These overviews do not follow the conference’s agenda (fatigue, pain, gender, sleep, etc.). Several of those sessions were undersubscribed and had papers on different subjects shoehorned in to fill them out. In order to obtain a more orderly presentation some new sections (cardiovascular/vascular, Exercise and CFS) are added in this overview while others are retained (Brain, Immune, etc.). Papers that I found most interesting are highlighted. Some overviews are found under more than one category.

**CONFERENCE HIGHLIGHT**

**A Biomarker For CFS?**


This paper appeared some time ago but it was difficult, given its highly technical nature, to understand its significance. It appears that it may be highly significant indeed. Visible and near infrared spectroscopy has been used in a wide variety of applications involving such diverse fields as agriculture, chemistry, pharmaceuticals and the petrochemical industries. Somehow these innovative researchers thought to try it out on CFS patients and it worked - in spades.

Thankfully, this study, with 92 CFS patients and 71 controls, was quite large and therefore probably quite robust. Two different statistical analyses identified 95% of the CFS serum samples (220/231) and 98% of the healthy serum samples (209/213) correctly. This is far more accurate than any other putative biomarker that has been proposed with respect to CFS. Rich Van Konyenburg queried Dr. Kuratsune about just what proteins the spectroscope was picking up but patent issues precluded him from divulging them.

This process is unbelievably easy to use. Dr. Sakudo noted that in contrast to the lengthy and subjective process now required to diagnose CFS patients that the NIH spectroscopy is objective, very rapid (takes less I second) and requires no experience and no skill (!). It looks like one simply attaches a probe to one’s thumb and the machine quickly analyses the data and spits out the answer! In his overview Dr. Lapp said it was like Star Trek!

What a breakthrough this would be. It would quickly and easily identify CFS patients, give researchers clues regarding its pathophysiology, further legitimize CFS, help build coherent sample sets, etc. It sounds almost too good to be true - and it may be. These researchers are pioneering the use of NIR Spectroscopy in the field of medical diagnostics. NIR spectroscopy has been used to document blood flows in the medical field but has not been used as a diagnostic tool. NIR spectroscopy’s failing in the past has been a lack of specificity that requires researchers to use sophisticated statistical tests to delineate its results.

This team, however, appears to be highly encouraged by their results. They talked about using it as a worldwide diagnostic tool and called for further international collaboration. They are also looking for and finding unique spectroscopic signatures in other diseases such as lupus. If they are successful, the implications of their work could obviously spread far beyond CFS - it’s no wonder they’re applying for patents.

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**A Clinical Trial Fails - and an Opportunity Opens**

Barry Hurwitz, Nancy Klimas, Rasha Lawrence, Nancy Gonzales, Alex Gonzalez, Anna Rusiewica, Johanna Klaus, George Sfakianakis and N. Schneiderman. Therapeutic effect of epoetin alpha on red blood cell volume, perceived fatigue and susceptibility to syncope in Chronic Fatigue Syndrome: Miami Epoetin Alpha Clinical Trial.

Dr. Hurwitz and his colleagues have been working on this major study on low red blood cell (RBC) volume sponsored by the NIH for over five years now. Low blood volume has been reported in CFS since about 2000. Several researchers have been able to increase the blood volume in CFS patients but have not seen much clinical benefit from doing so. This complex study assessed the level of RBC volume in about 60 CFS patients, tried to increase it using epoetin alpha, and then noted the effects of doing so.

They found that 70% of CFS patients had low RBC volume, an unusual condition called ‘normochromic normocytic anemia (NNA)’. This was a good start. It verified past study findings -something one cannot take for granted in CFS - and appeared to identify a possible subset. Epoetin alpha did increase CFS patients RBC levels to normal levels, but aside from a bit better performance on the tilt test, it had no effect on their fatigue or symptoms or quality of life; low blood volume is a secondary rather than a primary facet of CFS. That is, it does not cause CFS but is caused by whatever is causing CFS. The study, then, seemed to be something of a wash.

Yet this study did confirm that blood volume is decreased in most CFS patients. We can, therefore, think of LBV in the same light as a trail of bread crumbs through the forest; if you follow it closely enough it will lead you home. This team will, therefore, attempt to figure out what is causing this unusual problem. Dr. Hurwitz noted that pro-inflammatory cytokines can suppress red blood cell production and that’s where he’ll look next. So here we are back again at inflammation.

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**THE ANITIVRAL STUDIES**

**CONFERENCE HIGHLIGHT**

**Fixing CFS I**
Montoya, Jose, Kogelnik, A., Hoehg-Petersen, M., Rosso, F., and Hischei, C. Use of valganciclovir in patients with high antibody titers against human herpes virus 6 (HHV-6) and Epstein-Barr Virus (EBV) who were experiencing virus induced fatigue with CNS dysfunction (VIFCD).

This study will only apply to a subset of CFS patients but its findings were so compelling that it was one of the highlights of the conference. The authors identified their patients as having ‘virus induced fatigue with central nervous dysfunction’ – not CFS per se but if they didn’t have ‘CFS’ they must have been darn close. These patients had high antibody titers to two common, opportunistic viruses, the HHV-6 and Epstein-Barr viruses that have long been of interest in CFS. This small study contained just two patients.

These patients were treated with the antiviral drug Valganciclovir for six months. Interestingly not all had declines in their antibody levels; some in fact had increased antibody titers (!), and all felt worse between weeks two and four, but all reported greatly increased energy levels. In fact the energy scores were high enough to suggest that almost all were well or nearly well, and most remarkably, they appeared to stay that way even after the medication was discontinued. Dr. Montoya pointed out one patient who must have been bedridden (5% energy level) before the trial but who had essentially recovered her health by the end of it. She had been ill for over 7 years. The consistency of the improvement was dramatic. No side effects were seen.

This small study suggests, as others have, that well focused antiviral trials can be very effective in the right patient. Dr. Montoya warned that Valganciclovir is a serious drug that can have serious side effects. This was a pilot Study (there was no placebo group, etc.), but its results were positive enough that De Roche Pharmaceuticals is coughing up $1.3 million to study this issue further in a study beginning this year. If you’re this kind of CFS patient – which may only be a small subset of CFS patients – this study may end up being very good news indeed.

CONFERENCE HIGHLIGHT
Fixing CFS II


The above finding was probably not surprising to Martin Lerner, who has been finding that well targeted antiviral treatments have been effective in CFS for years. Dr. Lerner explained that he had been stricken with tremendous fatigue, light-headedness, muscle aches and exercise intolerance in 1988. An examination indicating his heart was dilated sparked his interest in cardiac issues in CFS. He was cured in an antiviral trial in the mid 1990’s. Dr. Lerner is quite old now - he walks with a stoop - but he gave an impressive presentation.

All his patients (37) meet the criteria for CFS and Dr. Lerner required that is study patients have initially high antibody titers to EBV and human cytomegalovirus (HMCV). Patients were given an oral form of the antiviral valganciclovir. Various measures of cardiac functioning and energy levels were assessed.

At six months energy had improved significantly and at three years was greatly improved with patients reporting energy levels at 7-8 out of 10. Antibody titers diminished over time and heart measures improved. Symptoms such as sore throat, fever, swollen lymph nodes, chest pain, fainting, palpitations and muscle aches either decreased or ‘more often’ disappeared. Dr. Lerner also stressed that treating the right CFS subset was critical to this protocol’s success.

THE FIRST FDA APPROVED DRUG FOR CFS?

David Strayer, Tom McCarron, Ying Han, William Carter, Staci Stevens. Meta-analysis of well-controlled, randomized, double-blinded, phase III/II clinical trials of Poly I:Poly C12U vs placebo in Chronic Fatigue Syndrome (poster).

It seems that Ampligen’s long and winding road through the Food and Drug Administration’s bureaucracy may finally have come to an end. Ampligen first crossed paths with CFS in the late 1980’s. It aroused great excitement in the early 1990’s but at one point appeared to be down for the count. Hemispherix Biopharma persevered, however, and the clinical trials of the last few years have been successful; Ampligen has now passed both Phase II and III clinical trials and appears set to become the first federally approved drug for CFS.

The number of CFS patients tested was quite large (326). The results were not overwhelming - a 24% increase in endurance versus a placebo group on a treadmill test but they were much better than other drugs that have gotten federal approval. Refreshingly, for an antiviral especially, side effects were mostly minimal and did not significantly differ between the placebo and the Ampligen group.

We know that CFS patients are a mixed bag and that some people respond very, very well to this drug and others don’t. This suggests that hidden within these rather modest results is a group of people who did very well. In contrast to the other antiviral trials, this study’s CFS patients did not have to display high antibody titers to a pathogen to enter the study; they simply had to have a high degree of disability and pass a treadmill test.


In a recent edition of Phoenix Rising we saw Lactobacillus acidophilus (LA) bacteria supplementation improve immune functioning in people with overtraining syndrome (click here). Here Dr. Sullivan states that LA can "normalize the cytokine profile" and has antioxidant effects. We have seen increasing evidence in this conference that if CFS is not an inflammatory disease, it at least has a strong inflammatory component. These researchers gave a probiotic product (Cultura Dofilus Natural Yoghurt, Arla Foods) to 15 CFS patients for 30 days and found that 40% of them reported improvement. The abstract did not say how much or where. If this is simply a yogurt product it’s interesting that such a weak formulation would be helpful; lactobacillus capsules, which are readily available in health food stores, contain far more probiotic bacteria than does yogurt.

Garth Nicolson. Lipid replacement and antioxidant therapy for restoring mitochondrial function in fatiguing illnesses and Chronic Fatigue Syndrome (poster) - Click here for an earlier overview of this study.

Jacob Teitlebaum, Clarence Johnson. Effective treatment of Chronic Fatigue Syndrome and Fibromyalgia with D-ribose (poster) - Click here for an earlier overview of this study.


D. Blockmans, P. Persoons, R. Ellithorpe, R. Settieneri. A randomized, double-blind, placebo-controlled cross-over study with Methylphenidate in sixty patients with Chronic Fatigue Syndrome (poster). Click here for an earlier overview of this study.
and that bringing down the heart rate went up about 20%. This patient was clearly able to exercise at higher levels while on IV saline. She reported improved activity. They found that her peak oxygen intake during exercise (peak VO2max) went up by 30-50%, her peak minute ventilation almost doubled and her peak and a half. These researchers at the Pacific Fatigue lab examined her cardiopulmonary responses to exercise as well as symptoms.

EPO and the Immune System

Ritchie Shoemaker and Margaret Maizel. Treatment of elevated C4a in patients with CFS using low doses of erythropoietin safely reduces symptoms and lowers C4a: a prospective clinical trial (poster).

One exercise study showed that CFS patients have increased levels of a powerful pro-inflammatory anaphylatoxic component (C4a) of the complement response after exercise. Despite its positive result this study seemed to be doomed to the dustbin of CFS research history as it has never been replicated and is now only rarely mentioned. Dr. Shoemaker certainly took notice of it, however, as he reports here that he has found that levels of the C4a protein have been commonly elevated in the 1000 CFS patients he has seen. Consider that earlier study replicated!

Erythropoietin (EPO), interestingly, given its function as a blood volume enhancer, is apparently also very effective at reducing C4a levels in inflammatory diseases. This lead to Dr. Shoemaker giving 60 CFS patients 8000 units of EPO five times over 15 days and then measuring their C4a and symptom levels.

The results had an interesting dichotomy; while the C4a levels in all the patients dropped, about 80% of the patients symptomatically improved while 20% did not. It turns out that the 20% who did not improve had exceptionally high C4a levels. Normal C4a levels are below 2830 ng/ml. The responders dropped their C4a levels from 8300 to near normal, about 1200 ng/ml. The non-responders initial levels were so high, about 19,500 ng/ml that even substantial improvement still left them with higher levels than the responders had at baseline (12,500 ng/ml). In short, it appeared that their C4a levels were too high for the EPO to give them relief at the dosage given.

What happens after CFS patients get off a drug is almost as important as what happens when they are on it. Dr. Shoemaker found that 2/3 of the responders relapsed while 1/3 of them did not. This short test of EPO appeared to fix the C4a problems in the non-relapsed group - their C4a levels remained low - but did not in those who relapsed - their C4a levels zoomed up again.

EPO and the Brain

Ritchie Shoemaker and Margaret Maizel. Treatment of CFS patients with elevated C4a using low dose erythropoietin corrects abnormalities in central nervous system metabolites and restores executive cognitive functioning (poster).

EPO has neuroprotective as well as anti-inflammatory (and blood volume) properties. There are two ways it protects nerve cells, both of which are of high interest in CFS; it improves blood flows in the capillaries and it prevents nerve cell apoptosis or suicide.

Dr. Shoemaker gave the same amount of EPO (5 doses of 8,000 units over two weeks) to 35 CFS patients and measured the metabolite levels in their hippocampus before and after treatment. Interestingly his initial testing found the same thing Paul Nestadt did in his MRS study (see Brain section); high lactate levels (77% of CFS patients) plus abnormal glutamate/glutamine ratios (97% of CFS patients).

He found that lactate levels normalized on EPO in all cases and glutamate/glutamine ratios normalized in just over half. He believes, in common with Dr. Park, that CFS is characterized by a systemic (central nervous system) inflammation and that bringing down the inflammation was the key to the cognitive improvements seen. He did note that the cognitive problems in his patients were not resolved. Both Dr. Natelson’s and Dr. Baraniuk’s cerebrospinal fluid studies may also suggest CNS inflammation is present.

Things Looking Up For The Men?

Ritchie Shoemaker and Margaret Maizel. Treatment of CFS patients with low levels of vasoactive intestinal polyptide (VIP) and shortness of breath with tadalafil improves exercise tolerance and pulmonary artery responses to exercise (poster).

Dr. Cheney, Dr. Park and Dr. Shoemaker all believe that elevated pulmonary artery pressure (PAP) plays a role in the cardiac problems seen in CFS. Dr. Cheney and Dr. Park have flagged cognition; here Dr. Shoemaker focuses on exercise intolerance. Dr. Shoemaker noted that drops in PAP during exercise allow for increased venous blood flows to the heart. Echocardiography tests provide indirect evidence that PAP does not drop in CFS patients during exercise. This suggests that reduced blood flows to the heart could play a role in the exercise intolerance seen in CFS.

Tadalafil also improves erectile dysfunction. Tadalafil is, in fact, the last of the big three drugs (Viagra, Levitra, Cialis) that have recently been introduced in the American market to improve male sexual performance. A study by the Los Angeles researcher, Dr. Friedman, is attempting to increase brain blood flows in CFS patient with Viagra.

Dr. Shoemaker gave 20 mg. tadalafil every 3 days to 30 CFS male patients for a total of 5 doses. Changes in erectile ‘behavior’ were noticed in 93% of males, symptom reduction occurred in 90% and PAP improved in 84%. Both shortness of breath and fatigue after exercise improved. Once again CFS patients appeared to respond quickly and positively to Dr. Shoemaker’s regime.

Summary - These were all preliminary studies; there were no control groups, no placebos, etc. We don’t know how much symptom improvement occurred in each or how much improvement in PAP was seen. We also don’t know what accounted for the different results in Dr. Hurwitz’s and Dr. Shoemaker’s EPO trials although Dr. Shoemaker did use about double the dose that Dr. Hurwitz did. We saw that even that dose was insufficient to help the CFS patients with very high C4a levels - perhaps Dr. Hurwitz’s dose was, despite its efficacy in bringing blood volume levels up to normal, still too low.

Researchers often gather preliminary data before they apply for a study. This is presumably what Dr. Shoemaker did here; he tried these drugs out in his patients - saw improvement - and then did a quick study that would hopefully help him secure funding for a full study.

Travis Stiles, Staci Stevens, Christopher Snell, Lucinda Bateman, Mark Van Ness. Intravenous saline administration improves physical functioning (poster).

This ‘study’ consisted of one patient who was given one liter per day of 0.9% saline solution via a central venous line thirteen times over a year and a half. These researchers at the Pacific Fatigue lab examined her cardiopulmonary responses to exercise as well as symptoms.

They found that her peak oxygen intake during exercise (peak VO2max) went by 30-50%, her peak minute ventilation almost doubled and her peak heart rate went up about 20%. This patient was clearly able to exercise at higher levels while on IV saline. She reported improved activity.
tolerance, reduced muscle pain and fatigue, and improved orthostatic intolerance and cognition. When they took her off the IV saline, she relapsed; when they put her back on it, she rebounded.

What could be causing these improvements? IV saline does increase blood volume but blood volume enhancement has failed to produce symptom reduction in several studies. IV saline also enhances sympathetic nervous system activity. Not only does SNS control blood flows to the tissues, it also regulates immune system activity.

In 1999 Dr. Bell reported that IV saline temporarily improved his patients but that the effect was lost within hours.

CONFERENCE HIGHLIGHT

An Old Treatment Renewed?

Tae Park. Comprehensive treatments with IVIG for CFS (poster).

Dr. Park gave one gram of IV gamma globulin in 500 cc of normal saline infused over 1 hour once a week to 50 CFS patients for six months, none of whom were working at the time. He also monitored their sleep, prescribing Klonopin and/or Prozac (10-20 mg.) if needed, and their activity levels and diet, accentuating organic foods and avoiding bread, canned foods, chocolate, MSG, aspartame and hot pepper. His patients were instructed to drink 2-3 liters of water a day with 2-3 teaspoons of salt, and walk no more than 1 hour a day.

His patients did very well; most returned to work or school. Karposky scores rose from the 40’s to the 80’s or 90’s and their cognition improved. Importantly, problems with sleep apnea improved greatly. Some of the younger patients essentially recovered in one to two months. Three to five years later Dr. Park said these patients still maintained their near complete recovery.

A Talk With Dr. Park - In his poster Dr. Park noted several IV gamma globulin trials that have failed in the past. I asked him in an e-mail why he thought his trial has worked while others had failed.

He said that he believes that CFS physicians and their patients underestimate how important it is to have a toxic free environment. He believes that an increasingly toxic environment is a main contributor to CFS; that it is the toxins we are exposed to in our air, foods and water that disrupt our immune systems allowing latent virus reactivation. He prohibits his patients from living in newly built houses. He stated he often sees enlarged livers (and noted, to his surprise, that few physicians in the U.S. know how to ‘palpate’ livers.)

Gamma globulin is the most important agent he has to treat central nervous system inflammation. He notes that many of his CFS patients present with stroke-like or Parkinson’s-like symptoms and sleep apnea even after using CPAP and all of them show improvement with intravenous gamma globulin. Three to six months of IV gamma globulin has also been effective in improving the low renal blood flows noted in Dr. Park’s poster (in the IACFS I: Cardiovascular and Exercise Studies click here). As described in that poster Dr. Park believes that CFS is a disease characterized by systemic microvascular inflammation.

Dr. Park runs the CFS Clinic of South Korea in Seoul.