CFS PHOENIX

PHOENIX RISING: A CFS/ FMS NEWSLETTER by Cort Johnson	**SPECIAL EDITION: LAYMEN'S GUIDE TO THE 8th IACFS CONFERENCE**
Subscribe to PHOENIX RISING!	**PART I : The Cardiovascular and Exercise Studies and Fatigue Overview**

These overviews do not follow the conferences 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.

The conference began on a high note with an overview on the state of fatigue science in Japan.

CONFERENCE HIGHLIGHT

A Model of CFS Emerges in Japan

Introductory Overview to the Fatigue Section – Yasuyoshi Watanabe - after a short introduction by Nancy Klimas the conference was started off by Dr. Watanabe, a member of the Japanese delegation. Dr. Klimas has said that the Japanese government is spending more on CFS right now than the U.S. Not only are the Japanese doing a great deal of work on CFS they are doing it in a cohesive and integrated manner.

The Japanese are not studying CFS out of the kindness of their hearts. The Japanese government has come to realize that chronic fatigue poses severe economic costs (>10 billion dollars/year) and that it is in their interest to resolve it. This has lead several government ministries to fund several large scale research projects including "The molecular/neural mechanisms of fatigue and the fatigue sensation and the way to overcome chronic fatigue" from 1999-2005 and another project from 2004-2009. They have three chronic fatigue research centers and are supported by laboratories in 26 universities and institutions. Among other things they are trying to find and/or develop anti-fatiguing foods and drugs.

The Japanese have been mostly focused on the central nervous system (CNS). Dr. Watanabe stated that lesions in several parts of the frontal cortex (Broadman's Area (BA) 10,11) may alter the operation of our sensory system and effect motivation in CFS patients.

The neuroendoimmune dysfunction in CFS appears to be most related to the abnormal activity of five substances two neurotransmitters – glutamate and serotonin, acetylcarnitine, transforming growth factor-b and interferon. Abnormal activation of the serotonergic system in the anterior cingulate appears to be particularly important. Dr. Watanabe believes problems in the prefrontal cortex and anterior cingulate play a key role in CFS. We will see the anterior cingulate come up several times in the conference.

The Japanese attempt to develop chronic fatigue animal models underscores how intensely they are studying chronic fatigue. They are the kind of basic research study one would have thought would have been done long ago in a disease characterized by post-exertional fatigue! They have been talked about for years in the U.S. These animal studies, which assess just what happens when organisms become fatigued, appear to be a kind of backdoor way of getting at CFS.

The Japanese have found that fatigued animals exhibit reduced glucose uptake in the forebrain, mitochondrial dysfunction, cytokine upregulation (IFN, TGF-B and ?), changes in gene expression and serotonergic dysfunction. All of these have been found in CFS.

These researchers also measured @100 biochemical factors and were able to us them to develop an "index of exhaustion". This included reduced glucose uptake in the brain, reduction of the dopaminergic fibers in the brain, degeneration of the pituitary melanotrophs, and ? Dopamine is an intermediate in tyrosine metabolism and precursor of norepinephrine and epinephrine (noradrenaline/adrenaline). Dopamine plays an especially important role in the basal ganglia; a part of the brain that has long been of interest in CFS. Norepinephrine/epinephrine are the central neurotransmitters of the sympathetic nervous system and play a central role in the stress response – another area of great interest. Pituitary melanotrophs produce melantropin, a hormone.

The reduction of dopaminergic nerve fibers in fatigued animals suggests that fatigue is associated with problems with basal ganglia and sympathetic nervous system functioning. There is evidence for both in CFS. But what might cause the brains of CFS patients to resemble those of exhausted laboratory rats? Dr. Watanabe will attempt to answer that question in his summary of the brain section.

They also had healthy volunteers undergo four hour exercise sessions and looked for biomarkers of fatigue. They noted that when fatigue reaches a certain state that motivation drops. They were able to relate decreased levels of the alanine amino acid to physical fatigue and reduced levels of the branched complex chain amino acids and tyrosine to mental fatigue. Tryptophan losses were correlated with a kind of complex fatigue associated with both physical and mental fatigue. Tryptophan is a precursor of serotonin. Researchers have suspected it is involved in fatigue for some time and some evidence suggests tryptophan levels are altered in CFS.

They have found, interestingly, that an aromatherapy substance called 'green odor' activated the anterior cingulate in the brain and seemed to relieve symptoms of fatigue. This was quite a presentation and a great way to start the conference. We will hear more from Dr. Kuratsune and the other Japanese researchers later.

CARDIOVASCULAR/VASCULAR SYSTEM

More and more studies suggest there is something the matter with the circulatory systems of CFS patients. There's evidence of low blood flows to the brain and muscles, abnormal skin blood flows, low blood volume and others. Dr. Hyde suggested many years ago that CFS is a kind of vasculitis – a disease afflicting the vascular system. Several studies at this conference suggest that he may, at least in part, be right.

Dr. Spence's talk on arterial stiffness and inflammation in CFS was shoehorned into the pain section. Later Dr. Spence laughed and said he had a good paper on pain that he could have presented here. Unfortunately Dr. Spence was only given half his allotted time – 7 ½ minutes – to give a talk that was for me the highlight of the conference.

CONFERENCE HIGHLIGHT

Connecting the Dots – A Central Paper in CFS?

Vance Spence, F. Khan, G. Kennedy, C. Underwood and J. Belch. Inflammation and arterial stiffness in patients with chronic fatigue syndrome.

This talk actually raised the hairs on the back of my neck. Dr. Spence's interest in arterial stiffness was prompted by a single finding in an otherwise largely unnoticed paper that concluded that connective tissue problems are not present in adolescent CFS. This team did, however, find greatly increased arterial stiffness, an abnormality it had no explanation for. Dr. Spence said that this caught his attention - arterial stiffness is rarely found in adolescents and certainly not to this extent; these young CFS patients had higher levels of arterial stiffness than diabetes patients do.

Dr. Spence's study looked at several inflammatory factors (cholesterol, free radical by-products, c-reactive protein) that are often associated with arterial stiffness. It found abnormally high levels of free radical by-products and C-reactive protein in CFS patients but not controls, as well as arterial stiffness that was increased, if my notes are right, by about 50% - an enormous amount. A further statistical analysis indicated that C-reactive protein was significantly correlated with increased arterial stiffness.

But how to explain this unusual finding? Dr. Spence noted that none of the usual suspects involved in arterial stiffness (increased age, diabetes, arteriosclerosis, etc.) could account for it in these CFS patients. So what could be stiffening the arteries of CFS patients? When he suggested neutrophil elastase my mouth gaped open. Elastase is a central factor in Dr. De Meirleir's RNase L paradigm and that he often finds it elevated in his patients. Dr. Baraniuk's fluid cerebrospinal proteome study suggests elastase is implicated in blood vessel problems in the brains of CFS patients. When Dr. Spence indicated that logical consequences of increased arterial stiffness are exercise intolerance and diastolic dystunction the hairs stood up on the back of my neck. Talk about paradigms starting to meet up.

Elastase dissolves elastin, a substance which gives blood vessels, tendons and ligaments their elasticity. Monocytes, for instance, secrete elastase in order to allow them to travel through connective tissues and get at infections. A recent study found that increased serum elastase levels are associated with increased arterial stiffness (See Sources of Orthostatic Intolerance for more on elastase).

A Talk With Dr. Spence - This paper was the result of an alert researcher picking up on an obscure finding and putting the pieces together. I was able to talk to Dr. Spence later. The founder of the MERGE research/advocacy group, he is an enormously engaging and enthusiastic researcher with a severe case of CFS. If my notes are correct, he believes that the circulatory problems seen in CFS – which MERGE has been studying for some time now – may originate in a dysfunction of the endothelial cells lining the blood vessels. These cells are not only involved in opening and closing the blood vessels but in the immune response as well, and they are often attacked by pathogens.

Funding, funding, funding - MERGE has been able to turn out several small studies a year and I asked him about his funding. He said it was all from CFS patients giving what they could. He noted that MERGE is trying to fund seed studies that major funders will pick up on and expand.

Funding is, of course, a big problem for CFS researchers. Dr. Evengaard several times during the conference noted the almost non-existent rate of governmental funding of non-behaviorally oriented CFS research in Europe. She said that (aside from Japan) the U.S. is the only country willing to fund biologically oriented research studies. I asked Dr. Hanna about the possibility of the NIH funding studies outside the U.S. and she said there was no problem with that, that she is simply looking for multidisciplinary studies that seek to explain, not simply characterize CFS. I asked both Dr. Spence and Dr. Kerr if they were considering attempting to secure funding through the NIH. They both were but the process is long and demanding and Dr. Spence, as mentioned earlier, has a severe case of CFS. These creative researchers desperately need more money. You can contribute to Vance Spence and MERGE by clicking here.

CONFERENCE HIGHLIGHT

Explaining CFS?

Tae Park. Decreased renal function in CFS patients (poster)

In his poster Dr Park states that he believes that the unexplained bright spots ('unidentified bright objects') sometimes found in the MRI's of CFS patients brains are evidence of an 'arteriolar vasculopathy' or an blood vessel disease. Specifically Dr. Park believes that CFS is not is a '*systemic micro-vascular inflammatory process*' - a process would affect not only the brain or the heart or the muscles but potentially every organ system in the body. Dr. Park put his money where his mouth is by looking at blood flows in a different organ – the kidneys. He found that all of the CFS patients in this small study demonstrated markedly reduced renal blood flows (40-60% of norms). Dr. Park believes that the problems with medication intolerance/toxicity in CFS relate to poor drug clearance by the kidneys.

He is not alone in his interest in the microvasculature. Both the MERGE research team and Dr. Stewart have found evidence of microvasculature problems in CFS. Recent studies have found that women are more prone to microvascular problems in the heart than men and of course many more women than men have CFS. Is CFS a 'systemic micro-vascular inflammatory process'?

A Talk with Dr. Park - Dr. Park was gracious enough to explain his theory further in an e-mail. He has seen evidence of capillary inflammation and something called 'perivascular cuffing' in the autopies of CFS patients. *Perivascular cuffing refers to the accumulation of immune cells surrounding the blood vessels that have presumably been injured.* **He notes that viruses such as HHV-6A and EBV are able to attack the endothelial cells lining the blood vessels. Then he stated something very interesting; that despite the low renal blood flows the typical CFS patient is not diabetic or hypertensive and shows no evidence of kidney disease.** *Does this pattern occur elsewhere? We seem to have diastolic dysfunction without heart failure or heart enlargement and low muscle blood flows without metabolic dysfunction. Is CFS a disease in which chronically low microvascular blood flows impair organ functioning but rarely cause overt organ disease?* **He believes the low renal blood flows he's finding reflect lowered brain and heart capillary blood flows as well. He noted that his treatment protocol incorporating IV gamma globulin resulted in both improved kidney blood blows and cognitive functioning.** *Dr. Park's treatment protocol is discussed in the Clinical Trials overview.*

Dr. Park believes the increased rates of patent foramen ovale and diastolic dysfunction (see Dr. Cheney below) in CFS are caused by reduced capillary blood flows and upper airway obstructions that elevate the pressure in the pulmonary artery during sleep. Increased pulmonary artery pressure should elevate diastolic pressure and pop open the foramen ovale. *In his sleep summary Dr. Lappe stated he was intrigued by findings of upper airway resistance syndrome in some CFS patients. Dr. Cheney ascribes a different cause to elevated pulmonary artery pressures in CFS (see below). Dr. Park stated he has successfully treated heart problems in CFS using his protocol.*

ANOTHER Syndrome? Metabolic Syndrome and CFS.

Elizabeth Maloney, DrPH, MS, James Jones, Chrisine Heim, Roumiana Boneva, William Reeves. CFS is associated with high allostatic load in Georgia.

This study extends the CDC work on allostatic stress in CFS. 'Allostatic load' is a measure of wear and tear on the body. The Wichita study showed that particularly with regard to cardiovascular factors CFS patients carry a high allostatic load **(click here)**. *In their Wichita studies the CDC took a broad brush approach to CFS research looking a wide variety of different factors. Intriguingly, given the recent findings from Vance Spence of MERGE and Dr. Cheney and others, cardiovascular factors jumped out.*

This study, which extended the CDC's look at these factors, found that both the CFS and CFS-like patients had significantly higher rates of allostatic load associated with the cardiovascular system than did the normal controls. My notes indicated Dr. Maloney found increased heart rate, SDB/DBP, and levels of albumin and, most importantly, c-reactive protein in CFS patients compared to age, sex and BMI matched controls.

The CFS patients in the Wichita studies looked a lot like metabolic syndrome patients, an idea explored in an earlier edition of Phoenix Rising (click here). Dr. Maloney explained that metabolic syndrome is characterized by high rates of abdominal obesity (waist-hip ratio), high triglyceride levels and high lipid levels. Spence has shown that CFS patients have high levels of the oxidized form of the 'bad' cholesterol and low levels of the 'good' cholesterol as well as high levels of oxidized stress. Dr. Maloney found that 33% of CFS patients (versus 14% of controls) met the criteria for metabolic syndrome and that females with CFS were particularly susceptible to doing so.

Low activity levels and weight gain can contribute to metabolic syndrome. I asked Dr. Maloney if she thought the inactivity and the weight gain seen in CFS was the cause of the metabolic syndrome found? She thought that inactivity could contribute to it but was more focused on the high levels of the inflammatory marker c-reactive protein (CRP). The fact that this substance also showed up in Vance Spence's study interested her greatly.

(The CDC is careful to have body mass index matched CFS patients and controls in its research studies. Since both CFS and healthy controls were equally overweight it appears that something other that weight gain is causing the increased rates of metabolic syndrome in these patients. The higher waist/hip ratio's in the CFS patients compared to the controls suggests they have a metabolic problem that causes greater fat deposition in the abdominal area. Fat in this area appears to be unusually active, pumping out increased pro-inflammatory cytokines such as II-6.)

A key player in metabolic syndrome may be a pro-inflammatory cytokine called IL-6. Fortuitously a paper examining IL-6 levels in CFS was presented by another CDC researcher. This study was a highlighted not only because of its findings but because of its innovative approach to this issue.

CONFERENCE HIGHLIGHT

A New Way to Research CFS?

Brian Gurbaxani, Kristin Singletary-Meadows, Andrew Miller, Dimitris Papanicolaou, Suzanne Vernon and William Reeves. Elevated pro-inflammatory IL-6 in patients with Chronic Fatigue Syndrome.

Dr. Gurbaxani gave an engaging and at times hilarious presentation. He represents the kind of innovative younger researcher that has been attracted to the CDC CFS research program in the last few years. His resume is most unusual; he has a B.S. in Applied and Engineering Physics and a Ph.D. in Molecular Biology and Bioinformatics. His background includes writing 'satellite mission control algorhythms and large scale simulations of space stations' (!). He is currently involved in writing data mining algorhythms for large data sets in CFS and other diseases…he is not your typical CFS researcher.

Dr. Gurbaxani has been studying an important but puzzling aspect of CFS – pro-inflammatory cytokines. If CFS has an inflammatory component then the levels of these cytokines should be increased but study results - and there have been many CFS cytokine studies – have been mixed. If Dr. Gurbaxani is right then he may have found an explanation why.

Dr. Gurbaxani's initial analysis indicated that IL-6 levels were increased in CFS patients but not significantly so. Ordinarily this would be the end of the study; it would be deemed a failure, simply another study indicating that cytokine up regulation does not play a role in CFS. But Dr. Gurbaxani knows his numbers and he thought that something was not quite right; he felt the CFS data was different in a ways that eluded standard statistical tests and so he did some unusual analyses on them. These indicated that IL-6 levels in the CFS patients were indeed different – significantly different.

Then he looked at several of the measures we have been talking about; c-reactive protein levels and waist to hip ratio and symptom severity, and found that IL-6 correlated with all three. Through the course of his work IL-6 went from an insignificant variable to a potentially central factor in not only the inflammation but in the increased rates of metabolic syndrome found as well.

Could Dr. Gurbaxani's techniques shed light on the mixed results of prior cytokine studies? I ask Dr. Gurbaxani about this and he stated he had seen data sets in which he thought the same process might be occurring.

Why would cytokine studies or studies on other subjects for that matter in CFS come up with these unusual results? Why would a CFS researcher need to go to such lengths? One reason could be the heterogeneous group of CFS patients he or she is studying. Most diseases are well defined; when breast cancer researchers study breast cancer patients they know they're studying breast cancer not prostrate or brain cancer. Researchers don't know that with regard to CFS; they know they are researching a disease characterized by extreme fatigue and some other symptoms but they don't know if the source of that fatigue – the disease process – differs from patient to patient. Dr. Gurbaxani stated that after hearing CFS patient stories at the conference he believes there are probably many triggers for CFS.

Dr. Gurbaxani's abstract ended with a sentence that will be well to keep in mind not only with regard to Dr. Levine's study later in the conference but with other puzzling CFS research results. '*..information theory analysis shows that the distribution of IL-6 in CFS is different than control(s) in all of its aspects (not just mean values) suggesting a different process is at work in CFS*"

This different distribution could simply reflect the presence of subsets in CFS. If one set of CFS patients had high IL-6 levels but others didn't then a means test will look interesting but it will not pass the rigorous criteria required for it to be called significant. I asked Dr. Gurbaxani if he thought that subsets could be driving these weird distributions? He did. Dr. Spence of MERGE has made this point as well. Dr. Gurbaxani believes identifying subsets is the biggest problem facing CFS research.

Paul Cheney and N. Lucki. Evidence for diastolic dysfunction in the Chronic Fatigue Syndrome enhanced by tilt echocardiography: a study of ninety consecutive cases.

Dr. Spence indicated that a logical outcome of increased arterial stiffness was diastolic dysfunction, a subject Dr. Cheney has focused on for the last three years.

Again (see Keynote Speech, Patient Conference) Dr. Cheney drew our attention to the fact that "preserved ejection fraction heart failure in women is epidemic, unexplained and deadly." *Preserved ejection fraction heart failure refers to cases of heart failure in which the pumping action of the heart (systole) is preserved but the filling phase (diastole) is impaired.* He believes that his scenario of impaired cellular energy production – which should, as he noted in the patient conference, affect diastolic functioning long before it affects systolic functioning – could explain the abrupt recent rise in diastolic heart failure.

He described a range of observed abnormalities in diastolic functioning found in his CFS patients during Tilt table tests. In a small study he found that echocardiography during Tilt best differentiates patients from controls. *There is some disagreement about how well some of these measures reflect cardiac functioning but one of the measures Cheney presented called E/e' ratio is well correlated with cardiac functioning.* Dr. Cheney also found a high degree of atrial cavitation (50% of CFS patients), reversal of blood flow into the pulmonary vein, and abnormal E/A ratio's.

He believes the striking similarities in diastolic dysfunction in CFS patients and young men exposed to low oxygen environments indicates that CFS patients exist in a state of 'functional hypoxia'.

A Layman's Speculations (pay it no special mind) - In his keynote address Dr. Cheney pointed out that he first conceived that diastolic dysfunction (DD) was present in CFS when he saw that the greatest difference in cardiac output between CFS and healthy controls in the Peckerman study occurred when they were lying down. It is my understanding that the filling defect in DD is most evident at times when the most blood is present in the heart, i.e. when one is lying down. Cheney is finding, however, that the DD is greatest in CFS patients when they are tilted, a period when paradoxically, blood flows to the heart, especially in CFS patients with low blood volume, are at their lowest – and when pressure on the left ventricle to expand to fill with blood, is at its lowest. This would at least at first blush seem to be an odd time to exhibit increased diastolic dysfunction.

How to explain this conundrum? This a very complicated subject that I am ill qualified to speak on but for whatever its worth one school of thought believes DD is more a function of extracardiac factors than with heart disease; that is, these researchers believe the problem with DD didn't start with the heart – it started elsewhere and that DD is more a function of increased wear and tear on the heart that it is with a disease of the heart muscle itself. That most problems in CFS are at their most severe when one is standing could perhaps suggest that the DD dysfunction in CFS is a function of them, not of a damaged heart (?).

Another Cardiac Abnormality in CFS

Paul Cheney and L. Nucki. Evidence of increased frequency of patent foramen ovale (PFO) in the Chronic Fatigue Syndrome and enriched oxygen modulation of the PFO (poster)

We noted that Dr. Cheney believes that CFS patients exist in a state of 'functional hypoxia' or low oxygen levels relative to their needs (see **Keynote Address, Patient Conference**). He believes that a left-shift on the oxy-hemoglobin dissociation curve should raise pulmonary artery pressure and that this, in combination with the low blood pressures often found in CFS, would result in increased rates of the patent foramen ovale. Poor diastolic functioning would then increase the severity of the PFO.

Looking at 41 consecutive CFS patients he found 81% of them had PVO – the highest percentage yet reported in a disease. Two thirds required a Valsalva maneuver to open them and one third exhibited it without doing the maneuver. *The Valsalva maneuver consists of blowing hard with the mouth and nose closed. This raises venous pressure and is used to investigate some aspects of cardiac functioning including decreased filling, i.e. diastolic dysfunction. Some PFOs only open during strain such as lifting, during sex, etc. That most PFO's opened only during the Valsalva maneuver would appear to suggest that they are usually closed in 2/3rds of CFS patients (?).* Dr. Cheney graded the PFOs in severity – most were of low to intermediate severity. *This finding appears to be very similar to that of diastolic dysfunction in CFS – it is very common in CFS but is usually of a mild to intermediate level of severity.* Giving oxygen to these patients closed the PFO in about a third of them.

Dr. Cheney believes that these PFOs are the source of the 'unidentified bright objects' seen on MRI scans.

It's hard to tell how important these PFOs are. Two recent large Mayo Clinic studies concluded that PFOs are not a risk factor for stroke, ischemic attack or a 'cerebrovascular event' (Petty et. al. 2006, Meissner et. al. 2006). Several moderately sized studies do suggest, however, that PFOs are a risk factor for migraine. We will see in the Gene Section of the Conference that a study indicated that migraine is much more commonly found among relatives of CFS patients than would normally be expected. Some researchers believe that both migraine and CFS are diseases of central sensitization; one causing pain and the other fatigue. Of course migraine is temporary in nature while the fatigue in CFS is chronic. Large scale studies examining the PFO/migraine connection are underway. Aside from this possible connection, PFOs are not, at least this point, associated with any known symptoms in healthy people including fatigue.

A Summary - Cardiovascular/Vascular Implications in CFS - *What does all this mean? Are the increased rates of abdominal fat, elastase, arterial stiffness, IL-6, c-reactive protein, metabolic syndrome and diastolic dysfunction in CFS related? Are these researchers converging on each other from different directions? At least at this point it does appear so. High Il-6 levels, c-reactive protein levels and arterial stiffness are found in metabolic syndrome and all three may be risk factors for diastolic dysfunction. This is a complex subject, one that Phoenix Rising will be covering in more detail as these studies are published.*

EXERCISE AND CFS

I loved the understatement made by the Snell group in one of their abstracts "*For many patients these problems are exacerbated following physical activity and adversely affect their work, social and even family lives. For such a prominent symptom of CFS research in this area has been limited. . . "*

Yes, it is amazing how little research has been done on what many CFS patients consider their most unique symptom – the crushing fatigue and/or pain and cognitive dysfunction, etc. that occurs after (too much) exercise. If someone had asked me what to study in CFS 20 years ago I would have said whatever you do find out what happens to me in the hours and days after I exercise. Give me an exercise test and start taking blood, start scanning my brain, etc.

There are some things we do know. One study suggested immune activation (complement system) occurs after exercise and a gene expression study found evidence of altered ion channel transport activity. *Please note that nothing in this section implies that CFS patients should not exercise to the extent that they can without relapsing.*

The CFS Brain on Exercise – Not a Happy Place

A. Garcia Quintana, A. Garcia-Burillo, J. Alegre-Martin, I Mena, J. Garcia-Quintana. Brain SPET quantification in Chronic Fatigue Syndrome: comparison of basal and post-stress studies.

The enterprising Garcia Quintana group from Spain used a SPET scan to examine brain activity before and after an exercise session. This is the first time, to my knowledge, that this has been done. It found that one area in particular, the Wernicke area, showed evidence of reduced activity after exercise. This area, which is found in the cerebral cortex, is thought to be 'essential for understanding and formulating coherent . . . speech.' Other areas in the temporal lobe were affected. Interestingly it was difficult to tell if the anterior cingulate region – a

region we will see mentioned time and time again with regard to CFS – was affected, because the activity in this region was too low to begin with.

Immune Activation During Exercise

J. Alegre-Martin,T. Soriano Sanchez, C. Javierre, J. Quintana, E. Ruiz, T. de Sevilla, K. De Meirleir, and A. Quintana. Study of biological markers, ergometric parameters and cognitive function in a cohort of patients with Chronic Fatigue Syndrome / Associations between biological markers, ergonometric parameters and cognitive function in a cohort of patients.

These studies found that the majority of the CFS patients had increased rates of RNase L activity (83%), RNase L fragmentation (88%) and a whopping 95% had increased elastase levels. They also have decreased 'functional reserve' and peak aerobic power. The high elastase readings were, of course, intriguing given Dr. Spence's supposition that elastase was driving the high levels of arterial stiffness he found. These researchers suggested that the RNase L abnormalities could contribute to the muscle symptoms found.

Dr. De Meirleir's research indicates that elastase is a key player in the responsible for the RNase L fragmentation found in CFS. High elastase levels alone will not fragment the RNase L enzyme; that process also requires that the RNase L enzyme be left in an unprotected state. I asked Dr. De Meirleir if high levels of a protease like elastase were, however, a necessary component of RNase L fragmentation and he said that it was. The question, then, becomes what is driving the increased elastase production?

The study that employed an exercise period found that RNase L activity in CFS was correlated with lactate concentrations, an intriguing finding given the increased lactate levels in the brain found earlier. *Blood lactate research in CFS has, however, had a decidedly mixed history with some studies showing elevated lactates and others not. This could suggest that a subset of CFS patients have elevated lactate levels.*

As we have and will see in this conference some researchers (Gurbaxani, Levine, Natelson, Lange, Klimas/Fletcher, De Meirleir) are starting to look for these subsets hidden within their study results. One can only imagine how much more significant research findings would be if more researchers tarted looking for and identifying 'anomalies' or subsets in their data – and then focusing on that set of patients. .

Klimas, N., Rosenthal, M and M. Fletcher. Immune effects of an acute exercise challenge in Gulf War Illness (poster).

This is a preliminary report from a large study focusing on immune markers and gene expression before and after exercise in GWI, CFS patients and healthy controls. It found that NK cell counts went way up following the exercise period but that T-cell counts remained the same. Unfortunately they don't tell us if this pattern was different in the controls versus the CFS or GWI illness subjects but this study does show that NK cells are sent into a tizzy after exercise and given the NK cell abnormalities found in CFS this is an interesting finding.

No More Messing Around - Taking Exercise Stress Tests to the Next Level

Rudi Vermeulen, Ruud Kird, Hans Scholte. A standardized test for post-exertional malaise in CFS? (poster)

This Dutch group carried the exercise testing regime one step or rather one day further by having CFS patients and healthy controls exercise three times over four days. It found that all the healthy controls and half the CFS patients improved their aerobic functioning in the second exercise trial. This would be enough for some CBT practitioners to say I told you so – that group is not sick! – and then instruct them to exercise their hearts out (perhaps literally). When these researchers extended the exercise test one day further, the test scores (VO2 max) of a big chunk of the CFS patients (25% more) declined - now 75% of the CFS patients were hurting. If they kept giving this test day after day they would surely find that all the CFS patients started falling apart.

This suggests what seems to be a rather obvious idea in retrospect, that one way to differentiate people with CFS from people with something else is through multiple day exercise testing. If post-exertional fatigue is a true marker of CFS and that fatigue is reflected by measures of aerobic output, then this test should differentiate 'true' CFS patients from others, or at least from any subgroup of CFS patients who do not exhibit post-exertional fatigue. Of course this test would have to be limited to people who are not completely disabled by CFS.

The SNELL EXERCISE STUDIES - The Snell group, which is associated with the Pacific Fatigue Lab in the University of the Pacific in California, has focused closely on the post-exercise period. They are sponsored by the CFIDS Association of America.

CONFERENCE HIGHLIGHT

Finally! A Stress Test That Works – Hope For Disability Seekers.

Margaret Ciccolella, Christiopher Snell, Staci Stevens, Travis Stile, Mark Van Ness. Pacific Fatigue Lab, University of the Pacific, Stockton, Ca. Chronic Fatigue Syndrome and the Abnormal Stress Test.

Documenting disability has been a real problem for CFS patients. The government believes that given their fatigued nature CFS patients should be unable to pass a stress test. Unfortunately CFS patients have shown a disturbing reluctance to failure them. Dr. Ciccolella reported one CFS patient who had four physicians testify as to his/her disability whose request for disability was nevertheless denied because he/she had passed a stress test. (This finding was overturned at the appellate level).

Dr. Ciccolella's theory was that since a single stress test would probably be insufficient to document disability in a disease characterized by post-exertional fatigue, they would do two, one 24 hours after the other. They found that while the control group did equally well at both tests, the exercise measures (Peak VO2, VO2 max) declined about 25% in CFS patients, far more than in other significant diseases such as COPD and heart failure (8%). This two-day stress test then provides objective evidence of disability in CFS and should provide, if it is accepted, major assistance to CFS patients attempting to get disability. This could be a real breakthrough.

Christopher Snell, Staci Stevens, Lucinda Bateman, Travis Stiles and J. Mark Van Ness. Using a reaction time paradigm to assess Neurocognitive Function in CFS.

So far we've found that if you test CFS patients after an exercise challenge, they exhibit declines in aerobic functioning and their NK cells proliferate wildly. Now the Snell group looks at cognition: CFS patients often complain that they have more trouble thinking after exertion. This study put that idea to the test; they measured a very simple measure of cognition – reaction time to both simple and complex stimuli - before and after an exercise test. It found that while CFS patients were slower, the results were not statistically significant. When they looked at all the test results together, however, there was a statistically significant difference. They also noted that variability within the CFS group was high while it was not in the control group. This suggests that some CFS patients did fairly well on these tests while others did not.

Perhaps the Dutch study noted above is informative in this regard. That study showed that a significant number of CFS patients who tolerated that first exercise test declined during the next one. Would a follow-up exercise test made their results more definitive?

It Hurts So Good? - No, It Doesn't

Staci Stevens, Christopher Snell, Lucinda Bateman, Travis Stiles and Mark Van Ness. Post-exertional malaise following an exercise test. (poster).

This was not an earth shattering study but it demonstrated very starkly how severely exercise affects CFS patients. After sedentary healthy controls and CFS patients exercised to capacity they were given SF-36 tests that characterize functioning in eight different areas: physical functioning, reduced activity levels because of physical problems, emotional problems, bodily pain, perception of general health, vitality (energy), social functioning and mental health. This study found that CFS patients reported significantly more problems in all eight areas compared to the flabby but still healthy controls. Only one of the 21 CFS subjects had recovered to baseline within 48 hours while all the healthy controls had. This, of course, indicates that the exercise problems in CFS are not due to simple inactivity – the healthy controls were sedentary as well - but are an integral problem of the disease itself.

No Immune Activation During Exercise?

J. Mark Van Ness, Christopher Snell, Staci Stevens, Lucinda Bateman and Travis Stiles. Metabolic and immune responses to exercise testing.

This was an attempt to examine immune, metabolic (blood glucose, lactate) and sympathetic nervous system (nasal rhinometry) functioning during exercise and, with regard to the immune measures (RNase L fragmentation, elastase), after the exercise period in CFS patients and controls.

In contrast to the others this study failed. While CFS patients had significantly lower cardiopulmonary scores (VO2 max, etc.), rates of RNase L fragmentation and elastase activity were not increased after the exercise test. Nor were the measures of sympathetic nervous system functioning or metabolism different.

This is, unfortunately, rather familiar territory for CFS. Here we have one study showing increased rates of RNase L fragmentation and lactate and one showing no difference. Which is correct? Do the large numbers of CFS patients in the Garcia-Quintana study trump the control group in the Snell study? Or vice versa? I have no idea.

Summary – We're seeing some real breakthroughs in the ability of extended exercise studies to reveal the disability present in CFS. These studies should give CFS greater credibility and new ammunition to use when applying for disability. Researchers are having more difficulty understanding what occurs during and after exercise in CFS. Explaining this problem seems to be one of the more difficult questions facing CFS researchers.

The brain scan study indicated reduced brain activity after exercise and the aerobic tests indicated similar declines in aerobic functioning. The role RNase L plays in exercise intolerance, however, is up in the air and tests of sympathetic nervous functioning and metabolism were negative.

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