*Compiled by R. Sanderson*

*Reviewed and edited by K. Casanova*

Dr. Nancy Klimas is Professor of Medicine at the University of Miami and the Director of Research for the Clinical AIDS/HIV Research at the Miami Veterans Affairs Medical Center. She has been a leader in the field of CFS/CFIDS/ME research, is a founding editor of the *Journal of Chronic Fatigue Syndrome*
[no longer published as of 2009] and is the current President of the International Association for CFS/ME (IACFS/ME). On Sunday, April 30, 2006, Dr. Klimas presented a lecture titled, "Research Advances in Chronic Fatigue Syndrome: Impact on Treatment," at the Connecticut CFIDS & FM Association's Spring Conference.

As much as everyone looks forward to hearing Dr. Klimas speak, such an event is never long enough. She always has a great deal of information to share with her audience, and it can be very hard to keep up with her. Therefore, please note that a lot of data was incorporated directly from a copy of her PowerPoint presentation (which includes complete information on the articles cited), along with elaborations made by Dr. Klimas on specific topics. In this way, we hope to provide you with as much information as is possible on recent research advances. Since CFS was the term used in the lecture, this name is used throughout this summary.

Dr. Klimas began her presentation with a brief review of issues that continue to affect our patient population: including the clinical case definition for CFS (Canadian Consensus Panel Clinical Case Definition for CFS/ME vs. the CDC 1994 criteria); CFS epidemiology and the high percentage of undiagnosed CFS cases; and the economic impact of CFS on productivity. She emphasized how these issues, along with the trivializing name, have negatively impacted treatment. Klimas acknowledged that many physician attitudes show a negative bias towards CFS due to its name. A survey of 811 GPs revealed that 44% did not feel confident making the diagnosis [of CFS], and 41% did not feel confident in treating it. Physicians had reported they would likely have more confidence in the diagnosis if they had a friend or family member with CFS. The doctors also reported that education that emphasizes acceptance of CFS as a real entity would improve their confidence in treatment. (Source: Bowen J *et al, Family Pract* April 1 (2005))

She provided an update regarding recent research advances and publications (2003 through early 2006) using her well-known model as a basis:

**Model for CFS Pathogenesis**

Genetic Predisposition
Triggering event/ infection
Mediators (Immune, endocrine, neuroendocrine, psychosocial)
Health Outcome/ Persistence

**Genetic Predisposition:**

Dr. Klimas went over some of HLA DR haplotypes identified in an earlier study of CFS patients that revealed these patients were at a 4 to 6 fold increased relative risk for haplotypes DR4, DR3, and DQ3 (Keller *et al,* 1992). Klimas explained that gene array data can separate patients into subgroups by their patterns of gene dysregulation in both immune and HPA gene clusters.

Technological progress has made it possible to analyze genes to a greater depth than we are presently able to medically understand what the data mean. Klimas further noted individuals with CFS cannot be lumped together, as they are part of subgroups and therefore should be treated differentially.

**Triggering event/infection:**

A brief review was done of prior studies that demonstrated an association between onset of CFS and an acute viral-like illness in 60-80% of patients (Komaroff and Buchwald). Furthermore, a percentage of patients remained sick after acute viral infections, such as EBV, Q fever or Ross River Virus (according to Australian and UK research). One of the newer theories of great interest to Dr. Klimas is the possibility that only fragments of viruses (like EBV) could “trash” [i.e., dysregulate] a patient’s system.

Ronald Glaser *et al*. have found evidence that regulatory peptides encoded by EBV are expressed in CFS despite the absence of replicating virus. These peptides are known to modulate immune function by inducing pro-inflammatory and Type-2 cytokines.

A. Martin Lerner and his group have found evidence of a two subgroups of CFS patients with incomplete viral multiplication (CMV viral “fragments” and EBV antigen.)

[The remainder of this discussion of Lerner’s recent paper (see citation below) departs from what Dr. Klimas presented in her lecture. We reviewed Lerner’s paper and we present some of his more interesting findings in the next three paragraphs. Then we return to Dr. Klimas' lecture.]

At the same time, Lerner has found abnormal oscillating cardiac T-waves (by 24 Holter monitor) in a significant percentage of CFS patients (as opposed to controls). A smaller percentage of patients had Abnormal Cardiac Wall Motion.

Lerner suggests that the findings of incomplete viral multiplication and cardiac anomalies may be causally linked in subsets of CFS patients. The link may be direct in terms of viral damage or mediated by immune system activity. He stresses that further research must be done in this area. He also notes that "one preliminary trial of antiviral therapy (valacyclovir) in a cohort of CFS patients with single virus Epstein-Barr Virus (EBV) persistent infection is promising." However, Lerner also notes that the other subset of patients with CMV incomplete viral multiplication did not respond to the antiviral. He says this makes sense because the antiviral is known to have anti-EBV effects, "but does not have significant anti-HCMV activity…"

Lerner, interestingly for CFS patients, also discusses Gunther Stent's theory regarding: "Premature scientific discovery. Premature scientific discoveries are met by the scientific community with resistance and ridicule." [Here Lerner is saying that much of the pioneering CFS research remains in the "premature scientific discovery" category.]

Glaser R *et al*, "Stress-associated Changes in the Steady-State Expression of Latent Epstein–Barr virus: Implications for Chronic Fatigue Syndrome and Cancer," *Brain, Behavior and Immunity*
19 (2) (2005): 91-103
.

Lerner AM *et al,* "Prevalence of Abnormal Cardiac Wall Motion in the Cardiomyopathy Associated with Incomplete Multiplication of Epstein-Barr Virus and/or Cytomegalovirus in Patients with Chronic Fatigue Syndrome," *In Vivo* Jul-Aug; 18(4) (2004): 417-24 .

Dr. Klimas indicated HHV-6 is another prevalent virus in individuals with CFS. It has been detected in 22% - 54% of patients in cross-sectional studies (Ablashi, Krueger, and Knox) and in 79% of CFS patients in longitudinal studies (HHV-6 PCR assay, Knox). Dr. Klimas emphasized that the only reliable lab for patient HHV-6 testing is the Wisconsin Viral Research Group in Milwaukee, WI. This is the laboratory in which Dr. Konstance Knox has done extensive research on the virus. However, Klimas cautioned HHV-6 does not respond to traditional antivirals, but requires aggressive treatment with very potent agents administered through IVs.

**Mediators (Immune, Endocrine, Neuroendocrine, Psychosocial):**

An Immune Cascade chart was used to illustrate how various immune response processes are activated in response to an infection. Basically, the helper T-cell function in individuals with CFS no longer remains balanced; instead, it shifts to a TH-2 pattern, which in turn, triggers pro-inflammatory cytokines.

More recent endocrinology studies show evidence of reduced cortisol output (by the adrenals) via several mechanisms, such as heightened negative feedback, heightened receptor function and impaired ACTH and cortisol responses to challenge. Research data also supports DHEA functional abnormality, abnormal serotonin function, and IL-6 increase associated with low cortisol. (The low cortisol is mediated by a hypothalamic dysregulation of Cortisol Releasing Hormone.) In spite of these findings, Dr. Klimas stated that cortisol treatment, especially long-term, is not being recommended. The following two studies address this issue:

Cleare AJ*, "*The Neuroendocrinology of Chronic Fatigue Syndrome," *Endocrine Reviews* 24 (2) (2003): 236-252.

Papanicolaou DA *et al* (representing a large US panel*), "*Neuroendocrine Aspects of Chronic Fatigue Syndrome," *Neuroimmunomodulation* 11(2) (2004): 65-74.

Some of the latest research on Autonomic Nervous System abnormalities in CFS (as shown on the chart for ANS) and other sources, are as follows:

- Haemodynamic Instability Score taken during tilt table testing predicts CFS with 90% sensitivity.
- Heart rate variability as a predictor of CFS.
- Gastric emptying delayed in 23 out of 32 CFS subjects.

Naschitz J, "The Head-up Tilt Test with Haemodynamic Instability Score in Diagnosing Chronic Fatigue Syndrome, " *QJM* 96(2) (2003): 133-42.

Yamamoto *et al, "*A Measure of Heart Rate Variability Is Sensitive to Orthostatic Challenge in Women with Chronic Fatigue Syndrome," *Experimental Biology and Medicine* 228 (2003):167-174

.

Burnet R*,* "Gastric Emptying is Slow in Chronic Fatigue Syndrome," *BMC Gastroenterology* 4 (2004): 32.

### Sleep Physiology

H. Modolfsky's early studies have documented a variety of circadian sleep disturbances in CFS patients, such as altered diurnal patterns in cortisol, prolactin, and NK cell function, as well as alpha wave intrusion on sleep EEG, and a reduced state of stage III and IV sleep. A more recent study by Nathanial Watson has shown a higher percentage of REM sleep in CFS twins (Twin Study of 22 discordant twins). This finding suggests an element of sleep-state dysregulation.

Dr. Klimas mentioned there are several new Stage IV sleep inducer medications being used. The strongest of these is Xyrem (a form of gamma hydroxybutyrate (GHB))—a beneficial drug in treatment of narcolepsy; but it is also known for its illegal use as a date-rape drug. Currently, it is only available through enrollment in a special program (not through retail pharmacies) and is so potent, it must be taken when already in bed. Remeron is a medication—actually, this is an antidepressant that promotes stage III and IV sleep—that Klimas has prescribed, often in ¼ doses. She recommended that individuals with sleep problems consult with sleep doctors and pointed out these physicians are in two specialties: pulmonology and neurology. It is also important to choose a doctor who will provide continuing care after the initial evaluation.

Watson *et al, "*Comparison of Subjective and Objective Measures of Insomnia in Monozygotic Twins Discordant for Chronic Fatigue Syndrome," *Sleep* May 1; 26(3) (2003): 324-8.

### Muscle

Though research findings pertaining to muscle function/ disturbances, including those of the heart, were not discussed in any great detail. A summary of these findings is included for your

information:

- An oxidative stress study measuring protein carbonyls suggested higher levels of protein oxidation in CFS subjects as opposed to controls.

- Exercise testing in 189 CFS subjects resulted in clinically significant subgroups with 50% of subjects showing moderate to severe functional impairment. An unexpected blunting of Heart Rate and Blood Pressure responses was noted.
- Sarcoplasmic reticulum defect: conduction and calcium transport abnormalities.

- Cardiac muscle—cardiac output found related to illness severity and the predicted exercise-induced relapse.

- Subset of CFS patients with IgM-EBV or CMV-Antibody found to be at risk for cardiac motility abnormalities and occasionally true cardiomyopathy.

- Raises the issue of incomplete viral replication activating immune responses as suggested by Glaser *et al*.

[Again. for a moment we depart from Klimas' lecture. Our review of Glaser's paper sheds somewhat more light on Klimas' note on his research. Glaser's team for a number of years has studied the workings of EBV and its effects in a variety of illnesses. In CFS, Glaser found strong indications that constituent components or expressions of the latent virus may by themselves account for immune dysregulation and symptoms in subgroups of CFS patients. The same process may occur for other viruses, including CMV and HHV-6.]

**Sources:**

Smirnova IV*,* "Elevated Levels of Protein Carbonyls in Sera of Chronic Fatigue Syndrome patients," *Mol Cell Biochem* Jun 248(1-2) (2003): 93-5.

Vanness JM *et al,* "Subclassifying Chronic Fatigue Syndrome through Exercise Testing." *Med Sci Sports Exerc.*
Jun 35(6) (2003): 908-913
.

Fulle S *et al,* “Modification of the Functional Capacity of Sarcoplasmic Reticulum Membranes in Patients Suffering from Chronic Fatigue Syndrome,” *Neuromuscular Disorders* 13 (2003): 479–484.

Peckerman A *et al*, "Abnormal Impedance Cardiography Predicts Symptom Severity in Chronic Fatigue Syndrome," *Am J Med Sci.* Aug 326(2) (2003): 55-60.

Lerner AM *et al*, "Prevalence of Abnormal Cardiac Wall motion in the Cardiomyopathy Associated with Incomplete Multiplication of Epstein-Barr Virus and/or Cytomegalovirus in Patients with Chronic Fatigue Syndrome," *In Vivo* 18( 4) (2004): 417-424.

Glaser R *et al, “*Stress-associated Changes in the Steady-state Expression of Latent Epstein–Barr virus: Implications for Chronic Fatigue Syndrome and Cancer,” *Br ain Behavior and Immunity*
19 (2) (2005): 91-103.

**New studies on the brain—Important research findings published over the last 12 months:**

- After a fatigue-inducing mental task, imaging studies showed decreased brain responsiveness to auditory stimulation (study of 6 male CFS patients and 7 male healthy controls carried out by researchers in Japan).
- Decreased absolute cortical blood flow in the brain (25 CFS patients, 7 controls). When stratified for psychiatric disorders, CFS subjects with psychiatric disorders had decreased blood flow in one region only (left cerebral artery) in contrast to CFS subjects without any psychiatric disorders who had reduced flow in both the right and left middle cerebral arteries. Therefore, those patients having CFS only (devoid of psychopathology) had the largest reduction in flow.

- Using more brain physiology to process tasks—A study using BOLD fMRI done in NJ (see the brief summary below).
- Reduced grey matter in the brain was linked to reduced activity (study done in the Netherlands of 2 groups of 15 females each, one group was younger than the other).

Briefly digressing from Dr. Klimas' lecture, information has been included about the specific findings of the New Jersey study (the 3rd one listed just above) by the researcher herself, Grudin Lange, PhD at one of the afternoon workshops. Lange's study group, that also included Drs. DeLuca and Natelson (Univ. of Medicine & Dentistry of NJ), looked at mental concentration in CFS patients. Using a particular type of imaging technique—Blood Oxygen Level Dependent (BOLD) functional MRI, they measured differences in blood flow in the brains of CFS patients compared to controls, especially when challenged with complex auditory processing while doing a simple task. This study shows that people with CFS have to exert more effort to process the same data as healthy controls and provides "evidence of increased neural resource allocation when processing more complex auditory information." This conclusion was taken from the study, which can be retrieved in its entirety at: http://www.cfids-cab.org/MESA/Lange.pdf. Dr. Klimas remarked Japan has become very active in CFS research and that more money is being spent on CFS research there than in the US.

Tanaka M *et al,* "Reduced Responsiveness is an Essential Feature of Chronic Fatigue Syndrome: a fMRI Study," *BMC Neurol* Feb 22; 6 (2006): 9.

Yoshiuchi K*,* "Patients with Chronic Fatigue Syndrome have Reduced Absolute Cortical Blood Flow." *Clin Physiol Funct Imaging* Mar 26(2) (2006): 83-6.

Lange G *et al*, *"*Objective Evidence of Cognitive Complaints in Chronic Fatigue Syndrome: a BOLD fMRI Study of Verbal Working Memory," *Neuroimage* Jun 26(2) (2005):513-24.

De Lange FP *et al,* "Gray Matter Volume Reduction in the Chronic Fatigue Syndrome," *Neuroimage*
Jul 1; 26(3)(2005): 777-81.

**Microarray Technology and Genes**

In microarray testing, samples are arranged in a grid-like order, within a defined area, on glass microscope slides. This technology allows a huge number of genes to be surveyed at one time. Samples appear as series of spots (that represent genes) which undergo a binding process and

produce signals relating to the gene still present from the samples. It is the intensity of these spots (like an on/off type of mechanism) that provide the data—so for example, the intensity of one spot (CFS) can be compared to the intensity of the corresponding spot (control). Agents are used to display the data in certain colors like red and green to help facilitate analysis. In one sample chart, Dr. Klimas pointed out how the red pattern was showing downregulated mitochondrial function, while the green one was showing upregulated cytokines. In that particular study, gene expression helped to demonstrate a difference between sudden and gradual onset of illness. The importance of this technology is that it will help to identify specific gene markers associated with CFS and ultimately lead to better treatments.

Gene research has provided meaningful information about CFS (again, as taken from Dr. Klimas' presentation chart):

A CDC study of 20,000 genes studied the activity of 26 genes—activity that could accurately predict which of 6 categories of chronic fatigue a patient had on the basis of symptoms and other clinical tests.

- Most of these genes are involved in immune system regulation, the adrenal gland, and the brain's hypothalamus and pituitary glands.
- Studies of hormones and immune factors confirm these findings.
- Kerr's study revealed differential expression of 35 genes in 25 patients as compared with 25 controls. The differential expression in patients suggested T-cell activation and disturbances of neuronal and mitochrondrial function.

Other studies have pinpointed 5 specific genes that correlate with an apparent susceptibility to chronic fatigue—more specifically with levels of serotonin and glutamate affected.

Speaking of the recent CDC study, Dr. Klimas felt newspapers had misreported the study findings and the role of stress. She stated there is a “huge difference” between stress as implied in these articles (assuming she meant how one might psychologically cope under pressure) and one’s stress response. In the latter, there are *biological defense* mechanisms called into action, which involve everything from the autonomic nervous system, the cardiovascular system, the neuroendocrine axis, and the immune system. These systems react automatically to stressors. Such stressors would include environmental triggers, infections, or disruptions caused by illness. Klimas also announced that on or around June 1st, the CDC is supposed to release another press release. She is optimistic this may have something to do with upcoming treatments.

**Management of CFS**

Time had run out by the time we got to this part of the presentation. Nearly a dozen charts summarized a variety of interventions, which were broken down into 4 major categories (pathogenisis directed): immune modulatory approaches, HPA-axis interventions, neurally mediated hypotension (NMH) treatment, and sleep. Since many of these were not discussed in detail, most have been left off because their use, benefit or status is uncertain. (A number of therapies are in various phases of study.)

Overall, Dr. Klimas indicated that sleep should be one of the first problems to be treated. Earlier, she talked about the Stage III and IV sleep inducers. She also mentioned Doxepin as another helpful medication for sleep. On her chart, it is noted that short acting hypnotics should be avoided (as they can “trap” a person in light alpha wave sleep).

Melatonin and Ritalin were also noted as still being studied for effectiveness in CFS, but the response/results to these appear to be rather poor. (In one study of 60 CFS patients,

placebo-controlled, using 10 mg. BID of Ritalin, only 17% of subjects reported decreased fatigue with 22% showing improvement in concentration.)

The following information on immune modulatory treatments comes not from her lecture, but directly from Klimas' PowerPoint notes. The text of the notes is as follows: "Ampligen, a immune modulator and antiviral (Phase 3 recently completed); Allergic immunotherapy to down regulate allergic drive; Future immunomodulators (trials underway): Isoprinosine, thalidomide, anti-TNF-alpha monoclonal Ab."

Dr. Klimas's PowerPoint notes (not mentioned in lecture) also state, under HPA-axis interventions—"Growth hormone study – was in Phase 1 (Antwerp study)."

Dr. Klimas mentioned a drug that is being used in Japan called Neurotropin is used to treat reflex sympathetic dystrophy and other painful conditions. Neurotropin is a "non-protein extract of cutaneous tissue from rabbits inoculated with vaccinia virus." There is some indication it may be helpful with CFS. However, the drug has not undergone clinical therapeutic testing in the United States." (Source: *Clinical Trials – NIH site*).

A survey was been done at the University of Iowa to determine things that patients have tried and found to be helpful. (Bentler SE, *J Clin Psychiatry* May 66(5) (2005): 625-32). A few supplements: Co-Q10, DHEA and ginseng were found to be helpful.
*[Ed. Note: Treatment with DHEA can have very serious side effects and must be managed and*

*monitored by a competent physician. Dr. Klimas has stated she is against such treatment. Also, there is some literature that of 3 types of ginseng, only one is helpful to CFS patients, while the other two types may worsen symptoms.]*
Vitamins predicted improvement. Yoga seemed to be the most helpful form of exercise and treatment. However, the subjects in this study were described as having "unexplained chronic fatigue of unknown etiology for at least 6 months"—hence participants may or may not have had CFS.

Another study at the Univ. of Georgia (Black CD and McCully KK, *Dynamic Medicine* Oct 28; 4 (2008): 10) examined how people with CFS were initially able to meet target goals in a prescribed daily walking program (for 4 to 10 days), but then these individuals developed exercise intolerance and worsening of symptoms. Dr. Klimas feels exercise is beneficial, but it is usually is best tolerated in short intervals (even 5 minutes at a time) with many rest breaks in between.

Dr. Klimas' PowerPoint presentation (not presented in lecture) also noted certain dangers of nutritional interventions including: "Licorice root—potassium deficiencies [that can affect the heart]; 'supplements' that are actually hormones [including DHEA]; 'supplements' that have iffy contents—eg., St. John's Wort, melatonin; products that make unsubstantiated claims; Under and overhydration." *[Ed. note: either of these states can be very serious. Having enough water is important, but drinking too much water can harm essential physiological systems and processes.]* Everyone should really exercise caution about taking supplements without a full appreciation of their side effects or interactions with current medications.

So, what we can take away from this latest presentation is that there have been ongoing studies to help better understand CFS/CFIDS/ME. The breadth and depth of biologically-based CFS/CFIDS/ME research is expanding. There is some promise of more effective

therapies—targeted to specific physiological systems—becoming available. Researchers conducting gene expression studies also hold out hope that their research may yield effective therapies.