PHOENIX RISING

A CFS/FMS/MCS NEWSLETTER

FROM CFS PHOENIX
Phoenix-cfs.org

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The Phoenix is a Mythical Bird That Rises Rejuvenated From Its Ashes

By Cort Johnson

Please Subscribe to Phoenix Rising

Phoenix Rising is a monthly newsletter committed to elucidating current CFS research, describing important events, telling patient stories, suggesting alternate treatments for CFS patients, etc. Please contribute to Phoenix Rising. Please send submissions, comments and/or clarifications to Phoenixcfs@yahoo.com)

NEWS

Free Canadian CFS/FM Legal Resource - FM-CFS Canada announces the launch of a new resource for patients and lawyers. The Law Zone: will give you 1) Free legal research, 2) Expert Questions & Answer, 3) Informative Links http://fm-cfs.ca/law/Legal-Index.html

FM-CFS Canada, Canadian lawyers, and law students are reviewing FM & ME/CFS cases in Canada. We're observing what does and doesn't work, patterns, judge histories, and more. We're doing this strategic review so your lawyer doesn't have to; so each lawyer doesn't have to reinvent the wheel. It's Free!

John Ernst, Executive Director, FM-CFS Canada. hope@fm-cfs.ca Toll-Free: 1-877-437-HOPE (4673), Direct - 1-613.565.2423, Charitable Registration No. 89241 7742 RR0001

New CFS Study – Some CFS physicians have believed for many years that poor mitochondrial functioning is very important in CFS but this topic has never been embraced by the research community. Finally we have a study looking at this issue. A USC physician is looking for people afflicted with CFS (and/of fibromyalgia) who would be interested in participating in this study. Participants will be asked to

(1) Fill out a short survey (3-4 pages) regarding your CFS/FM. (2) Fill out a second survey (4-5 pages) regarding symptoms (3) Provide a hair sample for DNA analysis (4) Invite family members (siblings, parents, children, grandparents, cousins, whomever might be available) to fill out the 2nd survey and possibly provide a hair sample for DNA analysis. (5) If necessary, provide a blood sample for a more in depth DNA analysis.

All of this can be done by mail, participants do not need to be from the Los Angeles area. If you are at all interested in participating in this study, please contact me by email at stbrown55@yahoo. com <mailto:stbrown55% 40yahoo.com> Stephen Brown, Ph.D.

Get Trained to Produce Results at the International Association for Chronic Fatigue Syndrome their *8th International IACFS Conference on chronic fatigue syndrome, fibromyalgia, Gulf War*

syndrome, and other related illnesses, Jan 10-14, 2007. The first day of the conference will be dedicated to Advocacy highlighted by the 2007 Advocates Extraordinaire! Program. It consists of an outstanding Advocacy and Leadership training, a first for our community in a patient conference for CFS as well as the presentation of the 2007 Sand Castles Awards. Nothing is more important for CFS than committed effective advocacy. Here is the link for complete information: http://www.pandoranet.info/THE8THIACFSCONFERENCE.html

Dr. Lloyd 'Talks' – Dr Lloyd is engaged in the fascinating Dubbo studies that are examining people as they lapse into CFS after getting infected with a pathogen. You can check out Dr. Lloyds powerpoint presentation at

http://www.mecfscanberra.org.au/actmecfs/act_science%20week.htm

New Jersey Chronic Fatigue Syndrome Conference - MANAGING SYMPTOMS & EXPLORING NEW RESEARCH FOR THE CFS PATIENT, Sunday, October 22, 2006, 11:30 am to 5:00 pm EST with Bernard Natelson, Lucinda Bateman, Susan Levine and others. For schedule and location - www.NJCFSA.org

Food for Brain Conference in London – will discuss how foods and food supplements can effect the brain and be used in treating diseases like CFS, autism, etc. Our own Dr. Basant Puri will be there among others.
http://www.foodforthebrain.org/content.asp?id_Content=1653

Cognitive Behavior Therapy Database available. This is a stand-alone comprehensive guide to the use of CBT and GET on patients with Myalgic Encephalomyelitis (or ICD-CFS). The database contains excerpts and links to literally hundreds of articles and research studies which expose the lack of scientific legitimacy underlying the 'behavioural' paradigm of M.E. You can download a copy of the entire 128 page database (or a 30 page summary) in Word or PDF formats and distribute paper copies.
http://www.ahummingbirdsguide.com/cbtandget.htm

US/Canadian DVD's Of London CFS Conference Available - Invest in ME has announced that an NTSC version of the ME Conference 2006 DVD will now be available from next week. This version will play on US/Canadian players/TVs without a converter.Both versions of the DVD (PAL and NTSC) will play on a PC using normal DVD software.

If you would like to confirm your order, or add to your order, or change your order to the NTSC version, then please email us at you convenience .www.investinme.org

Pat Fero Talks About the Reno CFS Research Center – Pat Fero, the director of the , recently participated in a . Read her report about the first state CFS research center to open in the US.

Support CFS Group Going National – the Denver CFIDS/FMS Suppoprt group, http://www.rmcfa.org/index.html is going national. Check out their beautiful website and support them in their efforts to engage national speakers, produce newspaper articles, expand 'RMCFA' support groups, create press releases, do radio interviews, sponsor a CFIDS/FMS

Convention in Denver, conduct research, etc. Lots of possibilities here! Please contact Mike Munoz, at mmunoz@rmcfa.org or 303/4cfsfms (303/423-7367)if you can help.

CFS, ME & FM Awareness Postcards – Series 2 – This is the CF-Alliance's next series of CFS postcards created by talented Chronic Fatigue Syndrome, Myalgic Encephalomyelitis, Fibromyalgia artists in order to raise awareness about Chronic Fatigue Syndrome, Myalgic Encephalomyelitis, etc/ The set contains ten glossy 4" x 6" postcards printed on heavy cardstock and are only $7.00. Each postcard beautifully depicts one of the four seasons. **http://www.cf-alliance.com/**

The PHOENIX RISING 'RESEARCHER OF THE YEAR'

Researchers must publish a paper in order to eligible to qualify for 'Researcher of the Year'. Researchers of the year are judged based on their past and present research efforts and the impact they make on the CFS community. For this reason researchers that make an effort to communicate with the CFS patient community are favored.

Dr. Jonathan Kerr

The B19 Parvovirus - Dr. Kerr's name has most recently been associated with gene expression studies but he came to CFS through his fascinating studies of how parvovirus B-19 infection can lead to CFS. He has studied parvovirus B-19 infection for over ten years. One of his studies found that 13% of those infected came down CFS two years later. Increased cytokine levels in these patients suggested that immune activation was the cause of their symptoms.

In 2005 Dr. Kerr elucidated a novel theory of post-infectious fatigue which suggested that these patients have been able to fight off the invader but that before it was destroyed it managed to insert parts of its genome into ours thus turning part of our genome pathogenic. *This theory is somewhat akin to those who suggest activated retroviral elements in our genome are at the heart of CFS.*

The Kerr Group is now charting gene expression changes in people who came down with CFS after parvovirus B19, Q-fever and enterovirus infection. This study should contribute enormously to our understanding of a very common trigger for CFS – infection.

The Gene Expression Studies - Dr. Kerr is most well known for his gene expression studies. His recent study found evidence of neuronal, immune and mitochondrial dysfunction in CFS. In an interview in The New Scientist he said his team's findings indicate that '*a significant part of*

the pathogenesis resides in the white blood cells' and that this new data '*will open the door to the development of pharmacological interventions*'.

The results of his first gene expression study were sufficiently encouraging for him to embark on a much (much!) larger, more comprehensive study that reportedly contains a thousand CFS patients! Early reports from this new study indicate the results are consistent, so far, with the old study.

Fortuitously Dr. Kerr has just published a paper summarizing his current studies.

Kerr, J., Christian, P., Hodgets, Langford, P., Devanur, L., Petty, R., Burke, B., Sinclair, L., Richards, S., Montgomery, J., McCermott, C., Harrison, T., Kellam, P., Nutt, D. and S. Holgate. 2006. Current research priorities in Chronic Fatigue Syndrome/Myalgic Encephalitis (CFS/ME): disease mechanisms, a diagnostic test and specific treatments. Journal of Clinical Pathology

Dr. Kerr's research team has three main goals.

- to gain a clear understanding of the genes associated with CFS
- To identify protein biomarkers for CFS
- To perform clinical trials on new and established drugs based on their gene expression results

Covering All The Bases - The Gene Expression Studies

Phase I – In this phase Dr. Kerr will attempt to identify genes associated with CFS. This phase will incorporate several gene techniques not commonly used in past gene expression studies.

Checking the Results - Dr. Kerr believes that most of the gene expression studies have had a serious flaw. He asserts that the gene microarrays commonly attribute the wrong genes to the RNA they pick up and that they cannot be trusted unless they are checked by real-time PCR. His is a minority opinion as most gene expression studies have not used this technique. The Whistler Pharmacogenomic study group, however, appeared to echo Dr. Kerr's critique when they stated in rather strong terms that a significant portion of the microarray data is inaccurate and that updating it is a matter of some urgency. Dr. Kerr's critique encompasses most of the CFS gene expression studies done to date including all the Pharmacogenomics studies, the CAMDA efforts, three more CDC studies and the Gow study. He will use real-time PCR to test his results.

This brings up an interesting question. Most of the gene expression studies have highlighted so many different types of genes that it has been difficult to use them to build a model of CFS of pathophysiology (click here). Could this be due to gene misclassification? An examination of the studies that used real-time PCR to check their results suggests not. Neither Dr. Kerr's nor the three other PCR-checked studies had more coherent results. One of them, in fact, found no differences in gene expression between CFS patients and controls.

Testing the Entire Genome - Dr Kerr believes that the inability of the prior gene expression studies to cover the entire genome has left important parts of the gene expression picture in CFS missing. No studies that I am aware of have gone so far as to test half the genome and most have examined far less. His studies will examine all 47,000 genes in the human genome.

When we talk about studying the entire genome we must be aware that researchers are restricted to examining one kind of cell. Because there is no obvious wound in CFS, gene

expression researchers have concentrated on immune cells in the blood that interact with many different areas of the body to get a snapshot of what is going on. While these cells appear to be the best choice available they can't give us a complete picture of everything that is happening in the body. A significant number of central nervous system genes, for instance, are not expressed in these cells.

(Dr. Sullivan is in the middle of a study that is examining gene expression in immune cells, serum and cerebrospinal fluid. This study should be completed in 2007. Click here).

Identifying New Genes – Most CFS gene expression studies identify RNA that is not yet associated with any known functional genes. These genes with as yet unknown functions could play a significant role in CFS. They made up a third of the genes in one CFS study and more than 50% of the genes highlighted in the Whistler Pharmacogenomic's fatigue study. Dr. Kerr will search for these novel gene sequences in his present study. Since this technique can also be used to test for viral genes he will also test for evidence of 28 different kinds of viral infection.

Phase Two – Phase one will hopefully end with the identification of a genetic signature associated with CFS. This will likely consist of a relatively small number of genes whose expression is either increased or decreased in CFS. Dr. Kerr will then test the distinctness of this genetic signature by examining if it is present in many more CFS patients, in people with idiopathic fatigue who do not meet the CDC criteria for CFS, and in people with diseases with some similarities to CFS (e.g. rheumatoid arthritis, osteoarthritis, depression). Dr. Kerr notes that this will probably winnow the down the number of genes first identified in CFS but will leave us with a core set of genes that are functioning abnormally in CFS patients.

Phase Three – the gene signature in CFS will be monitored over the period of a year in a set of CFS patients to determine if a) it fluctuates over time and b) and if certain symptoms are correlated with in the expression of certain genes.

Protein Biomarker – Dr. Kerr has completed a small pilot study which found evidence that reproducible protein biomarkers are present in the blood of CFS patients. This study is currently being repeated on a larger scale.

Two Clinical Trials of Pharmaceutical Drugs in CFS – Dr. Kerr is already fashioning clinical trials based on his gene expression results. Interferon-beta (IFN-b), an immunomodulatory cytokine that boosts the antiviral responses of cells, plays a key role in the early response to viruses. Several aspects of IFN-b make it of interest in CFS; it is known to boost NK cell functioning and to increase production of HLA I antigens. IFN-b has had some effectiveness in treating multiple sclerosis, a disease that often presents with high rates of severe fatigue. This will be the first IFN-b trial in CFS.

Much clinical research on **IFN-b** is currently focused on its use as a treatment for multiple sclerosis (MS). IFN-b1b is marketed as Betaseron and is currently available under the tradename Avonex (Goodkin, 1999).

IFN-b treatment appears to ameliorate autoimmune attacks by enhancing the function of the suppressor T-cells that damp down the immune response. IFN-B also appears to inhibit iNOS activity and improve the integrity of the blood brain barrier and these characteristics are believed to account for its success.

It is primarily used to treat multiple sclerosis, a disease often accompanied by severe fatigue. Several laboratory findings are similar in MS and CFS. Interferon-b treatment has been shown to have about a 30-35% reduction in the rate of MS relapses, and to slow the progression of disability in MS patients. It is not a cure and some MS patients show no effect. Flu-like symptoms are common but often decline over the course of treatment. Other much rarer side effects may include liver, thyroid and heart problems, depression and seizures.

Dr. Kerr is also beginning a trial involving a tumor necrosis factor (TNF) inhibitor called entanercept. We have had much discussion lately of TNF and its possible connection to CFS (s**ee Phoenix Rising**). TNF-a has been implicated in the fatigue not only in CFS but in MS and cholestatic liver disease as well. Etanercept was successful in a very small trial of CFS patients in 2000, but that study (as with so many others in CFS) has not been repeated.

Etanercept, a receptor for TNF-a, works by binding to and thus neutralizing TNF-a. A new drug only released in 1999, it has been used in such inflammatory diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, and ankylosing spondylitis. It is co-marketed by Amgen and Wyeth under the trade name **Enbrel**®.

Many side effects can occur including nausea, headache, etc. Because it is an immune suppressant people taking etanercept run the risk of developing infections – most are mild, but rarely, serious infections can occur. Other rare side effects include blood disorders and lymphoma. Etanercept can worsen a number of diseases including multiple sclerosis, diabetes, heart disease.

Both drugs have anti-inflammatory properties. Dr. Kerr notes the need, given the hypersensitive reactions CFS patients often have to drugs, to start CFS patients off at low doses.

Dr. Kerr ends this overview of his current studies on a note that will cheer many CFS patients. There is little equivocating here – Dr. Kerr expects these studies to play a very important role in advancing our understanding and treatment of CFS. He says that

> "In the **near** future, we can **expect** a diagnostic test for CFS, an understanding of the mechanisms of the disease, and treatments that **will work** in **most** cases of this tragic and all-too-common illness."

Those are big statements indeed: a diagnostic test, a real understanding of how this disease works and treatments that will work for most CFS patients and sooner rather later!!! Few researchers would be so bold. Let's hope Dr. Kerr is correct.

Summary **-** Dr. Kerr appears to be covering all the bases; he is examining the full genome (47,000 genes!), he is checking his results with real-time PCR to ensure that they are accurate, he is identifying novel genes, he is testing for protein analogues to the genes whose expression is increased in CFS and, if reports are correct, he is sampling an enormous number of CFS patients (1000!), and he is checking his results against a large number of control groups. It appears that at the conclusion of his work we will have a really good idea – for better or worse – how effective gene expression studies are in unraveling the mysteries of CFS.

His examination of how gene expression changes in patients who come down with CFS following parvovirus B19, Q-fever and enterovirus infection will also be important in unraveling the process of post-infectious fatigue.

This man is busy! Please support him and his team as best as you can. Studies of this magnitude are very expensive. You can contribute to Dr. Kerr's work through the CFS Research Foundation in the UK http://www.cfsrf.com/index.html
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RESEARCH

RESEARCH – *Unless otherwise noted the research summaries are by Cort Johnson, a laymen and CFS patient. Submissions from others are gratefully accepted. Comments, suggestions, clarifications, etc, negative or positive, only add to the editors and others understanding of CFS. Please send them to Phoenixcfs@yahoo.com).*

Research Summary:

Rating The Months Research - The thesis of this newsletter is that the most important studies deal with the pathophysiology of CFS. Each month is graded according to the following criteria;

A – several difference making papers on CFS pathophysiology
B – a difference making paper on CFS pathophysiology plus several important ones
C - several important papers on CFS pathophysiology
D – 1 or no important papers on CFS pathophysiology but several on other aspects of CFS
F – no important papers on CFS

Research Rating

Total Number of Papers -	**Country of Origin**
Epidemiology - 1	United States -2
Immune -	United Kingdom - 2
Clinical -1	Belgium - 1
Muscoskeletal - 1	Sweden - 1
Brain/CNS - 1	Germany - 1
Endocrine - 1	
Amino Acids - 1	

'PAPER' OF THE MONTH

Voted "Best Paper of the 2006 CAMDA Conference'

The analyses of the 2003 CDC Wichita data didn't stop with the publications in the Pharmacogenomic's Journal. While the CDC researchers and others took a stab at the data, the CDC apparently gave another group of independent researchers their shot at it. Unlike the researchers associated with the Pharmacogenomic's studies the CAMDA effort was international in scope. Researchers from Finland, Canada, the U.K., Italy, Australia, Korea and the U.S. presented their findings in a series of papers presented at the CAMDA conference at Durham, North Carolina in June of 2006.

The CAMDA conference takes the form of a contest in which the presenters vie to produce the best paper using the same gene microarray data set, in this case involving CFS. An enormous amount of very creative work resulted in a presentation of 10 papers and three posters seeking to elucidate biological characteristics unique to CFS, provide a biomarker, and open new avenues CFS research and treatment. They used much the same data set as did the Pharmacogenomic's researchers; gene microarray data from about half the genome, gene mutation data from about 50 neuroendocrine genes, extensive laboratory data focusing on the endocrine system, clinical data on fatigue, symptom severity, and psychological parameters, plus some other researchers had data on protein levels as well. *Proteome data - which provides information on current protein composition - is the analog to gene microarray data.* These the most complex single efforts yet made to understand CFS.

These are conference reports, not published papers, and as such they are less 'finished' than the Pharmacogenomics papers. You may access summaries of the other CAMDA conference papers by **clicking here**.

A Biomarker For CFS Found?

Presson, A., Sobel, E., Papp, J., Lusis, A., and S. Horvath. 2006. Integration of genetic and genomic approaches for the analysis of Chronic Fatigue Syndrome.

This group's goal was to find a potential gene expression biomarker in CFS. They took a much more rigorous approach to solving this problem than is usually done. Instead of simply evaluating which genes are more active in CFS, this group used a statistical process to create sets of genes called 'network modules' whose expression was correlated with each other. Within the modules (if I am reading this correctly), they identified particular gene or genes that displayed high 'connectivity'. These 'hub genes' were intimately involved in whatever kinds of unique type of gene activity that were occurring in the CFS patients.

They found five modules of genes whose expression rose and fell in the CFS patients. In order to check if these modules made any difference in the disease they used a statistical program to determine if any symptoms associated with CFS were correlated with them. Four of the five modules were associated with at least one symptom commonly found in CFS.

These researchers focused on one set of genes or one module whose expression was associated with increased levels of abdominal pain and for overall symptom severity. When they examined this group of genes from a functional standpoint they found it contained many genes involved in nitrogen metabolism and muscle development.

They then examined the frequency of 40 mutations (single nucleotide polymorphisms (SNPs)) in several neuroendocrine genes to determine which if any contributed significantly to symptom severity. They found that a mutation on the tryptophan hydroxylase gene was associated with more severe symptoms in CFS. An examination of the gene modules found that the tryptophan hydroxylase mutation was also most highly expressed in those genes associated with more

severe symptoms. *We have seen this gene before - researchers in the Pharmacogenomics studies also highlighted mutations in tryptophan hydroxylase. This enzyme breaks down serotonin, a neurotransmitter involved in pain perception, mood, libido, lung and gut functioning and others. An overactive enzyme would lead to decreased serotonin levels and vice versa.*

At this point, then, this group has uncovered two factors associated with increased symptom severity in CFS; a set of genes and an inherited mutation in the gene encoding the enzyme that breaks down the serotonin neurotransmitter.

The next step was to find a potential gene biomarker. To ensure that the putative biomarker was valid they required that it pass three tests; it also had to be associated with increased symptom severity, it had to be highly expressed in the subset of CFS patients carrying the tryptophan hydroxylase mutation, and it had to display high connectivity with other genes in the symptom severity module.

Eight genes passed those tests and this group focused on one - the FOXN1 gene – apparently because of its biological plausibility. This gene, called the Forkhead Box gene, plays a role in T-cell development and mutations in this gene have been shown to cause dysfunctional T-cells and an impaired immune response. This is an intriguing gene as we know that reduced levels of the main cytotoxic element in both T-cells and natural killer cells (NK), perforin, occur in CFS **(Click here)**. CFS patients also display increased T-cell activation – perhaps in response to impaired T-cell functioning. *Could the low perforin levels in CFS be caused by a mutation in this gene? Or does this gene simply indicate increased T-cell activation because of a pathogen or a problem with regulating the immune system*.

Despite the current emphasis on the HPA axis and neuroendocrine functioning and all the conflicting immune studies it seems that here we are again back scrutinizing the immune system. As noted above FOXN1 gene is particularly interesting because it can be connected with one of the few consistently found immune abnormalities in CFS – impaired NK cell functioning. This gene's association with a polymorphism that alters the rate of serotonin metabolism adds weight to the notion, now becoming fairly well expressed in the gene expression studies, of a disrupted neuro-immune interaction plays a role in CFS. This makes sense given all the multi-systemic symptoms in CFS. Serotonin is fascinating in its connections to brain induced fatigue, mood disorders and vascular problems, all of which may occur in CFS.

This gene may not be expressed in all CFS patients but it appears to be expressed in a subset of the most severely ill ones. It has not to my knowledge shown up in any of the gene expression studies. One very nice aspect of this gene is that because genomic and antibody markers are available for it should be easy to study in CFS.

As noted above this was only one of eight genes that this group thought might qualify as a biomarker and several of the others were quite intriguing. One, peroxisomal biogenesis factor (PEX6), is involved in the neurological system and metabolism. Peroxisomes play important roles in detoxification and in fatty acid breakdown and there is increasing evidence of fatty acid problems in CFS. *An upcoming issue of Phoenix Rising will focus on this subject.* Several peroxisomal genes have been highlighted in the gene expression studies. Another, the peroxiredoxin 3 (PRDX3) gene, is involved in antioxidant activities and another, myelin expression factor 2 (MYEF2), is involved in nerve cell development. All could fit in, in one way or another, with various findings in CFS..

Dr. Vernon's decision to focus on this paper in her presentation to the conference underscores its importance. There was some indication that she was going to bring additional evidence of the Forkhead Box gene's validity as a biomarker to the conference. Her powerpoint presentation suggested that she did but we can't be sure as we don't have the text to go with

it. If she had confirming evidence, this study certainly would have been the highlight of both the Pharmacogenomics and CAMDA conference's efforts.

A Cause of the Female Predominance in CFS Unmasked?

Grans, H., Nilsson, M., Dahman-Wright, K. and B. Evengard. 2006. Reduced levels of oestrogen receptor B mRNA in Swedish patients with chronic fatigue syndrome. JCP Online First 10.1136/jcp.2005.035956

The female predominance in CFS has long been noted but little investigated. This study begins to rectify this situation through its examination of estrogen receptor abundance and mutation levels.

Estrogen

Formed by the ovary, placenta, testes, and possibly the adrenal gland, the estrogens play a role in sexual development and reproduction, cardiovascular health, the central nervous system (memory, learning, fine motor skill, temperature regulation, mood, reproduction and depression!) and the immune system (!). Altered estrogen levels in the central nervous system could cause increased pain sensitivity, nausea, headache, dizziness, poor mood, etc.

Estrogen is also closely allied with serotonin. Some researchers have suggested that low estrogen levels could contribute to low serotonin. There is evidence of reduced serotonin functioning in CFS.

Given the immune abnormalities sometimes found in CFS it is intriguing that a similar gender bias is also found in several autoimmune disorders (e.g. multiple sclerosis (MS), rheumatoid arthritis, (RA)). A recent finding of increased anti-inflammatory (Th2) cytokine production in CFS suggested that impaired immunomodulation (aka altered autoimmunity?) occurred in CFS as well. Reports that CFS, MS and RA all improve during pregnancy when estrogen levels increase suggest that estrogen could also play a role in CFS and other diseases. *Perhaps the increased incidence of CFS in adults/adolescents vs children also suggest adult sex hormones play a role in CFS as well (?)*

We have two receptors for estrogen, ERa and ERb and a variant ERbcx. *Multiple receptors for a single substance are common.* The ERa and ERb receptors are both found on the endothelial cells and smooth muscles lining the blood vessels, the heart muscle cells and in the CNS and other parts of the body. *This means these parts of the body respond to estrogen.* The ERbcx variant, which inhibits estrogen activity, puts one at increased risk for several primarily female-oriented diseases (anorexia nervosa, bulimia, breast cancer, pre-eclampsia) as well as some diseases of the central nervous system (Parkinson's, Alzheimer's) and prostate cancer. Given the immune and CNS components present in CFS it appears that estrogen could play a role in CFS in any number of ways.

Methods -These researchers examined the mRNA levels for both receptor types and analyzed the frequency of the ERbcx mutation as well in CFS patients and healthy controls.

Findings – CFS patients had significantly reduced ERb mRNA levels relative to controls. Somewhat surprisingly given the association of the ERbcx mutation with disease it was not more commonly found in the CFS patients. *Low levels of the ERb receptor would presumably, however, result in the same outcome as does carrying the ERbcx variant, i.e. low estrogen*

activity. The authors appeared to think this was the case in CFS but noted that the low ERb receptor levels found could be a compensatory mechanism for high estrogen levels.

The authors asserted that the reduced ERb mRNA levels lend credence to the idea of an immunological basis for CFS. *Because estrogen is an immune system inhibitor low estrogen levels could result in the chronic immune activation that may be appearing in CFS.* They suggest that estrogen levels in CFS be checked and that estradiol treatment be tried. *Drugs used to increase estrogen activity in the body have been helpful in treating arthritis, rheumatoid arthritis and inflammatory bowel disease.*

> Estradiol. the most potent naturally occurring estrogen in mammals, is formed by the ovary, placenta, testis, and possibly the adrenal cortex. Estradiol is used in the treatment of menstrual disorders, menopause problems, etc.

Arghhhh!– Just as this study comes out one of the CDC gene expression studies published in the Pharmacogenomics Journal finds that one of the three most upregulated genes in CFS patients was, yes, the estrogen B receptor gene. Thus we appear to have two studies with diametrically opposite results. Perhaps someone who knows better than me can reconcile these two studies.

PERSONAL STORY

Part I: A BREAKTHROUGH EMERGING

By Cort Johnson

'Every cloud has a silver lining'. I generally resist aphorisms such as this but this one may turn out to be true. I faced my problems with carpal tunnel syndrome with dismay. A good deal of my day is taken up with projects that either involve or will involve word processing at some point. An ergonomic keyboard temporarily solved the problem but later the pain came back. I started to read.

Eventually I got a book on repetitive stress injury which, among other things, advocated looking for and massaging tight painful pressure points scattered along the muscles. I had been aware of these tender spots ever since I'd come down with CFS over 25 years ago. Oddly enough, one of my first practitioners, a chiropractor/kinesiologist, told me I had muscle abnormalities over my body, and that in general if I found a painful spot that I should massage it. I tucked that information away, however, and did nothing with it. I certainly had a lot more pressing symptoms - enormous fatigue, orthostatic intolerance, extreme sensitivities to foods and liquids, etc. - to deal with and his treatment did no immmediate discernable good anyway. Unless I probed for these points I was completely unaware of them.

Over time, however, I came to realize how common they were. The one I focused my attention first - only because I came across it while giving foot reflexology a try- is located at the top of my arch. This rather large lump of tight tissue seemed, at least according to the reflexology chart, to be associated with problems in my large intestine. Rubbing it, however, produced nothing more than a large blister. Exploring further, though, I found some exquisitely sensitive points on around my ankles and more points scattered densely along the inside of my shinbone. I also knew I had them on the top and inside of my elbow, and on my shoulder blades and just below my ears on my jawbone. Until a doctor told me otherwise, I believed this one simply marked the swollen and painful lymph nodes often found in CFS. After that I assumed it was, given my mother's struggle with Sjogren's syndrome, due to painful salivary glands. It was not

until a month or so ago, and I realized this painful spot was simply a group of unbelievably tight and clinched muscles.

Then I began to massage the ones on my wrists, arms, and shoulders. To my surprise one on my elbow loosened up in about two weeks. As it did, I could feel the muscles in my arms and shoulder relax. When the same thing happened with the several tender points scattered across my upper back I began to think about the big picture.

One of my key symptoms in CFS has always been my tight contracted muscles and one of my complaints over the years has always been my inability to really relax. It has seemed my body was always kind of 'jacked up', that it was always 'out of sorts', that my muscles often felt tight and heavy. Sometimes as I started out in the morning I could feel my muscles tighten and whatever relaxed feeling was present would quickly disappear. It also seemed that as my body went so did my mind – the more tight and uncomfortable was my body the less focused I was mentally and the more trouble I had concentrating.

Over time I became so disassociated with the feeling of relaxation that I literally forgot it existed. My attention became drawn to the fact that I existed in a rather agitated state some years after I got CFS only when a particularly strong treatment temporarily boosted me into a rare state of relaxation.

As I noted earlier I never reported these tender points to a CFS physician nor have I ever been asked about them. I have, however, told just about every doctor I've seen that my muscles feel tight and contracted and that I get a burning sensation from them after I exercise. Yet no doctor ever began to assess the prevalence of tender points. I am pretty sure, however, if these doctors knew that I had as many as 75 to 100 spots of painful contracted muscles all over my body they would have considered them clinically significant.

These tender points are not in the CDC definition nor are they mentioned in the extensive Canadian definition. They're not mentioned in most general guides to CFS but they are found in Fibromyalgia texts. Could I have FMS instead of CFS? The only assessment I had of FMS came not in a doctor's office but for a study I was engaged in as a CFS patients. This assessment – of the tender points in FMS - indicated I met the criteria for FMS but while I've had considerable discomfort from my muscles and even pain after I exercise too much, pain has never been a central issue in my illness. Fatigue has been a far more pervasive factor for me than pain, and I meet both the CDC and Canadian criteria for CFS.

Massaging the tender points on my upper body quickly lead to a noticeable feeling of relaxation, of an 'at-easeness' and suppleness in my muscles I hadn't associated with them for a long time. My chest seemed to broaden and my breath deepened. I began to wonder if I had stumbled onto something at the core of my CFS. Rubbing the spots on my feet I could feel my back loosen up. Rubbing some really painful ones on my hips caused a large portion of my midsection to relax. Rubbing points on my jaw caused it to loosen and swing down – surely it was these tight muscles were causing me to grind my teeth away. The more I explored and rubbed the more I could tell how 'locked up' my muscles truly were. I had tender points all over my face – below my chin, several places along my jaw bone, my eyebrows, below my eyes and scattered over my skull. My body was basically a mass of clenched and tightened muscles. No wonder I rarely felt relaxed.

This was very exciting and I proceeded to rub away. Over time I located over 100 tender points with really dense aggregations on my lower legs and feet, pelvis and head. Since I each one as a potential to get better, the more I found the happier I was. Some seemed fundamentally important – those on my hips really opened up my abdomen. The one scattered all around my pelvis? – well, I just could just imagine what those could do.

I suggest that everyone should check for these tender points. I have found them; top of my arch, inside outside of my ankles, at base of $3^{rd}/4^{th}$ toes, bottom inside and middle of shin, three spots on knee, two on thigh, all around the pelvis, two spots on hip bones, tip of bottom rib, two spots on forearm, elbow, upper arm, tip of shoulder blade, several around collarbone, upper back, below ears, two on jawbone, below chin, nose, eyes, inner eyebrows, several on forehead, top of head, edge of skull in back. I'm sure there are more.

The editor of the newsletter suggested the following book is a great introduction to dealing to these tender points.
Myotherapy, Bonnie Prudden's Complete Guide to Pain-Free Living

'**Days of the Bloggers'**

Website Updates