Highlights from Dr. Klimas' presentation to the Connecticut CFIDS & FM Association - "An Update on Chronic Fatigue Syndrome & Fibromyalgia - From Research to Management".

By R. Sanderson

On June 20, 2009, the Connecticut CFIDS & FM Association sponsored a lecture by the internationally renowned Dr. Nancy Klimas. Dr. Klimas is a leading researcher and clinician for CFIDS/ME (Chronic Fatigue and Immune Dysfunction Syndrome /Myalgic Encephalopathy), FM (Fibromyalgia) as well as Gulf War Illness (GWI). The conference hall at the Crowne Plaza Hotel in Cromwell, CT was filled to capacity with patients and family members, many of whom had traveled a substantial distance to hear her presentation. This year the focus was to provide an "Update on Chronic Fatigue Syndrome and Fibromyalgia - From Research to Management". This summary will provide the highlights on new research developments, new discoveries, and better ways to manage the illness.

First and foremost, Dr. Klimas emphasized how important it is to develop well-coordinated clinical and treatment guidelines for CFIDS. For example, when someone with CFIDS goes to an emergency room, there are currently no guidelines in place to describe what might be the most beneficial intervention for this patient. Something as simple as administering a saline IV is not common knowledge, even though this treatment can help to rehydrate, improve low blood volume or orthostatic hypotension, and stabilize a patient in an acute relapse. Klimas also recommends an extra liter of saline before surgery, to keep up blood volume during surgery, as well as after the procedure.

Dr. Klimas reviewed a few basic things such as reminding the audience that the 1994 clinical definition is still being used to diagnose CFIDS. However, she thinks post-exercise fatigue should be viewed as one of the key symptoms of CFIDS because this type of fatigue is distinctly unique to this illness. The degree of debilitation in CFIDS, according to Klimas, can be compared to the severity of active congestive heart failure. Contrary to earlier data and beliefs (that CFIDS affects primarily white women), the occurrence of CFIDS is found to be much higher in individuals of Hispanic and African-American origin and less frequent in those of Asian origin. One major problem remains in that as many as 85% of individuals who have CFIDS are not diagnosed. People still find it very difficult to find physicians who are knowledgeable enough to recognize, diagnose and treat this illness.

Fibromyalgia (FM), on the other hand, is an illness that presents primarily as widespread pain in all quadrants of the body. In Dr. Klimas' opinion, it is easier to diagnose FM during a physical exam when following the FM diagnostic criteria. Unlike CFIDS, it does not require the exclusion of so many other conditions in the diagnostic process. Recent FM research promotes a better understanding of the type of chronic pain experienced in FM-which is "centrally mediated". Pain in FM stems from the part of the brain which perceives pain as well as from increased sensory signals along the spinal cord. As a result, FM pain is not viewed as peripheral pain (i.e. pain resulting from injured tissues or chronic inflammation in joints) nor is it mediated by an immune system reaction.

Genomics research has greatly expanded over the past seven years (it is now possible to study 40,000 genes). This research methodology may assist in the recognition of many disease mechanisms. Specific gene patterns have been identified in CFIDS-88 genes have been associated with CFIDS and within these genes, there are 7 genomic subtypes. Dr. Jonathan Kerr's team in London, UK was the first group of researchers to make this discovery in CFIDS. They were even able to break down these clusters of genes into subtypes based on the number of activated genes and the characteristics and combination of dominant symptoms in each type. The subtypes correlate with the severity of symptoms. The most severe subtype presents as 8 major symptom groups (i.e. pain, infections, musculoskeletal symptoms, gastrointestinal symptoms, neurological symptoms, neurocognitive symptoms, sleep-related symptoms, and anxiety/ depression), while less severely impaired gene subtypes will have fewer symptom groups or will have one or two dominant symptom groups. All subtypes include fatigue. Dr. Klimas believes this sort of research will provide the biomarkers for diagnosis and will identify better treatments. She has also been working very closely with Gulf War Illness (the troops who became ill after their deployment to the Persian Gulf during 1990-91) in which a number of abnormal gene patterns have also been identified. She mentioned that the incidence of CFIDS is found to be 16-fold higher in individuals with GWI.

Dr. Klimas spoke about how gene activation does not happen on its own, but is greatly influenced by the state of a person's immune system. A lot also depends on "mediators"-substances or agents that will induce some type of biochemical activity-and the interaction of these mediators. In CFIDS, various mediators may have triggered the disruption of the homeostasis of internal systems and mechanisms. These systems would typically function within a range of values/set points, but when a mediator change, such as cytokine oversecretion, is encountered, this can throw the entire balance out of whack. So, what needs to be done in CFIDS is to find a way to reset the "set points" in patients in order to bring patients back to a healthy (or at least, healthier) state.

Recently there has been an attempt to use mathematical models in CFIDS research. The work of one scientist whose approach is unique and, Dr. Klimas feels, is most promising is that of

Gordon Broderick, PhD, at the University of Alberta's Institute for Biomolecular Design. Dr. Boderick has applied his engineering skills to test and demonstrate the expression of certain gene patterns as well as to "map out" and evaluate the interaction of various systems in CFIDS-particularly, in how these differ in CFIDS patients compared to healthy individuals. These advances in research methods and tools have left Dr. Klimas feeling increasingly more optimistic and excited about how CFIDS can be evaluated and about how best to determine effective treatment interventions.

Using exercise challenge and then evaluating gene expression patterns or monitoring specific symptoms before, during and after exercise is one of the best ways to capture valuable data about CFIDS. Sustained activity will quickly start to demonstrate changes in cytokine secretion and show overactive or underactive immune or neuroendocrine responses, with the results in CFIDS patients being quite the opposite of those found in healthy individuals (what should be turned on, is turned off, and vice versa). Taking this a step further, the Pacific Fatigue Lab in Stockton, CA has developed a very effective exercise protocol for CFIDS by testing patients' ability to produce energy while they are in a crash. This protocol requires that patients undergo a specific exercise routine on two consecutive days. It was discovered that some patients experienced up to a 50% drop in the amount of energy their bodies could produce on the second day. Other researchers are investigating the roles of neuropeptide Y and CD26 in CFIDS, especially since these markers are already used to evaluate and measure various biological processes (i.e. those in the cardiac, respiratory, immune, endocrine and nervous systems).

Viral persistence and reactivation continue to plague a segment of the CFIDS population. For example, Human Herpes virus 6 (HHV-6) has been detected in the spinal fluid in 20% of CFIDS patients (Peterson D). Epstein-Barr Virus-encoded dUTPase (that refers to deoxyuridine triphosphate nucleotidohydrolase) has been shown to induce immune dysregulation, to upregulate proinflammatory cytokines and in general, is thought to contribute to CFIDS symptoms (Glaser R). Enterovirus has been detected in 60% of stomach tissue biopsies (Chia JKS) as well as in 13% of muscle biopsies done on CFIDS/FM patients (Douche-Aourik F). Therefore, these studies confirm the presence of enterovirus and/or human herpes viruses (like EBV, aka HHV-4, and HHV-6) in CFIDS and FM.

Dr. Klimas first reviewed treatments (mainly anti-virals) which are still in clinical trials and/or which are approved for use in CFIDS outside of the U.S. Isoprinosine is an immunomodulator that helps to improve natural killer cell function. (It is available in Canada and Ireland). Ampligen is another immunomodulator that helps to improve RNase-L response to viral infection. (It is still awaiting FDA approval in the U.S., though it is used in Canada and some European countries). Valcyte (valganciclovir) is a type of anti-viral used to counteract Epstein-Barr virus reactivation (Montoya J). The FDA has approved this medication as

treatment of other conditions, but not for CFIDS. Phase II of a clinical trial for use in CFIDS was recently finished (results not yet published). This trial is a pharmaceutical company-sponsored study and considering the fact that the patent on Valcyte will run out in about 2 ½ years, there is concern about the CFIDS studies being completed before that happens.

Other clinicians, like Dr. Daniel Peterson, use anti-virals in an IV form. Dr. Klimas remarked anti-virals have demonstrated considerable improvement in a number of CFIDS patients, but these treatments carry a risk of fairly serious side effects.

Treatments that are more commonly used and/or prescribed by Dr. Klimas herself, include the following:

- Low-dose Naltraxone - this medication, at a regular dose, is used to block reception of opioid hormones in the treatment of opioid addiction, but at much lower doses, it can boost immune system response. It is also being studied in the treatment of neuropathic pain, because it blocks sensory fibers along the spinal cord. This drug, at the lower dose, can be obtained from compounding pharmacies.

- Low-dose Estrogen - Dr. Klimas supports the use of this hormone treatment, at the lowest dose, in women who are going through menopause, as long as there is no known cancer risk. She has found the changes of menopause can greatly exacerbate CFIDS symptoms.

- Xyrem - (sodium oxybate, a form of Gamma hydroxy butyrate (GHB), also known as the "date rape drug") is a central nervous system depressant with rapid onset, used to induce sleep. In fact, studies were recently completed for its specific use in CFIDS that demonstrated that this drug can help improve deep sleep and reduce sleep disturbances as well as fatigue (Univ. of Medicine and Dentistry, NJ and Jazz Pharmaceuticals). Its use requires special registration by prescribing physicians.

- Sleep medications - Dr. Klimas generally prefers to use medications that are not in the benzodiazepine family because they do not promote deepest level of sleep. She prescribes medications like Remeron or Trazodone (both of these are tetracyclic antidepressants), Doxepin in liquid form (its mechanism is similar to a tricyclic antidepressant), and the newer non-benzodiazepine hypnotics, like Lunesta or Ambien.

- Pain and combinations of FM symptoms - Dr. Klimas prescribes one of the newer medications, like Cymbalta or Savella (both are classified as serotonin-norepinephrine reuptake inhibitors, although the mechanism might be slightly different between the two of these products) for the multiple symptom relief provided by these medications. She also prescribes Lyrica and/or its predecessor, Neurontin. The benefits of Lyrica can be achieved at a lower dose than in Neurontin, but many patients do experience weight gain.

- Fatigue - Provigil (a unique central nervous system stimulant) was found to only modestly improve cognition in CFIDS, according to Dr. Klimas. Some CFIDS clinicians find it can negatively impact sleep, while several others prescribe it and find it to be fairly helpful.

- Supplements - the following three vitamins/dietary supplements are thought to be of particular importance in managing CFIDS, because so many CFIDS patients have been found to be deficient in these. Dr. Klimas recommends incorporating Vitamin D3 at 2000 I.U, B12 (in sublingual form) and Coenzyme Q10 (Co-Q10). Vitamin D helps to improve immune system function, maintain bone mass and muscle strength and provide protection against certain types of cancer. B12 in CFIDS patients can often be lower or even depleted at the cellular level as opposed to how it appears in serum. This vitamin can help with production of red blood cells, provide protection for nerve cells and their function, as well as boost energy. A recent Japanese study of Co-Q10 benefits was cited by Dr. Klimas which demonstrated increased performance and less fatigue after exercise. Co-Q10 at 60 mg can help to generate energy at cellular level as well as provide antioxidant protection.
[Editor's Note:
Even though only these particular three vitamins were highlighted during this presentation, it
is important to remember that
vitamins work together and depend on each other for proper absorption and optimal function within the body. Not taking the right combination could create imbalances and deficiencies in others.]

- Other interventions-exercise that focuses on muscle bulk/"core muscles" is recommended and it can be increased in small 5-minute increments. Neuromuscular massage can be very beneficial. This type of treatment focuses on trigger points and is achieved by applying steady pressure on fixed points and areas within taut bands of muscle.

In closing, Dr. Klimas made an exciting announcement: the "Centers for Chronic Fatigue & Immune Disorders" will open during Summer 2009 with Dr. Klimas serving as Chief Medical Officer. This is a new state-of-the-art medical clinic, located in the Miami area, which will focus on the assessment and treatment of CFIDS. She will be personally training the Center physicians with particular attention to the pathology and etiology of CFIDS. Some of the available services include the metabolic cart, tilt table test, sleep study, actigraph (a monitor worn by the patient that measures activity level and sleep time), DEXA scan and neurocognitive assessment. Patients will need to get a referral from their primary care physician in order to be seen at the clinic. The goal of this Center is not only to provide each patient with a very thorough evaluation, but to also create a custom treatment and maintenance program for each patient

We highly commend Dr. Klimas for her continued compassion, care and work with CFIDS and congratulate her on this outstanding accomplishment, making the Centers for Chronic Fatigue & Immune Disorders a reality.