

PHOENIX RISING

A CFS/FMS NEWSLETTER

FROM CFS PHOENIX (Phoenix-cfs.org)

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The Phoenix is a mythical bird that rises from the ashes of its own destruction

By Cort Johnson

(Please send submissions, comments and/or clarifications to Phoenixcfs@yahoo.com) 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.

NEWS

Senate Slams NIH and Praises CDC on CFS - The big Senate spending bill now going to the House conference committee has strong language a) commending the CDC on their work on CFS and b) slamming the NIH for allocating CFS funds to non-CFS projects. This bill gives the NIH 60 days to come up with a better accounting method for CFS grants and instructs them to open centers of CFS research. Plus they added \$1,000,000 dollars to the CDC's budget for CFS. Good for Senate and good for the CFIDS Association of America - it looks like its advocacy work is paying off.

Dr. Cheney Returns! - Dr. Cheney returns to Dallas in Sept to reprise his evocative findings on diastolic heart dysfunction in CFS. Among other subjects he will talk on "Chronic Fatigue Syndrome: The Heart of the Matter" a seminar by Paul R. Cheney, M.D., Ph.D. September 9th, 2006, 2 pm - 5 pm, Irving, TX

During his three-hour presentation, Dr. Cheney will discuss his latest research and treatment findings. These include (but are not limited to: Diastolic Dysfunction in CFS / Patent Foramen Ovaeles in CFS / Therapeutic Responses to Cellular Energy Therapy/Echocardiography / Oxygen therapy in CFS. This time a 2-DVD set will come out of this appearance. For more information click on the below URL.

Illness Closes Prominent CFS Web Site/ Chat Group - The CFSFMRsearch website has long been known to many CFS patients as a up to date source of information on CFS. Sadly the health of the sites webmaster, Nico Van Ende, has declined steadily over the past few years and as he is unable to update the website or run chat group, both have been closed. We send Nico our thanks for his work and our best wishes during these very difficult times. You can read Nico's goodbye at the below URL.

<http://listserv.nodak.edu/cgi-bin/wa.exe?A2=ind0607d&L=co-cure&T=0&P=4297>

Dr. De Meirleir Talks - Dr. Meirleir is one of the most innovative and important CFS researcher/physicians we have and there is much stimulating information from his latest talk in Canada. Dr. De Meirleir's ability to differentiate CFS patients from healthy controls, FMS, AIDS, MS, and cancer patients using RNase L fragmentation the most well tested biomarker in CFS. Just as we wondered, once again, what it will take to get the CDC or NIH interesting in

this test we hear that Dr. De Meirleir was able to differentiate 99% of CFS patients in a blind test of blood samples sent to him, yes, by the CDC! This could be big news. It would seem incredible that the CDC would not follow up on such dramatic results with research on its own. ([Click here](#) to find out more about RNase L and CFS). You can find out more from his talk by clicking [here](#) and can get presentations from his latest talk for patients (\$25) or physicians (\$80) by clicking on the below URL.

New CFS discussion group formed - "A forum for discussing the impact of politics on the search for the cause s of and treatments for disabling chronic illnesses of unknown etiology such as chronic fatigue syndrome (CFS), chronic immune dysfunction syndrome (CFIDS), myalgic encephalopathy (ME), myalgic encephalomyelitis (ME), fibromyalgia (FM) and multiple chemical sensitivity (MCS)."

Anyone can join the group by sending a blank email to:
CFS_politics-subscribe@yahoo.com Or you can join at the group's home page:

http://health.groups.yahoo.com/group/CFS_politics/

Kilimanjaro Trek to Aid CFS - On the 1st of September Simon Winnall and Ian Winstanley embark on a great expedition to North-East Tanzania to climb Mount Kilimanjaro, the highest peak in Africa at 5,895 m. All money raised will help fund the ME Research UK research programme.

Simon's sister, Nikki Winnall, <http://archive.thisisworcestershire.co.uk/2005/5/31/11841.html> has suffered from severe ME for the last 8 years and is currently bed-bound with bouts of total paralysis, hence their wish to use the expedition to raise funds for research. Her brother Simon said, "*When Nikki was fit she used to love the mountains; she once walked from North to South Wales to raise money for Great Ormond Street Hospital. I hope by attempting to climb Mount Kilimanjaro we can raise funds and the profile of ME research.*" You can sponsor them by visiting their own webpage to download a sponsorship form, or you can sponsor them online via their own just giving page <http://www.justgiving.com/winnall>. The guys will post a Kilimanjaro blog once they return so you can read about their adventures.

RESEARCH

RESEARCH - *Unless otherwise noted the research summaries are by Cort Johnson, a laymen and CFS patient. Submissions from others on any aspect of CFS 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.*

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
Psychological	United States
Immune	United Kingdom
Clinical	Belgium
Oxidation	Netherlands
Genes	Australia
Endocrine	
Treatment	

THE PAPERS

Special Edition - A Focus on Heredity in CFS

Are people born with a predisposition to CFS? How much of a role heredity plays in who gets CFS has puzzled researchers since its onset. Dr. Cheney reportedly thought it played a mild to moderate role. Several familial studies, however, found evidence that CFS tended to 'run in families'. These methods these studies employed, however, have been criticized.

A familial tendency towards CFS is also not synonymous with a genetic tendency towards it. This is because families share not only genes but a similar environment as well. Since it only takes one person to serve as a vector for a pathogen it is possible, for instance, for members of a family to face increased exposures to particular pathogen relative to the community around it.

Twin studies can also help disentangle the effects of heredity and environment. Five twin studies have indicated from low (25%) to moderate (43-51%) effects of heredity. The largest twin study, done in 2005 ([click here](#)) found that heredity played a modest role in CFS. Just as in the other studies, however, there are methodological limitations to twin studies.

Another way to look at the heredity question is to assess whether there are increased rates of mutation in specific genes thought to play a role in CFS; thus far five studies have examined single nucleotide polymorphism (aka gene mutations) in an array of endocrine, neurological and immune genes. These are the focus of this edition of Phoenix Rising

Single Nucleotide Polymorphism's

SNP's occur when a small spelling mistake occurs in one of the four nucleotide bases (ATCG) that make up our DNA. These mistakes are not uncommon - they occur - approximately 1 every 200 or so bases. In 1999, a consortium of pharmaceutical firms began a project to map 300,000 of the more common SNP's. When they finished several years later, they had mapped about 3 million of them but estimate as many as 30 million exist. For a variation to be considered a SNP it must occur in over one percent of the population.

These alterations are important because they can subtly or sometimes

dramatically alter the structure or function of the protein that the gene is coding for. Variations in SNP's have been shown to impact how people respond to such varied factors as diseases, pathogens, toxins and pharmaceutical

drugs. While some diseases are caused by single mutations, researchers believe it probably takes many mutations to increase ones risk for such complex diseases such as cancer, diabetes, vascular diseases (and CFS).

The gene polymorphism studies, then, examine how important heredity - the genetic makeup one is born with - may be in CFS. The gene expression studies, on the other hand, measure what which genes are active at a single point in time. Although the two are different measures they are not unrelated; researchers are finding that people with different genetic makeups can have different gene expression results as well.

Fortuitously, several immune and neuroendocrine gene mutation studies appeared at the same time. First we take a look at immune gene mutations.

Critical Immune Gene Mutations In CFS Uncovered?

Carlo-Stella, N., Badulli, C., De Silvestri, A, Bazzichi, L., Martinetti, M., Lorusso, L., Bombardieri, S., Salvaneschi, L. and M. Cucci. 2006. A first study of cytokine genomic polymorphisms in CFS: Positive association of TNF-857 and IFNgamma 874 rare alleles. Clin Exp. Rheumatol. 24, 179-182.

This study examined mutations in genes coding for the immune messengers called cytokines. Unfortunately I could only get the abstract of this paper.

Background - Cytokines and CFS - the cytokine picture in CFS is foggy. The high rates of allergy and sensitivity and indications of viral reactivation have led some to propose that CFS patients are Th2 dominant, that is, their immune systems produce predominantly anti-inflammatory cytokines. A recent study finding of increased Th2 cytokine production in response to an immune stressor suggested this was indeed so. Because the pro-inflammatory cytokines are largely responsible for battling intracellular infections, decreased Th1 cytokine production could result in increased levels of viral reactivation - a pattern some believe is occurring in CFS.

Cytokines

Cytokines are hormone-like immune messengers which regulate the immune response, i.e. they turn on or off different immune cells, interact with the HPA axis and the central nervous system, etc. Cytokine upregulation plays a role in many diseases including atherosclerosis, multiple sclerosis, autoimmune diseases, etc. As potent as hormones cytokines are difficult to measure accurately because of their very low levels. Possibly because of poor laboratory techniques cytokine studies have had mixed results in CFS.

On the other hand, increased levels of T cell activation suggest a pro inflammatory state is present in CFS. *Pro-inflammatory cytokines have recently been associated with fatigue and/or*

other fatiguing diseases such as multiple sclerosis and cholestatic liver diseases. They are also largely believed responsible for producing the symptoms one has when sick. Some studies have suggested tumor necrosis factor alpha (TNF-a) plays a role in CFS. The high levels of oxidative stress present in CFS could be the result of high pro-inflammatory cytokine activity.

Thus there is evidence for the existence of a pro or anti-inflammatory state in CFS. *De Meirleir has stated that the immune system in CFS is both under and over activated.* This paper does not resolve this issue but it is the first study - surprisingly given a long history of immune research in CFS - to assess whether or not CFS patients have a genetic predisposition towards pro-or anti-inflammatory cytokine activity.

The Study - These researchers examined the frequency with which 6 polymorphisms in 5 cytokines (pro-inflammatory - TNF-a; Anti - inflammatory - IL-10, IL-6, Other - IFN- γ) occurred in CFS patients and controls. They found that CFS patients had highly increased rates of the two tumor necrosis factor mutations (TNF-a) polymorphisms (308 G/A, -857 C/T) ($p < .002$) and reduced rates of CFS patients who were homozygous for IFN- γ polymorphism (857-TT).

Tumor necrosis factor (TNF)

TNF α is a member of a group of pro-inflammatory cytokines that help produce the early (acute phase reaction) to infection. It is a **very important** cytokine. By inducing the release of other cytokines (IL-1, 6, 8) it promotes further pro-inflammatory cytokine activity. TNF-a increases oxidative stress levels via its activation of the respiratory burst and degranulation in immune cells called neutrophils. *In the respiratory burst neutrophils rev up their engines in order to get ready to attack pathogens. Degranulation involves dumping the toxic contents of granules onto pathogens.* TNF-a also participates in a critical process cells use to destroy themselves when infected called apoptosis.

TNF-a also appears to trigger production of important inflammatory mediators called prostaglandins in the blood vessels of the brain. These prostaglandins could effect body fluids, energy, metabolism and blood oxygenation - all of which may be impaired in CFS. It is possible, therefore, that TNF-a could contribute to some of the central nervous system problems seen in CFS.

Some researchers also believe that increased levels of pro-inflammatory cytokines, including tumor necrosis factor- α , IL-1 β and IL-6, cause mental fatigue by inhibiting the clearance of glutamate in the brain, and through altering the permeability of blood brain barrier (BBB).

TNF-a or the effects of TNF-a may be able to be inhibited by a number of natural compounds, including curcumin (an ingredient in turmeric) and catechins (in green tea)

The TNF 308 G/A polymorphism found in CFS is associated with increased TNF-a production. Increased TNF-a production has been associated with fatigue in both multiple sclerosis and cholestatic liver disease ([click here](#)) and in the 'vital exhaustion' (fatigue, insomnia, unrefreshing sleep, irritability) sometimes seen following coronary angioplasty. suggests that some angioplasty patients respond to a stressor, in this case surgery, with high pro-inflammatory cytokine production, and are fatigued because of it. The increased rate of the TNF 308 G/A mutation in CFS they may respond to stressors in a similar way and be fatigued because of it.

TNF-a in CFS - Like many other immune measures studies examining TNF-a activity in CFS patients have had mixed results. A 2000 study indicated that a process designed to inhibit TNF-a production in the body is impaired in CFS but about only about half the studies examining TNF-a levels in CFS have shown increased levels.

Two studies using a more accurate test involving TNF-a production in response to an immune stimulant (lipopolysaccharides, endotoxins), found either normal or reduced TNF-a production in CFS while one early study (1991) found increased TNF-a production. While TNF-a levels were not increased in CFS relative to controls in a recent study, the response CFS patients had to TNF-a was. Thus instead of having higher levels of TNF-a, CFS patients appeared to display an exaggerated responses to it. (*What a twist that is! A similar situation occurs when rats with cholestatic liver disease respond to negligible amounts of the IL-1B cytokine with severe fatigue.*) Gaab posited that high levels of stress over time lead to a supersensitization to TNF-a and other cytokines in CFS. This suggests that even moderate amounts of TNF-a could be too much for CFS patients.

Interferon- γ (IFN- γ)

IFN- γ is produced by antigen presenting cells (APC's) and Th1 lymphocytes in response to pathogens. It activates Th1 cells, NK cells and macrophages and inhibits Th2 functions. IFN- γ behaves like a biological response modifier and is highly immunoregulatory.

Increased TNF-a levels could effect many problems seen in CFS including increased oxidative stress, chronic immune activation ('sickness behavior'), metabolism (obesity) and nervous system problems (fatigue, etc.)

A Key Genetic Anomaly in CFS?

Rajeevan, M Nathan., Smith, A., Dimulescu, I., Unger, E., Vernon, S., Heim, C. and W. Reeves. 2006. Glucocorticoid receptor polymorphisms and haplotypes associated with chronic fatigue syndrome. Genes, Brain & Behavior

This study takes a detailed look at how commonly mutations occur in the gene encoding the receptor for cortisol in CFS.

With fifteen studies to date and counting (one was released just last month) cortisol has been far and away the most well studied subject in CFS. This is the first full-court press the CDC has done on the mutations in a gene in CFS. Why have the CDC and others been so interested in cortisol?

Cortisol, the main adrenal stress hormone, not only increases the energy available to the tissues during stress but it also regulates the immune response and moderates HPA axis activity (the stress response). Thus cortisol not only ensures that the body has enough energy to cope with a stressful situation it also helps it decide when enough is enough, i.e., when the stress response, including the immune system response, should be ramped down. About half the studies done on the cortisol levels in CFS have found evidence of a mild hypocortisolism (See Hypocortisolism in CFS). Problems with cortisol could result in poor energy, an inability to handle all sorts of stresses well, chronic immune activation and the symptoms associated with that, etc. It is still unclear, however, how the mild hypocortisolism seen in some CFS patients could be responsible for its sometimes disabling symptoms.

The study focuses, however, not on the cortisol producing gene but on the gene producing the receptor for cortisol. Why examine a receptor for cortisol instead of cortisol itself? Because cells react to substances largely through the receptors they carry for them on their surfaces. Like turning a key in a car starts the engine filling a receptor on a cell turns on certain activities in that cell. If that receptor is rare or altered in any way a cell may not be able to respond properly to its environment. If, for instance, the receptor for cortisol is less active than usual then CFS patients could have a hard time turning off the immune response once it has become started.

Cortisol binds to two receptors on cells; it binds to the mineralocorticoid receptor (MR, NR3C2) when the body is at rest and to the glucocorticoid (GR, NR3C1) receptor when the body is under stress. The MR blocks further cortisol production but when the GR binds to cortisol it slips into the nucleus of the cell where it turns on genes involved in multiple activities in the body. A recent study found that GR's interact with more than 1300 genes in liver cells.

Methods - This study assessed how frequently nine mutations in the GR occurred in approximately equal numbers of CFS patients, idiopathic fatigue, and healthy controls. Seventy five percent of the CFS participants were female, the average age was 50.5 years and the average body mass index was 28.8 (overweight but not obese).

Findings - It found that CFS patients were significantly more likely to carry a mutation in the GR gene than were the other groups. The importance of this finding was assessed by determining if the mutations were correlated with increased symptom severity in CFS. If these mutations play a role in CFS then CFS patients with more of them should have worse symptoms. This study found that they did.

A closer examination indicated that five of the nine polymorphisms were significantly increased in CFS and that people homozygous for four of them were two or three times more likely to have either CFS or IF. *Everyone carries two forms of a gene. Being homozygous for a gene means carrying the same two forms.* One mutation in particular (A - rs1866388) was associated with increased fatigue, symptom severity and disability.

CFS patients also displayed increased rates of linkage disequilibrium in one section of the NR3C1 gene. A correlation analysis indicated that the patients with the most fatigue had the highest rates of linkage disequilibrium (LD).

As least so far as I understand it, linkage disequilibrium occurs when mutations cluster in one part of a chromosome instead of occurring randomly. Generally, the closer two mutations are to each other the more likely they will get passed down together. The increased rate of LD indicates one part of the NR3C1 gene is 'studded' with mutations in CFS.

The increased mutation rates in the gene coding for the cortisol receptor suggest that its function is altered in significant numbers of CFS patients. If this is so then the effects of the low cortisol levels seen in some CFS patients may be exacerbated by a reduced ability of their cells to respond to cortisol, i.e. these CFS patients may have difficulty utilizing the already low levels of cortisol available to them.

This was the most extensive exploration yet undertaken into the structure of a single gene in CFS and it was highly successful. Given the results - increased mutation rates in CFS patients, a positive association between gene mutation levels and symptom severity, the high levels of linkage disequilibrium present and their correlations with fatigue, and the identification of one particularly prominent polymorphism - it was not surprising that the CDC believes more analysis of this gene is called for. The authors proposed that a 'fine mapping effort' in the region of the gene where the linkage disequilibrium was found should be done.

Pharmacogenomics III: The Gene Polymorphisms in CFS

Inherited Neuroendocrine Gene Mutations Contribute to CFS?

Goertzel, B., Pennachin, C., Coelho, L., Gurbaxani, B., Maloney, E. and J. Jones. 2006. Combinations of single nucleotide polymorphisms in neuroendocrine effector and receptor genes predict chronic fatigue syndrome. Pharmacogenomics 7, 475-83.

Of all the Pharmacogenomics papers this one made the biggest splash in the press. It was this study that suggested CFS patients have a genetic predisposition to their disease centered in a group of mutations (single nucleotide polymorphisms (SNP's)) occurring in a set of neuroendocrine genes. Most studies attempting to determine if a mutation in a genes increases one's risk for a disease contrast how frequently that mutation occurs in patients versus controls. This study, like most others in these reports, took a systems approach. Instead of looking at whether one or a handful of polymorphisms were more commonly found in CFS patients, these researchers looked at a suite of about 50 inter-related neuroendocrine genes containing about 500 polymorphisms.

A Systems Approach - One of the central assumptions underlying the Pharmacogenomics projects seems to be that there is no silver bullet or single aberration waiting to be uncovered in CFS. Instead CFS is caused by a variety of problems, some subtle, some not-so-subtle, that combine together to create the condition we know as CFS. This idea is not unique to CFS - some researchers believe that broad systemic alterations underlie the problems in other complex, chronic diseases such as diabetes, heart disease, etc.

Findings - These researchers were able to differentiate CFS patients from healthy controls using a combination of 28 SNP's occurring in eight neuroendocrine genes. This finding appears to confirm the systemic nature of the neuroendocrine involvement in CFS; it took mutations in a large set of genes before they were able to detect significant differences between the neuroendocrine mutation rates in CFS patients and the healthy controls. *Does this suggest that the neuroendocrine vulnerability to CFS is both broad and shallow (?)*

The researchers singled out five genes of special-interest:

Neuronal tryptophan hydroxylase (TH2) gene - involved in tryptophan breakdown and serotonin production

5-hydroxytryptamine transporter (HTT) gene - involved in transporting serotonin metabolites out of the cell

- Serotonin - A vasoconstrictor and neurotransmitter, liberated by blood platelets, that inhibits gastric secretions and stimulates smooth muscle; present in relatively high concentrations in two areas of the central nervous system (basal ganglia, hypothalamus) that are of special interest in CFS (See **Central Fatigue in CFS**). Smooth muscles are found in the internal organs including the lungs and lining the blood vessels. The vast majority of serotonin is not found in the brain but in the plasma, gastrointestinal tract and immune tissues.
- An endocrinologist, Dr. Cleare, has posited that that reduced serotonin receptor activity (possibly in response to high serotonin levels) could cause a wide variety of involving sleep, pain, motivation and sexual activity among others in CFS and other diseases ([click here](#)). Reduced serotonin activity has been found in both depression and anxiety.
- A recent study finding of decreased gastric emptying in CFS suggests that low serotonin levels could also contribute to the gastrointestinal problems found in CFS. Both Dr.

Cheney and Dr. De Meirleir believe that gut problems can contribute significantly to CFS. Several studies also suggest that low serotonin may contribute to the pain in FMS. Serotonin also plays a role in the distribution of on body fat - an intriguing finding given the increased waist/hip ratio's found in CFS.

- The 2003 Narita study found increased rates of a mutation in the in a serotonin transporter gene that results in increased serotonin uptake. By reducing serotonin levels in the synapses of the nerves this mutation could also lead to reduced serotonin activity in CFS. A recent study also suggested that reduced serotonin activity contributes to the pain in FMS. It is conceivable that altered serotonin activity in different parts of the brain contributes to the fatigue and pain in CFS and FMS respectively.

The **catechol - O - methyltransferase (COMT)** gene involved in regulating norepinephrine and epinephrine levels. Increased mutations rates of the COMT gene occur in some mood disorders.

- Norepinephrine (NE) - a sympathetic nervous system (SNS) agent (catecholamine) produced in response to low blood pressure and physical stress, NE regulates blood flows (constricts blood vessels) and is an immune system regulator. Reduced NE levels could result in increased inflammation via increased TNF-a, IFN-y, nitric oxide production etc. Increased NE, on the other hand, could lead to reduced blood flows and predominantly anti-inflammatory cytokine production.
- Epinephrine (E) (adrenaline) - another SNS catecholamine, epinephrine causes increased heart rate and force of contraction, vasoconstriction or vasodilation, relaxation of the bronchiolar and intestinal smooth muscles, glycogenolysis, lipolysis, and other metabolic effects. Epinephrine also helps regulate (inhibit) the immune response.

The **cortisol receptor gene (NR31)** and two genes for **corticotropin releasing hormone receptors (CRHR1, CRHR2)**

- Corticotropin releasing hormone (factor) - sits at the top of the HPA axis. It stimulates the pituitary to produce ACTH which in turn prompts the adrenal glands to produce cortisol. A main initiator of the stress response, low CRH production could result in low cortisol levels.
- Cortisol - the main adrenal stress hormone increases blood glucose levels (energy), moderates immune activity and regulates HPA axis activity during stress.

There is evidence of altered serotonin activity in CFS, increased norepinephrine levels and sympathetic nervous activity in CFS, reduced cortisol levels, and reduced responsiveness of HPA axis (CRH). These findings, therefore, are consistent with much of what we know of neuroendocrine functioning in CFS.

It is perhaps notable that four of the five genes regulate immune functioning and three of the five affect blood flows. The authors were not interested in these features but briefly noted that these genes affect the way the body responds to internal signals through the process of interoception.

Interoception

The interoceptive system relates to the information conveyed to the spinal cord and the brain by sensory nerve cells returning from the organs, cardiovascular system, the skin and muscles.

The Aslakson group studying subsets in CFS proposed that one of the three subsets of CFS patients and one of the two subsets of idiopathic fatigue patients identified were characterized by altered interoception.

The interactions that serotonin, norepinephrine, epinephrine, cortisol and CRH have with the interoceptive system suggests to these researchers that it may come into play in CFS. An upcoming paper will examine what the interoceptive system is and how it might play a role in CFS.

This study appears to provide powerful evidence that CFS patients have inherited gene mutations that impair their responses to stressors such as exercise, infection, etc. How important these mutations are, however, is unclear. This study got the most attention in the press but was it the most significant? It was not a slam dunk. The authors stated that the accuracies - 75% accuracy in differentiating CFS patients from controls - did '*not look spectacular*' and noted that researchers really like to see a 90%+ classification success rate. Some outside researchers have questioned the validity of the results given the relatively low number of samples. Others questioned whether other sets of polymorphisms might have produced better results. The authors noted that their accuracy would have been improved not by winnowing out some of the CFS patients but by eliminating those healthy controls who now or earlier had suffered from a bout of long-term unexplained fatigue. Surprisingly this turned out to apply to about 15% of the healthy controls and suggests these factors do play a role in the production of fatigue.

Despite the low accuracy levels displayed, the authors appeared to be quite enthusiastic about their results, saying

"What is encouraging is that this rather mysterious and elusive illness called CFS appears to be finally yielding to attempts at biomarker discovery."

This study is being enlarged and replicated in a different group of CFS patients. We didn't have to wait long for a validation of its results. Just a month or so after the Pharmacogenomics studies were published we got word that another large research effort involving the same data base had been completed. In June the CAMDA (Critical Assessment of Microarray Data Analysis) conference met to report their results.

The Neuroendocrine Gene Mutations - A Summary From the CAMDA Conference - A presentation of the findings from that conference will appear shortly but a summary of them indicates that many of the same gene mutations were highlighted in both efforts. The five studies that successfully examined the gene mutation data highlighted the following genes (some studies did multiple analyses).

- Glucocorticoid receptor (cortisol) NR3C1 - 8
- Tryptophan hydroxylase (TH) - 5
- Corticotropin Releasing Hormone Receptor 2 (CRHR2) - 4

- Catechol-O-Methyltransferase (COMT) - 4
- Monoamine Oxidase B (MAOB) - 4
- Proopiomelanocortin (POMC) - 4
- Corticotropin Releasing Hormone Receptor 1 (CRHR1) - 2
- Corticotropin Releasing Hormone (CRH) - 2

Given the fairly large data set (50 genes/500 polymorphism) the congruence of the results is remarkable and suggests that alterations in genes involved in hormonal (cortisol, corticotropin releasing hormone) and neurotransmitter functioning (serotonin, norepinephrine/epinephrine, dopamine) interact in ways that predispose one to CFS.

Summary - This is all encouraging stuff. Finding increased levels of gene mutations in CFS patients points researchers in the direction of the disease - in this case they suggest CFS is a disease with impaired stress and immune responses. The confluence of neuroendocrine and immune gene mutations is particularly intriguing. In this case it suggests that CFS could both have a predisposition to produce more TNF-a than normal and a reduced ability to turn it off; i.e. CFS patients could, under the right circumstances, could have a tendency to chronic immune activation. Obviously there is more involved here than just inheritance - many CFS patients are, after all, completely healthy until they get felled by whatever causes CFS - but these studies have hopefully begun to unravel the unique vulnerabilities present in CFS and are pointing in the direction of whatever it is that brings things, often quite suddenly, to such a dramatic halt for so many CFS patients.

THE CFS STORIES

Claire's Story

My name is Claire. I cannot put my finger on the day/month/year that I came down with CFS.

I do know that I received antibiotic treatment as a baby for ear infections, and as a five-year old I received a vaccination when I moved into a just painted naval Quonset hut after having stayed with an abusive family for several weeks while my father was in the hospital. I began experiencing IBS symptoms the next year, and then when I was eight I began having bouts of pharyngitis and flu-like symptoms.

For five years in my teens I was put on various antibiotics for acne, and I dropped that treatment when I learned that antibiotics could cause stomach upset. The military doctors that I had been seeing had diagnosed me with a "nervous" stomach--totally ignoring the antibiotics I was on. Throughout this time my energy would go up and down. At 18 I went to an allergist and learned that I had a boat load of allergies; we--my family and I--attributed my bouts of flagging energy to the allergies.

When I left home at 20 my general health improved--that is, I had fewer episodes of flu-like symptoms. At 22, I was hit with an intense bout of fibromyalgia (of course there was no name for it back then and I waited the symptoms out, never seeing a doctor). I think I had had fibro symptoms before, but at 21 a car I was traveling in hit a tree at 65 mph and I think that was that.

By my early to mid 20s I got tired of doctors who had no answers as to why I kept getting the flu-like symptoms and also looked at me as if they wished I would just go away, and so I did--I quit going to doctors for about 8 years. By that time, I knew I had weird reactions to perfumes and household chemicals. I couldn't tolerate air fresheners. I was also experiencing odd symptoms all the time. My hands had not stopped hurting since the bad bout of fibro at 22; I'd

had problematic low blood pressure since my teens, continual headaches since childhood, bouts of dizziness, non-stop ringing in my ears starting at 22, etc.

I finally figured out that I was extremely sensitive to cigarette smoke (my health improved when I left home because I was no longer living with smokers), cats, and paint fumes, and also that each of these could trigger the exact same flu-like episodes and pharyngitis. I came to see these episodes as full-body immune responses, but my doctors simply looked at me.

For a number of years, I managed to avoid cats, paint, and cigarette smoke (quite a feat in the age before it was banned in most work places), and I found that I never had a sick day off from work. I felt bad all the time, but I did not experience the flu-like symptoms. Then, in my early 30's I had an accidental exposure to paint and was sick for three weeks. The allergist I consulted was "intrigued" by the oatmeal like matter that I would cough up from my lungs when exposed to paint, but his interest resulted in not so much as a "stay away from chemicals" because of his fear that he not plant the idea in my head that I might have chemical sensitivities. Around this time, I noticed that the bouts of flagging energy I'd been having was increasing--that is, I was having more of them.

Then at 34, I had another accidental paint exposure and this time I was sick for five weeks and the fatigue was extreme; I did not recover. I stayed seriously fatigued for two years. Of course, I chose to go ahead to law school *as planned*. Seriously, denial had become my best friend (how else does one live with non-stop pain, continual headaches, ringing in the ears, and a host of other strange symptoms), and I thought that the level of fatigue I was feeling was going to be life-long (after all I had watched the fatigue increase over the years).

Then, at the beginning of my second year of law school, I began experiencing explosive diarrhea after allowing my apartment to be sprayed for roaches several times in a couple of months. (Because I have minimal reactions to most other chemicals--other than Lysol, ammonia, moth balls, air fresheners, bleach, paint, polyurethane--, I thought I could handle pesticides.) This ongoing dis-ease led to some surgery and a terrible IBS diet, which I had to boot along with the doctor who suggested it (the same doctor who looked at me like I was crazy when I said that I thought the pesticides had caused the problem).

I did the allergy diet and discovered that my body was rejecting--of all things--foods that were not low in carbohydrates. So I researched all I could about nutrition and supplements, cut out sugar, made my own bread and mayonaise, went on a very low carb diet, gave up dairy and red meat, ate 75% raw foods, and took handfuls of supplements several times a day. After about six months, the diarrhea stopped and one bright and glorious day my energy returned. (One way the body can rid itself of pesticides is through rapid weight loss; it seemed my body knew this and rejected carbohydrates. A very low carbo diet will result in rapid weight loss, but don't try this at home without a doctor's supervision because it can kill you. I did this on my own because I could not find a sympathetic doctor and I was willing to risk death to find health.)

And then at 39 (after being run over by a car as a pedestrian, my dog dying, leaving my husband, moving, my brother being diagnosed with AIDS, and my being laid off), my health began to deteriorate again, and--duh!--I thought that the diet and nutritional supplements weren't working. Actually, I noticed a severe dip in my energy when I started working full-time again after taking a year off after law school (and the car accident). (Funny, as physically exhausting and difficult as law school is, I found it less stressful than WORK even though I put in more hours in school.)

...and so I gave up the diet and the supplements (I thought it was just something else that worked for a while and then failed...like antihistamines). And my energy went up and down and up and down.

By this point in my life I had never had a cold, and as an adult, never had a virus other than the stomach flu three times, and then at 39, I had my first non-stomach-flu virus as an adult. At 44, I think I may have gotten mono, and my doctor did not test me for it because I had an anaphylactic angioedema allergic reaction to a cough medicine at the time I went to see him with what I now believe were the initial viral symptoms, and this reaction caused my neck/glands to really swell up. (I am allergic or sensitive to many drugs; this particular drug--a cough suppressant--is recommended by some to stop reactions to petro-chemicals and paints right in their tracks...and I'm allergic to *IT...sigh*) And the fatigue I felt after those initial viral symptoms felt just like more of the same only worse.

When the (mono?) fatigue finally left (that is, when it finally lessened) after 4 1/2 months (I worked the whole time, although I would cry when no one was around because I was so fatigued), I realized that I had to stop pushing myself. I had to save all of my energy for employment (for that all important paycheck), and so I gave up all volunteer work. By now, I'd become incredibly good at "faking it." As far as I was concerned I was going to fake myself into an early grave, and an early grave was preferable to figuring out how I was going to support myself without an income. (Or live a dull and unfulfilling life.)

Within two years of that probable bout of mono I was going down and not coming back up. I asked my employer to let me work from home, and finally months later when I asked to work 3/4 time from home for 3/4 pay, my employer let me work full time at home. But it was too late. That winter I had the second non-mono virus as an adult. And by spring I was in full denial mode. I had a mortgage, law school loans, and I couldn't see how I would survive without a paycheck.

Also, up until this time, my biggest fear had been that my chemical sensitivities would cause me to have to work from home and that I would be unable to find suitable employment, and here I was with a decent paying job working from home and I was unable to do my work. My migraines had taken over my life, my fibromyalgia was coming on with a vengeance, I lacked energy, and worse yet, I lacked the brain power, and it scared me to death. And so I faked it even more. (Lucky for me I was--note the *was*--pretty bright and so for a long time, I put the hard stuff off until moments when my brain wasn't fogged and skated by on residual intelligence for everything else; my ex-husband used to say that my 40% was like others 110%. I don't take credit for my past smarts; it was one way in which I was blessed in life.)

Not long after I turned 48--just two years after I started working from home--, I mentioned to a co-worker that I thought I had mono again. This was at the beginning of a five-day, 67 work week, where I was on my feet most of the time managing a conference (although I was working from home, I was still responsible for four week-long conferences each year). I proceeded to have these viral symptoms on and off for six weeks when my partner begged me to see my doctor. (By the end of the six weeks I was lying across my keyboard with only enough energy to answer my email.) Although my doctor was skeptical--"most people do not have mono more than once"--, he tested me and found that I had a new mono virus.

And so, I finally allowed myself to crash, and I have been disabled ever since. I never thought then that I would still be so sick now. (I was confident I'd recover in a couple of months--such denial!) I never thought that I'd continue to lack brain power. Although it should have been obvious to me that I have been on a downward spiral all these years (that even my ups had become less up over time)--obvious to me had I not had a long-term affair with denial--, I had always managed to work, to support myself.

Luckily for me, my mother (though she doesn't have much) had a small home in my town that she bought as an investment, and she gave that home to me (the rent from that home wouldn't pay my mortgage, but it allowed me to sell my home and get out from under all of my debt).

Thank God for my mother's intervention, as I had planned suicide at the prospect of losing my home and being forced to move into sub-standard housing with my partner in order to live. After years of trying to control my environment and finally being able to do so by owning my own home, I was facing having to rent. And I couldn't face having to stand up to landlords who wanted to use pesticides or buildings that required painting. I couldn't be as sick as I was/am and have to fight for my right to live at the same time. (I would have never gone to my mother and asked for help, as I knew my mother intended that home to bring income to my disabled brother after she died. *My brother has since died and so my need did not rob him of his financial future.*)

Finally, after years of denial, I accept the fact that I have an illness that is made worse by stress, and I think that diet and supplements do help. As I look to the future, I look forward to learning how to enjoy life more and stress less. And if I recover a semblance of normal energy, it seems clear to me that full-time work combined with the errands required for every day life is more than my body can take.

I've dreamed about lots of jobs I'd like to have--lots of ways I could contribute in life. As if it meant something, I used to say, "If I didn't have chemical sensitivities, then I could do thus and so." Then, one day, I realized that I could NOT do thus and so because there was no Claire *without* chemical sensitivities: she did not exist. It's taken my years to substituted CFS for chemical sensitivities in that sentence.

Obviously, this is not the life I wanted or worked for. I have multiple talents just not the ability. The spirit is willing but the body is not able. I suspect this is true for many people who are ill.

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Life is good. Regardless of the vagaries of living, life is worth living if only to have the opportunity to smell the sweet lemon-vanilla scent of magnolia blossoms, to see one paper-thin periwinkle butterfly flutter about, to feel one cool breeze dance across your skin on a warm summer day, to hear one chickadee call out for a mate, or to taste the juicy sweet nectar of one ripe peach. Joy--the possibility of joy--is abundant even in times of sorrow if only we use our senses. Love life back. – Claire Prideaux

'Days of the Bloggers' - Both Sue and Zona come to grips with the frustration caused by the huge gap between they want to do (and even need to do) and they can do with CFS and Zona decides to just tear up that list of things that need doing.