected Chronic Fatigue Syndrome/Chronic Fatigue and Immune Dysfunction Syndrome/Myalgic Encephalopathy (CFS/CFIDS/ME) researcher and clinician, and a member of the federal CFS/CFIDS/ME Coordinating Committee, presented a thorough review of the latest scientific information on CFS research and treatment. At the end of her lecture the Massachusetts CFIDS/ME & FM Association presented Dr. Klimas with a substantial donation for her work. This donation would not have been possible without the support of our members and contributors.*

*Dr. Klimas emphasized that CFIDS/ME patients have good reason to be hopeful since CFS/CFIDS/ME research has advanced in these last few years as a result of more research funding. Dr. Klimas stressed that the political and advocacy work of patient organizations are a key to obtaining future research funds. Political pressure pushes the federal government to provide the CFS/CFIDS/ME research funds critical to future progress. (Since this lecture, Dr. Klimas has received an NIH CFIDS Research Center grant.)*

### **CFIDS/ME and Overlapping Illnesses**

Dr. Klimas outlined the progress that has been made in properly classifying CFIDS/ME patients under the very broad 1994 case definition. Researchers have found that there are a variety of illness subgroups under the definition's large umbrella that probably include many patients who do not have CFIDS/ME. Dr. Klimas said that the two symptom criteria that are most characteristic of CFIDS/ME are post-exertional malaise and unrefreshed sleep. Thus she questions whether a person really has CFIDS/ME in the absence of these symptoms.

Dr. Klimas next compared CFIDS/ME and fibromyalgia (FM). While many CFIDS/ME patients have FM and many FM patients have CFIDS/ME, there are a "vast majority" of FM patients who do not have CFIDS/ME. Therefore, while *CFIDS/ME and FM are somewhat overlapping illnesses, they are not the same illness.*

### **CFIDS/ME Disease Process**

Dr. Klimas next turned to an in-depth discussion of the pathophysiology of the CFIDS/ME illness process. First, she presented a general model of the stages of the disease process.

The model indicates that CFIDS/ME is triggered, in a genetically susceptible person, by an infection or some other event. Next, in response to the trigger, the immune, endocrine, and neuroendocrine systems are mobilized. However, these systems remain activated or in a state of imbalance. According to this theory, CFIDS/ME is not a disease involving an ongoing infection or continuous triggering process. Instead, CFIDS/ME is the body's prolonged response to the original triggering events. This prolonged neuroimmune and endocrine activation then sets up the cascade of physiological events to follow.

### **Possible Genetic Predisposition**

As of 1999, there has been only one study (Keller *et al.*) that assessed genetic factors in CFIDS/ME. The results showed that CFIDS/ME has at least one component that runs 4 to 6-fold higher than normal controls for three gene types (HLA DR haplotypes: DR4, DR3, and DQ3) - which happen to be the same three gene types that are associated with juvenile rheumatism, arthritis, juvenile diabetes and Sjogren's Syndrome. These are genes that are connected with immune regulation—thus there might be an autoimmune piece to CFIDS, since these other illnesses are autoimmune in nature.

### **CFIDS/ME Triggers**

Sixty to 80% of CFIDS/ME patients can date their illness onset to an acute viral-like illness or infection. (However, only 18% of fibromyalgia patients report having an infection just prior to becoming ill.) There is clear documentation that a percentage of patients developed CFIDS/ME after contracting an Epstein-Barr virus (EBV) or a cytomegalovirus (CMV) infection. However, instead of recovering, the patients remained sick.

In Australia, Dr. Andrew Lloyd has undertaken a large prospective study to identify CFIDS/ME triggers by looking at patients who get EBV; Q Fever or Ross River viral infections. The latter two illnesses have chronic courses similar to mononucleosis. At onset of their illnesses, Dr. Lloyd is doing a comprehensive battery of immunological tests, and then is following the subjects over time to see what factors could predict patients' failure to recover. Early findings indicate that those subjects with decreased cell-mediated immunity are most likely to have ongoing, persistent symptoms. Cell-mediated immunity is tested by delayed hypersensitivity skin testing. The test consists of an intradermal injection under the skin and is similar to TB, candida, and other allergy testing.

One hypothesis that might explain these findings, according to Dr. Klimas, is that many CFIDS/ME patients may have an underlying immune abnormality that impedes normal recovery from infections. Dr. Klimas stressed that, as a matter of treatment, it is more important to focus on the "mediators"—the chemicals produced by the neuroimmune and endocrine systems in response to the triggers—because these chemicals can be changed as opposed to invariants such as genetics or triggering events.

### **Immune System Involvement**

The following chart presents the two different immune response processes (or cascades) that occur following various infections.

The chart shows that the immune system has two subsystems: Th-1 and Th-2. Each is designed to activate according to the type of microorganism or antigen involved. The Th-2 system responds particularly against bacteria and parasites. The system's cytokine patterns activate B-cells to make antibodies. However, if there are too many B-cells, then autoantibodies may be produced, that can trigger autoimmune diseases, or profound allergic reactions. The inflammatory cytokines, such as IL-10 linked to the Th-2 response, are found to be closely linked to CFIDS/ME.

In CFIDS the immune response appears to be shifted improperly and persistently to the Th-2 system. The Th-1 pattern produces Natural Killer (NK) cells and cytotoxic T-cells that help to clear viruses. The Th-1 system is not functioning well. One form of therapy would be to try to shift the overworking Th-2 response to an improved Th-1 response. Dr. Klimas is exploring treatments that would accomplish this shift.

### **Immune System Dysregulation**

The evidence, according to Dr. Klimas, is substantial and irrefutable. Hundreds of scientific articles have been published, nationally and internationally, confirming evidence of immune activation, natural killer cell dysfunction, Th-2 cytokine patterns, and the poor functioning of the Th-1 system.

Dr. Klimas summarized some of the evidence.

1. Immune dysregulation in CFIDS/ME:

A. Up-regulation of macrophages

B. CD-4 cell activation, CD-8 activation

C. Th-2 shift, B-cell derived illness (allergy)

D. Th-1-dependent poor function, NK-cell dysfunction

E. Pro-inflammatory cytokine release

2. Evidence of chronic immune activation

A. Activation markers on cells

B. Products of activated cells (cytokines, etc.)

C. Enzyme systems of up-regulation (e.g., interferon, 2,5a-RNaseL activity)

D. Messenger RNA up-regulation of cell products (cytokines)

Dr. Klimas particularly noted the dramatic up-regulation of the anti-viral enzyme systems. The work of Dr. Suhadolnik on the 2,5a-RNaseL pathway in CFIDS/ME has shown that the cells and

the enzymes are so activated that the reaction, instead of taking 1-2 minutes to digest a viral protein, occurs almost instantly, in as few as 3 seconds.

Dr. Klimas praised Dr. Suhadolnik's research. His Ampligen research findings have been confirmed by four other studies. And not only has he been able to discover enzyme system diagnostic markers for CFIDS/ME, he has even been able to correlate these markers to the severity of illness. Dr. Suhadolnik included other illness subgroups in his research, but found that CFIDS/ME subjects have the highest level of activation in the antiviral RnaseL pathway ever reported in the medical literature. Fortunately, he has recently received NIH research funding to continue his groundbreaking work.

### **Viral Persistence: Reactivation of HHV-6**

In concluding her discussion on the role of the immune system in CFIDS/ME, Dr. Klimas reviewed the recent work of Dr. Konstance Knox, who has shown that the Human Herpes Virus 6 (HHV-6) is periodically reactivated in some CFIDS/ME patients. The work is especially intriguing, since many patients and a number of CFIDS/ME researchers have suspected that a major component of CFIDS/ME involves chronic viral persistence.

Dr. Knox and her team conducted a significant study involving 4 sites with a total number of 368 subjects. Thirty-five percent of the CFIDS/ME subjects expressed the HHV--6 virus in their serum while no HHV-6 virus was found in the control group. While this finding was significant, it really did not demonstrate expression of this virus as a fundamental key to the illness, since two-thirds of CFIDS/ME patients did not show expression.

An interesting discovery was when 26 CFIDS/ME patients, who had first tested negative were re-tested, they were then found to have reactivated virus. The testing technique in the study involved the direct identification of the virus itself, rather than antibodies to it. These results may be significant in identifying a characteristic of the disease process, since periodic reactivation of HHV-6 may occur in more than 37% of CFIDS/ME patients.

Dr. Knox and her colleagues then did a smaller study of 35 subjects with CFIDS/ME who had neurological problems. They looked for HHV-6 in the patients' central nervous systems and found the virus actively expressing in 7 patients. Therefore, at least in some patients, the virus is getting into the brain. According to Dr. Klimas, the virus has the propensity to go into the tiny little vessels in the brain that supply blood and cause inflammatory reactions. In CFIDS/ME patients, abnormalities in PET, MRI, and SPECT scans often show decreased blood perfusion.

This decreased perfusion may be caused by local inflammatory responses caused by HHV-6. Interestingly, Drs. Ablashi, Krueger, and Knox found no active expression of the HHV-7 or HHV-8 virus in CFIDS/ME patients.

### **Other Herpes Viruses**

The Herpes family of viruses may play a role in the pathophysiology of CFIDS/ME. Dr. Klimas already cited EBV (HHV-3) and cytomegalovirus (CMV or HHV-4) as known triggers for CFIDS/ME. The viruses in this family are generally latent viruses. An individual usually is first infected in childhood or adolescence. At this age, the initial infection is usually quickly overcome by the immune system, but the virus itself manages to "hideout" in some part of the body's tissues, becoming inactive or "latent".

For instance, HHV-6 hides out in natural killer cells. Dr. Klimas theorized about HHV-6 and CFIDS/ME: why would someone at age 20, 30, or 40 begin to express a virus that should be latent? Something must have happened immunologically to allow the virus to reactivate. She recalled Dr. Lloyd's hypothesis that people can get infections which then persist if the immune system is already not performing properly.

If HHV-6 were active in some CFIDS/ME patients, would the virus be contagious? Dr. Klimas said she has not found anything in the secretions of CFIDS/ME patients that is infectious or contagious, including HHV-6, EBV, or any-thing else.

### **HPA-Axis Dysregulation: Hormones**

Dr. Klimas emphasized that it is incorrect to separate the immune, endocrine, and nervous systems. In fact, all three form one complex system where the component parts interact with intricate feedback loops. A major portion of the hormonal or endocrine system is the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus and the pituitary glands are in the brain, while the adrenal glands sit atop the kidneys. The hypothalamus is the master gland; it tells the pituitary when a particular hormone is needed. The pituitary, in turn, sends signals to the adrenals and other glands. The problem in CFIDS/ME is that activity of the hypothalamus is blunted and hormone-producing signals are not produced properly.

At the 1998 AACFS conference in Cambridge, MA, Dr. Ted Dinan presented a preliminary but extraordinary piece of research in which CAT scans showed very shrunken adrenal glands in CFIDS/ME patients. In contrast, both depressed persons and healthy controls showed entirely normal-sized adrenals. Furthermore, the CFIDS/ME patients showed hypothalamic and pituitary

dysfunction in addition to the shrunk-en adrenals.

The hypothalamus is also dysfunctional in fibromyalgia patients. Dr. Robert Bennett, a leading fibromyalgia researcher, was irked by critics of studies demonstrating organic deficits in FM. The constant criticism was that the studies were invariably too small, so he decided to respond. In a study of 500 patients, Dr. Bennett demonstrated abnormal hypothalamic function. In a sub-sample he found that it was the hypothalamus, not the pituitary, which was not functioning properly.

### **Dysfunction in the Autonomic Nervous System**

The autonomic nervous system is divided into two segments: *the sympathetic and parasympa-thetic systems*. The sympathetic system mobi-lizes the flight or fight response; adrenalin is produced and blood is sent to the muscles and brain. The parasympathetic system, on the other hand, puts the body into a state of relax-ation, allowing the body to recuperate and restore itself. Dr. Klimas stated that in CFIDS/ME patients the sympathetic and parasympathetic systems are not in proper balance with each other. The regulation of blood pressure by these systems is often dysfunctional. The evidence for this has come from research at Johns Hopkins (Drs. Calkins, Rowe *et al*) and from the blood volume/cell studies by Drs. Bell and Streeten.

### **Cognitive Dysfunction**

Dr. John LaManca *et al.* administered IQ tests to CFIDS/ME patients and to a control group four hours and 24 hours after treadmill testing. The CFIDS/ME patients experienced a cognitive loss four hours after treadmill, which continued to persist for 24 hours. Usually when cognitive testing is repeated, learning occurs and there is a gain in score. The control group had a good improvement in score while the CFIDS/ME patients had scores that went down as they relapsed fol-lowing the treadmill testing.

### **Neurally-Mediated Hypotension in CFIDS/ME**

Dr. Klimas gave a short description of this con-dition. Normally, when a person stands up much of the blood volume goes to the legs and feet. As a result, there is a very brief reduction of blood volume available to the heart; sensors in the heart respond by sending a sympathetic nerve signal to the brain calling for increased blood pressure and pulse. The brain sends the signal to provide increased blood flow, and within a couple of minutes, having obtained blood it needs, the heart should send a second message to the brain calling for a small parasympathetic response to reduce blood flow to prevent any overshooting or hypertensive response.

In CFIDS/ME, upon standing, everything happens properly until the final parasympa-thetic response. The parasympathetic response, instead of providing a small downward adjust-ment in blood pressure, is way overstated and you get a big blood pressure and pulse drop. The blood pressure can go to 60/30 or under and the pulse to 40. Many doctors fail to diagnose this condition, because they ask if the patient actually has had instances of fainting. If the CFIDS/ME patient has been able to prevent actual fainting and answers no, then the doctor moves on. The doctor fails to ask if the patient has felt like fainting.

### **Blood Volume and Red Blood Cell Mass**

Similarly, Drs. Bell and Streeten found an intriguing set of abnormalities in their work on PWC's blood volume. They did sophisticated tests that tagged red blood cells to make a count of the entire number of RBCs in the body. At the same time, they measured the volume of blood plasma. Bell and Streeten found abnor-mal numbers both in plasma and RBCs.

If the number of red cells is much lower, then the cells have to try to deliver less oxygen much more quickly. This can result in tachycardia and other circulatory difficulties. If blood volume or plasma volume is low, then the blood goes to the feet and there is greater difficulty get-ting blood to the heart and head.

The kidneys control blood volume. They determine how much liquid goes out through the urine and how much stays in. The kidneys also make erythropoetin (EPO), a hor-mone that tells the bone marrow to make more red blood cells. The sympathetic nervous system is responsible for signaling the kidneys to retain or excrete liquid, thereby altering blood volume.

Dr. Klimas is doing a partially funded NIH study to determine if the sympathetic tone of kidneys is affected in CFIDS/ME, and if there is a therapeutic intervention She has commenced EPO clinical trials, by injection, to induce more red blood cell formation (in people with docu-mented low RBC). She hopes the trials will show efficacy of the treatment.

### **Interventions for Low Blood Volume**

If a PWC has low blood volume or neurally mediated hypotension (NMH), there are basical-ly two therapeutic approaches. The whole sys-tem can be visualized as a system of pipes and a pump. The first approach would be to fill up all the space in the pipes, so that the heart would not experience the temporary loss in volume. Water, salt and the drug Florinef would be the



therapeutic means to increase the blood volume. The alternate approach is to regulate the heart (pump). The cardiologist can give beta blockers, that make the heart beat at an even 60 beats per minute all the time. This allows the heart a little more time to fill between beats, so it more fully fills. But beta blockers can have the side effect of fatigue. Therefore the physician must balance the risk vs. the benefit of the therapy.

Dr. Klimas outlined her approach for increasing blood volume. First, over a two-week period, substantially increase the intake of water and salt, using salt tablets. She clearly warned that water should not be increased without also taking salt, since increased water by itself acts as a diuretic (you will pee out more fluid; in so doing, you will reduce blood volume and become sicker). Also, you must take proper amounts of water and salt. Too much salt can result in hypertension. Your blood pressure will go down when you stand up. If you overshoot, you will do so when you are lying down. The blood pressure must be monitored, both lying down and standing up.

In addition to water and salt a physician may prescribe Florinef. However, Florinef causes the body to lose potassium. Potassium loss can be serious. The result can be terrible fatigue, heart arrhythmias, or skeletal muscle malfunction and paralysis. You must have your doctor monitor your potassium levels regularly.

One aid for NMH is to elevate the head of your bed 30 degrees or higher. The elevation maintains a signal in your brain all night long that you're a little upright. This keeps the tone in the vessels a little tight all night, preventing a relaxation in the venous tone of the legs. As a result, when you rise in the morning, the blood supply is not pushed entirely into the legs and there is less of a drop in blood pressure.

### **A Minimal and Achievable Exercise Program**

Again, in relation to blood pressure, the body's muscles help to control the tone of the blood vessels. For this reason and many others, it is very important to take care of the body's muscles. CFIDS/ME patients need to find ways to do even the most minimal exercise. Here is the approach recommended by Dr. Klimas. To start, determine how many minutes you have during a good part of your day to do minimal movement before you start to feel tired. This is the amount of time you will exercise at the beginning. There are two types of exercise: aerobic and strengthening.

#### **Aerobic Exercise**

Aerobic exercise consists of body movement that increases the heart rate, such as swimming, bicycling, even walking. Dr. Klimas highly recommends swimming since the water compresses vascular space, thereby encouraging circulation throughout the body. Swimming also cools and prevents overheating. Your goal is to prevent deconditioning. Start with your minimal, fixed amount of time and do the same exercise every day for two weeks. Don't try to advance the amount of time or push yourself for the first 2 weeks. After two weeks, add 7 minutes of the exercise at a different time of day. After another two weeks or so, you can begin to exercise a third time a day for another 7 minutes. When you feel absolutely ready, you can increase the number of minutes in each period, but be flexible. If you're having a relapse, don't make yourself worse by forcing yourself to stick to your schedule. But as soon as you feel better, get back to your program. By sticking with it, over time, you will improve physically. In six months, you may be able to exercise moderately for 15 minutes, two to three times per day. For many CFIDS/ME patients this is a rational goal that can be achieved without undue relapsing.

### **Strengthening with Isometric or Weightlifting Exercise**

A major problem for CFIDS/ME patients is the loss of muscle tone due to inactivity. Strengthening exercises are a very good way to maintain tone, and these exercises are not as difficult for the patient since they require less blood flow and oxygenation. Moreover, the exercises should only be done every other day. To start take a one-pound can of soup and do repetitions (biceps curls) with one hand until your arm is a little tired, then stop. Remember how many repetitions you did. Next, move on to the next muscle group and do the same thing. Rest the next day, since the rest allows the muscle to strengthen. For the first week don't change the number of repetitions. You will need a book of weight exercises to teach you how to progress. Dr. Klimas recommends the *FM Survivors Guide* by Dr. Mark Pellegrino that outlines an excellent exercise program.

### **Medications for Compressing the Vascular System**

Besides exercise, the vascular system can be compressed using various medications. Many patients use caffeine or Sudafed. The problem is these substances can cause tachycardia. Midodrine, a prescription medication, is a more specific vasoconstrictor, especially in the legs. It shunts blood to the head, but some patients can't tolerate it. Dr. Klimas said she has had good experience with it. It is best to start at very low doses. PWCs should divide the standard dose by 4 or 10. Dr. Klimas starts patients at one half or quarter tablet the 1st day. If the patient does well, then she gives the same dose in the morning and at lunch. The next increase is to morning, lunch, and then mid-afternoon.

There is a timing issue involved in taking Midodrine. Blood pressure shifts after meals, and the blood supply is then shunted to the gut. Therefore, it is best to take the medication before meals. Don't take Midodrine before bed since it raises blood pressure 10-20 points. If your blood pressure is normal lying down, you don't need this medication. If your pressure is too low

when you are lying down, then Midodrine might help you.

### **Sleep Disorder and CFIDS/ME**

Dr. Klimas said that sleep was one of the most critical factors affecting the illness: "If you can't get sleep under control and help the patient get restorative sleep, you really can't help the patient make any substantial improvement with any real speed. Every effort must be made to help the patient get restorative sleep."

The problem of sleep best highlights the interactive involvement of the brain, hormonal, and immune systems in CFIDS/ME. If a person has a severe sleep disorder, his or her immune and hormonal systems may be severely out of balance and dysfunctional. Sleep sets the circadian rhythms of the immune and endocrine systems. When normal sleep is disrupted, the diurnal patterns of cortisol and prolactin production are altered, as are the diurnal patterns of NK-cell function. Alpha-wave intrusion on sleep EEG also occurs.

### **Sleep Therapies**

It is necessary to work to reestablish the body's circadian rhythm by reestablishing a regular sleep pattern. The goal is to set a bedtime for the same time each night, and then to fall asleep shortly after going to bed. Her idea is to create a conditioned response—to associate being in bed only with nighttime sleeping. If one is only in bed to sleep, then getting into bed is more likely to result in sleep. To establish this conditioned response, the PWC must avoid using the bed for resting or reading during the day. Dr. Klimas says this approach will help you fall asleep at the same time each day. The approach may not help you stay asleep or help you obtain the proper restorative sleep.

If you do need medication, Klimas advises, "avoid using the short-acting hypnotics." These medications, like Ambien and Restoril, are designed to help you fall asleep. The problem is they don't help you stay asleep. Moreover, these medications trap people in the lighter alpha sleep. CFIDS/ME patients need a drug to induce deeper sleep—stages 3 and 4. The drug also needs to last 8 hours so the person will remain asleep. Tricyclics in low doses, like Elavil and especially Doxepin, are very good choices. Doxepin has the added benefit of having antihistamine and anticholinergic properties. It comes in a liquid so PWCs can control the dosage by adjusting it to just drops.

Dr. Klimas warned that PWCs must be careful in using the Selective Serotonin Reuptake Inhibitors (SSRIs) for sleep, i.e., the Prozac class. These drugs can be either sedating or

activating. It is important to know which of these drugs sedate and in what doses. Prozac is an activating drug. If you take it in the morning, it will peak in the evening and then you won't be able to sleep. You should take it at night so it will activate in the morning.

The new drug Serzone is used to improve stage 3 and stage 4 sleep. Klonopin can help with restless leg syndrome. Flexeril can be used to relax the muscles at night.

### **Treatment of Pain in CFIDS/ME**

The effective treatment of pain has to be a high priority. Months and years of moderate and severe pain can take a serious toll physically and mentally. Most doctors rely on NSAIDs (nonsteroidal, anti-inflammatory drugs) like ibuprofen, which don't work very well with CFIDS/ME. Tricyclics (Elavil, Doxepin) can help with pain thresholds so there is less perception of pain. Opiates, from codeine to morphine, are sometimes used to control pain. The use of opiates is controversial because of the fear of addiction. Dr. Klimas, however, argued that because of the serious consequences of pain in CFIDS/ME, sometimes the use of opiates must be risked. She said, "I have never lost anyone to CFIDS/ME, but I have lost people to pain. The people who die of CFIDS/ME die from suicide, and typically people don't kill themselves unless there is a big pain piece to their illness." She would argue vehemently that opiates have a role for some patients, though not a majority of patients. When serious pain control is needed, Dr. Klimas often prefers to use longer acting, low-dose morphine that lasts 12 hours or the new 24-hour type. Shorter-acting Percocet may be more addicting. New neurotransmitter analogs like Neurontin also have a role and are not addictive. She'll try these first.

Dr. Klimas also emphasized that it's essential to understand the interactions of the various medications the patient is taking. The interactions themselves could be causing symptoms and affecting the individual's sleep.

### **Other Therapies-Self-Help for Cognitive Symptoms**

The prescription for cognitive dysfunction is: practice, practice, practice. There are many patients who become isolated and reduce their cognitive challenges. Do crossword puzzles, volunteer, go to a class, tutor, go to meetings, do something fun. Try not to sit by yourself at home all day. Listen to book tapes. Know your best time of day to do intellectually challenging work.

### **Pregnancy and CFIDS/ME**

Blood volume increases dramatically during pregnancy so most PWCs who are pregnant feel

better. They often relapse after delivery, so supports need to be in place. Dr. Klimas feels that breast-feeding is not a good idea. There is the exhaustion from having to get up at night, and there is also the potential of the baby's exposure to virus at too young an age.

### **Vaccination**

Dr. Klimas' advice is to get vaccinated if you can tolerate it. The medication Amantadine can treat half of the various influenza strains as well as prevent them. She gives patients Amantadine during the flu season.

### **Who Gets Better?**

Some studies say the younger the patient, the better the recovery. But Dr. Dedra Buchwald found that this is not true. A CDC study says chances for improvement are higher if the patient is ill less than 3 years. Buchwald's study says the duration of illness is not a predictor of prognosis.

Dr. Klimas did say, "What we really do know is that people who are depressed do worse than people who are not. Depression is treat-able. CFIDS/ME patients may be reluctant to get this part of the illness treated because of the stigma of depression. Half of CFIDS/ME patients do not have any depression. Those that do, most often have a secondary depression.